Toxicology of Solvents

Edited by

Maeve McParland
and Nicola Bates

RAPRA
TECHNOLOGY LTD.

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First Published 2002 by

Rapra Technology Limited

Shawbury, Shrewsbury, Shropshire, SY4 4NR, UK

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A catalogue record for this book is available from the British Library.

ISBN: 1-85957-296-0

Typeset by Rapra Technology Limited
Printed and bound by Polestar Scientifica, Exeter, UK

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All contributors are staff of the Medical Toxicology Unit, London and the UK National Poisons Information Service (NPIS). The authors are Specialists in Poisons Information.

The Medical Toxicology Unit is part of Guy's and St Thomas' Hospital in South London. The Unit, formerly known as the Guy's Poisons Unit and the National Poisons Unit, was formed from the Information Service and Medical Service in 1965. The Poisons Unit was expanded in 1967 with the addition of the Poisons Reference Laboratory.

The Unit offers a complete poisons centre service with medical, information, laboratory and research capacity. Uniquely, in the United Kingdom it offers information, out-patient and in-patient tertiary referral medical toxicology services. The services are offered to support NHS medical and other healthcare professionals as well as selected services to other governmental, quasi-governmental and commercial organisations.

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Acknowledgements

First, all the authors gratefully acknowledge the invaluable assistance of Helaina Checketts, Librarian of the Medical Toxicology Unit.

We are also grateful to our colleagues Alessandro Barelli, Alexander Campbell, Monique Mathieu-Nolf and Sarah McCrea for their work translating papers.

We would also like to thank the information team for their help and support, particularly Nick Edwards and Bethan Redmond. A special thank you to Shaun Greene and Robie Kamanyire.

Introduction

The chapters in this book contain an overview of the toxicity of a number of individual solvents or, in the case of glycol ethers and their acetates, a group of solvents. The emphasis is on occupational exposure, although not exclusively so, as examples and information are drawn from other areas. Definitions of some of the terms used are given in the glossary. Each chapter has the same layout, with information under the following headings.

SUMMARY

This includes a brief outline of the main features and risks of the chemical described.

DESCRIPTION

This section outlines the physical and chemical properties and lists the synonyms and identification numbers (CAS, UN, RTECS, EINECS) of the chemical or chemicals described in the chapter. These properties can influence the toxicity of a chemical. Odour thresholds (the lowest concentration of a vapour or a gas in air that can be detected by odour) are also included, but reported odour thresholds may vary widely. Where this is the case all the figures are quoted with the relevant reference. Several lists of odour thresholds for a number of chemicals have been published (e.g., Amoore and Hautala, 1983; Ruth, 1986).

OCCUPATIONAL EXPOSURE

Exposure limits

Exposure limits are set as the concentration in air of a chemical in the workplace that is thought to be safe. This means that most workers can be exposed at the given concentration or lower without harmful effects. These limits are intended for use as guidelines or recommendations in the control of potential workplace health hazards.

There are several different types of exposure limit. For most of the chemicals described here, the UK and USA time-weighted averages (TWA) are listed. The TWA is the concentration that could be tolerated by an average worker for a 40 hour working week (8 hours a day, 5 days a week). UK limits are quoted from EH40/2000, an annual list of occupational exposure limits published by the Health and Safety Executive (HSE). The American limits quoted are those set by the American Conference of Governmental Industrial Hygienists (ACGIH) in their publication *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. Many countries produce their own lists of occupational exposure limits and an extensive list of international standards and exposure limits is given in the Appendix of *Patty's Toxicology* (Bingham *et al.,* 2001).

Some exposure limits are also given a skin notation because of the risk of dermal absorption in addition to inhalation. This designation does not include substances that can cause dermal irritation, and it should be noted that absorption may be greater through damaged skin.

Biomonitoring

Biomonitoring is used to measure individual exposure to a chemical in addition to air sampling. It involves measurement of the concentration of a chemical determinant in the expired air, blood or urine of exposed workers. The determinant may be the chemical itself, a metabolite or a reversible biochemical change induced by the chemical. The biological exposure index (BEI) generally indicates a concentration of the chemical determinant below which nearly all workers should not experience adverse health effects. They are guidance values for assessing biological monitoring results and apply to 8 hour exposures over a 5 day working week.

BEIs usually represent concentrations which are most likely to be observed in healthy workers exposed to chemicals to the same extent as workers with inhalation exposure at the threshold limit value (TLV). A TLV is a term used by the ACGIH to express the airborne concentration of a material to which nearly all workers can be exposed day after day without adverse effects.

Undue weight should not be placed on a single evaluation of a BEI because of the variability of biological specimens. However, removal from exposure pending further investigation may be considered following a single determination if significant exposure is thought to have occurred. If measurements from a worker persistently exceed the BEI, investigation and action is recommended to reduce exposure. Investigation is also warranted where the BEIs of a group of subjects working in the same area and/or same shift exceed the designated concentration. In addition, samples below the BEI do not necessarily indicate the absence of risk to health (ACGIH, 2000).

BEIs are not intended to be used as a measure of adverse effects or a diagnosis of occupational illness, but they can be used to detect and determine dermal or gastrointestinal absorption in addition to inhalation exposure, to assess body burden, to determine past exposure in the absence of other means, to detect non-occupational exposure in workers, to test the effectiveness of personal protective equipment and engineering controls and to monitor work practices (ACGIH, 2000).

Various notations are included in the ACGIH BEIs. These are as follows:

- B (background) - The determinant may be present in samples from individuals who have not been occupationally exposed. Consequently, this may affect interpretation of the result and these background concentrations are incorporated in the BEI value.

- Nq (non-quantitative) - Biological monitoring should be considered for this chemical but due to insufficient data a specific BEI could not be determined.

- Ns (non-specific) - The determinant is non-specific for a single chemical as it may be detected following exposure to other chemicals.

- Sq (semi-quantitative) - The determinant is an indicator of exposure but the quantitative interpretation is ambiguous. The determinant may be used as a screening test if a quantitative test is impractical, or as a confirmatory test where the quantitative test is non-specific and the origin of the determinant is in question.

TOXICITY

The individual risk from a particular chemical is determined by a number of factors including the route of exposure, dose, duration of exposure, work environment (e.g., temperature, humidity, hygiene practices) and individual factors of the victim (e.g., genetic factors, body mass, age, gender, pre-existing disease, concurrent exposure, correct use of protective equipment) and the chemical (physical and chemical properties). Toxicokinetics including the absorption, distribution, metabolism and elimination of a chemical also influence toxicity (IPCS, 2000). For many chemicals, for example benzene, hexane and dimethylformamide (DMF), it is not the chemical itself but one or more metabolites that are known or thought to be responsible for its toxic effects. In these cases, toxicity may therefore be influenced more by the extent of metabolism rather than the dose.

A solvent may also vary in its constituents and contaminants, and these can also influence toxicity. In some cases investigators have not been specific about the solvent they are studying. For example, white spirit may contain aromatic as well as aliphatic compounds, and these are not always specified; xylenes are available in three isomers or as a mixture and it is not always stated which is under investigation. Toxicity information, particularly in the older literature may relate to contaminants rather than the solvent of interest. This is the case with toluene and xylenes, where the haematological effects reported were probably due to benzene contamination.

Where it has been possible information on human exposure has been used. In some cases this information is lacking and data on animal toxicity has been used although this has its limitations, for example species differences in body size, metabolism, dosing, toxicokinetics, and susceptibility (IPCS, 1999). Information from experimental animals has also been used to support findings from human studies.

Many toxicity studies have limitations involving small sample size, lack of appropriate controls, lack of measurement of exposure concentrations and non-exclusion of confounding factors. These problems have been highlighted where appropriate. Studies on occupational exposure to chemicals are further complicated by the fact that in many situations workers are exposed to a number of different substances and in many cases the effects of an individual solvent cannot be determined.

Mode of action

This section outlines the known and suggested mechanisms of toxicity of the solvents. However, for many of the chemicals described the mode of action has not been fully established and information is limited. In contrast, for some solvents, such as benzene, there is a large quantity of literature on the possible mechanisms of action that are multifactorial and complex.

Metabolic interactions

Many different solvents are metabolised by the same metabolic pathways and consequently may interact with each other. Co-exposure to other substances including tobacco smoke, ethanol or pharmaceuticals can also affect the toxicokinetics or toxicity of a solvent. In some cases the solvent itself may be of relatively low toxicity but can increase the toxicity of other substances. The classic example of this is methyl ethyl ketone (MEK), which can potentiate the toxicity of other substances, making them more hazardous at a lower concentration. In this section studies investigating the extent and possible hazards of metabolic interactions are outlined and each substance is discussed separately. Studies reporting no metabolic interaction are also included.

CASE REPORTS

Case reports are included to provide an overview of poisoning from the solvents discussed. The emphasis is on accidental exposure in the workplace and the case reports serve to demonstrate the variable clinical picture that can result and the circumstances in which poisoning can occur. These include exposure due to faulty equipment, spills, leaks and fires, incorrect use of protective equipment, intentional abuse, formulation changes, lack of knowledge of the risks involved and failure of industrial hygiene practices.

CLINICAL EFFECTS

This section is divided into acute and chronic exposure and details the clinical effects by route of exposure (inhalation, dermal, eye and ingestion). In the industrial situation inhalation is the most common route of exposure (Proctor, 1996; Harbison, 1998) and ingestion is uncommon. However, it is included here for the sake of completeness and because of the potential for accidental or intentional ingestion. For some of the

chemicals described, such as methanol, severe poisoning is most likely from ingestion rather than any other route of exposure, and the majority of the information on the toxicity of the chemical is derived from cases of intentional ingestion. Where similar clinical features can occur from more than one route of exposure, particularly ingestion and inhalation, these effects are described under the heading of systemic effects, to avoid repetition.

In some instances (e.g., toluene, trichloroethane) much of the information on clinical effects in the literature relates to solvent abuse. Whereas exposure in the industrial setting usually involves chronic low level exposure, abuse is usually intermittent inhalation of a very high (often unmeasured) concentration. However, we have tried to make it clear in these chapters what aspect of toxicology is being discussed.

Carcinogenicity

For most of the solvents discussed there is only relatively limited information on the risks of cancer. The exception is benzene. One group of workers exposed to benzene have been the subject of numerous studies and they are the most intensively studied group in occupational epidemiology (Paustenbach *et al*., 1992). For the other solvents most information derives from a small number of case reports and case series. Carcinogenicity is often difficult to evaluate in human populations because of the long lag time between exposure and onset. This makes it particularly difficult to correlate dose to effect, and there are also numerous confounding effects including exposure to other chemicals, socioeconomic factors, alcohol intake and smoking habits that further complicate the picture.

The International Agency for Research on Cancer (IARC), part of the World Health Organization (WHO), publishes authoritative independent assessments by international experts of the carcinogenic risks posed to humans by a variety of agents, mixtures and exposures. The evidence is evaluated from human and experimental animal data and the substance or exposure is categorised. The categories reflect the strength of the evidence derived from these studies and other relevant data. The IARC categories (IARC, 2001) have been stated for the chemicals described, where available. They are defined as follows:

- **Group 1:** The agent is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans.

  This category is used when there is *sufficient evidence* of carcinogenicity in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is *sufficient evidence* of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

- **Group 2**

  This category includes agents, mixtures and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents, mixtures and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data.

- **Group 2A**: The agent is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans.

  This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of *limited evidence* of carcinogenicity in humans.

- **Group 2B**: The agent is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.

  This category is used for agents, mixtures and exposure circumstances for which there is *limited evidence* of carcinogenicity in humans and less than *sufficient evidence* of carcinogenicity in experimental animals. It may also be used when there is *inadequate evidence* of carcinogenicity in humans but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is *inadequate evidence* of carcinogenicity in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

- **Group 3**: The agent is not classifiable as to its carcinogenicity to humans.

  This category is used most commonly for agents, mixtures and exposure circumstances for which the *evidence of carcinogenicity is inadequate* in humans and *inadequate or limited* in experimental animals. Exceptionally, agents for which the *evidence of carcinogenicity is inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category.

- **Group 4**: The agent is probably not carcinogenic to humans.

  This category is used for agents or mixtures for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents or mixtures for which there is *inadequate evidence* of carcinogenicity in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

  The evidence relevant to carcinogenicity from studies in humans (that is, the terms in italics in the above descriptions of the IARC categories) are defined as follows (IARC, 2001):

  - *Sufficient evidence of carcinogenicity*: The Working Group considers that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding factors could be ruled out with reasonable confidence.

  - *Limited evidence of carcinogenicity*: A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding factors could not be ruled out with reasonable confidence.

  - *Inadequate evidence of carcinogenicity*: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

  - *Evidence suggesting lack of carcinogenicity*: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent, mixture or exposure circumstance and any studied cancer at any observed level of exposure. A conclusion of 'evidence suggesting lack of carcinogenicity' is inevitably limited to the cancer sites, conditions and levels of exposure and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

  The evidence relevant to carcinogenicity in experimental animals is defined separately and classified into one of the following categories (IARC, 2001):

- *Sufficient evidence of carcinogenicity*: The Working Group considers that a causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms, or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, tumour type or age at onset.

- *Limited evidence of carcinogenicity*: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, for example, (a) the evidence of carcinogenicity is restricted to a single experiment; or (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent or mixture increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

- *Inadequate evidence of carcinogenicity*: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

- *Evidence suggesting lack of carcinogenicity*: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent or mixture is not carcinogenic. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the species, tumour sites and levels of exposure studied.

Genotoxicity

There are many different types of tests for evaluation of the genotoxic properties of chemicals including tests involving bacteria (usually *Salmonella typhimurium*), yeast (*Saccaromyces cerevisiae*), fruit flies (*Drosophila melanogaster*), cultured mammalian cells and experimental animals (Carere *et al*., 1995). These data have not been evaluated here and only summary information is given. However, information from studies involving exposed workers has been used.

Reproductive toxicity

This section discusses toxicity affecting the reproductive system, including effects on males and females, and the embryo and fetus during pregnancy. In most cases data on humans are lacking or inconclusive and animal data is discussed. However, in many studies the animals are exposed to high doses, sometimes for prolonged periods, and this does not reflect the industrial situation. Consequently, these studies must be interpreted with caution.

RISK GROUPS

Some individuals may be more at risk of adverse health effects following exposure to a particular chemical. This may be due to a variety of factors including body mass, pre-existing disease, gender, age, ethnic differences and genetically determined variation in enzyme activities. The risk groups for a particular chemical are outlined in this section, but in many cases specific studies investigating these confounding factors are lacking.

HOSPITAL MANAGEMENT

Treatment is outlined only briefly and is intended as a guide only; expert advice should always be sought, for example from a poisons information service.

The management of most cases of poisoning is symptomatic and supportive. Gastric decontamination with activated charcoal or gastric lavage is usually only worthwhile within one hour of ingestion (AACT/EAPCCT, 1997a,b). Activated charcoal is made from organic material such as coconut shells, peat or wood that has been burned and then heated to a very high temperature in steam, air or carbon dioxide. The result is a finely divided powder with an extensive pore structure and a large surface area (1,000 m^2/g) that can adsorb a wide range of substances. A substance adsorbed by charcoal is less available to be absorbed systemically, rather, it is carried through the gastrointestinal tract and excreted. However, activated charcoal is unlikely to be of benefit with most solvents because they are not adsorbed, and activated charcoal will therefore be ineffective in reducing absorption from the gastrointestinal tract. Administration of activated charcoal may sometimes result in vomiting and this may increase the risk if the solvent is an aspiration hazard, because of the possibility of pulmonary damage if the chemical enters the lungs. Similarly, where gastric lavage is undertaken, and it will usually only be necessary following an intentional ingestion, the airway must be protected if the solvent is an aspiration hazard.

A small number of substances have specific antidotes and these have been discussed briefly in the appropriate chapters. Treatment of chronic exposure is outlined briefly and in most cases is symptomatic and supportive.

FURTHER INFORMATION

Numerous organisations including those listed here, publish documents on aspects of chemical toxicity and testing, including monographs on specific chemicals.

- **The Environmental Health Criteria (EHC) Series**
  The Concise International Chemical Assessment (CICAD) Series

  These documents are published under joint sponsorship of the UN Environmental Programme, the International Labour Organization and the World Health Organization and within the framework of the Inter-Organization Programme for the Sound Management of Chemicals. Further information is available from: Marketing and Dissemination, World Health Organization, 1211 Geneva 27, Switzerland. Website www.who.int/pcs/index.htm

- **Toxicological Profiles from the Agency for Toxic Substances and Disease Registry (ATSDR)**

  Further information is available from: The Agency for Toxic Substances and Disease Registry, Division of Toxicology/Toxicology Information Branch, 1600 Clifton Road NE, E-29, Atlanta, Georgia 30333, USA. Website www.atsdr.cdc.gov

- **European Centre for Ecotoxicology and Toxicology of Chemicals**

  Several different types of publication are available including Joint Assessment of Commodity Chemicals (JACC) Reports, Technical Reports (TR) and monographs. Further information is available from: ECETOC, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium. Website www.ecetoc.org

REFERENCES

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits.* American Conference of Governmental Industrial Hygienists.

AACT/EAPCCT. 1997a American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position statement: gastric lavage. *Clin Toxicol* 35 (7):711-719.

AACT/EAPCCT. 1997b American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position statement: single-dose activated charcoal. *Clin Toxicol* 35 (7):721-741.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Bingham E, Cohrssen B, Powell CH (editors). 2001 Appendix: United States and international standards. In: *Patty's Toxicology,* fifth edition, Volume 8. John Wiley & Sons Inc., New York, pp. 1103-1326.

Carere A, Mohn GR, Parry JM, Sors AI, Nolan CV. 1995 *Methods and Testing Strategies for Evaluating the Genotoxic Properties of Chemicals*. European Commission Report EUR 15945 EN.

EH40/2000. *Occupational Exposure Limits*. Health and Safety Executive, TSO, London.

Harbison RD. 1998 Diagnosis of occupational disease. In: *Hamilton & Hardy's Industrial Toxicology*, fifth edition. RD Harbison (editor). Mosby, St Louis.

IARC. 2001 International Agency for Research on Cancer website at www.iarc.fr.

IPCS. 1999 *Environmental Health Criteria 210. Principles for the Assessment of Risks to Human Health from Exposure to Chemicals*. International Programme on Chemical Safety, World Health Organization, Geneva.

IPCS. 2000 *Environmental Health Criteria 214. Human Exposure Assessment*. International Programme on Chemical Safety, World Health Organization, Geneva.

Paustenbach DJ, Price PS, Ollison W, Blank C, Jernigan JD, Bass RD, Peterson HD. 1992 Reevaluation of benzene exposure for the pliofilm (rubberworker) cohort (1936-1976). *J Toxicol Environ Health* 36:177-231.

Proctor NH. 1996 Toxicologic concepts - setting exposure limits. In: *Proctor and Hughes' Chemical Hazards of the Workplace*, fourth edition. Hathaway GJ, Proctor NH, Hughes JP (editors). John Wiley & Sons Inc., New York.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

First Aid

SUMMARY

- Terminate exposure and support vital functions
- The victim should be moved to an uncontaminated area
- Rescuers should, ideally, be trained personnel and must be careful not to put themselves at risk and so wear appropriate protective clothing and, if available, breathing apparatus
- If the casualty is unconscious a clear airway should be established and maintained; give 100% oxygen if available
- **Inhalation exposure:** If the patient stops breathing, expired air resuscitation should be started immediately using a pocket mask with a one-way valve, if available. It is important where the face is contaminated that expired air resuscitation (i.e., mouth-to-mouth) is NOT attempted unless an airway with rescuer protection is used
- **Dermal exposure:** Remove contaminated clothing, if possible under a shower and place in double, sealed, clear bags and label; store the bags in a secure area away from patients and staff
- Wash skin thoroughly with copious amounts of water
- **Eye exposure:** Irrigate thoroughly with water or saline (normal, 0.9% NaCl) for 15 minutes
- **Oral exposure:** If the patient/victim is conscious and alert and able to cooperate, encourage small quantities of oral fluids (no more than 50-100 ml in total)

Only general information on first aid is given below. In an emergency call for medical assistance and take steps to limit exposure to others.

DECONTAMINATION

Decontamination is essential following a chemical spill. Although some chemicals can be absorbed through the skin it is more likely that a greater proportion will be absorbed through the lungs from inhalation of the chemical from contaminated skin and clothing.

Dermal decontamination

Contaminated clothing should always be removed and place in double, sealed, clear polythene labelled bags. They should be stored in a secure area to prevent further contamination. Clothing should not be removed if it is stuck to the skin as this may cause further damage. Copious amounts of water should be used, if possible a shower, in cases of extensive contamination. Care should be taken to ensure the runoff water is disposed of appropriately and does not contaminate others.

Eye decontamination

Water or normal saline (0.9% NaCl) should be used for irrigation. Eye washes should be available in the workplace. It is essential to ensure that the whole eye has been irrigated including under both lids. The head should be positioned to ensure that the contaminated irrigating fluid does not run into the other eye or the mouth.

Ingestion

The victim should **not** be made to vomit. Many solvents are an aspiration hazard and may pose more of a risk if they enter the lungs than by ingestion. Aspiration may occur when drinking the solvent or if the victim subsequently vomits. If the victim is conscious and alert and able to cooperate, with no evidence of oral burns, a small drink of water may be given, but they should not be forced to drink. Ingestion of large quantities of oral fluids is not recommended because this may result in vomiting. Care should be taken to avoid contact with vomit as it may be contaminated and it should be removed from the victim's face and clothing.

Inhalation exposure

Removal from the source of exposure is essential. Rescuers should take care not to put themselves at risk. There are many cases reported where the initial rescuers on scene have needed to be rescued themselves as a result of overexposure. Protective equipment should be used to remove a victim from a contaminated area. Some solvents are heavier than air (those with a relative vapour density of more than 1) and will collect in low areas, for example, at the bottom of storage tanks. In these cases it is particularly important to use protective equipment. It should be noted that the extra effort and exertion that may be required to lift or drag an unconscious victim away from the source of the exposure, may increase the respiratory uptake of the solvent by rescuers.

GENERAL POINTS

If the victim is unconscious they should be placed in the recovery position. It is essential to ensure the airway is clear and to remove any obstruction (e.g., vomit, false teeth). Ensure the tongue is not blocking the airway. Nothing should be given by mouth to an unconscious or convulsing victim and nothing should be placed in the mouth of a victim who is convulsing.

In the case of a chemical incident such as a spill or leak it is essential to determine the chemical(s) involved to ensure that a proper risk assessment of the situation can be made.

1 Acetone

Jennifer Butler

SUMMARY

- Acetone is absorbed by all routes; inhalation is the main route of exposure in the workplace
- Vapour exposure leads to irritation of the mucous membranes, eyes, nose and throat
- Systemically, acetone is a central nervous system (CNS) depressant leading to dizziness, confusion and drowsiness which can progress to stupor and coma depending on the concentration and length of exposure
- Toxicity following acetone exposure is non-specific; systemic effects may be confused with other medical conditions
- Acetone has not been reported to increase the risk of cancer in occupationally exposed individuals
- Although animal studies suggest that acetone at high concentrations may be teratogenic, there is very little information to suggest that it has the same effects in humans

DESCRIPTION

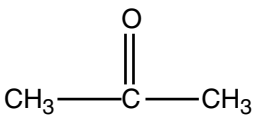
Synonyms

Acetone, dimethyl formaldehyde, dimethyl ketal, dimethyl ketone, ketone propane, methyl ketone, propanone, pyroacetic acid, pyroacetic ether, beta ketopropane, 2-propanone, allylic alcohol, ketone propane, acetone oil

Identification numbers

CAS	67-64-1
UN	1090
RTECS	AL 3150000
EINECS	2006622

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	C_3H_6O
molecular formula	
molecular mass	58.09
physical form	volatile, highly flammable liquid
relative vapour density (air = 1)	2.00
flash point (°C)	–18

boiling point (°C)	56.5
autoignition temperature (°C)	465
refractive index	1.356
explosive limits in air (%v/v)	2.6–12.8

Odour threshold

A wide range of odour thresholds have been documented for acetone ranging from 13 to 680 ppm (Amoore and Hautala, 1983; Ruth, 1986; Morgott, 2001). There may be a degree of tolerance in the perception of acetone odour. Workers with previous occupational exposure to acetone had reduced perception of the intensity of acetone at a concentration of 800 ppm, than non-exposed control subjects (Dalton *et al.*, 1997).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK): 750 ppm (1810 mg/m^3)
TWA (ACGIH): 500 ppm (1190 mg/m^3)

Conversion factors

1 ppm = 2.37 mg/m^3
1 mg/l = 421 ppm
1 mg/m^3 = 0.421 ppm

Biological monitoring

The ACGIH biological exposure index for acetone is an end of shift urinary acetone concentration of 50 mg/l (ACGIH, 2000). Acetone can occur naturally in humans as a by-product of metabolism (giving a blood concentration of up to 10 mg/l), and may be present in the urine of individuals who have been exposed to other agents; this must be taken into account when interpreting blood and urine results (ACGIH, 2000; Baselt, 2000).

TOXICITY

Acetone is ubiquitous; in addition to its extremely wide use as a solvent, it is a naturally occurring metabolite in plants and animals. In humans, it is produced in the breakdown and use of stored fats. Industrially, its role can be divided into three main areas; use as chemical feedstock, as a formulating solvent for commercial products, and as an industrial process solvent. Owing to its many useful properties it is the preferred formulating solvent for a huge range of paints, varnishes, inks, car-care products, coatings and even for use in health and beauty products.

Acetone is absorbed by all routes, but in the industrial setting, toxicity is most likely by the inhalation route, and then only in exceptional circumstances. Acetone toxicity does not have a characteristic syndrome and signs of intoxication may be confused with other medical conditions (Foley, 1985; Morgott, 2001).

Normal blood acetone concentrations can be up to 10 mg/l (Baselt, 2000). The amount of acetone present can be affected by many physiological, clinical and chemical factors such as, pregnancy, lactation, dieting, vigorous physical exercise/exertion, starvation, diabetes mellitus and prolonged vomiting (Morgott, 2001). In relation to the workplace, an important contributing factor is increased physical effort, which may increase acetone production and this should be taken into account when interpreting blood and urine concentrations.

Following exposure to acetone, blood concentrations may not correlate with clinical effects. In a case reported by Wijngaarden *et al.* (1995) an acetone concentration of 290 mg/l was associated with decreased levels of consciousness. The patient was reported to have a Glasgow coma scale (GCS) of 8 with a blood acetone concentration of 490 mg/l. The patient was acidotic (pH 7.11), and this may also have been a contributing factor to her altered level of consciousness. An alcoholic patient, who had ingested an unknown quantity of isopropanol, was awake and conversant with an acetone concentration in excess of 1,600 mg/l (Gaudet and Fraser, 1989). A concentration of 4,450 mg/l was recorded in a child who had ingested an estimated 160 ml of nail varnish remover (acetone 60%, isopropanol 10%). The patient was comatose, with areflexia and respiratory depression (Gamis and Wasserman, 1988). Ingestion of 5,440 mg acetone (80 mg/kg) in a male volunteer (an estimated 7 ml of pure acetone) had no reported ill effects. Acetone was detected in the blood soon after exposure at a concentration of 720 mg/l (Haggard *et al.,* 1944).

Fatalities following exposure to acetone are extremely rare and patients can survive massive exposure with good supportive medical management (Strong, 1944; Gitelson *et al.,* 1966; Gamis and Wasserman, 1988; Gaudet and Fraser, 1989; Wijngaarden *et al.,* 1995).

Absorption

Acetone is rapidly absorbed via the lungs. It has a high blood:air partition ratio, suggesting that a large portion of inhaled acetone is absorbed (Haggard *et al.,* 1944). Volunteers exposed to acetone vapours at concentrations of 100 and 500 ppm had peak blood concentrations of 100-700 mg/l at two hours post exposure (Baselt, 2000).

On ingestion acetone is rapidly absorbed. Ingestion of 10,000 mg of acetone, on an empty stomach achieved a peak blood acetone concentration of 327 mg/l, at ten minutes post ingestion (Baselt, 2000).

Distribution

There is very little information on the distribution of acetone. However, it is a non-ionic substance, miscible with water, and these properties allow it to passively diffuse across cell membranes, and distribute throughout body fluids (IPCS, 1998; Morgott, 2001). The volume of distribution for acetone is 0.8 l/kg (Baselt, 2000).

Metabolism

Acetone is metabolised by a variety of routes. The three main routes have been identified as the lactate, methylglycoxal and propanediol pathways. It is metabolised by these pathways via several intermediates. Most of the intermediates and final metabolites are not considered to be toxic (Harbison and Garvey, 1998; IPCS, 1998; Morgott, 2001). Acetone is gluconeogenic, i.e., it can be used as a material source for the biosynthesis of glucose. The body also utilises the metabolites of acetone for the synthesis of other endogenous compounds.

The first step in acetone metabolism is cytochrome P450 oxidation to acetol by the enzyme acetone monooxygenase. The acetol is further metabolised by either of two pathways, an intrahepatic methylglycoxal pathway or an extrahepatic propanediol pathway. The oxidation of acetol to methylglycoxal is also cytochrome P450-dependent. At larger acetone concentrations, above those resulting from normal metabolic processes, the activity of cytochrome P450 CYP2E1 is induced, and consequently functions at a much higher rate. This in turn increases the enzymatic elimination of acetone. This self-induction allows acetone to regulate its own metabolism (Morgott, 2001).

Elimination

Endogenous acetone is eliminated via metabolic pathways (IPCS, 1998; Morgott, 2001). At higher concentrations, these pathways can become saturated, and elimination is mainly via the lungs (Morgott, 2001). This was confirmed by human volunteer studies carried out by Nomiyama and Nomiyama (1974). The authors studied the elimination of seven organic solvents via the respiratory tract. Acetone was found to have a high ratio of eliminated to retained solvent, suggesting that acetone is eliminated unchanged via the lungs with a small portion retained in the blood. The remaining acetone is eliminated via the kidneys and by its metabolic pathways.

The elimination half-life of acetone is variable but usually falls in the range 18-27 hours (Natowicz *et al.*, 1985; Sakata *et al.,* 1989; Jones, 2000). Acetone is removed by haemodialysis at a rate of 7,000 mg per hour (using a 1.0 m^2 standard dialyser). This is approximately 40 times the rate of urinary elimination (Rosansky, 1982). Urinary elimination of acetone is linearly related to the amount of acetone absorbed (Pezzagno *et al.,* 1986).

Mode of action

The mechanism of toxicity of acetone is not fully understood. It appears to be moderately toxic to the liver causing haematological effects, but the mechanism of these effects is unknown. In rodent studies, acetone has been reported to be nephrotoxic possibly due to hyaline droplet formation, but this mechanism is not relevant in humans. Liver and kidney weights are increased in experimental animals exposed to acetone. This may be a result of acetone induction of microsomal enzymes (reviewed in IPCS, 1998 and Morgott, 2001).

The CNS effects witnessed in acetone intoxication may be attributed in part to the metabolic acidosis caused by acetone. Accumulation of ketones can occur in certain disease states, e.g., in diabetic and alcoholic ketoacidosis. The resultant acidosis can cause CNS effects such as lassitude, dizziness, delirium, and drowsiness.

Metabolic interactions

Acetone can interact with other agents in two main ways:

Enzyme induction

Acetone is an inducer of cytochrome P450 CYP2E1 and other microsomal enzymes (IPCS, 1998; Morgott, 2001). As many other industrial chemicals are metabolised via this enzyme system, increased activity can increase the potential toxicity of other workplace chemicals.

'Co-solvency'

Geller *et al.* (1979) have suggested a mechanism of 'co-solvency', which may be particularly significant for nervous system tissue, where there are barriers between the circulation and the nerve cells. Membranes with a high fat content such as myelin, preferentially take up hydrophobic molecules, whereas penetration to the cytoplasm of the nerve cell bodies is facilitated by a hydrophilic molecule. In some instances combinations of solvents may have a synergistic effect, acting as a single agent. This synergism is not limited to interactions involving acetone.

- **Carbon tetrachloride (CCl_4)**

  Acetone is considered a major potentiator of CCl_4 toxicity (Folland *et al.*, 1976; IPCS, 1999). This may be related to acetone-induced enzyme induction, increasing the production of the reactive metabolites of CCl_4.

- **Hexane and methyl *n*-butyl ketone (MnBK)**

  Both hexane and MnBK are metabolised to the neurotoxic metabolite, 2,5-hexanedione. The serum and nerve concentration of 2,5-hexanedione was significantly increased in rats treated with 2,5-hexanedione in combination with acetone compared to 2,5-hexanedione alone. The effect with acetone was weaker than that of methyl ethyl ketone but stronger than that of toluene (Zhao *et al.*, 1998).

- **Methylene chloride**

  One of the routes of metabolism of methylene chloride is a microsomal oxidation process (involving cytochrome P450). Carbon monoxide is formed by this microsomal oxidation pathway (Gargas *et al.,* 1986) and concurrent exposure to acetone may increase the production of carbon monoxide, by the induction of this pathway.

- **Methyl ethyl ketone (MEK)**

  In volunteer studies, exposure to a mixture of MEK and acetone had no effect on neurobehavioural performance. MEK does not potentiate the effect of acetone and there is no pharmacokinetic interaction between the two ketones (Brown *et al.,* 1987; Dick *et al*., 1988; Dick *et al*., 1989).

- **Trichloroethylene**

  Trichloroethylene is metabolised principally in the liver by two pathways, one of which is by oxidation via cytochrome P450. Induction of this isoenzyme system by acetone may increase the metabolism of trichloroethylene to its toxic metabolites. The toxic metabolites of trichloroethylene may affect dopaminergic transmission in the brain resulting in CNS dysfunction (Mutti and Franchini, 1987).

CASE REPORTS

Coma and metabolic acidosis following application of a muscle liniment

A 47 year old woman presented to a rural hospital with a 2 to 3 week history of increased weakness, dizziness and fatigue. The main concern at the time of presentation was a 24 hour history of decreasing level of consciousness. At presentation the patient had normal vital signs but a GCS of 8 to 10. Initial blood biochemistry showed an anion gap acidosis, with a normal blood glucose concentration (5.1 mmol/l). The patient required intubation and was transferred to a regional hospital. On arrival at the emergency department, she had a GCS of 10. The only other striking feature was a marked metabolic acidosis (pH 7.09-7.11). Aspartate aminotransferase (AST) and creatinine were slightly elevated. The patient underwent haemodialysis. Further blood results showed an acetone concentration of 8 mmol/l (464 mg/l). After 10 hours of dialysis her mental status improved considerably. Blood acetone concentrations 6 hours post dialysis were 3 mmol/l (174 mg/l). The following morning her level of consciousness deteriorated again. Acetone concentrations were repeated and were 5 mmol/l (290 mg/l). She was dialysed for a further 6 hours, with a post dialysis acetone concentration of 1 mmol/l (58 mg/l). The acetone concentrations remained at this level for a further 24 hours with the patient awake and well. On closer questioning it was discovered that the patient had, for a 1–2 week period, been applying a muscle liniment for leg discomfort. The most recent application had occurred on the day before admission. On examination the liniment in question was found to be 70% v/v acetone. Inhalation, as well as the dermal route, was thought to be significant in this case (Wijngaarden *et al.,* 1995).

Acute inhalation of acetone

Several workers became unwell after occupational exposure to acetone. They had been involved in cleaning out a pit into which water from a burst water main had flowed 10 days previously. Near the pit there were four 10 gallon tanks which were ultrasonically agitated. Two tanks contained acetone and two contained 1,1,1-trichloroethane. The water from the burst pipe had escaped into the pit, joining water which had seeped through the foundations. Four workers began removing the 4 inch depth of water from the bottom of the pit. Two shovelled water into a bucket which was pulled out of the pit on a rope. Two of the workers noticed a sickly sweet smell and one complained of weakness and a headache. The other complained of eye irritation and feeling drunk. After returning from an hour lunch break he collapsed in the pit. One of the workers who had been pulling the bucket out of the pit went to help him. However, he felt faint and sent another worker for help. Four other workers helped the two men in the pit. These workers complained of dizziness, eye irritation, chest tightness and weakness. The two workers who had spent longest in the pit were admitted to hospital. One was unconscious with vomiting and a poor pulse. The other who had been the first to collapse, was drowsy, nauseated, vomiting, confused and ataxic. Both recovered. Measurements in the pit 3 hours, 18 hours and one week later found air concentrations of acetone in excess of 12,000 ppm and 1,1,1-trichloroethane up to 50 ppm. It was thought that the acetone had gradually evaporated from the tanks, moved along the floor to the pit and some had become dissolved in the water. Agitation of this water by shovelling into a bucket had increased the concentration in the pit by releasing dissolved acetone (Ross, 1973).

CLINICAL EFFECTS

Acute exposure

Inhalation

Human volunteers exposed to acetone vapours of 200 ppm considered it satisfactory for an eight hour exposure period. A concentration of 300 ppm produced slight irritation, and at 500 ppm the subjects complained of irritation to the eyes, nose and throat, but considered the atmosphere still tolerable (Nelson *et al.,* 1943). Workers exposed to acetone concentrations in excess of 12,000 ppm over a period of several hours developed dizziness, confusion, drowsiness, ataxia, and in one case coma (Ross, 1973). Application of a synthetic plaster cast using an acetone based solvent lead to systemic toxicity in the treated patients (Hift and Patel, 1961). See systemic effects below.

Acetone exposed workers may develop a tolerance to the irritant effects of acetone. In a study of occupationally versus non-occupationally exposed individuals, the perceived irritant effects of acetone (800 ppm) were significantly lower in the occupationally exposed group. While the control group complained of a wide range of symptoms including skin irritation, nasal congestion, itching and sweating, the occupationally exposed group had fewer complaints, with nasal irritation the only symptom described as exceeding the rating of 'weak' (Dalton *et al.,* 1997).

Keisswetter *et al.* (1996) studying the effects of night-shift work and solvent exposure, found that acetone exposed workers (average air concentration, 1,000 ppm) complained more of tiredness, tension and annoyance compared to the control and mixed solvent groups. In a primate study, baboons exposed to 500 ppm acetone for 24 hours per day for seven days, had reduced response times at tasks, but there was no effect on the accuracy of the tasks (Geller *et al.,* 1979).

Systemic effects are unlikely from occupational inhalation exposure except in exceptional circumstances and at concentrations vastly exceeding the current workplace exposure limits.

Dermal

Acetone is a skin irritant. With prolonged contact it may have a defatting action on the skin. Topically applied acetone left on human subjects for 30 to 90 minutes caused considerable damage to the skin, with recovery by 72 hours post exposure (BUA, 1997).

Acetone is absorbed dermally. Systemic effects have been reported in patients exposed to acetone during the application of synthetic casts and from the topical application of a muscle liniment. In these cases however, inhalation may also have played a role in the absorption of the acetone (Strong, 1944; Hift and Patel, 1961; Wijngaarden *et al.,* 1995).

Eye

Acetone at concentrations exceeding 500 ppm caused irritation to the eyes of volunteers (Nelson *et al.,* 1943; Dalton *et al.,* 1997).

Direct splash contact to the eye causes an immediate stinging sensation. Serious effects are unlikely if the eye is promptly irrigated. Patchy epithelial injury may occur but usually recovers over 24 to 48 hours (Grant and Schuman, 1993).

Ingestion

Acetone is irritating to mucous membranes. On ingestion it causes pain and redness to the mouth and throat. Ingestion of 200 ml caused swelling of the throat with erosions to the soft palate and entrance to the oesophagus (Gitelson *et al.,* 1966). Acetone is quickly absorbed from the gastrointestinal tract with systemic effects likely via this route.

No toxic effects were reported in adults after oral administration of 40–80 mg/kg (Haggard *et al.*, 1944). Ingestion of 200 ml of pure acetone caused coma and respiratory depression (Gitelson *et al.,* 1966).

Acetone is not an aspiration risk (Panson and Winek, 1980), however, there may be a risk of aspiration of stomach contents in an acetone-poisoned patient, with altered mental status.

Systemic effects

There are many reports describing the clinical effects of acute acetone intoxication (Strong, 1944; Hift and Patel, 1961; Gitelson *et al.,* 1966; Gamis and Wasserman, 1988; IPCS, 1998; Morgott, 2001). Acetone is a CNS depressant leading to dizziness, lethargy, confusion and drowsiness. These effects may progress through stupor to coma, depending on the concentrations and length of exposure. Pupils may be pin-point.

Gastrointestinal effects include nausea, abdominal pain, and late onset vomiting which may contain blood. There is risk of aspiration of stomach contents in the sedated patient. Commonly, the breath has a strong fruity odour. In severe cases Kussmaul breathing and respiratory depression occur. Acidosis is a common feature, and the patient may also be sweating, flushed and tachycardic.

As endogenous acetone is involved in the biosynthesis of glucose, hyperglycaemia may occur following large exposures. In cases where intoxication has been severe, hyperglycaemia may persist after the patient has recovered from the acute phase of toxicity. The persistence of hyperglycaemia has been reported to last from 4 days to 4 months (Strong, 1944; Gitelson *et al.,* 1966).

The clinical picture of acetone intoxication is not specific and can be confused with other medical conditions, e.g., diabetic and alcoholic ketoacidosis (Foley, 1985; Morgott, 2001).

The reports of renal effects following acetone exposure are conflicting. In animal models, acetone has been observed to cause renal toxicity. However, renal effects have not been reported in cases where patients have had high blood acetone concentrations. Hawley and Falko (1982) reported a case of elevated serum creatinine in the absence of renal damage following ingestion of isopropanol. This deranged level was attributed to high acetone concentrations (acetone is a metabolite of isopropanol), possibly interfering with the assay, rather than a direct toxic effect by the parent chemical or its metabolite. The renal effects reported in some cases of acetone poisoning may be secondary to muscle breakdown in the deeply sedated patient.

Chronic exposure

Inhalation

There are very few reports to indicate that prolonged inhalation of low vapour concentrations result in any serious chronic effects in humans. Workers exposed to 1,000 ppm 3 hours per day for 7 to 15 years complained of inflammation of the respiratory tract, stomach and duodenum (Vigliani and Zurlo, 1955).

Immunotoxicity

Acetone has provided conflicting results in sensitisation tests in animals and there are no data available on a sensitising effect in humans. It did not give a positive result in a mouse ear swelling test. This test is performed to judge the allergenic potential by observing the amount of swelling occurring after a topical challenge (BUA, 1997).

Dermal

Acetone is a skin irritant. With prolonged contact it may have a defatting effect. Topically applied acetone left on human subjects for 30 to 90 minutes caused considerable damage to the skin, with recovery by 72 hours post exposure. Acetone has provided conflicting results in sensitisation tests in animals and there are no data available on a sensitising effect in humans. However, as acetone is an endogenous compound present in relatively high concentrations in the normal population, as well as having a role in metabolism, a sensitising effect from acetone is unlikely (BUA, 1997).

Eye

No information available.

Ingestion

No information available.

Carcinogenicity

Acetone has not been evaluated by the IARC as a human carcinogen. A review of the literature by Morgott (2001) found that workers exposed to acetone in various industries did not show any significant increase in the incidence of mortality from non-Hodgkin's lymphoma, multiple myeloma or breast cancer.

Genotoxicity

Various mutation studies, with and without metabolic activation, were negative for various *Salmonella typhimurium* and *Bacillius subtilis* strains exposed to 1-10 mg acetone per plate or well. There were also negative findings for a range of sister chromatid exchange assays (reviewed by BUA, 1997 and IPCS, 1998).

Reproductive toxicity

There is very little information on the effects of acetone on reproduction and developmental effects in the human population. The majority of studies have involved workers with co-exposure to multiple solvents.

Agnesi *et al.* (1997) investigated 108 women exposed to 12 solvents involved in shoe making. The risk of spontaneous abortion was found to be higher in the exposed group compared to controls. However, in a similar study by Taskinen *et al.* (1989) there was no significant increase in the risk of spontaneous abortion in acetone-exposed workers. This conclusion was reiterated in a later study involving female laboratory workers (Taskinen *et al.*, 1994).

In animal and embryo studies acetone has been found to produce mild reproductive and developmental changes. However, these studies involved the use of acetone at extremely high concentrations (reviewed in Morgott, 2001).

RISK GROUPS

There are no specific risk groups for acetone. However, acetone is an inducer of CYP2E1 and may increase the toxicity of other workplace chemicals metabolised via this enzyme.

HOSPITAL MANAGEMENT

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Gastric lavage is not necessary following ingestion of acetone. Activated charcoal is not of benefit. If there has been any vomiting, coughing or wheezing in a patient with altered mental status, then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive. See below for management of systemic effects.

Systemic effects

Treatment for acetone intoxication is essentially supportive. It is important to ensure the patient is adequately hydrated. The electrolytes, blood glucose and blood gases should be monitored. Acidosis should be treated aggressively with bicarbonate. If facilities allow, blood should be taken for the determination of blood acetone concentrations. In patients with decreased mental status the renal function should be monitored. Respiratory depression may require ventilation. Haemodialysis removes acetone at approximately 40 times the rate of urinary elimination, and should be considered in patients with severe CNS, respiratory or metabolic toxicity.

Antidotes

There is no specific antidote for acetone.

Chronic exposure

In most cases of chronic poisoning clinical effects resolve gradually once exposure has ceased. Treatment is symptomatic and supportive care.

REFERENCES

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Agnesi R, Valentini F, Mastrangelo G. 1997 Risk of spontaneous abortion and maternal exposure to organic solvents in the shoe industry. *Int Arch Occup Environ Health* 69:311-316.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6): 272-290.

Baselt RC. 2000 *Disposition of Toxic Drugs and Chemicals in Man*, fifth edition. Chemical Toxicology Institute, California.

Brown WD, Setzer JV, Dick RB, Phipps FC, Lowry LK. 1987 Body burden profiles of single and mixed solvent exposures. *J Occup Med* 29 (11):877-883.

BUA (Beratergremium für Umweltrelevante Altstoffe). 1997 *Acetone*. BUA Report 170 (June 1995). S Hirzel, Stuttgart.

Dalton P, Wysocki CJ, Brody MJ, Lawley HJ. 1997 Perceived odor, irritation, and health symptoms following short-term exposure to acetone. *Am J Ind Med* 31:558-569.

Dick RB, Brown WD, Setzer JV, Taylor BJ, Shukla R. 1988 Effects of short duration exposures to acetone and methyl ethyl ketone. *Toxicol Lett* 43 (1-3):31-49.

Dick RB, Setzer JV, Taylor BJ, Shukla R. 1989 Neurobehavioural effects of short duration exposures to acetone and methyl ethyl ketone. *Br J Ind Med* 46:111-121.

Foley RJ. 1985 Inhaled industrial acetylene. A diabetic ketoacidosis mimic. *J Am Med Assoc* 254 (8):1066-1067.

Folland DS, Schaffner W, Ginn HE, Crofford OB, McMurray DR. 1976 Carbon tetrachloride toxicity potentiated by isopropyl alcohol. Investigation of an industrial outbreak. *J Am Med Assoc* 236:1853-1856.

Gamis AS, Wasserman GS. 1988 Acute acetone intoxication in a pediatric patient. *Pediatr Emerg Care* 4 (1):24-26.

Gargas ML, Clewell HJ, Andersen ME. 1986 Metabolism of inhaled dihalomethanes *in vivo*: Differentiation of kinetic constants for two independent pathways. *Toxicol Appl Pharmacol* 82:211-223.

Gaudet MP, Fraser GL. 1989 Isopropanol ingestion: case report with pharmacokinetic analysis. *Am J Emerg Med* 7 (3):297-299.

Geller I, Gause E, Kaplan H, Hartmann RJ. 1979 Effects of acetone, methyl ethyl ketone and methyl isobutyl ketone on a match-to-sample task in the baboon. *Pharmcol Biochem Behav* 11 (4):401-406

Gitelson S, Werczberger A, Herman JB. 1966 Coma and hyperglycaemia following drinking of acetone. *Diabetes* 15 (11):810-811.

Grant WM, Schuman JS. 1993 *Toxicology of the Eye,* fourth edition. Charles C Thomas, Springfield, Illinois.

Haggard HW, Greenberg LA, McCullough Turner J. 1944 Physiological principles governing the action of acetone together with determination of toxicity. *J Ind Hyg Toxicol* 26 (5):133-151.

Harbison RD, Garvey GJ. 1998 Aldehydes and Ketones. In: *Hamilton and Hardy's Industrial Toxicology*, fifth edition. Harbison RD (editor). Mosby, St Louis.

Hawley PC, Falko JM. 1982 'Pseudo' renal failure after isopropyl alcohol intoxication. *S Med J* 75 (5):630-631.

Hift W, Patel PL. 1961 Acute acetone poisoning due to a synthetic plaster cast. *S Afr Med J* 35:246-250

IPCS. 1998 *Environmental Health Criteria 207. Acetone*. World Health Organization, International Programme on Chemical Safety, Geneva.

IPCS. 1999 *Environmental Health Criteria 208. Carbon Tetrachloride*. World Health Organization, International Programme on Chemical Safety, Geneva.

Jones AW. 2000 Elimination half-life of acetone in humans: case reports and review of literature. *J Anal Toxicol* 24:8-10.

Kiesswetter E, Seeber A, Blaszkewicz M, Sietmann B, Vangala RR. 1996 Neurobehavioural effects of solvents and circadian rhythms. *Neurotoxicol* 17 (3-4):777-784.

Morgott DA. 2001 Acetone. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Mutti A, Franchini I. 1987 Toxicity of metabolites to dopaminergic systems and the behavioural effects of organic solvents. *Br J Ind Med* 44:721-723.

Natowicz M, Donahue J, Gorman L, Kane M, McKissick J, Shaw L. 1985 Pharmacokinetic analysis of a case of isopropanol intoxication. *Clin Chem* 31 (2):326-328.

Nelson KW, Ege JF Jr, Ross M, Woodman LE, Silverman L. 1943 Sensory response to certain industrial solvent vapors. *J Ing Hyg Toxicol* 25:282-285.

Nomiyama K, Nomiyama H. 1974 Respiratory elimination of organic solvents in man. Benzene, toluene, *n*-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. *Int Arch Arbeitsmed* 32:85-91.

Panson RD, Winek CL. 1980 Aspiration toxicity of ketones. *Clin Toxicol* 17:271-317.

Pezzagno G, Imbriani M, Ghittori S, Capodaglio E, Huang J. 1986 Urinary elimination of acetone in experimental and occupational exposure. *Scand J Work Environ Health* 12:603-608.

Rosansky SJ. 1982 Isopropyl alcohol poisoning treated with hemodialysis: kinetics of isopropyl alcohol and acetone removal. *Clin Toxicol* 19 (3):265-271.

Ross DS. 1973 Acute acetone intoxication involving eight male workers. *Ann Occup Hyg* 16 (1):73-75.

Ruth JH. 1986 Odor thresholds and irritation levels of several chemical substances: a review. *Am Ing Hyg Assoc J* 47:142-151.

Sakata M, Kikuchi J, Haga M. 1989 Disposition of acetone, methyl ethyl ketone and cyclohexanone in acute poisoning. *Clin Toxicol* 27 (1-2):67-77.

Strong GF. 1944 Acute acetone poisoning. *Can Med Assoc J* 51:359-362.

Taskinen H, Anttila A, Lindbohm M-L, Sallmén M, Hemminki K. 1989 Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand J Work Environ Health* 15:345-352.

Taskinen H, Kyyrönen P, Hemminiki K, Hoikkala M, Lajunen K, Lindbohm M-L. 1994 Laboratory work and pregnancy outcome. *J Occup Med* 36 (3):311-319.

Vigliani EC, Zurlo N. 1955 *Arch Gewerbepath Gewerbrhyg* 13:528-534. Cited in BUA (Beratergremium für Umweltrelevante Altstoffe). 1997 *Acetone*. BUA Report 170 (June 1995). S Hirzel, Stuttgart.

Wijngaarden M van, Mock T, Dinwoodie A, LeGatt D, Yatscoff R. 1995 Coma and metabolic acidosis related to the use of muscle liniment. *Crit Care Med* 23 (6):1143-1145.

Zhao W, Misumi J, Yasui T, Aoki K, Kimura T. 1998 Effects of methyl ethyl ketone, acetone, or toluene coadministration on 2,5-hexanedione concentration in the sciatic nerve, serum, and the urine of rats. *Int Arch Occup Environ Health* 71 (4):236-244.

2 Benzene

Nicola Bates

SUMMARY

- Acute benzene exposure results in irritation and CNS depression
- The most significant chronic health effects are haematotoxicity, immunotoxicity and carcinogenicity
- Benzene causes bone marrow toxicity varying from mild effects to aplastic anaemia
- Benzene is known to cause cancer, particularly of the lymphatic and haematopoietic systems
- Benzene is a genotoxic carcinogen
- The metabolites of benzene are thought to be responsible for toxicity; the mechanisms of toxicity are complex and multifactorial
- Individual susceptibly to benzene toxicity is variable

DESCRIPTION

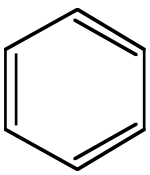
Synonyms

Annulene, benzol, benzole, coal naphtha, cyclohexatriene, phenyl hydride, pyrobenzol, pyrobenzole. Note: Benzin and benzine have been used as synonyms for benzene but now refer to a low-boiling petroleum distillate consisting mainly of aliphatic hydrocarbons (Hamilton, 1922; Greenburg, 1926; Barlow and Sullivan, 1982).

Identification numbers

CAS	71-43-2
UN	1114
RTECS	CY1400000
EINECS	2007537

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	C_6H_6
molecular formula	
molecular mass	78.11
physical form	clear, colourless liquid
relative vapour density (air=1)	2.7
flash point (°C closed cup)	-11.1

boiling point (°C)	80.1
autoignition temperature (°C)	498
refractive index	1.5016
explosive limits in air (%v/v)	1.3-7.1

Odour threshold

Odour threshold has been measured as 12 ppm (Amoore and Hautala, 1983), 4 ppm (Jex and Wyman, 1996), 1.1 ppm (Gusev, 1965) and 1.4-84 ppm (Ruth, 1986).

OCCUPATIONAL EXPOSURE

Exposure limits

Country	**TWA**
Sweden	0.5 ppm
UK	3 ppm (to be lowered to 1 ppm by 27 June 2003)
USA	1 ppm

Conversion factors

1 ppm = 3.2 mg/m^3

1 mg/m^3 = 0.31 ppm

1 mg/l = 310 ppm

Biomonitoring

Biomonitoring of benzene exposure usually involves measurement of one or more of the urinary metabolites (outlined below) as this is less invasive than measuring concentrations in blood. However, as the occupational exposure limits have decreased and workers are exposed to lower concentrations of benzene, so the sensitivity of benzene biomarkers has been questioned. This is a particular problem for exposures to concentrations of less than 1 ppm benzene.

Ong *et al*. (1996) investigated the specificity of various biomarkers for biological monitoring of workers exposed to low benzene concentrations (<1 ppm). They measured environmental benzene concentrations, benzene concentrations in blood and urine and urinary concentrations of *trans,trans*-muconic acid, catechol, phenol and hydroquinone. Significant correlation was shown between all urinary biomarkers, except catechol, and air benzene concentrations. The strongest correlation was between air and urinary benzene concentrations, followed by blood benzene concentrations. Of the urinary phenol and hydroquinone concentrations, the latter was more strongly correlated to the air benzene concentration. However, when the exposure was low (<0.25 ppm) only urinary benzene concentrations were significantly correlated to air concentrations. No significant differences were found in non-exposed controls compared to subjects occupationally exposed to low benzene concentrations. Consequently, they concluded that the currently used biomarkers are unable to differentiate between subjects exposed to ≤0.25 ppm benzene and those with only background exposure.

The problem is further complicated by evidence which suggests that at low benzene concentrations the proportion of the different metabolites produced is a function of the exposure dose. Rothman *et al*. (1998) compared the concentrations of urinary metabolites in workers exposed to benzene at ≤25 ppm and >25 ppm. In the group with the higher exposure, the ratio of phenol and catechol to total metabolites increased by 6% and 22.2% compared with the lower exposure group, whereas the hydroquinone and *trans,trans*-muconic acid decreased by 18.8% and 26.7%, respectively.

Measurement of non-metabolised benzene in body fluids following exposure to low concentrations is problematic because there is often interference from exposure to tobacco smoke. The average concentration of benzene in blood or urine is generally 3-5 times higher in smokers (Ong and Lee, 1994). In addition, benzene is a ubiquitous environmental pollutant and smoking, both active and passive, is a significant source of exposure (Wallace, 1989; Wallace, 1996). Consequently, in some cases, occupational exposure to benzene may actually be *lower* than that from environmental sources.

Adequate monitoring of benzene exposure may depend on the use of more than one biomarker (ATSDR, 1997). For a review of the various biomarkers and the different analytical techniques used to measure them, see Ong and Lee (1994) or Angerer and Hörsch (1992).

- **Phenol**

  Phenol is the main urinary metabolite of benzene and has been the most commonly used biological exposure indicator. However, its use as a biomarker for benzene is limited to exposure concentrations above 5 ppm (Angerer and Hörsch, 1992; Boogaard and van Sittert, 1995; Ong *et al*, 1995). This is because phenol may also be present in urine from endogenous production (e.g., from the metabolism of amino acids), and dietary, pharmaceutical and environmental exposure (Lee *et al*., 1993a; Ong and Lee, 1994; Boogaard and van Sittert, 1996).

- **Hydroquinone (quinol)**

  Good correlation has been reported between hydroquinone concentrations and benzene exposure in the range 1-68 ppm (Ong *et al*., 1995). However, in some studies this biomarker was unable to distinguish between those exposed at 10 ppm benzene and individuals without exposure (Inoue *et al*., 1988b). The urinary hydroquinone concentration is higher in smokers (Lee *et al.,* 1993b).

- **Catechol**

  There is poor correlation between catechol concentrations and benzene exposure in the range 1-68 ppm (Inoue *et al*., 1988b; Ong *et al*., 1995). The urinary catechol concentration is higher in smokers (Lee *et al.,* 1993b).

- ***trans,trans*-Muconic acid (2,4-hexadienedioic acid)**

  trans,trans-Muconic acid is a minor urinary metabolite of benzene. Between 2% (Inoue *et al.,* 1989a) and 3.9% (range 1.9-7.3%) (Boogaard and van Sittert, 1995; Boogaard and van Sittert, 1996) of absorbed benzene is excreted as *trans,trans*-muconic acid and the half-life is less than 6 hours (Johnson and Lucier, 1992; Boogaard and van Sittert, 1995; Boogaard and van Sittert, 1996).

  Urinary concentrations of *trans,trans*-muconic acid in exposed workers correlate with the air benzene concentration (Inoue *et al*., 1989a; Bechtold *et al.,* 1991; Ducos *et al.,* 1992; Lee *et al*., 1993a; Ong *et al.,* 1995; Liu *et al*., 1996), even in the range 0.25-3.5 ppm (Ong *et al*., 1996). Although Lee *et al*. (1993a) found correlation with a benzene concentration below 0.1 ppm, a more recent study found that at concentrations below 0.25 ppm this biomarker was unable to distinguish between occupationally exposed and control subjects (Ong *et al.,* 1996). Other studies have also found *trans,trans*-muconic acid a less reliable biomarker for benzene exposure because of its relatively short half-life (Boogaard and van Sittert, 1996). There is also evidence for preferential formation of *trans,trans*-muconic acid at low benzene exposure concentrations (Johnson and Lucier, 1992).

  High background concentrations of *trans,trans*-muconic acid may be due to other compounds interfering with the analysis. This is a particular problem with the urine of smokers, and further complicated by the finding that smokers have higher urinary *trans,trans*-muconic acid concentrations than non-smokers (Lee *et al*., 1993a; Ruppert *et al*., 1995). In addition, sorbic acid (*trans,trans*-2,4-hexadienoic acid) in food is metabolised to *trans,trans*-muconic acid and this may affect results. However, in a small volunteer study the interference with background *trans,trans*-muconic acid concentrations after ingestion of 200 mg of sorbic acid was minimal (Ducos *et al*., 1990).

For benzene exposure concentrations greater than 1 ppm, *trans,trans*-muconic acid is a suitable biomarker and may be preferred because it is relatively straightforward to measure (Boogaard and van Sittert, 1995).

- **S-phenylmercapturic acid (*N*-acetyl-*S*-phenyl-*L*-cysteine)**

  The minor urinary metabolite *S*-phenylmercapturic acid has been found to be a sensitive biomarker of benzene exposure at concentrations below 1 ppm and even down to 0.3 ppm (van Sittert *et al*., 1993; Boogaard and van Sittert, 1995). It is not detected in the urine of individuals without exposure to benzene (Inoue *et al.,* 2000). In some studies smoking did not influence the urinary *S*-phenylmercapturic acid concentration (van Sittert *et al*., 1993; Inoue *et al.,* 2000), however it did in others (Boogaard and van Sittert, 1995). The average urinary elimination half-life of *S*-phenylmercapturic acid is 9 hours and the average proportion of inhaled benzene excreted in the urine as *S*-phenylmercapturic acid is 0.11% (range 0.05-0.26%) (van Sittert *et al*., 1993; Boogaard and van Sittert, 1995; Boogaard and van Sittert, 1996). The urinary concentrations of S-phenylmercapturic acid and phenol were strongly correlated (van Sittert *et al*., 1993). Detection of this compound usually requires sophisticated testing equipment (e.g., gas chromatography-mass spectrometry) and although it is a sensitive method it is not routinely available. However, a simpler high performance liquid chromatography (HPLC) method has recently been developed (Inoue *et al.,* 2000), which may make routine testing of this biomarker more practical.

- **1,2,4-Benzenetriol (hydroxyquinol, 1,2,4-trihydroxybenzene)**

  This compound is not found in the urine of individuals with no occupational exposure to benzene. There is correlation between exposure and the urinary concentration of 1,2,4-benzenetriol. However, the method of measuring this compound is difficult and the potential use of 1,2,4-benzenetriol as a biomarker is further complicated by the observation that excretion is suppressed by co-exposure to toluene (Inoue *et al.,* 1989b). Consequently 1,2,4-benzenetriol is not recommended as a biomarker for benzene exposure.

- **Benzene in blood**

  In the study by Perbellini *et al*. (1988) the benzene exposure concentration significantly correlated with the blood benzene concentration but not with the concentration in the breath. This is not the case for smokers. Another study found that, although breath and blood concentrations were correlated, the breath, but not the blood concentration, correlated with the exposure concentration (Brugnone *et al*., 1989). Brugnone *et al*. (1998) found that it was not possible to distinguish between occupational and environmental exposure using the blood benzene concentration when the benzene concentration in the workplace was less than 0.03 ppm. However, these workers state that, although it is difficult to measure, the blood benzene concentration is a useful biomarker for benzene exposure (Brugnone *et al*., 1999). One of the main problems is that smoking complicates interpretation because smokers have higher blood benzene concentrations (Perbellini *et al*., 1988; Pekari *et al*., 1992; Brugnone *et al*., 1998; Brugnone *et al*., 1999). Ong and Lee (1994) argue that methods of measuring benzene in the blood lack specificity and sensitivity and do not recommend them for routine use.

- **Benzene in breath**

  Benzene breath concentrations are usually higher in smokers (Perbellini *et al*., 1988). The benzene concentration in breath is correlated with the blood concentration but not the exposure concentration (Perbellini *et al*., 1988). However, Drummond *et al.* (1988) found that breath benzene concentrations are more reliable than blood concentrations as a marker of exposure. The method used (gas chromatography-mass spectrometry) was sensitive and sophisticated but is not routinely available.

- **Benzene in urine**

  Ong *et al.* (1995) found significant correlation between the exposure concentration and the urinary concentration of benzene, but there was insufficient data for evaluating exposure to concentrations of less than 1 ppm.

- **Other monitoring**

  Regular monitoring of the haematological parameters is essential in benzene-exposed workers. All parameters are affected including white blood cell count, red blood cell count, absolute lymphocyte count, haematocrit, mean corpuscular volume (MCV) and platelets. However, the absolute lymphocyte count is the most sensitive indicator of benzene-induced haematotoxicity with a 32% decrease in one study. All other parameters were decreased, except the MCV which was significantly increased, compared to controls (Rothman *et al*., 1996a).

TOXICITY

Exposure to benzene has long been known to pose a risk to health (Rinsky *et al*., 1987; Paustenbach *et al*., 1993; Ross, 1996; Smith, 1996a). The earliest reports of chronic benzene toxicity are in the European literature and date from 1897 (Le Noire and Claude, 1897; Santesson, 1897). Benzene was imported into the USA from Germany until World War I and it was after this, when the USA began producing its own benzene, that the risks of toxicity began to be fully appreciated (Greenburg, 1926) and there were calls to control exposure (Hamilton, 1922). The first case of leukaemia attributed to benzene exposure was reported in 1928 (Delore and Borgomano, 1928). Humans can tolerate relatively high concentrations of benzene and it is this fact that lead to the widespread use of benzene as an industrial solvent (Paustenbach *et al*., 1993).

Acute inhalation or oral exposure can result in CNS depression, and death can occur within minutes of massive inhalation exposure (Avis and Hutton, 1993). Acute benzene exposure has been reported following chemical spills (Clare *et al*., 1984), industrial accidents on cargo ships (Midzenski *et al.,* 1992; Avis and Hutton, 1993; Barbera *et al*., 1998), the use of a benzene-containing product without adequate protection (Drozd and Bockowski, 1967) and solvent abuse (Winek *et al*., 1967; Winek and Collom, 1971).

The most common route of exposure to benzene is inhalation (Marcus, 1990). Most information on benzene toxicity concerns long-term inhalation exposure. The most significant health effects of benzene are haematotoxicity, immunotoxicity, neurotoxicity and carcinogenicity (International Programme on Chemical Safety (IPCS), 1993). Benzene toxicity is characterised by either early reversible haematotoxicity or irreversible bone marrow damage due to prolonged exposure (Snyder and Hedli, 1996). In early studies of benzene-exposed workers high numbers had evidence of haematotoxicity to varying degrees (reviewed in Smith, 1996a). It is well recognised that exposure to benzene concentrations greater than 30 ppm can cause haematotoxicity (ECETOC, 1984). Benzene is sometimes described as a radiomimetic toxin because the myelotoxic effects resemble that of ionising radiation. Bone marrow effects are of three types: bone marrow depression, chromosome changes and carcinogenicity (IPCS, 1993). It was suggested in the 1950s that benzene could cause leukaemia but clear evidence for this was not available until the 1970s (Paustenbach *et al*., 1993). With improved industrial hygiene and, consequently, lower concentrations of benzene in the workplace, more recent studies have generally found a much smaller proportion of workers, and in some cases none, with evidence of haematotoxicity. However, occasional outbreaks of benzene-induced haematotoxicity still occur (e.g., Aksoy *et al*., 1987). There is limited information on haematotoxicity after short-term or chronic oral or dermal exposure (IPCS, 1993).

Benzene toxicity varies between species. Although metabolism in all species studied is qualitatively similar, there are quantitative differences in the proportion of benzene metabolised by different pathways (reviewed in Henderson, 1996). In all species studied it has been found that a greater proportion of absorbed benzene is converted to hydroquinone and ring-opened metabolites following low dose compared to high dose exposures. Mice have a greater capacity to metabolise benzene than rats or primates. Mice and monkeys metabolise a greater proportion of absorbed benzene to hydroquinone metabolites than rats or chimpanzees. Non-human primates metabolise less benzene to *trans*,*trans*-muconic acid than rodents or humans. Consequently, there is no suitable animal model for benzene toxicity in humans (Snyder *et al*., 1993; Harbison, 1998; Golding and Watson, 1999). On the basis of the available evidence, a small increase in leukaemia mortality in workers exposed to low benzene concentrations cannot be distinguished from a no-risk situation (IPCS, 1993). Consequently it is impossible to define a no-effect level for benzene exposure (ECETOC, 1984; Marcus, 1990).

The history of the establishment of occupational exposure limits has been complex and in the USA, controversial (Feitshans, 1989). In 1978, OSHA in the USA reduced the permissible occupational exposure limit from 10 ppm to 1 ppm on the basis of information from case reports and two epidemiological studies (Infante *et al.*, 1977; Ott *et al.*, 1978). The US Supreme Court overturned this in 1980 on the basis that there were insufficient data on quantitative dose-response relationships. However, in the light of further studies, particularly that of Rinsky *et al.* (1987), OSHA re-imposed the 1 ppm exposure limit in 1987. Nicholson and Landrigan (1989) estimated that this 10 year delay in lowering the exposure limit may ultimately result in between 30 to 490 excess leukaemia deaths in the USA following exposure to benzene at concentrations >1 ppm between 1978-1987. In addition, deaths from other diseases that may occur following benzene exposure (e.g., aplastic anaemia) will increase this total.

Benzene is no longer used as a general solvent in Europe and North America. However, it is still widely used in some countries. A review of 50,000 workplaces in China found the average concentration of benzene to be 5.6 ppm. Of 508,818 benzene-exposed workers examined, 2,676 cases of benzene poisoning were identified, an incidence of 0.5% (Yin *et al.*, 1987b).

There is a huge amount of literature on benzene toxicity spanning over a century and it has been the subject of several large reviews. For more information see ECETOC (1986), Askoy (1988), Marcus (1990), Paustenbach *et al.* (1993), IPCS (1993), Snyder *et al.* (1993), ATSDR (1997) or Snyder (2000). The risk assessments of benzene exposure, in particular, have been extensively reviewed and studied; for further details and criticisms see Brett *et al.* (1989), Byrd and Barfield (1989), Lamm *et al.* (1989) and ATSDR (1997).

Absorption

Benzene is readily absorbed by inhalation and ingestion. The proportion of benzene absorbed ranges from approximately 50 to 90% (Srbová *et al.*, 1950; Pekari *et al.,* 1992; Ong *et al.*, 1995).

Benzene can be absorbed dermally but not as well as inhalation or oral exposure (ATSDR, 1997). In an experimental study, the absorption of benzene vapour through the skin was less than 1% of the amount absorbed through the lungs under similar conditions (Hanke *et al.,* 2000). Absorption through the skin of liquid benzene was low at 0.4/mg/cm^2/hour. This is unlikely to result in acute poisoning, but there is risk of chronic toxicity from this route (Hanke *et al.,* 2000).

Distribution

Benzene is highly lipid soluble. In three cases of inhalation and dermal exposure where the victims died within minutes the highest concentrations of benzene were found in the body fat, brain and blood (Avis and Hutton, 1993). In a similar case, but where death occurred after approximately 30-45 minutes high concentrations of benzene were found in the liver, heart and brain with lower concentrations in kidney, blood and lungs. The urine contained a very small concentration (2.26 mg/l) of benzene (Barbera *et al.*, 1998). Blood concentrations of benzene in these cases of acute poisoning were 30-120 mg/l (Avis and Hutton, 1993) and 31.7 mg/l (Barbera *et al.*, 1998).

Blood concentrations of benzene in individuals who have died after inhalational abuse range from 0.94-20 mg/l (Winek *et al.*, 1967; Winek and Collom, 1971).

Metabolism

The fraction of benzene metabolised following absorption depends on the route of exposure and the dose (Paustenbach *et al.*, 1993). Metabolism of benzene occurs mainly in the liver involving the enzyme P450 CYP2E1, but other organs including the bone marrow are also involved (Smith *et al.,* 1989; Paustenbach *et al.*, 1993). A reduction in liver metabolism by partial hepatectomy reduces benzene metabolism and toxicity in rats, demonstrating the importance of the liver and benzene metabolism for toxicity (Sammett *et al.*, 1979).

Benzene is oxidised to benzene oxide which is unstable (Smith, 1996b). This compound either binds directly to cellular constituents and ultimately forms phenylmercapturic acid (Cox, 1991), or is hydrated to form

dihydrodiol leading to the formation of catechol. Benzene oxide can undergo non-enzymatic rearrangement to form phenol. Phenol is hydroxylated to hydroquinone (quinol) which can then produce *p*-benzoquinone and 1,2,4-benzenetriol. Phenol can also be hydroxylated to catechol, which can also form *o*-benzoquinone. A large number of metabolites are present in the urine (see below). The major metabolites are phenol, hydroquinone and catechol which are excreted as sulphates and glucuronides. They account for approximately 25% of the absorbed benzene (Inoue *et al.*, 1988b). The benzene aromatic ring is relatively stable and only small quantities of ring-opened metabolites are formed as a consequence (Snyder, 1987). The urinary metabolites of benzene include (Snyder and Hedli, 1996):

- Hydroxylated metabolites (phenol, hydroquinone and catechol) excreted as glucuronide or sulphate conjugates
- Ring-opened metabolites, e.g., *trans,trans*-muconic acid and 6-hydroxy-*trans,trans*-2,4-hexadienoic acid
- Mercapturic acids including L-phenylmercapturic acid, 6-*N*-acetylcysteinyl-*S*-2,3-cyclohexadienol and 2,5-diOH-phenylmercapturic acid
- DNA adduct residues including N^7-phenylguanine and 8-hydroxy-2-deoxyguanosine.

The dose-dependent metabolism of benzene is probably due to competition between benzene and phenol for the same oxidative enzyme systems. Benzene and its metabolite phenol are both substrates for the enzyme P450 CYP2E1 and because the benzene concentration (as the parent compound) is higher than that of phenol, benzene can inhibit phenol oxidation and decrease the formation of hydroquinone conjugates (Medinsky *et al.*, 1996).

Elimination

The fraction of benzene eliminated unchanged via the lungs varies between 12% and 50% (Srbová *et al.*, 1950; Nomiyama and Nomiyama, 1974; Pekari *et al.,* 1992; Ong and Lee 1994). A very small amount of benzene (0.1-0.2%) is excreted unchanged in the urine (Srbová *et al.*, 1950; Ong and Lee, 1994).

In workers exposed to 0.02-4.1 ppm (85% of samples <1ppm), benzene was detectable in the breath 16 hours after cessation of exposure (before the start of the next shift). There was poor correlation between the concentrations of benzene in the breath and prior exposure. An increase in the benzene concentration in the breath was found during the working week (Money and Gray, 1989).

The elimination of benzene has been reported to be triphasic. The half-lives of these phases are approximately 1 hour, 3-6 hours and >15 hours (Nomiyama and Nomiyama, 1974; Pekari *et al.*, 1992). During exposure to benzene the blood concentrations were higher in males than females, while end-exhalation breath concentrations were equivalent. However, four hours after cessation of exposure the blood and exhaled breath concentrations were higher in females. This may be due to the greater quantity of body fat in females (Sato *et al.*, 1975).

Of the benzene absorbed the proportion of urinary metabolites is as follows:

- Phenol 13.2%, hydroquinone 10.2%, catechol 1.6% (Inoue *et al.*, 1986; 1988b),
- *trans,trans*-Muconic acid 2-4% (Inoue *et al.,* 1989a; Boogaard and van Sittert, 1995; 1996),
- 1,2,4-Benzenetriol 0.5% (Inoue *et al.*, 1989b),
- *S*-phenylmercapturic acid 0.1% (van Sittert *et al.*, 1993; Boogaard and van Sittert, 1995; 1996).

However, it should be noted that these proportions may vary with the exposure concentration.

Mode of action

The mechanism of benzene toxicity is complex and has not been fully elucidated. Benzene itself is not directly toxic and toxicity is believed to involve benzene metabolites and multiple mechanisms (Yardley-Jones *et al.*, 1991). Many benzene metabolites have been identified but it is not known which are ultimately responsible

for the bone marrow toxicity of benzene (Schrenk *et al.,* 1996). Myelotoxic metabolites are thought to be formed by hepatic metabolism and then transported to the bone marrow where further transformation may occur (Irons *et al.,* 1980). Since the metabolites are the cause of toxicity the fraction metabolised, rather than the quantity of benzene involved in an exposure, is probably a better measure of risk (Bois *et al*., 1996).

Some of the mechanisms proposed for benzene toxicity are described below with supporting evidence. It is important to note that the mechanisms that produce chronic haematological effects, genotoxic effects and leukaemia may not be the same (Goldstein, 1989). The phenol metabolites of benzene (phenol, catechol, hydroquinone and 1,2,4-benzenetriol) can all be metabolised by myeloperoxidase which could result in highly toxic semiquinone radicals and quinones. These compounds may be the ultimate metabolites of benzene responsible for its toxicity (Smith, 1996b).

Mechanisms of toxicity

- **Covalent binding of a reactive intermediate(s) to DNA or oxidative damage to DNA, followed by one or more proliferative steps resulting in stimulation of genetically altered cells.**

  The concentration of peripheral lymphocyte 8-hydroxy-2-deoxyguanosine (a sensitive marker of DNA damage due to hydroxyl radical attack) in exposed workers with normal leucocyte counts was found to correlate with the air benzene and urinary *trans,trans*-muconic acid concentration (Liu *et al*., 1996). Another study found the urinary concentration of 8-hydroxy-2-deoxyguanosine also correlated with the benzene concentration in exposed workers (Lagorio *et al*., 1994).

- **Alkylation by benzene metabolites of cellular components including DNA.**

  The benzene metabolites *trans,trans*-muconaldehyde (a precursor of the urinary metabolite *trans,trans*-muconic acid) and 6-hydroxy-*trans,trans*-2,4-hexadienal are multifunctional alkylating agents which have the potential to cross-link cellular DNA and protein. They also react with and deplete glutathione (GSH), which is an important cellular antioxidant (Witz *et al*., 1996). Alkylation of DNA could result in mutation or chromosome damage.

- **Inhibition of topoisomerase II.**

  Topoisomerases are a group of important chromosomal proteins involved in maintaining the shape and structure of DNA by breaking and resealing strands. They are also involved in chromosome segregation, DNA replication and repair and other cellular processes. Topoisomerase II is believed to play a role in genomic stability and interference with topoisomerase II activity at critical stages of the cell cycle could cause chromosome breakage, aneuploidy or cell death (Chen and Eastmond, 1995b). Phenol and its peroxidation metabolites 2,2′-biphenol and 4,4′-biphenol, have shown inhibitory effects on topoisomerase II but not topoisomerase I. Other benzene metabolites (1,4-benzoquinone and 1,2,4-benzenetriol) also inhibited topoisomerase II, but at higher concentrations (Chen and Eastmond, 1995b).

- **Mitotic recombination.**

  Rothman *et al*. (1995; 1996b) found an increase of mutations in the glycophorin A (GPA) locus in benzene exposed workers. This assay identifies stem cell or precursor erythroid cell mutations expressed in peripheral erythrocytes. The authors suggested that this finding may be due to mitotic recombination in longer-lived stem cells. The mutation frequency was related to cumulative benzene exposure not to current exposure (Rothman *et al*., 1995).

- **Inhibition of cell division by interfering with microtubules.**

  Microtubules are polymers of the protein tubulin. They are involved in spindle formation during cell division, maintenance of cell shape, cell growth, intracellular movement of organelles and secretion of cellular products. Hydroquinone (but not phenol or catechol), has been shown *in vitro* to inhibit microtubule polymerisation. This was an oxidative process where hydroquinone competes for sulphydryl dependent guanosine triphosphate (GTP)-binding sites on the protein (Irons and Neptun, 1980).

- **Interference with the differentiation of stem and progenitor cells in the bone marrow.**

  Haematopoiesis is regulated through a process of proliferation and differentiation in which immature stem cells give rise to a larger quantity of progressively more differentiated cells. These processes are strictly controlled by multiple growth factors or cytokines that work together to control haematopoiesis. An altered response to haematopoietic cytokines is an early feature of the leukaemogenic process. *In vitro* studies on bone marrow cells suggest that hydroquinone (but not catechol, phenol or *trans,trans*-muconic acid), alters stem cell differentiation (Irons and Stillman, 1996a; 1996c).

- **Increased concentrations of prostaglandins which results in down-regulation of haematopoiesis and inhibition of the synthesis of interleukin 1.**

  Both prostaglandins and interleukin 1 are involved in normal bone marrow function. Prostaglandins act by down-regulating haematopoiesis, whereas interleukin 1 enhances haematopoiesis. Indomethacin is a non-steroidal anti-inflammatory drug that inhibits the cyclooxygenase component of prostaglandin synthase and prevents synthesis of prostaglandins. In mice benzene caused an increase in prostaglandins in bone marrow. But co-administration of indomethacin with benzene completely prevented bone marrow depression. Similar results were found with aspirin and meclofenamate. None of these drugs, alone, had any affect on bone marrow cellularity (Kalf *et al*., 1996). Indomethacin also had a protective effect against benzene-induced genotoxicity (Wierda and Gaido, 1986; Kalf *et al*., 1996). Indomethacin has also been shown to reduce hydroquinone toxicity to stromal cell function (Gaido and Wierda, 1987).

- **Activation of protein kinase C.**

  Benzene has been shown to activate protein kinase C *in vitro* and in intact platelets (Da Silva *et al*., 1989). Protein kinase C is an enzyme essential in signal transduction; a number of tumour promoters also enhance this enzyme.

- **There is a synergistic effect between the metabolites (Goldstein, 1989; Snyder *et al*., 1989; Smith, 1996b).**

  Bone marrow has high concentrations of myeloperoxidase (MPO) and the myeloperoxidase-dependent metabolism of hydroquinone to the reactive metabolite 1,4-benzoquinone is stimulated by phenol (Eastmond *et al*., 1987; Smith *et al*., 1989). A synergistic genotoxic effect (induction of micronuclei) has been observed between catechol and hydroquinone in human lymphocytes (Robertson *et al*., 1991). In animals hydroquinone and *trans,trans*-muconaldehyde given together were more effective at inhibiting erythrocyte production than each compound alone (Snyder *et al*., 1989). Similarly, phenol and hydroquinone when given together produce bone marrow toxicity resembling that of benzene. This was not the case when they were given alone (Eastmond *et al*., 1987). These two metabolites have been shown to be more genotoxic (measured as the formation of micronuclei in bone marrow erythrocytes) when given together compared to the effect when given alone (Chen and Eastmond, 1995a). Also, 1,4-benzoquinone and *trans,trans*-muconaldehyde are chemically similar (they are α,β-unsaturated diketones) and may have similar molecular targets and toxic effects (Smith, 1996b). In combination these two metabolites have been shown to severely inhibit red cell production (Guy *et al*., 1991).

  Cox (1991) outlines five hypotheses for benzene-induced carcinogenesis (**Table 2.1**). These hypotheses are not mutually exclusive. Smith (1996b) summarises the proposed mechanisms of benzene carcinogenesis as follows: The phenolic metabolites acting synergistically produce DNA strand breaks, topoisomerase II inhibition and damage to the mitotic spindle. This results in genotoxic effects including mitotic recombination, chromosome translocations and aneuploidy. This in turn causes activation of key proto-oncogenes, loss of heterzygosity and inactivation of tumour suppressor genes. If this occurs in the bone marrow or early progenitor cells a leukaemic clone will develop which has a selective growth advantage. Epigenetic effects of benzene (occurring without direct effect on the chromosomes) on the bone marrow stroma and progenitor cells may also be involved in the establishment of a leukaemic clone of cells.

Table 2.1 Hypotheses for benzene induced carcinogenesis (Cox, 1991)
Hypothesis 1 Benzene metabolites initiate cancer by reacting with cellular DNA, creating DNA adducts that represent heritable carcinogenic damage to the somatic cell line. The resulting cells fail to respond normally to regulatory signals instructing them to differentiate instead of proliferating.
Hypothesis 2 The compensating proliferation of stem cells, created by the cytotoxic effects of benzene metabolites on partially differentiated cells, increases the likelihood of carcinogenic damage, assuming that stem cells are at greater risk of carcinogenic damage while they are in their normal, quiescent state.
Hypothesis 3 Cytotoxic damage to the stromal microenvironment impairs its ability to regulate stem cell proliferation and differentiation. Initiated and/or malignant stem cells are allowed to proliferate uncontrollably.
Hypothesis 4 Cytotoxic damage to the immune system allows tumour cells that would normally be detected and killed to survive and proliferate, leading to a variety of carcinogenic endpoints.
Hypothesis 5 Benzene metabolites initiate cancer through their effects on stem cell chromosomes. These chromosomal aberrations may activate oncogenes or inactivate anti-oncogenes.

Metabolic interactions

Several animal studies (reviewed in Snyder *et al*., 1989; Marcus, 1990) have shown that reduction of benzene metabolism decreases benzene toxicity. Various methods were used to decrease benzene metabolism including hepatectomy, co-administration of other solvents (e.g., toluene, xylene) metabolised by the same mechanisms or administration of anti-oxidants. Benzene, styrene, xylene and toluene are metabolised by the same enzyme systems and may competitively inhibit the metabolism of each other (Cohr and Stokholm, 1979; Tardif *et al.,* 1992). Consequently, there may be an increased concentration of unchanged solvent in the blood and decreased or delayed urinary excretion of metabolites (Tardif *et al.,* 1991; Tardif *et al.,* 1992). This may result in overestimation of the toxic risk where blood concentrations are used for monitoring, or underestimation where the urinary metabolites are used (Tardif *et al.,* 1992).

- **Ethanol**

  Ethanol enhances the metabolism and the toxicity of benzene in animals (Baarson *et al*., 1982; Nakajima *et al*., 1985). Increased severity of benzene-induced anaemia, lymphopenia and bone marrow aplasia were observed in benzene-treated mice given ethanol (Baarson *et al*., 1982). Both ethanol and benzene are inducers of P450 CYP2E1. The enhancement of benzene-induced haematotoxicity is of particular concern for benzene-exposed workers who consume ethanol, since benzene can interfere with the elimination of ethanol and co-exposure may result in CNS depression (ATSDR, 1997).

- **Methylene chloride**

  Studies in rats have shown that a single oral administration of an aromatic hydrocarbon (benzene, toluene or *m*-xylene) 16-24 hours before the administration of methylene chloride increases the peak concentration of carboxyhaemoglobin (formed by carbon monoxide, a metabolite of methylene chloride, combining with haemoglobin). The half-life of methylene chloride in blood was shorter, indicating that the metabolic degradation of methylene chloride is enhanced by the aromatic hydrocarbons. This effect on the peak carboxyhaemoglobin concentration was dependent on the time interval between aromatic hydrocarbon and methylene chloride treatment, since earlier administration of toluene or *m*-xylene decreased the

carboxyhaemoglobin elevation. Disulfiram treatment blocked carboxyhaemoglobin elevation completely and corresponding increases in the concentration and half-life of methylene chloride were observed (Kim and Kim, 1996).

- **Toluene**

  Benzene and toluene are metabolised by the same enzyme systems and may competitively inhibit the metabolism of each other (Cohr and Stokholm, 1979). In the case of benzene and toluene this is unlikely to be a problem if exposure is minimised, e.g., if concentrations remain below the threshold limit values (Sato and Nakajima, 1979).

  Metabolism of benzene to phenolic compounds and toluene to hippuric acid and *ortho*-cresol has been shown to be suppressed in workers exposed to a mixture of both (Inoue *et al*., 1988a). The benzene urinary metabolites *trans,trans*-muconic acid (Inoue *et al*., 1989a), 1,2,4-benzenetriol (Inoue *et al.,* 1989b), phenol and hydroquinone (Inoue *et al.,* 1988a) are reduced in workers with co-exposure to toluene. In the study by Liu *et al.* (1996), the concentration of peripheral lymphocyte 8-hydroxy-2-deoxyguanosine (a marker of DNA oxidative damage) was found to be negatively correlated with the air concentration of toluene in benzene exposed workers. In another study co-exposure to xylene and toluene did not influence the urinary concentration of 8-hydroxy-2-deoxyguanosine in benzene exposed workers (Lagorio *et al*., 1994).

CASE REPORTS

Fatal acute accidental exposure

While opening a valve in a cofferdam of a chemical cargo ship four crew members were exposed to benzene fumes that had collected in the pipe from the previous cargo. None of the victims were wearing protective clothing. Three of the four men died. One victim, seeing the other three incapacitated, attempted a rescue wearing a facemask and oxygen tank. Having rescued one man, he returned but was overcome and died. The exposure concentration was unknown, but death occurred within minutes of exposure. Postmortem examination revealed second degree chemical burns to the face, trunk and limbs, and haemorrhagic airless lungs with alveolar haemorrhage and pulmonary oedema (Avis and Hutton, 1993).

Acute accidental exposure

Acute exposure to benzene (>60 ppm) occurred over several days in 15 men who were removing residual fuel (degassing) from shipboard fuel tanks. The clinical effects reported included mucous membrane irritation (80%), dyspnoea (67%), dizziness (60%), nausea (47%), chemical taste (47%), headache (33%), cough (27%), drowsiness (20%) and fatigue (20%). Workers exposed for more than two days were more likely to report dizziness and nausea. Repeated laboratory analyses over the following four months found at least one haematological abnormality consistent with benzene exposure in nine (60%) of the workers. One year later 6 workers (40%) had persistent abnormality. However, there was no correlation between the presence of haematological abnormalities and the exposure duration (Midzenski *et al.,* 1992).

CLINICAL EFFECTS

Acute exposure

Inhalation

Acute exposure to benzene causes CNS depression with dizziness, euphoria, nausea, vomiting, headache, drowsiness and ataxia (Anon, 1988; Marcus, 1990; Midzenski *et al*., 1992; Harbison, 1998). Haematuria has been reported (Drozd and Bockowski, 1967). Exposure to a high concentration may result in coma. Deaths have been reported from acute benzene exposure (Hamilton, 1922; Greenburg, 1926; Avis and Hutton, 1993; Barbera *et al*., 1998) and are usually attributed to asphyxiation, respiratory arrest, central

Table 2.2 The effects of acute inhalation of benzene in humans (Gerarde, 1960)	
Exposure concentration and duration	**Effects**
25 ppm for 8 hours	no effect
50-150 ppm for 5 hours	headache, lassitude, fatigue
500 ppm for 60 minutes	symptoms of illness
1,500 ppm for 60 minutes	serious symptoms
7,500 ppm for 30 minutes	dangerous to life
19,000-20,000 for 5-10 minutes	fatal

nervous system depression or cardiac arrest. Benzene sensitises the myocardium to endogenous catecholamines (Gerarde, 1960).

Benzene concentrations up to 1,000 ppm are tolerable for a short period. Concentrations of 500-1,000 ppm can be tolerated for longer periods by acclimatised workers (Paustenbach *et al.*, 1993). See **Table 2.2** for the effects of acute inhalation of benzene at different exposure concentrations.

The CNS effects of benzene are rapidly reversed on removal from exposure and there is no evidence that acute benzene intoxication results in long-term neurological damage (Marcus, 1990). Acute benzene exposure does not appear to cause significant haematological effects in the short-term but this does not rule out the possibility of long-term haematological changes (Midzenski *et al.*, 1992).

Postmortem examination of individuals who have died following acute benzene exposure, from either occupational exposure or abuse, has shown haemorrhagic pulmonary oedema, cerebral oedema and multi-organ congestion (Winek *et al.*, 1967; Winek and Collom, 1971; Avis and Hutton, 1993; Barbera *et al.*, 1998).

Dermal

Dermal contact with benzene may cause irritation (Wolf *et al.*, 1956; Midzenski *et al.*, 1992), erythema, oedema and blistering (Gerarde, 1960; Harbison, 1998). Severe burns can occur from exposure to the liquid or vapour (Avis and Hutton, 1993).

Eye

Benzene is a moderate eye irritant (Wolf *et al.*, 1956). It causes a burning sensation and transient injury of the epithelial cells. Recovery is rapid (Grant and Schuman, 1993).

Optic neuritis has been associated with benzene toxicity in one acute and one chronic case. However, it is not clear if benzene was the cause of the ocular effects (Grant and Schuman, 1993).

Ingestion

Ingestion of benzene may cause local irritation of the mucous membranes of the mouth, throat, oesophagus and stomach (Gerarde, 1960). Gastrointestinal ulceration (Appuhn and Goldeck, 1957), gastritis and pyloric stenosis (Greenberg, 1926) have been reported. Congestive gastritis was found on postmortem examination of an 18 year old male who died after intentionally inhaling benzene (Winek and Collom, 1971).

Benzene is an aspiration hazard and may cause pulmonary haemorrhage and oedema if aspirated into the lungs (Gerarde, 1960).

Chronic exposure

Inhalation

Haematological effects

Benzene causes bone marrow toxicity and appears to follow a dose-response relationship (IPCS, 1993). Duration of exposure does not appear to be a factor influencing haematological effects (Aksoy et al., 1971). Bone marrow toxicity can vary from mild effects to aplastic anaemia. There are numerous studies in benzene-exposed workers demonstrating haematological effects, including anaemia (decreased red blood cells), thrombocytopenia (decreased platelets), leucopenia (decreased white blood cells/leucocytes) and pancytopenia (decrease in all cell types). Aplastic anaemia, the ultimate form of bone marrow depression, is characterised by pancytopenia and bone marrow necrosis. The bone marrow ceases to function and stem cells do not mature. It is rapidly fatal (Anon, 1988). Pancytopenia is usually associated with irreversible bone marrow aplasia (Snyder and Hedli, 1996).

Benzene-exposed workers may progress through aplastic anaemia to a myelodysplastic phase to frank leukaemia (Paustenbach *et al*., 1993), but this is not always the case (Rangan and Snyder, 1997). In one study, aplastic anaemia developed in 4 of 221 workers who had been exposed to benzene for an average of 118.5 days and an estimated daily mean concentration of 1035.6 mg/m^3 (324 ppm) (Yin *et al*., 1987b). In individuals who survive aplasia the bone marrow is usually dysplastic (Snyder and Hedli, 1996).

Results of bone marrow biopsies in benzene-poisoned workers are very variable (Aksoy, 1989). Bone marrow may be acellular, hypocellular, hypercellular or normocellular. There may be maturation arrest in the myeloid or erythroid series or both. Vacuolation may be observed in the myeloid and/or erythroid elements (Aksoy *et al.,* 1971; Aksoy *et al.,* 1972).

Clinical effects in patients with bone marrow depression include headache, inappetance (lack of appetite) and abdominal discomfort. In severe cases there may be weakness, fatigue, pale skin and mucous membranes, blurred vision and dyspnoea on exertion. Coagulopathy may result in petechiae, bruising, epistaxis (nose bleed) and bleeding from the gums and gastrointestinal tract. Vaginal bleeding may occur in women (Hunt, 1979). Death in patients with aplastic anaemia may occur from infection or haemorrhage (Aksoy *et al*., 1972). Haemorrhagic complications of pregnancy have also been reported, particularly in the older literature, in women with benzene toxicity (Hunt, 1979).

A study of haematological screening data of a cohort of rubber workers over a 35 year period found a strong correlation between benzene exposure and a low leucocyte count. The relationship between benzene exposure and a low erythrocyte count was weaker. The maximum estimated daily benzene exposure concentration was 34 ppm (Ward *et al.,* 1996). In a study of 459 workers exposed between 1940 and 1975, significant decreases in leucocytes, erythrocytes and haemoglobin were recorded between 1940 and 1948 when the exposure was 75 ppm. However, this was not observed for the period 1949-75 when the exposure concentration was 15-20 ppm (Kipen *et al*., 1989).

There were no significant abnormalities in haematological parameters in 66 workers exposed to low average concentrations of benzene (less than 10 ppm) for more than 5 years (Yardley-Jones *et al*., 1988b). Other studies of benzene-exposed workers similarly found no differences in haematological findings compared to controls (Hancock *et al*., 1984; Collins *et al.,* 1997). In the study by Hancock *et al.* (1984) this was true even when the workers were divided by cumulative exposure concentrations equivalent to average benzene concentrations of <1 ppm, 1-10 ppm and >10 ppm for a 20 year employment.

It is likely that the haematological effects reported with some other organic solvents, such as toluene, are the result of benzene contamination (Hayden *et al.,* 1977; Cohr and Stokholm, 1979; King, 1982).

Neurological effects

Neurological examination in six workers with aplastic anaemia after exposure to benzene (0.5-8 years, mean 6 years) found abnormalities in four workers. There was decreased vibration sense and global atrophy of the lower extremities and exaggerated reflexes of both sides. Some workers had also been exposed to lower concentrations of toluene (Baslo and Aksoy, 1982).

Kellerova (1985) observed an increased frequency of abnormal and threshold EEG findings in benzene-exposed workers compared to controls. There was sleep disturbance with faster onset of deep sleep stages and frequent lability of background EEG activity.

Immunotoxicity

Benzene immunotoxicity is related to bone marrow depression (described below). This results in changes in both humoral and cellular immunity (IPCS, 1993).

A study of 35 painters exposed to benzene, toluene and xylene found that they had significantly lower immunoglobulin A (IgA) and IgG concentrations, but increased IgM levels. This was thought to be due to a suppressive action of benzene on immunoglobulin-producing cells, resulting in inhibition of DNA synthesis (Lange *et al.,* 1973a). In addition 10 workers were found to have autoleucocyte agglutinins suggesting an immunological component to benzene toxicity (Lange *et al*., 1973b). Serum complement concentrations were also decreased in 62 of 79 workers exposed to benzene, toluene and xylene for 0.25 to 18 years (Smolik *et al*., 1973).

The number of T-cell lymphocytes was low in a study of workers exposed to benzene, toluene and xylene. The number of B and null lymphocytes was normal (Moszcyznski, 1981). In a study of workers exposed to low average concentrations of benzene there was no difference in the cell cycle kinetics of phytohaemagglutinin-stimulated lymphocytes in exposed workers compared to controls (Yardley-Jones *et al.,* 1988a).

Other effects

Hepatotoxicity is not a feature of benzene exposure (ATSDR, 1997), although hepatosplenomegaly has been reported in two workers with benzene-induced pancytopenia (Aksoy *et al*., 1972). There are very little data on the renal effects of benzene (ATSDR, 1997).

Dermal

Chronic dermal exposure to benzene may cause dermatitis (Gerarde, 1960). Repeated application of benzene to rabbit skin caused erythema, oedema, exfoliation, blistering and moderate necrosis (Wolf *et al*., 1956).

Porokeratosis of the scrotum, natal cleft and inner thighs was reported in a 70 year old male who was exposed to benzene for 14 years (until the age of 48 years). Porokeratoses are a group of disorders of epidermal keratinisation which may progress to malignancy. This individual had been involved in remoulding tyres during which the rotating tyres were splashed with a solution of benzene and crude rubber. Each day about 200 litres of solution were used. His overalls became heavily soiled particularly around the thighs and lower abdomen and they were only replaced every 3-4 weeks. He had left his job after 14 years because of pancytopenia (Trcka *et al*., 1998).

Eye

Optic neuritis has been associated with benzene toxicity in one acute and one chronic case. However, it is not clear if benzene was the cause of the ocular effects (Grant and Schuman, 1993).

Ingestion

Benzene was used to treat leukaemia prior to 1913. It was given orally in gelatin capsules starting at a dose of 43 mg/kg/day and increasing to 71 mg/kg/day. These patients developed leucocytosis and multiple haemorrhages with severe anaemia. However, it is not clear whether this was due to the disease itself or to benzene toxicity (ATSDR, 1997).

Carcinogenicity

Benzene is a known human carcinogen and is associated particularly with leukaemias (Infante *et al*., 1977; Ott *et al.,* 1978; Rinsky *et al.,* 1981; Bond *et al*., 1986; Paci *et al*., 1989; Rinsky *et al.,* 1987; Yin *et al*., 1987a; 1989; Rinsky 1989; Hayes *et al*., 1996; Yin *et al*., 1996, 1997). These are a heterogeneous group of neoplasms arising from the haematopoietic (blood-forming) cells.

Some risk assessments and studies on workers exposed to relatively low benzene concentrations (Thorpe, 1974; Hurley *et al*., 1991) found no excess leukaemia deaths. However, interpretation of negative epidemiological studies is complicated and may for example, be due to problems with the methodology. One of the major problems with benzene studies is the quantitative exposure data, particularly where there may be a very long latency period. The assessment of risk is further complicated by the possibility that low cumulative exposure may result in well-differentiated malignancy (e.g., multiple myeloma), whereas higher exposure leads to leukaemia (Rinsky, 1989). The risk of cancer from exposure to low concentrations of benzene has yet to be established. However, there is no doubt that chronic exposure to high concentrations of benzene (usually above 10 ppm) increases the risk of leukaemia (Swaen and Meijers, 1989). On the basis of the available evidence a small increase in mortality from leukaemia in workers exposed to low benzene concentrations cannot be distinguished from a no-risk situation (IPCS, 1993).

Occupations involved

- **Workers using benzene-based glue**

  Many cases of benzene carcinogenicity involve shoemakers, and garment and leather industry workers handling benzene-containing glue (Aksoy *et al*., 1984; Aksoy 1985; Maltoni *et al*., 1989; Paci *et al*., 1989).

- **Chemical workers**

  Many of the studies from North America involve workers manufacturing Pliofilm, which is a product made from natural rubber (rubber hydrochloride) suspended in a solvent containing benzene (Infante *et al*., 1977; Rinsky *et al.,* 1981; Rinsky *et al*., 1987; Schnatter *et al*., 1996b). The product is a glossy membrane used mainly for packaging (Crump, 1996). These cohort studies have been repeatedly re-analysed with additional years of follow-up data and re-estimates of exposure concentrations (e.g., Austin *et al*., 1988; Lamm *et al*., 1989; Paustenbach *et al*., 1992; Crump, 1994; Paxton *et al*., 1994a,b Crump, 1996; Paxton, 1996), making these workers the most intensively studied group in occupational epidemiology (Paustenbach *et al*., 1992). The workers are from three different facilities in Ohio (one in St Mary's and two in Akron). These re-analyses all confirm an increased risk of leukaemia from benzene exposure. However, in one study the leukaemia deaths occurred in workers who started work prior to 1950 suggesting that early occupational environments differed from those experienced by workers who started after this date (Paxton *et al*., 1994a; Paxton, 1996). This finding is consistent with a threshold mechanism for benzene-induced leukaemia.

  An increased frequency of leukaemia following exposure to benzene in other chemical workers has also been reported (Ott *et al.,* 1978; Decouflé *et al.,* 1983; Wong, 1987a,b).

- **Petroleum transportation and distribution**

  There are case reports of workers with leukaemia (Brandt *et al.,* 1977; Infante *et al.,* 1990; Lumley *et al*., 1990) and studies which show an increased risk of leukaemia in workers in the petroleum industry (petrol pump attendants and distributors) exposed to benzene in petrol (Fleming, 1990; Rushton and Romaniuk, 1997). However, other studies have found no increased risk (Thorpe, 1974; Rushton and Alderson, 1981; Raabe and Wong, 1996; Schnatter *et al*., 1996a).

Exposure concentrations

Workers who have developed leukaemia have been exposed to concentrations of benzene of 16-680 ppm (Rinsky *et al*., 1981) and even as low as 3 ppm (Yin *et al*., 1987a). As stated previously, a no-effect level has not been defined for benzene exposure (ECETOC, 1984; Marcus, 1990).

Latency

There may be a long delay between exposure to benzene and the onset of leukaemia (Marcus, 1990), however, it is very variable. Rinsky *et al.* (1987) report an average latency of 20.5 years with a range of 13.5-37 years for acute myelogenous leukaemia. In another study the average latency for onset of leukaemia was 11.4 years with a range of 0.8-49.5 years (Yin *et al.*, 1987a).

Myelodysplastic syndrome (previously called preleukaemia syndrome)

Some individuals exposed to benzene are initially diagnosed as having myelodysplastic syndrome (MDS). This is a term for any haematological syndrome which may in time develop into leukaemia but at the time of assessment cannot be classified as leukaemia. The criteria for diagnosis of myelodysplastic syndrome vary but usually include refractory anaemia, usually hypochronic and often associated with thrombocytopenia or pancytopenia, normal or slightly increased percentage of myeloblasts in bone marrow and the presence of few blast cells in the peripheral blood film (Aksoy, 1985). A myelodysplastic syndrome may arise without previous aplastic anaemia (Rangan and Snyder, 1997).

Types of cancer

Benzene exposure is particularly associated with acute myelogenous leukaemia (AML) (Snyder, 1987), but other leukaemias and malignant diseases have also been reported (reviewed in Linet *et al.*, 1996); see **Table 2.3**. However, some authors question these findings (Smith and Norelle Lickiss, 1980) and state that AML and its variants are the only cancers consistently associated with benzene exposure (Lamm *et al.*, 1989; Crump, 1994). The other cancers reported with benzene exposure may reflect exposure to other chemicals or population and genetic differences in susceptibility (Linet *et al.*, 1996). Other cancers reported following exposure to benzene include:

Table 2.3 Types of cancers reported following exposure to benzene.
The role of benzene in some of these cancers is controversial, see text for details.

Acute lymphoblastic leukaemia (ALL)
Acute myelogenous leukaemia (AML) acute myeloblastic leukaemia acute myelomonocytic leukaemia
Chronic myelogenous leukaemia (CML)
Erythomyelosis
Erythroleukaemia
Hodgkin's disease
Lung cancer
Malignant lymphoma
Multiple myeloma
Non-Hodgkin's lymphoma (NHL; lymphosarcoma)
Note: The terms acute and chronic do not refer to the duration of disease but to the degree of cell differentiation, i.e., little or none and well differentiated, respectively.

- **Lung cancer**

  Some mortality studies on benzene exposure have identified individuals with lung cancer (Aksoy, 1985; Yin *et al.*, 1989; Hayes *et al.*, 1996; Yin *et al.*, 1996). However, the relative risk of lung cancer from benzene exposure is difficult to distinguish from the risks associated with cigarette smoking.

- **Lymphoma**

  Some studies on benzene exposure and leukaemia have coincidentally shown an increase in the relative risk of lymphoma, including Hodgkin's disease and non-Hodgkin's lymphoma (Vianna and Polan, 1979; Decouflé *et al.,* 1983; Rinsky *et al.*, 1987; Wong, 1987a; Yin *et al.*, 1996). More studies are required to determine whether benzene exposure does increase the risk of lymphoma (Young, 1989). Increasing environmental benzene concentrations may have a role in the increased incidence of non-Hodgkin's lymphoma (O'Connor *et al.*, 1999).

- **Multiple myeloma**

  Multiple myeloma, which is characterised by multiple bone marrow tumours, has been reported in workers exposed to benzene, both in case reports (Torres *et al.*, 1970; Aksoy *et al.*, 1984) and in epidemiological studies (Decouflé *et al.,* 1983; Rinsky *et al.*, 1987; Rinsky 1989). However, benzene exposure and the association with an increased risk of multiple myeloma is a controversial subject (Bergsagel *et al.*, 2000; Goldstein and Shalat, 2000). Several studies using analysis of raw data (Bond *et al.,* 1986; Wong, 1987a,b; Yin *et al.*, 1996; Paci *et al.*, 1989), published cohort data (Bezabeh *et al.*, 1996, Wong and Raabe, 1997), updating previous cohort studies (Paxton *et al.*, 1994a; Paxton, 1996) and evaluation of the literature (Bergsagel *et al.*, 1999) have found no association.

Genotoxicity

Although a number of gene mutation assays have shown benzene to be weakly or non-mutagenic (Dean, 1985; Goldstein, 1989; Parke, 1989), this is contradicted by studies in exposed workers. These have shown chromosome aberrations, mostly breaks, gaps and sister chromatid exchanges (SCE), in benzene exposed workers (e.g., Tough and Court Brown, 1965; Forni *et al.*, 1971a, 1971b; Funes-Cravioto *et al.*, 1977; Yardley-Jones *et al.*, 1990; Karacic *et al.,* 1995; Tunca and Egeli, 1996). There appears to be no correlation between the duration of exposure and the frequency of chromosome changes (Forni *et al.*, 1971a; Tunca and Egeli, 1996; Seiji *et al.*, 1990). Genotoxicity has also been demonstrated in *in vitro* and *in vivo* animal studies (reviewed in Snyder, 1987; Ludewig *et al.,* 1989).

A higher mutation frequency has been observed in benzene-exposed workers using a test to identify stem cell or precursor erythroid cell mutations expressed in peripheral erythrocytes (Rothman *et al.*, 1995; 1996b; Smith, 1996b). The mutation frequency was related to cumulative benzene exposure rather than current exposure (Rothman *et al.*, 1995).

Benzene has been reported to cause chromosome specific aneuploidy, the loss or gain of whole chromosomes. Numerical changes in C-group chromosomes 6-12 and X have been observed in the blood and bone marrow of individuals with benzene induced myelogenous leukaemia, myelodysplastic syndrome (preleukaemia) and pancytopenia (Smith, 1996b). Aneuploidy of chromosome 9 has been reported in workers exposed to benzene concentrations >31 ppm, but not in those with exposure to lower concentrations. Aneuploidy correlated with the air concentration of benzene, the urinary concentration of phenol and decreased lymphocyte count in exposed workers (Zhang *et al.*, 1996).

A significantly increased incidence of hyperdiploidy (a gain in chromosome number) of both chromosomes 8 and 21 was observed in the lymphocytes of benzene-exposed workers. The effect was mainly in the form of trisomy (3 copies of the chromosome). There was also an increase in translocations. In workers exposed to >31 ppm benzene there was a 15-fold increase in translocations between chromosome 8 and 21 compared to controls. In this study chromosome aberrations correlated with current (previous 6-12 months) exposure, not to cumulative life-time exposure (Smith *et al.*, 1998). Changes in chromosomes 8 and 21 are common in patients with acute myeloid leukaemia. In addition, cytogenic abnormalities with loss of all or part of

chromosomes 5 and 7 are found in patients with myelogenous leukaemia after antineoplastic therapy or benzene/solvent exposure (Irons and Stillman, 1996b).

Follow-up of workers after they had suffered severe benzene haematotoxicity demonstrated that increased chromosome-type aberrations (with normal blood counts) were still present even 30 years after they had recovered from benzene toxicity. This study also investigated 31 subjects with a history of benzene toxicity and 31 controls. There were eleven deaths in the exposed group including five deaths from cancer. The deceased subjects had had significantly higher rates of chromosome-type aberrations than those still living, and those that had died from cancer had the highest rates of chromosome-type aberrations in the last cytogenetic examination before the diagnosis of cancer or their death (Forni, 1996).

Several studies have shown slight or no genotoxic effects in workers exposed to low concentrations of benzene (Watanabe *et al*., 1980; Sarto *et al*., 1984; Jablonická *et al.,* 1987; Yardley-Jones *et al*., 1988b; Seiji *et al*., 1990). There was no increase in sister chromatid exchanges (SCEs) in peripheral lymphocytes in workers exposed to a maximum of 40 ppm of benzene for 1-20 years (Watanabe *et al*., 1980). Similarly there was no significant increase in SCE in workers exposed to benzene at 0.2-12.4 ppm (Sarto *et al*., 1984). There was no significant increase in SCE in 10 workers exposed to a single acute high exposure to benzene. However, the study was done 3 months after the incident and the number of workers was small (Clare *et al*., 1984).

In vitro studies on human lymphocytes exposed to various benzene concentrations found no increase in SCEs or the number of chromosome aberrations (Gerner-Smidt and Friedrich, 1978).

Reproductive toxicity

Although some animal studies have shown benzene to be embryotoxic and fetotoxic (Murray *et al*., 1979; Nawrot and Staples, 1979; Kuna and Kapp, 1981), it is not a potent reproductive toxin (Snyder, 1987; IPCS, 1993) and in most cases effects only occur at concentrations resulting in maternal toxicity (Schwetz, 1983). Some studies have implicated benzene as a reproductive toxin in humans (reviewed in Barlow and Sullivan, 1982; ATSDR, 1997), but the studies are limited and no conclusions can be drawn. There are no data to suggest a reproductive risk at benzene concentrations encountered in the workplace or environment (Paustenbach *et al*., 1993).

Stücker *et al*. (1994) analysed the frequency of spontaneous abortion and paternal exposure to benzene (graded as <5 ppm and ≥5 ppm benzene). The frequency of spontaneous abortion was not significantly higher in either of the benzene-exposed groups compared to controls.

Benzene crosses the placenta and is present in cord blood in concentrations equal to or greater than that of maternal blood (Dowty *et al*., 1976).

A 22 year old pregnant worker developed severe pancytopenia and chromosome abnormalities following benzene exposure in the previous year. She had serious haemorrhagic complications during delivery but gave birth to a healthy boy. The following year she delivered a normal girl. All chromosome studies on the mother were abnormal but no aberrations were found in cytogenetic examination of the newborn boy (Forni *et al.,* 1971b). Other cases of haemorrhagic complications of pregnancy have been reported, particularly in the older literature, in women with benzene toxicity (Hunt, 1979).

RISK GROUPS

There are cases that demonstrate differences in individual susceptibility to benzene toxicity. An example is that of a husband and wife who manufactured whistles by dipping plastic material into a bucket of benzene (88.42% and toluene 9.25%). The wife developed severe aplastic anaemia after 6 months, whereas the husband developed no haematological abnormalities even after 14 years of exposure (Baslo and Aksoy, 1982; Aksoy, 1985). This was probably due to genetic differences. This is further supported by reports of a familial connection in some cases of benzene poisoning. Aksoy (1985) described cases of benzene toxicity involving cousins, an uncle and nephew, and a father and son.

Although there are various factors that may make some individuals more likely to develop benzene toxicity (listed below), it is believed that all humans are susceptible to the pancytopenic effects of benzene (ATSDR, 1997).

- **Pre-existing bone marrow disease.**

  Benzene is a bone marrow toxin. Individuals with haematological disease, e.g., beta-thalassaemia, may be more at risk from the toxic effects of benzene (Aksoy *et al*., 1971). Folic acid deficiency may be a risk factor for megaloblastic erythropoiesis in patients with benzene-induced pancytopenia (Aksoy *et al.,* 1972).

- **Rapid synthesis of bone marrow (Marcus, 1990) and high bone marrow myeloperoxidase activity (Snyder, 2000).**

  Benzene accumulates in bone marrow and individuals rapidly synthesising bone marrow are at greater risk of benzene toxicity (Marcus, 1990). This includes fetuses, infants and individuals with anaemia and related blood disorders.

- **Low NAD(P)H:quinone oxidoreductase 1 (NQO1) concentrations (Rothman *et al.*, 1997; Moran *et al.* 1999; Snyder, 2000).**

  NQO1 is an inducible enzyme involved in the detoxification of a number of compounds. It is capable of detoxifying quinones (produced by the oxidation of phenolic metabolites of benzene) by maintaining them in their reduced forms. Recently, a polymorphism in NQO1 has been identified and individuals homozygous for this mutation have no NQO1 activity. It has been suggested that such individuals may be more susceptible to benzene toxicity. A study of benzene exposed workers in China supported this hypothesis (Rothman *et al.*, 1997). Moran *et al*. (1999) suggest NQO1 is induced in human bone marrow cells after exposure to benzene metabolites. They found that induction of NQO1 was not observed in cells of individuals who are homozygous for the mutation. In addition, these individuals are more susceptible to other forms of chemical induced toxicity and cancer. The proportion of individuals with this mutation varies between different ethnic groups. This is a relatively new area of study and many questions have still to be answered (Ross, 1996; Smith, 1999).

- **High P450 CYP2E1 activity (see Smith 1996a).**

  A higher rate of P450 CYP2E1-dependent metabolism will increase the rate of formation of benzene metabolites (Snyder, 2000). In the study by Rothman *et al*. (1997) CYP2E1 polymorphism did not affect benzene metabolism or influence the risk of benzene poisoning, except in those individuals with high CYP2E1 activity who were also homozygous for the NQO1 mutation (see above).

- **Low GSH transferase concentrations (Snyder, 2000).**

  Glutathione (GSH) is involved in the detoxification of many substances. GSH transferase is responsible for catalysing the reaction converting GSH to GS^-. A low concentration of GSH transferase will delay detoxification.

  It should be noted however, that the relative activities of these enzymes (CYP2E1, NQO1, GSH transferase, bone marrow myeloperoxidase) determines an individual's susceptibility to benzene toxicity since there may be compensation. For example, an individual with a high concentration of NQO1 combined with a high CYP2E1 activity may not be more susceptible to benzene toxicity (Snyder, 2000).

- **Gender**

  It has long been suggested that women may be more susceptible to benzene toxicity (Barlow and Sullivan, 1982). Data from physiological-based pharmacokinetic (PBPK) modelling supports this. Although females have lower blood benzene concentrations under the same exposure conditions than males, they metabolise a greater percentage (23-26% difference). Consequently, they may be exposed to higher concentrations of benzene metabolites (Brown *et al*., 1998). A number of observations support this. In the study by Liu *et al*. (1996) the concentration of peripheral lymphocyte 8-hydroxy-2-deoxyguanosine (a measure of DNA oxidative damage) was higher in females compared to males when exposed to the same benzene

concentration. However, there was no difference in the 8-hydroxy-2-deoxyguanosine concentration, lymphocyte micronuclei (a measure of genotoxicity) or leucocyte count (a measure of myelotoxicity) between males or females in the control group.

No gender differences in haematopoietic and lymphoproliferative cancers were observed in Chinese workers exposed to benzene, although the number of leukaemias and other diseases was small (Li *et al*., 1994).

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Benzene is an aspiration hazard and gastric lavage should only be attempted if the airway is protected. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive.

Antidote

There is no specific antidote for benzene.

Chronic exposure

Referral to a haematologist is recommended for any worker with evidence of bone marrow depression.

REFERENCES

Aksoy M. 1985 Malignancies due to occupational exposure to benzene. *Am J Ind Med* 7:395-402.

Aksoy M (editor). 1988 *Benzene Carcinogenicity*. CRC Press, Boca Raton.

Aksoy M. 1989 Hematotoxicity and carcinogenicity of benzene. *Environ Health Perspect* 82:193-197.

Aksoy M, Dinçol K, Akgün T, Erdem S, Dinçol G. 1971 Haematological effects of chronic benzene poisoning in 217 workers. *Br J Ind Med* 28:296-302.

Aksoy M, Dinçol K, Erdem S, Akgün T, Dinçol G. 1972 Details of blood changes in 32 patients with pancytopenia associated with long-term exposure to benzene. *Br J Ind Med* 29:56-64.

Aksoy M, Erdem S, Dinçol G, Kutlar A, Bakioglu I, Hepyüksel T. 1984 Clinical observations showing the role of some factors in the etiology of multiple myeloma. *Acta Hematol* 71:116-120.

Aksoy M, Özeris S, Sabunchu H, Inanici Y, Yanardag R. 1987 Exposure to benzene in Turkey between 1983 and 1985: a haematological study on 231 workers. *Br J Ind Med* 44:785-787.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Angerer J, Hörsch B. 1992 Determination of aromatic hydrocarbons and their metabolites in human blood and urine. *J Chromatog B* 580:229-255.

Anon. 1988 Benzene. *Rev Environ Contam Toxicol* 106:9-19.

Appuhn E, Goldeck H. 1957 Früh- und Spätschäden der Blutbildung durch Benzol und seine Homologen [Early and late disorders of haematopoiesis caused by benzene and its homologues]. *Arch Gewerbepathol Gewerbehyg* 15:399-428.

ATSDR. 1997. *Toxicological profile for benzene (update)*. Agency for Toxic Substances and Disease Registry. US Department of Health and Human Services.

Avis SP, Hutton CJ. 1993 Acute benzene poisoning. *J Forensic Sci* 38 (3):599-602.

Austin H, Dellzell E, Cole P. 1988 Benzene and leukemia: a review of the literature and a risk assessment. *Am J Epidemiol* 127 (3):419-439.

Baarson KA, Snyder CA, Green JD, Sellakumar A, Goldstein BD, Albert RE. 1982 The hematological effects of inhaled benzene on peripheral blood, bone marrow, and spleen cells are increased by ingested ethanol. *Toxicol Appl Pharmacol* 64:393-404.

Barbera N, Bulla G, Romano G. 1998 A fatal case of benzene poisoning. *J Forensic Sci* 43 (6):1250-1251.

Barlow SM, Sullivan FM. 1982 *Reproductive Hazards of Industrial Chemicals. An evaluation of animal and human data*. Academic Press, London.

Baslo A, Aksoy M. 1982 Neurological abnormalities in chronic benzene poisoning. A study of six patients with aplastic anemia and two with preleukemia. *Environ Res* 27:457-465.

Bechtold WE, Lucier G, Birnbaum LS, Yin SN, Li GL, Henderson RF. 1991 Muconic acid determinations in urine as a biological exposure index for workers occupationally exposed to benzene. *Am Ind Hyg Assoc J* 52 (11):473-478.

Bergsagel DE, Wong O, Bergsagel L, Alexanian R, Anderson K, Kyle RA, Raabe GK. 1999 Benzene and multiple myeloma: appraisal of the scientific evidence. *Blood* 94 (4):1174-1182.

Bergsagel DE, Wong O, Bergsagel LP, Alexanian R, Anderson KC, Kyle RA, Raabe GK. 2000 Benzene and multiple myeloma: scientific evidence [authors' reply]. *Blood* 95 (4):1513-1514.

Bezabeh S, Engel A, Morris CB, Lamm SH. 1996 Does benzene cause multiple myeloma? An analysis of the published case-control literature. *Environ Health Perspect* 104 (Suppl 6):1393-1398.

Bois FY, Jackson ET, Pekari K, Smith MT. 1996 Population toxicokinetics of benzene. *Environ Health Perspect* 104 (Suppl 6):1405-1411.

Bond GG, McLaren EA, Baldwin CL, Cook RR. 1986 An update of mortality of chemical workers exposed to benzene. *Br J Ind Med* 43:685-691.

Boogaard PJ, van Sittert NJ. 1995 Biological monitoring of exposure to benzene: a comparison between *S*-phenylmercapturic acid and *trans-trans*-muconic acid, and phenol. *Occup Environ Med* 52:611-620.

Boogaard PJ, van Sittert NJ. 1996 Suitability of *S*-phenyl mercapturic acid and *trans-trans*-muconic acid as biomarkers for exposure to low concentrations of benzene. *Environ Health Perspect* 104 (Suppl 6):1151-1157.

Brandt L, Nilsson PG, Mitelman F. 1977 Non-industrial exposure to benzene as a leukaemogenic risk factor [letter]. *Lancet* 2:1074.

Brett SM, Rodricks JV, Chinchilli VM. 1989 Review and update of leukemia risk potentially associated with occupational exposure to benzene. *Environ Health Perspect* 82:267-281.

Brown EA, Shelley ML, Fisher JW. 1998 A pharmacokinetic study of occupational and environmental benzene exposure with regard to gender. *Risk Anal* 18 (2):205-213.

Brugnone F, Perbellini L, Faccini GB, Danzi FPB, Maranelli G, Romeo L, Gobbi M, Zedde A. 1989 Benzene in the blood and breath of normal and occupationally exposed workers. *Am J Ind Med* 36:385-299.

Brugnone F, Perbellini L, Romeo L, Bianchin M, Tonello A, Pianalto G, Zambon D, Zanon G. 1998 Benzene in environmental air and human blood. *Int Arch Occup Environ Health* 71:554-559.

Brugnone F, Perbellini L, Romeo L, Cerpelloni M, Bianchin M, Tonello A. 1999 Benzene in blood as a biomarker of low level occupational exposure. *Sci Total Environ* 235:247-252.

Byrd DM, Barfield ET. 1989 Uncertainty in the estimation of benzene risks: application of an uncertainty taxonomy to risk assessment based on an epidemiology study of rubber hydrochloride workers. *Environ Health Perspect* 82:283-287.

Chen H, Eastmond DA. 1995a Synergistic increase in chromosomal breakage within the euchromatin induced by an interaction of the benzene metabolites phenol and hydroquinone in mice. *Carcinogenesis* 16 (8):1963-1969

Chen H, Eastmond DA. 1995b Topoisomerase inhibition by phenolic metabolites: a potential mechanism for benzene's clastogenic effects. *Carcinogenesis* 16 (10):2301-2307.

Clare MG, Yardley-Jones A, Maclean AC, Dean BJ. 1984 Chromosome analysis from peripheral blood lymphocytes of workers after acute exposure to benzene. *Br J Ind Med* 41:249-253.

Cohr K-H, Skokholm J. 1979 Toluene. A toxicologic review. *Scan J Work Environ Health* 5 (2):71-90.

Collins JJ, Ireland BK, Easterday PA, Nair RS, Braun J. 1997 Evaluation of lymphopenia among workers with low-level benzene exposure and the utility of routine data collection. *J Occup Environ Med* 39 (3):232-237.

Cox LA Jr. 1991 Biological basis of chemical carcinogenesis: insights from benzene. *Risk Anal* 11 (3):453-464.

Crump KS. 1994 Risk of benzene-induced leukemia: a sensitivity of the pliofilm cohort with additional follow-up and new exposure estimates. *J Toxicol Environ Health* 42 (2):219-242.

Crump KS. 1996 Risk of benzene-induced leukemia predicted from the Pliofilm cohort. *Environ Health Perspect* 104 (Suppl 6):1437-1441.

Da Silva C, Fan X, Castagna M. 1989 Benzene-mediated protein kinase C activation. *Environ Health Perspect* 82:91-95.

Dean BJ. 1985 Recent findings on the genetic toxicology of benzene, toluene and xylene. *Mutat Res* 154:153-181.

Decouflé P, Blattner WA, Blair A. 1983 Mortality among chemical workers exposed to benzene and other agents. *Environ Res* 30:16-25.

Delore P, Borgomano C. 1928 Leucémie aiguë au cours d'intoxication benzénique. Sur l'origine toxique de certaines leucémies aiguës et leurs relations avec les anémies graves [Acute leukaemia following benzene

intoxication. The toxic origin of certain acute leukaemias and their relationship to serious anaemias]. *J Med Lyon* 9:227-233.

Dowty BJ, Laseter JL, Storer J. 1976 The transplacental migration and accumulation in blood of volatile organic constituents. *Pediatr Res* 10:696-701.

Drozd J, Bockowski EJ. 1967 Acute benzene poisoning. *J Occup Med* 9 (1):9-11.

Drummond L, Luck R, Afacan AS, Wilson HK. 1988 Biological monitoring of workers exposed to benzene in the coke oven industry. *Br J Ind Med* 45:256-261.

Ducos P, Gaudin R, Robert A, Francin JM, Maire C. 1990 Improvement in HPLC analysis of urinary *trans,trans*-muconic acid, a promising substitute for phenol in the assessment of benzene exposure. *Int Arch Occup Environ Health* 62:529-534.

Ducos P, Graudin R, Bel J, Maire C, Francin JM, Robert A, Wild P. 1992 *trans,trans*-Muconic acid, a reliable biological indicator for the detection of individual benzene exposure down to the ppm level. *Int Arch Occup Environ Health* 64:309-313.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 1986 Benzene. *Technical Report No. 16*.

Eastmond DA, Smith MT, Irons RD. 1987 An interaction of benzene metabolites reproduces the myelotoxicity observed with benzene. *Toxicol Appl Pharmacol* 91:85-95.

Feitshans IL. 1989 Law and regulation of benzene. *Environ Health Perspect* 82:299-307.

Fleming AF. 1990 Benzene in petrol: a continuing hazard [letter]. *Lancet* 336:1076-1077.

Forni A, Pacifico E, Limonta A. 1971a Chromosome studies in workers exposed to benzene or toluene or both. *Arch Environ Health* 22:373-378.

Forni AM, Cappellini A, Pacifico E, Vigilani EC. 1971b Chromosome changes and their evolution in subjects with past exposure to benzene. *Arch Environ Health* 23:385-391.

Forni A. 1996 Benzene-induced chromosome aberrations: a follow-up study. *Environ Health Perspect* 104 (Suppl 6):1309-1312.

Funes-Cravioto F, Zapata-Gayon C, Kolmodin-Hedman B, Lambert B, Lindsten J, Norberg E, Nordenskjöld M, Olin R, Swensson Å. 1977 Chromosome aberrations and sister chromatid exchange in workers in chemical laboratories and a rotoprinting factory and in children of women laboratory workers. *Lancet* 2:322-325.

Gaido KW, Wierda D. 1987 Suppression of bone marrow stromal cell function by benzene and hydroquinone is ameliorated by indomethacin. *Toxicol Appl Pharmacol* 89 (3):378-90.

Gerarde HW. 1960 *Toxicology and Biochemistry of Aromatic Hydrocarbons*. Elsevier, Amsterdam.

Gerner-Smidt P, Friedrich U. 1978 The mutagenic effects of benzene, toluene and xylene studied by the SCE technique. *Mutat Res* 58:313-316.

Golding BT, Watson WP. 1999 Possible mechanisms of carcinogenesis after exposure to benzene. *IARC Sci Pub* 150:75-88.

Goldstein BD. 1989 Introduction: Occam's razor is dull. *Environ Health Perspect* 82:3-6.

Goldstein BD, Shalat SL. 2000 The causal relationship between benzene exposure and multiple myeloma [letter]. *Blood* 95 (4):1512-1513.

Grant WM, Schuman, JH. 1993 *Toxicology of the Eye,* fourth edition. Charles C Thomas, Springfield, Illinois.

Greenberg L. 1926 Benzol poisoning as an industrial hazard. *Public Health Reports* 41:1357-1375.

Gusev IS. 1965 Reflective effects of microconcentrations of benzene, toluene and xylene and their comparative assessment. *Hyg Sanit* 30:331-336.

Guy RL, Hu P, Wizt G, Goldstein BD, Snyder R. 1991 Depression of iron uptake into erythrocytes in mice by treatment with the combined benzene metabolites *p*-benzoquinone, muconaldehyde and hydroquinone. *J Appl Toxicol* 11 (6):443-446.

Hamilton A. 1922 The growing menace of benzene (benzol) poisoning in American industry. *J Am Med Assoc* 78 (9):625-630.

Hancock DG, Moffitt AE, Hay EB. 1984 Hematological findings among workers exposed to benzene at a coke oven by-product recovery facility. *Arch Environ Health* 39 (6):414-418.

Hanke J, Dutiewicz T, Piotrowski J. 2000 The absorption of benzene through human skin. *Int J Occup Environ Health* 6 (2):104-110. [Reprinted in translation from *Medycyna Pracy* 1961 12 (5):413-426.]

Harbison RD. 1998 Aromatic hydrocarbons. In: *Hamilton and Hardy's Industrial Toxicology*, fifth edition. Harbison RD (editor). Mosby, St Louis.

Hayden JW, Peterson RG, Bruckner JV. 1977 Toxicology of toluene (methylbenzene): review of current literature. *Clin Toxicol* 11 (5):549-559.

Hayes RB, Yin SN, Dosemeci M, Li GL, Wacholder S, Chow WH, Rothman N, Wang YZ, Dai TR, Chao X-J, Jiang ZL, Ye P-Z, Zhao HB, Kou QK, Zhang WY, Meng JF, Zho JS, Lin XF, Ding CY, Li CY, Zhang Z-N, Li DG, Travis LB, Blot WJ, Linet MS. 1996 Mortality among benzene-exposed workers in China. *Environ Health Perspect* 104 (Suppl 6):1349-1352.

Henderson RF. 1996 Species differences in the metabolism of benzene. *Environ Health Perspect* 104 (Suppl 6):1173-1175.

Hunt VR. 1979 *Work and the Health of Women*. CRC Press, Boca Raton.

Hurley JF, Cherrie JW, Maclaren W. 1991 Exposure to benzene and mortality from leukaemia: results from coke oven and other coal product workers [letter]. *Br J Ind Med* 48:502-503.

Infante PF, Rinsky RA, Wagoner JK, Young RJ. 1977 Leukaemia in benzene workers. *Lancet* 2:76-78.

Infante PF, Schwartz E, Cahill R. 1990 Benzene in petrol: a continuing hazard [letter]. *Lancet* 336:814-815.

Inoue O, Seiji K, Kasahara M, Nakatsuka H, Watanabe T, Yin S-G, Li G-L, Jin C, Cai S-X, Wang X-Z, Ikeda M. 1986 Quantitative relation of urinary phenol levels to breathzone benzene concentrations: a factory survey. *Br J Ind Med* 43:692-697.

Inoue O, Seiji K, Watanabe T, Kasahara M, Nakatsuka H, Yin S, Li G, Cai S, Jin C, Ikeda M. 1988a Mutual metabolic suppression between benzene and toluene in man. *Int Arch Occup Environ Health* 60:15-20.

Inoue O, Seiji K, Kasahara M, Nakatsuka H, Watanabe T, Yin S-N, Li G-L, Cai S-X, Jin C, Ikeda M. 1988b Determination of catechol and quinol in the urine of workers exposure to benzene. *Br J Ind Med* 45:487-492.

Inoue O, Seiji K, Nakatsuka H, Watanabe T, Yin S-N, Li G-L, Cai S-X, Jin C, Ikeda M. 1989a Urinary *t*,*t*-muconic acid an indicator of exposure to benzene. *Br J Ind Med* 46:122-127.

Inoue O, Seiji K, Nakatsuka H, Watanabe T, Yin S-N, Li G-L, Cai S-X, Jin C, Ikeda M. 1989b. Excretion of 1,2,4-benzenetriol in the urine of workers exposed to benzene. *Br J Ind Med* 46:559-565.

Inoue O, Kanno E, Kakizaki M, Watanabe T, Higashikawa K, Ikeda M. 2000 Urinary phenylmercapturic acid as a marker of occupational exposure to benzene. *Ind Health* 38:195-204.

IPCS. 1997 *Environmental Health Criteria 150. Benzene*. International Programme on Chemical Safety, World Health Organization, Geneva.

Irons RD, Dent JG, Baker TS, Rickert DE. 1980 Benzene is metabolized and covalently bound in bone marrow *in situ*. *Chem Biol Interact* 30:241-245.

Irons RD, Neptun DA. 1980 Effects of the principal hydroxy-metabolites of benzene on microtubule polymerization. *Arch Toxicol* 45:297-305.

Irons RD, Stillman WS. 1996a The effects of benzene and other leukaemogenic agents on haematopoietic stem and progenitor cell differentiation. *Eur J Haematol* 57 (Suppl):119-124.

Irons RD, Stillman WS. 1996b The process of leukemogenesis. *Environ Health Perspect* 104 (Suppl 6): 1239-1246.

Irons RD, Stillman WS. 1996c Impact of benzene metabolites on differentiation of bone marrow progenitor cells. *Environ Health Perspect* 104 (Suppl 6):1247-1250.

Jablonická A, Vargová M, Karelová J. 1987 Cytogenetic analysis of peripheral blood lymphocytes in workers exposed to benzene. *J Hyg Epidem Microbiol Immunol* 31 (2):127-133.

Jex TT, Wyman DO. 1996 A mini review of benzene. *Toxic Subs Mechan* 15:135-143.

Johnson ES, Lucier G. 1992 Perspectives on risk assessment impact of recent reports on benzene. *Am J Ind Med* 21:749-757.

Kalf GF, Schlosser MJ, Renz JF, Pirozzi SJ. 1989 Prevention of benzene-induced myelotoxicity by nonsteroidal anti-inflammatory drugs. *Environ Health Perspect* 82:57-64.

Karacic V, Skender L, Bosner-Cucancic B, Bogadi-Sare A. 1995 Possible genotoxicity in low level benzene exposure. *Am J Ind Med* 27:379-388.

Kellerova V. 1985 Electroencephalographic findings in workers exposed to benzene. *J Hyg Epidemiol Microbiol Immunol* 29:337-346.

Kim SK, Kim YC. 1996 Effect of a single administration of benzene, toluene or *m*-xylene on carboxyhaemoglobin elevation and metabolism in rats. *J Appl Toxicol* 16(5):437-444.

King MD. 1982 Neurological sequelae of toluene abuse. *Hum Toxicol* 1:281-287.

Kipen HM, Cody RP, Goldstein BD. 1989 Use of longitudinal analysis of peripheral blood counts to validate historical reconstructions of benzene exposure. *Environ Health Perspect* 82:199-206.

Kuna RA, Kapp RW. 1981 The embryotoxic/teratogenic potential of benzene vapor in rats. *Toxicol Appl Pharmacol* 57:1-7.

Lagorio S, Tagesson C, Forastiere F, Iavarone I, Axelson O, Carere A. 1994 Exposure to benzene and urinary concentrations of 8-hydroxydeoxyguanosine, a biological marker of oxidative damage to DNA. *Occup Environ Med* 51:739-743.

Lamm SH, Walters AS, Wilson R, Byrd DM, Grunwald H. 1989 Consistencies and inconsistencies underlying the quantitative assessment of leukemia risk from benzene exposure. *Environ Health Perspect* 82:289-297.

Lange A, Smolik R, Zatoński W, Szymańska J. 1973a Serum immunoglobulin levels in workers exposed to benzene, toluene and xylene. *Int Arch Arbeitsmed* 31:37-44.

Lange A, Smolik R, Zatoński W, Glasman H. 1973b Leucocyte agglutinins in workers exposed to benzene, toluene and xylene. *Int Arch Arbeitsmed* 31:45-50.

Lee B-L, New A-L, Kok P-W, Ong H-Y, Shi C-Y, Ong C-N. 1993a Urinary *trans,trans*-muconic acid determined by liquid chromatography: application in biological monitoring of benzene exposure. *Clin Chem* 39 (9):1788-1792.

Lee BL, Ong HY, Shi CY, Ong CN. 1993b Simultaneous determination of hydroquinone, catechol and phenol in urine using high-performance liquid chromatography with fluorimetric detection. *J Chromatog B* 619:259-266.

Le Noire MM, Claude H. 1897 Sur un case de purpura attribué à l'intoxication par le benzene [A case of purpura attributed to benzene intoxication]. *Bull Mem Soc Med Hop Paris* 3:1251. Cited in: Smith MT. 1996a Overview of benzene-induced aplastic anaemia. *Eur J Haematol* 57 (Suppl):107-110.

Li G-L, Linet MS, Hayes RB, Yin S-N, Dosemeci M, Wang Y-Z, Chow W-H, Jiang Z-L, Wacholder S, Zhang W-U, Dai T-R, Chao X-J, Zhang X-C, Ye P-Z, Kou Q-R, Meng J-F, Zho J-S, Lin X-F, Ding C-Y, Wu C, Blot WJ. 1994 Gender differences in hematopoietic and lymphoproliferative disorders and other cancer risks by major occupational group among workers exposed to benzene in China. *J Occup Med* 36 (8):875-881.

Linet MS, Yin S-N, Travis LB, Li C-Y, Zhang Z-N, Li D-G, Rothman N, Li G-L, Chow W-H, Donaldson J, Dosemeci M, Wacholder S, Blot WJ, Hayes RB, the Benzene Study Group. 1996 Clinical features of hematopoietic malignancies and related disorders among benzene-exposed workers in China. *Environ Health Perspect* 104 (Suppl 6):1353-1364.

Liu L, Zhang Q, Feng J, Deng L, Zeng N, Yang A, Zhang W. 1996 The study of DNA oxidative damage in benzene-exposed workers. *Mutat Res* 370:145-150.

Ludewig G, Dogra S, Glatt H. 1989 Genotoxicity of 1,4-benzoquinone and 1,4-naphthoquinone in relation to effects on glutathione and NAD(P)H levels in V79 cells. *Environ Health Perspect* 82:223-228.

Lumley M, Barker H, Murray JA. 1990 Benzene in petrol [letter]. *Lancet* 336:1318-1319.

Maltoni C, Ciliberti A, Cotti G, Conti B, Belpoggi F. 1989 Benzene, an experimental multipotential carcinogen: results at the Bologna Institute of Oncology. *Environ Health Perspect* 82:109-124.

Marcus WL. 1990 Chemical of current interest - benzene. *Adv Mod Environ Toxicol* 17:127-188.

Medinsky MA, Kenyon EM, Seaton MJ, Schlosser PM. 1996 Mechanistic consideration in benzene physiological model development. *Environ Health Perspect* 104 (Suppl 6):1399-1404.

Midzenski MA, McDiarmid AM, Rothman N, Kolodner K. 1992 Acute high dose exposure to benzene in shipyard workers. *Am J Ind Med* 22:553-565.

Money CD, Gray CN. 1989 Exhaled breath analysis as a measure of workplace exposure to benzene ppm. *Ann Occup Hyg* 33 (2):257-262.

Moran JL, Siegel D, Ross D. 19991 A potential mechanism underlying the increased susceptibility of individuals with a polymorphism in NAD(P)H:quinone oxidoreductase 1 (NQO1) to benzene toxicity. *Proc Natl Acad Sci* 96:8150-8155.

Moszczynski P. 1981 Organic solvents and T-lymphocytes [letter]. *Lancet* 1:438.

Murray FJ, John JA, Rampy LW, Kuna RA, Schwetz BA. 1979 Embryotoxicity of inhaled benzene in mice and rabbits. *Am Ind Hyg Assoc J* 40:993-998.

Nakajima T, Okuyama O, Yonekura I, Sato A. 1985 Effects of ethanol and phenobarbital administration on the metabolism and toxicity of benzene. *Chem Biol Interact* 55:23-38.

Nawrot PS, Staples RE. 1979 Embryo-fetal toxicity and teratogenicity of benzene and toluene in the mouse [abstract]. *Teratology* 19:41A.

Nicholson WJ, Landrigan PJ. 1989 Quantitative assessment of lives lost due to delay in the regulation of occupational exposure to benzene. *Environ Health Perspect* 82:185-188.

Nomiyama K, Nomiyama H. 1974 Respiratory elimination of organic solvents in man. *Int Arch Arbeitsmed* 32:85-91.

O'Connor SR, Farmer PB, Lauder I. 1999 Benzene and non-Hodgkin's lymphoma. *J Pathol* 189:448-453.

Ong C-N, Lee B-L. 1994 Determination of benzene and its metabolites: Application in biological monitoring of environmental and occupational exposure to benzene. *J Chromatog B* 660:1-22.

Ong CN, Kok PW, Lee BL, Shi CY, Ong HY, Chia KS, Lee CS, Luo XW. 1995 Evaluation of biomarkers for occupational exposure to benzene. *Occup Environ Med* 52:528-533.

Ong CN, Kok PW, Ong HY, Shi CY, Phoon WH, Tan KT. 1996 Biomarkers of exposure to low concentrations of benzene: a field assessment. *Occup Environ Med* 53:328-333.

Ott MG, Townsend JC, Fishbeck WA, Langner RA. 1978 Mortality among individuals occupationally exposed to benzene. *Arch Environ Health* 33:3-10.

Paci E, Buiatti E, Costantini AS, Miligi L, Pucci N, Scarpelli A, Petrioli G, Simonato L, Winkelmann R, Kaldor JM. 1989 Aplastic anemia, leukemia and other cancer mortality in a cohort of shoe workers exposed to benzene. *Scand J Work Environ Health* 15:313-318.

Parke DV. 1989 Introduction: session on metabolism. *Environ Health Perspect* 82:7-8.

Paustenbach DJ, Price PS, Ollison W, Blank C, Jernigan JD, Bass RD, Peterson HD. 1992 Reevaluation of benzene exposure for the pliofilm (rubberworker) cohort (1936-1976). *J Toxicol Environ Health* 36:177-231.

Paustenbach DJ, Bass RD, Price P. 1993 Benzene toxicity and risk assessment, 1972-1992: Implications for future regulation. *Environ Health Perspect* 101 (Suppl 6):177-200.

Paxton, MB, Chinchilli VM, Brett SM, Rodricks JV. 1994a Leukemia risk associated with benzene exposure to the pliofilm cohort. I Mortality update and exposure distribution. *Risk Anal* 14 (2):147-154.

Paxton, MB, Chinchilli VM, Brett SM, Rodricks JV. 1994b Leukemia risk associated with benzene exposure to the pliofilm cohort. II. Risk estimates. *Risk Anal* 14 (2):155-161.

Paxton MB. 1996 Leukemia risk associated with benzene exposure in the Pliofilm cohort. *Environ Health Perspect* 104 (Suppl 6):1431-1436.

Perbellini L, Faccini GB, Pasini F, Cazzoli F, Pistoia S, Rosellini R, Valsecchi M, Brugnone F. 1988 Environmental and occupational exposure to benzene by analysis of breath and blood. *Br J Ind Med* 45:345-352.

Pekari K, Vainiotalo S, Heikkilä P, Palotie A, Luotamo M, Riihimäki V. 1992 Biological monitoring of occupational exposure to low levels of benzene. *Scand J Work Environ Health* 18:317-322.

Raabe GK, Wong O. 1996 Leukemia mortality by cell type in petroleum workers with potential exposure to benzene. *Environ Health Perspect* 104 (Suppl 6):1381-1392.

Rangan U, Snyder R. 1997 Scientific update on benzene. *Ann NY Acad Sci* 837:105-113.

Rinsky RA. 1989 Benzene and leukemia: an epidemiologic risk assessment. *Environ Health Perspect* 82:189-199.

Rinsky RA, Young RJ, Smith AB. 1981 Leukemia in benzene workers. *Am J Ind Med* 2:217-245.

Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. 1987 Benzene and leukemia. An epidemiological risk assessment. *N Engl J Med* 316:1044-1050.

Robertson ML, Eastmond DA, Smith MT. 1991 Two benzene metabolites, catechol and hydroquinone, produce a synergistic induction of micronuclei and toxicity in cultured human lymphocytes. *Mutat Res* 249:210-209.

Ross D. 1996 Metabolic basis of benzene toxicity. *Eur J Haematol* 57 (Suppl):111-118.

Rothman N, Haas R, Hayes RB, Li G-L, Wiemels J, Campleman S, Quintana PJE, Xi L-J, Dosemeci M, Titenko-Holland N, Meyer KB, Lu W, Zhang LP, Bechtold W, Wang Y-Z, Kolachana P, Yin S-N, Blot W, Smith MT. 1995 Benzene induces gene-duplication but not gene-inactivating mutations at the glycophorin A locus in exposed humans. *Proc Natl Acad Sci* 92:4069-4073.

Rothman N, Li G-L, Dosemeci M, Bechtold WE, Marti GE, Wang YZ, Linet M, Xi L-Q, Lu W, Smith MT, Titenko-Holland N, Zhang L-P, Blot W, Yin S-N, Hayes RB. 1996a Hemotoxicity among Chinese workers heavily exposed to benzene. *Am J Ind Med* 29:236-246.

Rothman N, Smith MT, Hayes RB, Li G-L, Irons RD, Dosemeci M, Haas R, Stillman WS, Linet M, Xi L-Q, Bechtold WE, Wiemels J, Campleman S, Zhang L, Quintana PJE, Titenko-Holland N, Wang Y-Z, Lu W, Kolachana P, Meyer KB, Yin S. 1996b An epidemiologic study of early biologic effects of benzene in Chinese workers. *Environ Health Perspect* 104 (Suppl 6):1365-1370.

Rothman N, Smith MT, Hayes RB, Traver RD, Hoener BA, Campleman S, Li G-L, Dosemeci M, Linet M, Zhang L, Xi L, Wacholder S, Lu W, Meyer KB, Titenko-Holland N, Stewart JT, Ross D. 1997 Benzene poisoning, a risk factor for hematological malignancy, is associated with NQO1 ^{609}C→T mutation and rapid fractional excretion of chlorzoxazone. *Cancer Res* 57:2839-2842.

Rothman N, Bechtold WE, Yin S-N, Dosemeci M, Li G-L, Wang Y-Z, Griffith WC, Smith MT, Hayes RB. 1998 Urinary excretion of phenol, catechol, hydroquinone and muconic acid, by workers occupationally exposed to benzene. *Occup Environ Med* 55:705-711.

Ruppert T, Scherer G, Tricker AR, Rauscher D, Adlkofer F. 1995 Determination of urinary *trans-trans*-muconic acid by gas chromatography-mass spectrometry. *J Chromatogr B* 666:71-76.

Rushton L, Alderson MR, 1981 A case-control study to investigate the association between exposure to benzene and deaths from leukaemia in oil refinery workers. *Br J Cancer* 43:77-84.

Rushton L, Romaniuk H. 1997 A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. *Occup Environ Med* 54:152-166.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Sammett D, Lee EW, Kocsis JJ, Snyder R. 1979 Partial hepatectomy reduces both metabolism and toxicity of benzene. *J Toxicol Environ Health* 5:785-792.

Santesson CG. 1897 Über chronische Vergifttung mit Steinkohlenteerbenzin: vier Todesfälle [Chronic poisoning with coal tar gasoline: four fatal cases]. *Arch Hyg Berl* 31:336-376. Cited in: Smith MT. 1996a Overview of benzene-induced aplastic anaemia. *Eur J Haematol* 57 (Suppl):107-110.

Sarto F, Cominato I, Pinton AM, Brovedani PG, Merler E, Peruzzi M, Bianchi V, Levis AG. 1984 A cytogenetic study on workers exposed to low concentrations of benzene. *Carcinogenesis* 5:827-832.

Sato A, Nakajima T, Fujiwara Y, Murayama N. 1975 Kinetic studies on sex differences in susceptibility to chronic benzene intoxication - with special reference to body fat content. *Br J Ind Med* 32:321-328.

Sato A, Nakajima T. 1979 Dose-dependent metabolic interaction between benzene and toluene *in vivo* and *in vitro*. *Toxicol Appl Pharmacol* 48:249-256.

Schnatter AR, Armstrong TW, Thompson LS, Nicolich MJ, Katz AM, Huebner WW, Pearlman ED. 1996a The relationship between low-level benzene exposure and leukemia in Canadian petroleum distribution workers. *Environ Health Perspect* 104 (Suppl 6):1375-1379.

Schnatter AR, Nicolich MJ, Bird MG. 1996b Determination of leukemogenic benzene exposure concentrations: refined analyses of the Pliofilm cohort. *Risk Anal* 16 (6):833-840.

Schrenk D, Orzechowski A, Schwarz LR, Snyder R, Burchell B, Ingelman-Sunberg M, Bock KW. 1996 Phase II metabolism of benzene. *Environ Health Perspect* 104 (Suppl 6):1183-1188.

Schwetz BA. 1983 A review of the developmental toxicity of benzene. *Adv Med Environ Toxicol* 4:17-21.

Seiji K, Jin C, Watanabe T, Nakasuka H, Ikdea M. 1990 Sister chromatid exchanges in peripheral lymphocytes of workers exposed to benzene, trichloroethylene or tetrachloroethylene, with reference to smoking habits. *Int Arch Occup Environ Health* 62:171-176.

Smith MT, Yager JW, Steinmetz KL, Eastmond DA. 1989 Peroxidase-dependent metabolism of benzene's phenolic metabolites and its potential role in benzene toxicity and carcinogenicity. *Environ Health Perspect* 82:23-29.

Smith MT. 1996a Overview of benzene-induced aplastic anaemia. *Eur J Haematol* 57 (Suppl):107-110.

Smith MT. 1996b The mechanism of benzene-induced leukemia: a hypothesis and speculations on the causes of leukemia. *Environ Health Perspect* 104 (Suppl 6):1219-1225.

Smith MT. 1999 Benzene, NQO1 and genetic susceptibility to cancer. *Proc Natl Acad Sci* 96:7624-7626.

Smith PR, Norelle Lickiss J. 1980 Benzene and lymphomas [letter]. *Lancet* 1:719.

Smith MT, Zhang L, Wang Y, Hayes RB, Li G, Weimels J, Dosemeci M, Titenko-Holland N, Xi L, Kolachana P, Yin S, Rothman N. 1998 Increased translocations and aneusomy in chromosomes 8 and 21 among workers exposed to benzene. *Cancer Res* 58:2176-2181.

Smolik R, Grzybek-Hryncewicz K, Lange A, Zatonski W. 1973 Serum complement level in workers exposed to benzene, toluene and xylene. *Int Arch Arbeitsmed* 31:243-247.

Snyder CA. 1987 Benzene. In: *Ethel Browning's Toxicity and Metabolism of Industrial Solvents*, second edition, Volume 1: Hydrocarbons. R Snyder (editor). Elsevier Science Publishers, Amsterdam.

Snyder R. 2000 Recent developments in the understanding of benzene toxicity and leukemogenesis. *Drug Chem Toxicol* 23 (1):13-25.

Snyder R, Dimitriadis E, Guy R, Hu P, Cooper K, Bauer H, Witz G, Goldstein BD. 1989 Studies on the mechanism of benzene toxicity. *Environ Health Perspect* 82:31-35.

Snyder R, Witz G, Goldstein BD. 1993 The toxicology of benzene. *Environ Health Perspect* 100:293-306.

Snyder R, Hedli CC. 1996 An overview of benzene metabolism. *Environ Health Perspect* 104 (Suppl 6): 1165-1171.

Srbová J, Teisinger J, Skramovsky S. 1950 Absorption and elimination of inhaled benzene in man. *Arch Ind Hyg Occup Med* 2 (1):1-8.

Stücker I, Mandereau L, Aubert-Berleur MP, Déplan F, Paris A, Richard A, Hémon A. 1994 Occupational paternal exposure to benzene and risk of spontaneous abortion. *Occup Environ Med* 51:475-478.

Swaen GMH, Meijers JMM. 1989 Risk assessment of leukaemia and occupational exposure to benzene. *Br J Ind Med* 46:826-830.

Tardif R, Laparé S, Plaa GL, Brodeur J. 1991 Effects of simultaneous exposure to toluene and xylene on their respective biological exposure indices in humans. *Int Arch Occup Environ Health* 63:279-284.

Tardif R, Goyal R, Brodeur J. 1992 Assessment of occupational health risk from multiple exposure: review of industrial solvent interaction and implication for biological monitoring of exposure. *Toxicol Ind Health* 8 (1/2):37-52.

Thorpe JJ. 1974 Epidemiological survey of leukaemia in persons potentially exposed to benzene. *J Occup Med* 16 (6):375-382.

Torres A, Giralt M, Raichs A. 1970 Coexistencia de antecedentes benzólicos crónicosy plasmocitoma multiple. Presentatión de dos casos [Coexistence of chronic benzol contacts and multiple plasmacytoma. Presentation of 2 cases]. *Sangre* 15:275-279.

Tough IM, Court Brown WM. 1965 Chromosome aberrations and exposure to ambient benzene. *Lancet* 1:684.

Trcka J, Petteke-Rank CV, Bröcker E-B, Hamm H. 1998 Genitoanocrural porokeratosis following chronic exposure to benzene. *Clin Exp Dermatol* 23:28-31.

Tunca BT, Egeli Ü. 1996 Cytogenetic findings on shoe workers exposed long-term to benzene. *Environ Health Perspect* 104 (Suppl 6):1313-1317.

van Sittert NJ, Boogaard PJ, Beulink GDJ. 1993 Application of the urinary *S*-phenylmercapturic acid test as a biomarker for low levels of exposure to benzene in industry. *Br J Ind Med* 50:460-469.

Vianna NJ, Polan A. 1979 Lymphomas and occupational benzene exposure. *Lancet* 1:1394-1395.

Wallace LA. 1989 Major sources of benzene exposure. *Environ Health Perspect* 82:165-169.

Wallace L. 1996 Environmental exposure to benzene: an update. *Environ Health Perspect* 104 (Suppl 6): 1129-1136.

Ward E, Hornung R, Morris J, Rinsky R, Wild D, Halperin W, Guthrie W. 1996 Risk of low red or white blood cell count related to estimated benzene exposure in a rubberworker cohort (1940-1975). *Am J Ind Med* 29:247-257.

Watanabe T, Endo A, Kato Y, Shima S, Watanabe T, Ikeda M. 1980 Cytogenetics and cytokinetics of cultured lymphocytes from benzene-exposed workers. *Int Arch Occup Environ Health* 46:31-41.

Wierda D, Gaido K. 1986 Indomethacin protects against *in vivo* benzene inhibition of stromal cell function [abstract]. *Toxicologist* 6:286.

Winek CL, Collom WD. 1971 Benzene and toluene fatalities. *J Occup Med* 13 (5):259-261.

Winek CL, Collom WD, Wecht CH. 1967 Fatal benzene exposure by glue-sniffing [letter]. *Lancet* 1:683.

Witz G, Zhang Z, Golstein BD. 1996 Reactive ring-opened aldehyde metabolites in benzene hematotoxicity. *Environ Health Perspect* 104 (Suppl 6):1195-1199.

Wolf MA, Rowe VK, McCollister DD, Hollingsworth RL, Oyen F. 1956 Toxicological studies of certain alkylated benzenes and benzene. *Arch Ind Health* 14:387-398.

Wong O. 1987a An industry wide mortality study of chemical workers occupationally exposed to benzene. I. General results. *Br J Ind Med* 44:365-381.

Wong O. 1987b An industry wide mortality study of chemical workers occupationally exposed to benzene. II. Dose response analyses. *Br J Ind Med* 44:382-395.

Wong O, Raabe GK. 1997 Multiple myeloma and benzene exposure in a multinational cohort of more than 250,000 petroleum workers. *Regul Toxicol Pharmacol* 26:188-199.

Yardley-Jones A, Anderson D, Jenkinson P. 1988a Effect of occupational exposure to benzene on phytohaemagglutinin (PHA) stimulated lymphocytes in man. *Br J Ind Med* 45:516-522.

Yardley-Jones A, Anderson D, Jenkinson PC, Lovell DP, Blowers SD, Davies MJ. 1988b Genotoxic effects in peripheral blood and urine of workers exposed to low level benzene. *Br J Ind Med* 45:694-700.

Yardley-Jones A, Anderson D, Lovell DP, Jenkinson PC. 1990 Analysis of chromosomal aberrations in workers exposed to benzene. *Br J Ind Med* 47:48-51.

Yardley-Jones A, Anderson D, Parke DV. 1991 The toxicity of benzene and its metabolism and molecular pathology in human risk assessment. *Br J Ind Med* 48:437-444.

Yin S-N, Li G-L, Tain F-D, Fu Z-I, Jin C, Chen Y-J, Luo S-J, Ye P-Z, Zhang J-Z, Wang X-C, Wu H-N, Zhong Q-C. 1987a Leukaemia in benzene workers: a retrospective cohort study. *Br J Ind Med* 44:124-128.

Yin S-N, Li Q, Liu Y, Tain F, Dy C, Jin C. 1987b Occupational exposure to benzene in China. *Br J Ind Med* 44:192-195.

Yin S-N, Li G-L, Tain F-D, Fu Z-I, Jin C, Chen Y-J, Luo S-J, Ye P-Z, Zhang J-Z, Wang G-C, Zhang X-C, Wu H-N, Zhong Q-C. 1989 A retrospective cohort study of leukemia and other cancers in benzene workers. *Environ Health Perspect* 82:207-213.

Yin SN, Hayes RB, Linet MS, Li G-L, Dosemeci M, Travis LB, Zhang Z-N, Li D-G, Chow W-H, Wacholder S, Blot WJ. 1996 An expanded cohort study of cancer among benzene-exposed workers in China. Benzene Study Group. *Environ Health Perspect* 104 (Suppl 6):1339-1341.

Yin SN, Hayes RB, Linet MS, Li G-L, Dosemeci M, Travis LB, Li C-Y, Zhang Z-N, Li D-G, Chow W-H, Wacholder S, Wang Y-Z, Jiang Z-L, Dai T-R, Zhang W-Y, Chao X-J, Ye P-Z, Kou Q-R, Zhang X-C, Lin X-F, Meng J-F, Ding C-Y, Zho J-S, Blot WJ. 1997 A cohort study of cancer among benzene-exposed workers in China: overall results. *Am J Ind Med* 29:227-235.

Young N. 1989 Benzene and lymphoma. *Am J Ind Med* 15:495-498.

Zhang L, Rothman N, Wang Y, Hayes RB, Bechtold W, Venkatesh P, Yin S, Wang Y, Dosemeci M, Li G, Lu W, Smith MT. 1996 Interphase cytogenetics of workers exposed to benzene. *Environ Health Perspect* 104 (Suppl 6):1325-1329.

3 Carbon Disulphide

Maeve McParland

SUMMARY

- Carbon disulphide is potentially very toxic
- It is a potent neurotoxin and is narcotic at high concentrations
- Toxicity from carbon disulphide is primarily by inhalation, but toxicity following ingestion and dermal exposure can occur
- The target organs are the central nervous system, cardiovascular system, peripheral nervous system, liver, eyes and skin
- Carbon disulphide neurotoxicity manifests in three ways: encephalopathy, peripheral and cranial nerve dysfunction, and movement abnormalities
- Carbon disulphide causes skin irritation and potentially severe chemical burns
- Coronary heart disease occurs more frequently in workers exposed to carbon disulphide
- Chronic carbon disulphide exposure causes retinopathy
- Carbon disulphide can adversely effect both male and female reproductive function; one study reported birth defects in humans
- It not thought to be carcinogenic

DESCRIPTION

When pure, carbon disulphide is a colourless liquid with a sweet ether-like odour. The crude technical product is a yellowish liquid with a disagreeable odour, which has been described as similar to that of decaying radishes.

Synonyms

CS_2, carbon disulfide, carbon bisulphide, carbon bisulfide, dithiocarbonic anhydride, carbon sulphide, carbon sulfide

Identification numbers

CAS	75-15-0
UN	1131
RTECS	FF 6650000
EINECS	2008436

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	CS_2
molecular formula	S═C═S
molecular mass	76.14
physical form	colourless/yellowish volatile liquid
relative vapour density	2.67
flash point (°C) (closed cup)	-29.62
boiling point (°C)	46.3
auto ignition temperature (°C)	100
refractive index (at 20 °C)	1.62546
explosive limits in air (%v/v)	1-50

Odour threshold

0.11 ppm (Amoore and Hautala, 1983).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK) and TWA (ACGIH): 10 ppm (31.2 mg/m^3)

Conversion factors

1 mg/m^3 = 0.321 ppm
1 mg/l = 320 ppm
1 ppm = 3.12 mg/m^3

Biomonitoring

The biological exposure index (BEI) for carbon disulphide is 5 mg/g creatinine of 2-thiothiazolidine-4-carboxylic acid (TTCA) in urine at the end of a shift (ACGIH, 2000). Biological exposure indices have not been established for blood or alveolar air.

TOXICITY

The toxicity of carbon disulphide has been extensively studied. Research initially concentrated on its neurological effects and it was only later that the cardiovascular effects of carbon disulphide became apparent. Exposure is almost exclusively confined to occupational situations and chronic exposure has been extensively studied from an industrial hygiene perspective.

Historically, literature on the toxicity of carbon disulphide comes from its use in the cold vulcanisation of rubber and in the manufacture of viscose rayon, the incidence of poisoning roughly paralleling its industrial use in various countries. The toxicity of carbon disulphide first became apparent in the 1800s when it was used for cold vulcanisation of rubber in Europe. This process was never in common use in the US (where the heat cure method of rubber vulcanisation was favoured). In the US occupational exposure to carbon disulphide appeared with the viscose rayon manufacturing industry and practically all epidemiological studies to date have been conducted on viscose rayon workers.

In 1856, Delpech, a physician in Paris, presented the first study on the effects of carbon disulphide. He described a variety of nervous system and mental disorders, and reported that workers typically had an early stage of excitation followed by a period of depression, and he termed the syndrome 'carbon disulphide neurosis'. Towards the end of the nineteenth century and in the beginning of the twentieth century reports began to appear in the German literature. A landmark paper by Laudenheimer describing 50 cases of carbon disulphide 'insanity' resulted in the occupational exposure limit being reduced from several hundred to less than 30 ppm. As a result of this reduction it was said that the general morbidity among rubber workers during the early 1900s declined by 75% and their mental disorders by 86% (Gordy and Trumper, 1938; Davidson and Feinleib, 1972; Spyker *et al.,* 1982). Due to further improved working and hygiene conditions in the industrial environment, adverse effects from carbon disulphide exposure are now less frequent and less pronounced. Recent studies have concluded that the current TLV of 10 ppm is sufficient to protect workers from the neurotoxic (DeFruyt *et al.*, 1998) and cardiovascular (Franco *et al.,* 1982; Drexler *et al.,*1996) effects of carbon disulphide.

Toxicity from acute exposure to carbon disulphide is rare and most adverse effects have been reported from chronic exposure. Carbon disulphide is a potent neurotoxin and is narcotic at high concentrations. Target organs are the central and peripheral nervous systems, including the optic and auditory nerves, the liver, heart, testes and skin. Less pronounced are the toxic effects of carbon disulphide on the pancreas, kidney, the haematopoietic system and the hormonal regulatory system. At high concentrations carbon disulphide is embryotoxic. Epidemiological studies of workers in the viscose rayon industry have shown that the main toxic effects are on the neurological system (both central and peripheral) and the cardiovascular system (coronary heart disease and ECG changes). Ocular effects are also widely reported (alterations in the retinal microvasculature and impaired colour discrimination) and liver and kidney damage can occur (WHO, 1979; BUA, 1991; Gehring *et al.*, 1991; Feldman, 1999).

Carbon disulphide is formed in the body from degradation of other sulphur xenobiotics such as disulfiram and this presents a potential source of minor exposure to carbon disulphide (Dalvi, 1988). Disulfiram is converted enzymatically to carbon disulphide. Carbon disulphide is known to cause neurofilamentous distal axonopathy in animals. Similar changes in human nerve tissue after disulfiram administration, suggest that carbon disulphide is the toxic agent (Ansbacher *et al.*, 1982).

There is a huge amount of literature on carbon disulphide toxicity spanning over a century and it has been the subject of many studies. For a comprehensive review see Beauchamp *et al.* (1983).

Absorption

The main route of absorption for carbon disulphide is inhalation, however, it is also readily absorbed from the gastrointestinal tract as evidenced by clinical effects following ingestion (Foreman *et al.,* 1886; Yamada, 1977). Carbon disulphide may be absorbed through the skin as a vapour or liquid (Coppock and Buck, 1981).

There is considerable variation between individuals, but absorption seems to be proportional to the concentration of carbon disulphide in the inhaled air. Equilibrium between the carbon disulphide concentration of inhaled and exhaled air is reached within 1-2 hours. Equilibrium after inhalation takes 60-120 minutes. However, it varies with the carbon disulphide concentration inhaled (Coppock and Buck, 1981). At this point the percentage retained is approximately 40-50%, and carbon disulphide is then distributed in the organism by the bloodstream, where twice as much is taken up by the erythrocytes as by the plasma (WHO, 1979).

Carbon disulphide is readily absorbed by inhalation, at exposure concentrations of 17-30 ppm - at least 80% of an inhaled dose is absorbed during the first 15 minutes of exposure. After 30 minutes the concentration absorbed drops to approximately 55% (Teisenger and Soucek, 1949; Davidson and Feinleib, 1972, Beauchamp *et al.*, 1983; Coppock and Buck, 1981). Pulmonary absorption increases with physical activity, however the percentage of inhaled carbon disulphide retained decreases as the blood and tissues become saturated (Teisinger and Soucek, 1949).

The rate of absorption of carbon disulphide from the gastrointestinal tract is not known but from the limited clinical evidence it appears to be rapid (Foreman, 1886).

Workers exposed to an average carbon disulphide level of 10 ppm had acid-labile blood concentrations of 332.6 µg/l (Campbell *et al.,* 1985).

Distribution

As carbon disulphide is readily fat and lipid soluble and binds to amino acids and proteins, it disappears rapidly from the bloodstream and has a higher affinity for all tissues and organs (WHO, 1979). It is readily soluble in lipids and its retention increases in individuals with a high percentage of body fat (Rosier *et al.,* 1987a). Carbon disulphide can cross the placenta to the fetus. It has been detected in breast milk and the urine of infants of exposed mothers (Cai and Bao, 1981).

Metabolism

Carbon disulphide is extensively metabolised, irrespective of the route of administration. Approximately, 70% to 95% of absorbed carbon disulphide is metabolised, the rest is excreted by lung and kidneys (Davidson and Feinleib, 1972).

The metabolism of carbon disulphide occurs by two distinct pathways. In the primary pathway carbon disulphide spontaneously reacts directly with free amine and sulphydryl groups of cellular amino acids and polypeptides. The products of these reactions are dithiocarbamates (from reaction with amine and amino acids), and trithiocarbamates (from the reaction with sulphydryl groups). Both the dithocarbamates and trithiocarbamates are water-soluble and are excreted by the kidney. The second pathway is the microsomal oxidation of carbon disulphide to reactive intermediates, which then covalently bind to cell macromolecules (Bus, 1985).

Some carbon disulphide is metabolised to inorganic sulphides including thiourea, 2-mercapto-2-thiazolin-5-one and 2-thiothiazolidine-4-carboxylic acid (TTCA) (McKee *et al*., 1943; Baselt, 2000). TTCA is found in the urine of workers exposed to carbon disulphide (Van Doorn *et al*., 1981; Meuling *et al*., 1990). The urinary concentration of TTCA is quantitatively related to the uptake of carbon disulphide (Campbell *et al*., 1985). Campbell *et al*. (1985) calculated that at a carbon disulphide exposure concentration of 30 mg/m^3 (9.6 ppm), less than 6% is metabolised to TTCA.

Inhaled carbon disulphide undergoes significant metabolism to non-volatile compounds and the elimination of these acid-labile metabolites is sufficiently prolonged to suggest their accumulation on repeated exposures (McKenna and DiStefano, 1977).

Elimination

Following inhalation, the primary route of excretion for unmetabolised carbon disulphide is exhalation from the lung. Approximately, 5% to 30% of carbon disulphide is excreted unchanged by the lungs (McKee *et al,* 1943; Teisinger and Soucek, 1949; Davidson and Feinleib, 1972; Baselt, 2000). Elimination is rapid (Baselt, 2000). Studies indicate that there is a 25% reduction in blood concentrations in one hour and concentrations approach zero at 2 hours (Teisinger and Soucek, 1949). In a volunteer study, elimination of inhaled carbon disulphide was characterised by an initial fast rate giving a half-life of 1.1 minutes, followed by a relatively slow rate with a half-life of 109.7 minutes (Rosier *et al*., 1987a).

Carbon disulphide is deposited in the body in free and bound forms and its elimination rate is determined by the route of exposure, and the ratio of these two forms in the body (Coppock and Buck, 1981).

Only about 0.05% is excreted unchanged by the kidneys (Teisinger and Soucek, 1949). About two thirds of this is excreted in a bound form, and requires acidification and aeration of urine for its release. Metabolised carbon disulphide appears primarily in the urine as inorganic sulphur-containing metabolites, thiourea, 2-mercapto-2-thiazolin-5-one and 2-thiothiazolidine-4-carboxylic acid (TTCA); the latter two compounds are

conjugates with glycine and cysteine, respectively (Baselt, 2000). Urinary TTCA accounts for 1-2% of an absorbed dose of carbon disulphide (Rosier *et al*., 1987b), but the concentration does not appear to correlate with the environmental concentration of carbon disulphide (Kitamura *et al*., 1993).

On evaluating the effect of an 8 hour inhalation exposure to 2 mg/l (640 ppm) of carbon disulphide in rats, McKenna and DiStefano (1977) reported that although tissue concentrations of free carbon disulphide reached a plateau within 4-5 hours, tissue concentrations of the acid labile metabolites continued to increase throughout the 8 hour exposure. The study also showed that acid-labile metabolites were eliminated slowly after termination of exposure, which is a significant finding in that it suggests that these metabolites may accumulate in the body after repeated carbon disulphide exposure.

Mode of action

The biological mechanisms of the adverse effects of carbon disulphide are largely unknown, but there are a number of possible mechanisms. Carbon disulphide can react with various biological molecules. The toxic effects may be based on reactions with sulphydryl and amino groups of proteins, amino acids and catecholamines leading to impairment or disturbance of various biochemical parameters. In addition to toxicity from the direct reaction of carbon disulphide with biological molecules, another possible toxic mechanism is that a reactive intermediate may be formed during oxidative metabolism. Disturbance of lipid metabolism may occur and there may be interaction with the microsomal drug-metabolising system. It is thought that liver toxicity from carbon disulphide exposure may be partly explained by the destruction of cytochrome P450 (WHO, 1979; Bus, 1985; BUA, 1991; Feldman, 1999).

Three mechanisms have been proposed to explain the central and peripheral system neurotoxicity produced by carbon disulphide.

1. Dithiocarbamate formed by the reactions of carbon disulphide with amines can chelate the divalent cations of copper and zinc and inhibit critical metabolic enzymes such as dopamine-β-hydroxylase (McKenna, 1977; Bus, 1985; BUA, 1991). Dopamine-β-hydroxylase contains copper and this metalloenzyme is inhibited by carbon disulphide, resulting in a build up of dopamine, which leads to the Parkinson-like features seen in carbon disulphide toxicity. Although the toxicological consequences of the changes in nerve copper concentrations have not been fully identified, altered metalloenzyme activity within the neurone may be a possibility (Bus, 1985). Other evidence for metalloenzyme inhibition was found in a study of grain workers who self-presented because of neurological symptoms, where two were found to have abnormal zinc excretion (Peters *et al.,* 1986). The effect of supplementing the diet with trace metals has been inadequately explored as a method of preventing carbon disulphide-induced neurotoxicity (Beauchamp *et al*., 1983).

2. Carbon disulphide (or the oxidative metabolites) can react directly with the amine and thiol groups on proteins and hence disrupt normal protein function and metabolism (Davidson and Feinleib, 1972; Bus, 1985; BUA, 1991).

3. Carbon disulphide can react with the free amine group pyridoxamine and produce a neuropathy similar to that observed in vitamin B_6 deficiency (Bus, 1985).

Liver toxicity is thought to be connected with the formation of reactive sulphur from carbon disulphide, which can bind onto sulphydryl groups and thus inactivate enzymes and other SH-proteins. Although the mechanism is not fully understood it is known that this reactive sulphur is responsible for reducing cytochrome P450 activity (BUA, 1991).

Metabolic interactions

Carbon disulphide inhibits the cytochrome P450 redox enzyme complex and affects the metabolism of all compounds dependent on that system for their detoxification, toxicity, or therapeutic action (Cox *et al*., 1998).

- **Ethanol**

  Carbon disulphide has been shown to inhibit the activity of the enzyme aldehyde dehydrogenase; thus concurrent exposure to carbon disulphide and ethanol can increase blood acetaldehyde concentrations (Freundt *et al*, 1976). It is thought that workers exposed to carbon disulphide may experience a disulfiram-like reaction when subsequently exposed to ethanol (Rainey, 1977).

- **Carbon tetrachloride (CCl_4)**

  Exposure to carbon disulphide decreases the toxicity of carbon tetrachloride, which is metabolised by cytochrome P450 to toxic intermediates. Rats dosed simultaneously with carbon disulphide and carbon tetrachloride displayed hepatic effects resembling those due to carbon disulphide alone (ATSDR, 1994). This is thought to be due to destruction of the hepatic P450 metabolic system by carbon disulphide, such that activation of the carbon tetrachloride to toxic metabolites was much reduced. Similar results have been reported in workers exposed to an 80:20 mixture of carbon tetrachloride and carbon disulphide used to fumigate grain (Peters *et al.,* 1987). The neurological effects observed in these individuals resembled those caused by carbon disulphide alone, and there was no evidence of carbon tetrachloride-induced hepatotoxicity (Peters *et al.,* 1987; ATSDR, 1994).

CASE REPORTS

Chronic exposure and multiple system atrophy

A 60 year old male first presented with insidious onset of balance disturbance, impotence, irritability and emotional lability. His balance and coordination worsened until, by age 62, he had difficulty with walking, manual dexterity and speech. He also noted severe nightmares. There was no tremor, no changes in facial expression, cogwheel rigidity, or bradykinesia, and he had no impairment of hearing or vision. A magnetic resonance image (MRI) at age 63 gave equivocal results (variously interpreted as normal or mild cerebellar atrophy). However, a repeat MRI a year later showed definite cerebellar and brainstem atrophy. Thyroid function, urinary lead and mercury concentrations, serum vitamin B_{12} concentrations and electroencephalography were all normal.

A neurologist evaluated the patient at age 64 years. Blood pressure was normal without orthostatic changes. Speech was slightly slurred, cognition was generally intact with normal emotional responses; cranial nerve function was normal. Motor examination revealed normal strength without involuntary movements, but with rippling movements of large muscles in the chest and lower extremities. There were impairments of finger-to-nose, heel-knee-shin and rapid alternating movements. The patient was unable to tandem walk and was unstable when standing with his feet close together, even with his eyes open. Deep tendon reflexes were normal, and no pathological reflexes were present. A computerised tomography (CT) scan showed atrophy of the cerebellar and pontine regions. He was diagnosed with olivopontocerebellar atrophy of the sporadic type. In the next few years, the patient experienced progressive deterioration in function and dysphagia, dysarthria and ataxia increased.

By age 67 he was unable to walk and had little functional independence. He also suffered multiple medical problems including rectal bleeding, neurogenic bladder with chronic urinary infections requiring intermittent catheterisation, a fungal infection of the mouth, peptic ulcer disease, bronchitis with dysphagia, gynaecomastia (probably secondary to ranitidine use) and hiccups. A repeated MRI scan of the brain at age 68 showed advanced cerebellar atrophy and prominent atrophy in the posterior tracts and nuclei of the pons. The patient died at the age of 69. No autopsy was performed.

Previous medical history was remarkable only for benign positional vertigo, hiccups, some orthostatic hypotension, peptic ulcer disease and prostatic hypertrophy. He was a lifelong non-drinker and non-smoker. The patient had been employed from age 25 to age 59 in a viscose rayon production plant. During most of this time, he worked in the spinning room. Although measurements of carbon disulphide concentrations from his plant were not available, the spinning room has been reported as having some of the highest carbon disulphide concentrations in rayon manufacturing, ranging from 10 to 20 ppm and sometimes reaching 30 ppm or higher (Frumkin, 1998).

Cerebral damage following a single high exposure to carbon disulphide

The patient was a 48 year old man, previously healthy and employed as the head of a petrochemical laboratory. He had no history of trauma to the head, CNS infection or abuse of drugs or alcohol. His work was almost exclusively administrative, and there had been no previous exposure of importance to carbon disulphide or other neurotoxic agents.

In February 1979 a fire started in a galvanised bucket, which contained 100-150 ml of carbon disulphide and during the fire carbon disulphide fumes were evolved. The patient kicked the burning bucket along the floor for 20 minutes to get it out of the building, he was in the room for approximately 20 minutes and it was calculated that he was exposed to a minimum concentration of 400 ppm and a maximum concentration of 470,000 ppm carbon disulphide. He lost consciousness for approximately 10 minutes and was subsequently observed for 24 hours in a hospital, but no objective findings were recorded.

After a few asymptomatic days he then had progressive complaints of anxiety, nightmares, intermittent blurred vision lasting a few seconds, reduced memory and concentration, and headache, resulting in absences from work 2-3 times a week. Precordial pain and impotence occurred, symptoms which the patient had never previously experienced. As the symptoms progressed the patient was referred to an occupational medicine clinic. Neuropsychological examination established dementia in the form of reduced ability to learn and memorise, reduced rate in simple reaction time as well as in more complex tasks, and a reduction in abstract thinking. There were no focal neurological signs.

In a subsequent examination one year later no signs of progression were found. He had a slight decrease in strength in the left arm and leg, slightly decreased coordination in the left-sided finger-nose test, and a mild reduction of vibration sense in the left leg. Regional cerebral blood flow showed reduced cortical flow in the sensory-motor area on the right side. The left hemispheric flow was considered to be normal. CT scanning presented slight cortical atrophy of the cerebrum, and a slight, but significant, right central atrophy. Ocular symptoms were suggestive of optic neuritis, but at the time of the examination there were no objective ocular findings. Twenty-one months after the accident the symptoms were still present and, in spite of treatment, the patient was unable to manage his previous work and was forced to retire (Kruse *et al.*, 1982).

Polyneuropathy induced by chronic carbon disulphide exposure

A 48 year old man worked at a viscose rayon plant as a fibre cutter for 23 years. In June 1992, he developed progressive numbness of both feet which then ascended to both knees, and was associated with muscle weakness. Two months later, numbness and clumsiness of both hands were noted and he was unable to perform his job. On evaluation, his muscle strength was diminished in all four limbs and he could not walk on his toes or heels and had difficulty climbing stairs. His handgrip was weak and there was a generalised absence of tendon reflexes. Impairment of light touch, pinprick, temperature, position, and vibration sensory modalities was evident in a glove and stocking distribution. Study of nerve conduction velocities (NCV) disclosed a prolonged distal latency (DL), decreased amplitudes of compound muscle and sensory nerve action potentials, and slowing of NCVs in median, ulnar, peroneal, tibial and sural nerves suggesting a mixed axonal and demyelinating polyneuropathy. There was no sign of diabetes mellitus, porphyria, Guillain- Barré syndrome or radiculopathy. He had consumed alcohol socially for 10 years.

His occupational history showed that he had worked in a poorly ventilated room with exposure to relatively high concentrations of carbon disulphide. Gloves and respirators were not routinely used during the operation. Several of his co-workers had similar symptoms of numbness and weakness in distal limbs; polyneuropathy due to occupational exposure to carbon disulphide was suspected. During the three year follow-up, motor deficits resolved slowly. One year later he was able to walk on toes and heels, however three years later 'tightness' of both legs still persisted. Tendon reflexes were absent in his lower limbs but present in upper limbs, and sensory impairment was only minimally improved (Chu *et al.*, 1995).

Carbon disulphide nephropathy

A 45 year old non-diabetic man presented with features resembling diabetic triopathy. Clinical abnormalities included peripheral and central nervous system abnormalities as well as retinopathy, dyslipidaemia,

cardiovascular disease and nephrotic syndrome. At age 50 he developed congestive heart failure and progressive neuropsychiatric abnormalities, including memory failure, apathy, homicidal ideation and impotence. Over the next 5 years he developed progressive renal failure and dementia. Haemodialysis was initiated and a right nephrectomy was performed because of the presence of a renal mass. Renal tissue remote from the mass showed focal sclerosing glomerulonephritis and extensive interstitial changes. He developed end stage renal disease and progressive dementia, because of the dementia his family decided to withdraw dialysis support and he died of renal failure. The patient had been employed for 15 years in the spinning department of a viscose rayon manufacturing plant. Air sampling at the plant detected high carbon disulphide concentrations (200-500 ppm), well above the occupational exposure limits (Klemmer and Harris, 2000).

CLINICAL EFFECTS

Acute exposure

There is limited information on the effects of acute carbon disulphide exposure.

Inhalation

After acute inhalation, patients may experience, nausea, vomiting, dizziness, fatigue, headache, mood changes, lethargy, blurred vision, agitation, delirium, hallucinations and convulsions (Vanhoorne *et al.,* 1992).

The symptoms reported in 27 people acutely exposed to carbon disulphide (mostly emergency workers attending a fire on a railroad tank leaking carbon disulphide) were headache, dizziness, nausea, burning of the throat, lips or skin, shortness of breath or chest pain, impotence and vomiting (Spyker *et al*., 1982).

Cerebral damage was reported in a 48 year old man exposed to carbon disulphide fumes evolved during a fire accident (Kruse *et al.,* 1982; see case report).

Dermal

Carbon disulphide can cause erythema and pain in mild exposures, but full thickness burns can result from significant skin exposure. Carbon disulphide causes burns because of its excellent fat solvent properties, and it can be absorbed through the skin and cause systemic effects. Dermatitis and vesiculation may occur from skin contact with the liquid or vapour (Hathaway *et al*., 1996). A burning sensation followed by anaesthesia has also been reported from dermal contact with carbon disulphide (Gordy and Trumper, 1938).

Eye

Splashes of carbon disulphide liquid in the eye may cause immediate and severe irritation (Hathaway *et al.,* 1996).

Ingestion

Cases of ingestion of carbon disulphide are rare and only a few reports exist of accidental or intentional ingestion. Foreman *et al*. (1886) reported a fatal case in a 63 year old man who intentionally drank approximately 0.5 oz (14 ml) of carbon disulphide. He became unconscious soon afterwards and died at approximately two hours post ingestion. Postmortem examination revealed minute haemorrhages of the gastric mucosa. The liver, kidneys and spleen were normal.

A 42 year old woman accidentally drank about 5 ml of the carbon disulphide stored in a soft drink bottle. She induced vomiting mechanically, and five hours later she vomited again and experienced numbness of the lips. At twelve hours post ingestion, she had abdominal discomfort and went to hospital. Examination revealed agitation, accentuated tendon reflexes, bilateral positive Babinski reaction and hyperaesthesia. By 16 hours post ingestion, transient sinus tachycardia and sharp P waves were observed on the ECG. Non-specific EEG abnormalities were present between the second and sixth day of illness. On the fifth day she developed

delusions with confusion and memory loss that continued intermittently for one week. Following discharge the patient remained normal for eight days and then for two days experienced an intermittent return of agitation, illusions and delusions. Two months post ingestion she had recovered fully (Yamada, 1977).

Chronic exposure

There is a vast amount of literature on the chronic effects of carbon disulphide mainly generated from epidemiology studies on viscose rayon workers. A brief summary of the main points is given below with references for further reading.

Inhalation

Cardiac effects

Chronic exposure to carbon disulphide has been associated with increased atherosclerosis and coronary atherosclerotic heart disease (CAHD). It is purported that carbon disulphide causes hypertension, hypercholesterolaemia and/or an antifibrinolytic effect (Rosenman, 1984). Specific electrocardiographic changes, including ST-T wave abnormalities, have also been noted by some workers (Davidson and Feinleib, 1972).

The atherosclerosis and ischaemic heart disease that has been reported from chronic carbon disulphide exposure are associated with vascular changes similar to those of artherosclerosis in older age groups (Vigliani, 1954), and these changes mainly affect the blood vessels supplying the brain and heart muscle (WHO, 1979). However, the current TLV (10 ppm) for carbon disulphide exposure should protect workers from development of carbon disulphide-induced cardiac effects. Studies in workers exposed to 10 ppm or less have found no increase in coronary heart disease or atherosclerotic findings (Franco *et al.,* 1982; Drexler *et al.,* 1996).

Tiller *et al.* (1968) undertook a study of deaths from cardiovascular diseases among employees of 5 British viscose rayon factories. They found a 2.5-3 fold excess mortality due to coronary heart disease, among workers who had worked primarily in the viscose spinning process, where exposure to carbon disulphide was greatest. Similar increased mortality rates have been demonstrated from epidemiological studies in other countries including Norway, Finland and the United States (Franco, 1982). Hernberg *et al.* (1976) in Finland, found an excess of coronary deaths among 48 men who had been exposed to carbon disulphide for at least 5 years, and who died under 65 years of age.

Examination of 343 viscose rayon workers who were matched with control subjects from a paper mill, demonstrated that the subjects exposed to carbon disulphide, had higher blood pressures and a slightly higher prevalence of ECG abnormalities. The authors concluded that their findings suggest that carbon disulphide may be an aetiological factor in the pathogenesis of coronary heart disease (Tolonen *et al.*, 1975).

The pathological lesions observed on postmortem examination are those of atheromatous plaque formation, general atherosclerosis, glomerulosclerosis, and changes in the retinal arteries resembling those seen in hypertension (Davidson and Feinleib, 1972).

Animal studies investigating the effects of carbon disulphide on the myocardium showed alterations in the coronary arteries (capillary proliferation and vessel wall hypertrophy), plus vacuolar degeneration, fatty degeneration and haemorrhages of the myocardium.

Other reports investigating the cardiovascular effects of carbon disulphide include: Lieben *et al.,* 1974; Oliver and Weber, 1984; Nurminen and Hernberg, 1985; Sweetnam *et al.,* 1987; McMahon and Manson, 1988; Phillips, 1992; Liss and Finkelstein, 1996; Price *et al.,* 1997; Guidotti and Hoffman, 1999.

Neurological effects

The most widely known and extensively studied aspect of carbon disulphide toxicity is its neurological effects. The nervous system is one of the main targets of carbon disulphide toxicity. Neurotoxicity manifests as psychological and behavioural changes followed by neurological changes, both in the brain and peripheral nerves (WHO, 1979).

Relatively short exposures are predominantly associated with psychiatric and neurological symptoms including extreme irritability, uncontrolled anger, rapid mood changes, hallucinations, paranoic and suicidal tendencies and manic delirium. Other symptoms include memory defects, severe insomnia, nightmares, fatigue, loss of appetite and gastrointestinal effects (Braceland, 1942; Davidson and Feinleib, 1972; Klemmer and Harris, 2000).

Long-term exposure over many years produces the syndrome of chronic poisoning characterised by signs and symptoms arising from adverse effects on different organ systems, including the nervous system and the cardiovascular system. Less frequently, there are symptoms suggesting involvement of the gastrointestinal and endocrine systems (WHO, 1979).

Measurable neurological changes have been demonstrated in workers who have never been exposed to more than 20 ppm (the occupational exposure limit at the time of the study) (Spyker *et al.*, 1982). Symptoms of moderate to severe intoxication have appeared in individuals chronically exposed to vapour concentrations averaging slightly in excess of 20 ppm (Kleinfeld and Tabershaw, 1955). De Fruyt *et al.* (1998) studied the neuropsychological effects of occupational exposure to carbon disulphide. Only the study group exposed to values exceeding three times the recommended TLV for carbon disulphide (i.e., more than 30 ppm) had significant impairments in both the speed and quality of psychomotor performance. However, on evaluation of the effects of occupational carbon disulphide exposure in a sample of 156 male viscose rayon workers (maximum exposure concentration 7.6 ppm) small, but statistically significant, decreases in sensory and motor nerve conduction velocities were reported (Johnson *et al.*, 1983). These findings suggest that even chronic low level exposure to carbon disulphide may result in neurological changes.

Aaserud *et al.* (1990) investigated the neurological symptoms of 24 men formerly and currently employed in the manufacture of viscose rayon. When clinical neurological examinations were performed with the 16 subjects still employed in rayon production, only one was considered normal. Nine had minor neurological deficits. Six had facial palsy, reduced coordination, asymmetrical reflexes, or a positive Romberg's test.

Chapman *et al.* (1991) studied index finger tremor in 19 age-matched control subjects and in 19 grain industry employees chronically exposed to carbon disulphide-based fumigants. The findings in this study suggest that amplitude and frequency abnormalities characterise finger tremor in subclinical and early clinical carbon disulphide parkinsonism. The authors suggest that tremor differences may be able to serve as an early warning in adverse chemical exposures, when overt manifestations are not present.

Peters *et al.* (1987) investigated the neurological effects of carbon disulphide fumigants in granary workers. They found that 50-80% exhibited a range of symptoms, including cogwheel rigidity, intention and resting tremulousness and conduction abnormalities. Hänninen *et al.* (1971; 1976) showed visual-perceptual, psychomotor and cognitive integration deficits in carbon disulphide exposed workers.

In observing workers in viscose rayon factories Vigliani (1954) concluded that chronic exposure to carbon disulphide may result in peripheral neuropathy characterised by a glove and stocking sensory impairment. Absence or a decrease of tendon reflexes, and muscle weakness was also observed. Polyneuropathy of workers in the viscose rayon industry has been studied by other authors (Alpers and Lewey, 1940; Vasilescu, 1976; Aaserud *et al.*, 1990; Chu *et al.*, 1995; Klemmer and Harris, 2000).

Huang *et al.* (1996) reported a detailed neurological investigation of 10 patients with polyneuropathy and various neuropsychiatric symptoms following carbon disulphide exposure. Clinical and laboratory examinations included electroencephalography (EEG), brain computerised tomography (CT), brain magnetic resonance images (MRI) and carotid duplex sonography. In four cases, brain MRI revealed lesions of the basal ganglia and corona radiata, 6 patients had mild atherosclerosis with plaques (<20% stenosis) of extracranial vessels. Clinically, headache, nightmares, memory impairment, fatigue, anorexia and emotional lability were common and two patients had stroke episodes. The authors concluded that encephalopathy, cerebrovascular disease, and polyneuropathy may all occur after chronic carbon disulphide exposure.

Psychiatric examination of 120 workers in the viscose rayon industry where the subjects had varying degrees of exposure to carbon disulphide concluded that the onset of psychosis was acute and frequently occurred when the patient was at work. However, this was usually preceded by gradual personality change observed first by family and friends (Braceland, 1942). Mancuso and Locke (1972) found an association between exposure to carbon disulphide and an increase in the suicide rate in viscose rayon workers employed between 1938 and 1948.

For a comprehensive review of the neuropsychological and psychological effects of carbon disulphide see Grasso *et al.* (1984) or Feldman (1999).

Renal effects

Klemmer and Harris (2000) reported nephropathy in a man occupationally exposed for 15 years to carbon disulphide. Ten years after his last carbon disulphide exposure, the patient developed end-stage renal disease (ESRD) due to the combined effect of focal segmental glomerulosclerosis (FSGS) and unilateral nephrectomy, necessitated by the presence of a renal mass.

Hepatic effects

Fatty degeneration of the liver was found in early animal studies by Lewey *et al.* (1941). In a control study, Vanhoorne *et al.* (1992) found hepatomegaly and raised γ-glutamyltransferase in carbon disulphide exposed viscose rayon workers.

Gastrointestinal effects

Vanhoorne *et al.* (1992) reported a greater prevalence of gastrointestinal complaints (anorexia, nausea, vomiting, flatulence) in viscose rayon workers when compared to controls.

Ototoxicity

On auditory examination, Zenk (1970) concluded that workers exposed to carbon disulphide had a reduction of thresholds to high frequencies and that this should be regarded as an early symptom of intoxication.

Other effects

Diabetes mellitus is a risk factor for atherosclerosis, which is a feature of chronic carbon disulphide poisoning. Glucose tolerance testing in carbon disulphide exposed workers indicated an increased prevalence of decreased glucose tolerance (i.e., latent diabetes) in the carbon disulphide exposed workers (73%) compared to the control group (17%) (Franco *et al.*, 1978).

Dermal

Prolonged contact with the skin produces second and third degree burns and a local neuritis (Gordy and Trumper, 1938). Carbon disulphide can be absorbed through the skin and cause toxicity.

Eye

The ocular manifestations of chronic carbon disulphide exposure are characterised by impaired colour vision and alterations in the retinal microvasculature. The retinal capillary anomalies are very similar to diabetic retinopathy, and although it has been postulated that the retinopathy had a possible aetiologic relationship with disturbed glucose metabolism due to carbon disulphide exposure, the pathogenesis is still unknown (Sugimoto *et al.*, 1976a; 1976b).

Fundus anomalies, and subnormal or supranormal electroretinograms (ERGs) were found in viscose rayon workers chronically exposed to carbon disulphide. The fundus anomalies consisted of either discrete pigmentary changes in the posterior pole or microvascular retinal lesions (DeLaey *et al.,* 1980).

A study of 338 workers of a viscose rayon plant demonstrated that the prevalence of retinopathy increased with both increasing carbon disulphide exposure and concentration (Sugimoto *et al.,* 1976a). In a separate study the same authors repeated direct ophthalmoscopic/colour fundus photographic examinations (three times in five years) on 214 carbon disulphide exposed workers, to determine the effects of exposure cessation on the course

of retinopathy, and develop a prognosis for retinopathy in workers continually exposed for years. Progression to a more developed stage of retinopathy occurred in 21.3% of the 134 workers still exposed to carbon disulphide. Among 80 workers no longer exposed to carbon disulphide, the prevalence of progression was 13.7%. Resolution or improvement to a milder stage of retinopathy occurred in 1.5% of the group still exposed to the chemical and in 11.3% of the group of workers removed from exposure. It was recommended that exposure to carbon disulphide should not continue for longer than 10 years and if retinopathy is found, the worker should immediately be transferred to work without exposure (Suigimoto *et al.,* 1976b).

Raitta *et al.* (1981) studied the effect of chronic carbon disulphide exposure on the optic nerve in 62 workers (mean age 43.5 years) in a Finnish viscose rayon plant. The exposure history ranged from 6-36 years with a mean of 16 years. Carbon disulphide exposure did not relate to specific pattern defects in colour discrimination, but impaired colour discrimination occurred significantly more often in the exposed group compared to controls. The abnormal findings suggest impairment in the receptiveness of the ganglion cells or demyelination of the optic nerve fibres. However, in a later study, Ruijten *et al.* (1990) found no impairment of colour discrimination in their study group. Along with other peripheral and autonomic nervous system function tests, they evaluated colour discrimination in 45 workers (mean age 49 years) with an average of 20 years exposure to carbon disulphide in the viscose rayon industry. The mean cumulative exposure was calculated to be 165 ppm-years (a measure of exposure and duration). The difference in results between the two studies could be explained by differences in the sensitivity of testing methods (the method used by Riatta *et al*. was more sensitive), and the fact that subjects in the Riatta *et al*. study had higher mean exposure concentrations (generally below 20 ppm).

An ophthalmological examination of 123 male carbon disulphide exposed viscose rayon workers (with at least 1 year exposure) found strong associations between exposure and reduced colour vision discrimination, and an excess of microaneurysms. The findings were not thought significant enough to cause incapacity, but could serve as possible early indicators of serious ophthalmological, vascular or neurological damage (Vanhoorne *et al.,* 1996).

Ingestion

No information available.

Carcinogenicity

There is little information on the potential carcinogenicity of carbon disulphide. It has not been evaluated by the IARC. In a review of the studies of leukaemia and solvent exposures in the rubber industry, Checkoway *et al*. (1985) reported that the risk association of carbon disulphide exposure and lymphocytic leukaemia was greater than that for benzene.

Genotoxicity

From the limited mutagenicity data there is no evidence that carbon disulphide is genotoxic (BUA, 1993).

Reproductive toxicity

Several studies have examined the effects of occupational exposures to carbon disulphide on human reproductive function. Acute and prolonged exposure may produce adverse effects in males and females. Reported adverse effects include menstrual abnormalities, spontaneous abortions and premature births. Some of these studies are limited by lack of exposure measurements, concomitant exposure to other chemicals and lack of appropriate controls. However, there is some evidence that carbon disulphide may act as a reproductive toxin (ATSDR, 1992).

Male reproductive effects

In an epidemiological study of the effects of carbon disulphide on male sexuality and reproduction, Vanhoorne *et al*. (1994) found that exposure had a significant effect on libido and potency, but no effects were noted on fertility nor on semen quality. In contrast, Lancranjan (1972) reported hypospermia and abnormal sperm

morphology (asthenospermia, teratospermia) in men (mean age 30 years), attributed to chronic carbon disulphide exposure in an artificial fibre factory.

Le and Fu (1996) investigated human sperm chromosome mutagenesis induced by carbon disulphide and concluded that high concentrations of carbon disulphide may directly cause mutagenesis of the germ cell. Structural aberrations consisted of breaks, deletions, centric rings, fragments and chromatid exchange.

Female reproductive effects

In a study in China, Bao *et al.* (1991) demonstrated that carbon disulphide may contribute to increased birth defects. The study investigated 682 women (comprising 1,112 births in total), occupationally exposed to carbon disulphide for at least 6 months prior to and during pregnancy. Carbon disulphide exposure did not influence the incidence of spontaneous abortion, prematurity, stillbirth, low birth weight or neonatal perinatal death, but the incidence of birth defects in infants of exposed workers was 2.6-fold higher than that in the control group. No specific syndrome of defects was identified, but cardiovascular and central nervous system defects and inguinal hernias occurred in high prevalence.

Animal studies

Tabacora and Hinkova (1976) studied male and female rat offspring from mothers exposed throughout gestation to different concentrations of carbon disulphide (50, 100, 200 mg/m^3; 16, 32, 64 ppm). Behavioural patterns in the offspring were tested at days 21, 30 and 90 of life (periods of weaning, growth and maturity). Decreases in vertical and horizontal motor activity were found on day 30 of life in all treated groups, as well as prolonged periods of grooming and increased defecation at 100 mg/m^3 (32 ppm) and 200 mg/m^3 (64 ppm). Investigational activity was lower at 200 mg/m^3 (64 ppm). There were no significant differences in the groups on day 90 of life.

RISK GROUPS

It has been reported that retention of inhaled carbon disulphide in individuals not previously exposed is greater than in those chronically exposed. Although the mechanism of decreased retention is unknown, the observation does suggest caution in extrapolating acute human exposure data to chronic (Beauchamp *et al.*, 1983).

As carbon disulphide is readily soluble in lipids its retention increases in individuals with a high percentage of body fat (Rosier *et al.*, 1987a).

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Gastric lavage may be considered if ingestion was recent, however, because of the risk of aspiration a cuffed endotracheal tube must be used to protect the airway. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to see if aspiration has occurred. Treatment is supportive. See below for management of systemic effects.

Systemic effects

Monitor ECG, vital signs, and fluid and electrolyte status. Baseline liver function tests and renal function should be determined. Symptomatic and supportive. Neurological follow-up may be required.

Antidotes

There is no specific antidote for carbon disulphide.

Chronic exposure

Neurological and ophthalmological assessment may be required in workers chronically exposed to carbon disulphide. MRI study may detect brain lesions particularly in the sub-cortical white matter areas, before the occurrence of stroke (Huang *et al.*, 1996). Some investigators believe that changes in the microcirculation of the eye are diagnostic of carbon disulphide overexposure (Tolonen, 1974). Treatment is supportive.

REFERENCES

Aaserud O, Gjerstad L, Nakstad P, Nyberg-Hansen R, Hommeren OJ, Tvedt B, Russell D, Rootwelt K. 1988 Neurological examination, computerized tomography, cerebral blood flow and neuropsychological examination in workers with long-term exposure to carbon disulphide. *Toxicology* 49:277-282.

Aaserud O, Nakstad P, Russell D, Rootwelt K. 1990 Carbon disulphide exposure and neurotoxic sequelae among viscose rayon workers. *Am J Ind Med* 10:25-37.

ACGIH. 2000 *Threshold Limit values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Alpers BJ, Lewy FH. 1940 Changes in the nervous system following carbon disulfide poisoning in animals and man. *Arch Neurol Psychiatr* 44:725-739.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Ansbacher LE, Bosch EP, Cancilla PA. 1982 Disulfiram neuropathy: a neurofilamentous distal axonopathy. *Neurology* 32:424-428.

ATSDR. 1992 *Toxicological profile for carbon disulphide*. Agency for Toxic Substances and Disease Registry. US Department of Health and Human Services.

ATSDR. 1994 *Toxicological profile for carbon tetrachloride*. Agency for Toxic Substances and Disease Registry. US Department of Health and Human Services.

Bao YS, Cai S, Zhao SF, Xhang XC, Huaang MY, Zheng O, Jiang H. 1991 Birth defects in the offspring of female workers occupationally exposed to carbon disulphide in China [abstract]. *Teratology* 43:452-452.

Baselt RC. 2000 *Disposition of Toxic Drugs and Chemicals in Man*, fifth edition. Chemical Toxicology Institute, California.

Beauchamp RO, Bus JS, Popp JA, Boreiko CJ. 1983 A critical review of the literature on carbon disulphide toxicity. *CRC Crit Rev in Toxicol* 11:169-278.

Braceland FJ. 1942 Mental symptoms following carbon disulphide absorption and intoxication. *Ann Intern Med* 16:246-261.

BUA (Beratergremium für umweltrelevante Altstoffe). 1993 *Carbon disulphide*. BUA Report 83 (August 1991). S Hirzel. Stuttgart.

Bus JS. 1985 The relationship of carbon disulphide metabolism to development of toxicity. *Neurotoxicology* 6 (4):73-80.

Campbell L, Jones AH, Wilson HK. 1985 Evaluation of occupational exposure to carbon disulphide by blood, exhaled air, and urine analysis. *Am J Ind Med* 8:143-153.

Cai SX, Bao YS. 1981 Placental transfer, secretion into mother milk of carbon disulphide and the effects on maternal function of female viscose rayon workers. *Ind Health* 19 (1):15-29.

Chapman LJ, Sauter SL, Henning RA.1991 Finger tremor after carbon disulfide-based pesticide exposures. *Arch Neurol* 48:866-870.

Checkoway H, Wilcosky T, Wolf P, Tyroler H. 1984 An evaluation of the associations of leukemia and rubber industry solvent exposures. *Am J Ind Med* 5:239-249.

Chu CC, Huang CC, Chen RS, Shih TS. 1995 Polyneuropathy induced by carbon disulphide in viscose rayon workers. *Occup Environ Med* 52:404-407.

Coppock RW, Buck WB. 1981 Toxicology of carbon disulfide: A review. *Vet Hum Toxicol* 23 (5):331-336.

Cox C, Que Hee SS, Tolos WP. 1998 Biological monitoring of workers exposed to carbon disulfide. *Am J Ind Med* 33:48-54.

Davidson M, Feinleib M. 1972 Carbon disulfide poisoning: a review. *Am Heart J* 83:100-114.

De Fruyt F, Thiery E, De Bacquer D, Vanhoorne M. 1998 Neuropsychological effects of occupational exposure to carbon disulfide and hydrogen sulfide. *Int J Occup Environ Health* 4 (3):139-146.

De Laey JJ, De Rouck H, Priem H, Vanhoorne M. 1980 Ophthalmological aspects of chronic CS_2 intoxication. *Int Ophthal* 3 (1):51-56.

Delpech A. 1863 Industrie du caoutchouc soufflé: recherches sur l'intoxication spéciale que détermine le sulfure de carbone [The inflated rubber industry: research on the special intoxication determined by carbon disulphide]. *Ann Hyg Publ Med Leg* 19:65-183. Cited in: Davidson M, Feinleib M. 1972 Carbon disulphide poisoning: a review. *Am Heart J* 83:100-114.

Drexler H, Ulm K, Hardt R, Hubmann M, Goen T, Lang E, Angerer J, Lehnert G. 1996 Carbon disulphide IV. Cardiovascular function in workers in the viscose industry. *Int Arch Occup Environ Health* 69:27-32.

Feldman RG. 1999 *Occupational and Environmental Neurotoxicology*. Lippincott-Raven, Philadelphia.

Foreman W. 1886 Notes of a fatal case of poisoning by bisulphide of carbon. *Lancet* 2:118-122.

Franco G, Tullio M, Angelo P 1978 Glucose tolerance and occupational exposure to carbon disulphide [letter]. *Lancet* 2:1208.

Franco G, Tullio M, Germani L, Candura F. 1982 Assessment of coronary heart disease risk among viscose rayon workers exposed to carbon disulphide at concentrations of about 30 mg/m^3. *Scand J Work Environ Health* 8 (2):113-120.

Freundt KJ, Lieberwirth K, Netz H, Pohlmann E. 1976 Blood acetaldehyde in alcoholized rats and humans during inhalation of carbon disulphide vapor. *Int Arch Occup Environ Health* 1976 37 (1):35-46.

Frumkin H. 1998 Multiple system atrophy following chronic carbon disulphide exposure. *Environ Health Perspect* 106 (9):611-613.

Gehring PJ, Nolan PG, Watanabe PG, Schumann AM. 1991 Solvents, Fumigants, and related products In: *Handbook of Pesticide Toxicology*. Volume 2. Hayes WJ, Laws ER (editors). Academic Press, London.

Gordy ST, Trumper M. 1938 Carbon disulfide poisoning with a report of 6 cases. *J Am Med Assoc* 110 (19):1543-1549.

Grasso P, Sharratt M, Davies DM, Irvine D. 1984 Neurophysiological and psychological disorders and occupational exposure to organic solvents. *Fd Chem Toxicol* 22 (10):819-852.

Guidotti TL, Hoffman H. 1999 Indicators of cardiovascular risk among workers exposed to high intermittent levels of carbon disulphide. *Occup Med* 48 (8):507-515.

Hänninen H. 1971 Psychological picture of manifest and latent carbon disulphide poisoning. *Br J Ind Med* 28:374-81.

Hänninen H, Eskelinen L, Husman K, Nurminen M. 1976 Behavioral effects of long-term exposure to a mixture of organic solvents. *Scand J Work Environ Health* 2 (4):240-255.

Hathaway GJ, Proctor NH, Hughes JP. 1996 *Proctor and Hughes' Chemical Hazards of the Workplace,* fourth edition. John Wiley & Sons Inc, New York.

Hernberg S, Tolonen M, Nurminen M. 1976 Eight-year follow-up of viscose rayon workers exposed to carbon disulfide. *Scand J Work Environ Health* 2:27-30.

Huang C, Chu C, Chen R, Lin S, Shih T. 1996 Chronic carbon disulphide encephalopathy. *Eur Neurol* 36:364-368.

Johnson BL, Boyd J, Burg JR, Lee ST, Xintaras C, Albright BE. 1983 Effects on the peripheral nervous system of workers: exposure to carbon disulphide. *Neurotoxicology* 4:53-66.

Kitamura S, Ferrari F, Vides G, Filho DCM. 1993 Biological monitoring of workers occupationally exposed to carbon disulphide in a rayon plant in Brazil. *Int Arch Occup Env Health* 65:S177-S180.

Klenfield M, Tabershaw IR. 1955 Carbon disulphide poisoning. *J Am Med Assoc* 159 (7):677-679.

Klemmer PJ, Harris AA. 2000 Carbon disulphide nephropathy. *Am J Kidney Dis* 36 (3):626-629.

Kruse A, Borch-Johnsen K, Pedersen LM. 1982 Cerebral damage following a single high exposure to carbon disulphide. *J Soc Occup Med* 32: 44-45.

Lancranjan I. 1972 Alterations of spermatic liquid in patients chronically exposed by carbon disulphide. *Med Lav* 63 (1-2):29-33.

Le J, Fu X. 1996 Human sperm chromosome analysis - study on human sperm chromosome mutagenesis induced by carbon disulfide. *Biomed Environ Sci* 9 (1):37-40.

Lewey FH. 1941 Experimental chronic carbon disulfide poisoning in dogs. A clinical, biochemical and pathological study. *J Ind Hyg Toxicol* 23 (9):415-436.

Lieben J, Menduke H, Flegel EE, Smith F. 1974 Cardiovascular effects of CS_2 exposure. *J Occup Med* 16 (7):449-453.

Liss GM, Finkelstein MM. 1996 Mortality among workers exposed to carbon disulfide. *Arch Environ Health* 51 (3):193-200.

MacMahon B, Monson BB. 1988 Mortality in the US rayon industry. *J Occup Med* 30:698-705.

Mancuso TF, Locke BZ. 1972 Carbon disulfide as a cause of suicide: epidemiological study of viscose rayon workers. *J Occup Med* 14 (8):595-606.

McKee R, Kiper C, Fountain J, Riskin AM, Drinker P. 1943 A solvent vapor: carbon disulfide – absorption, elimination, metabolism, and mode of action. *J Am Med Assoc* 122 (4):217-222.

McKenna MJ, DiStefano V. 1977 Carbon disulphide. I. The metabolism of inhaled carbon disulphide in the rat. *J Pharmacol Exp Ther* 202: 245-252

Meuling WJA, Bragt PC, Braun CLJ. 1990 Biological monitoring of carbon disulfide. *Am J Ind Med* 17:247-254.

Nurminen M, Hernberg S. 1985 Effects of intervention on the cardiovascular mortality of workers exposed to carbon disulphide: a 15-year follow-up. *Br J Ind Med* 42:32-35.

Oliver LC, Weber RP. 1984 Chest pain in rubber chemical workers exposed to carbon disulphide and methaemoglobin formers. *Br J Ind Med* 41:296-304.

Peters HA, Levine RL, Matthews CG, Sauter S, Chapman L. 1986 Synergistic neurotoxicity of carbon tetrachloride/disulfide (80/20 fumigants) and other pesticides in grain storage workers. *Acta Pharmacol Toxicol* 57 (Suppl 7):535-546.

Peters HA, Levine RL, Matthews CG, Chapman LJ. 1987 Extrapyramidal and other neurologic manifestations associated with carbon disulfide fumigant exposure. *Arch Neurol* 45:537-540.

Phillips M. 1992 Detection of carbon disulfide in breath and air: a possible new risk factor for coronary artery disease. *Int Arch Occup Environ Health* 64:119-123.

Price B, Bergman TS, Rodríguez M, Henrich RT, Moran EJ. 1997 A review of carbon disulfide exposure data and the association between carbon disulfide exposure and ischemic heart disease mortality. *Reg Toxicol Pharmacol* 26:119-128.

Rainey JM. 1977 Disulfiram toxicity and carbon disulphide toxicity. *Am J Psychiatry* 134 (4):371-378.

Raitta C, Henrik T, Tolonen M, Nurminen M, Helpiö E, Malström S. 1981 Impaired colour discrimination among viscose rayon workers exposed to carbon disulphide. *J Occup Med* 23 (3):189-192.

Rosier J, Veulemans R, Masschelein R, Vanhoorne M, Van Peteghem C. 1987a Experimental human exposure to carbon disulphide. I. Respiratory uptake and elimination of carbon disulphide under rest and physical exercise. *Int Arch Occup Environ Health* 59:233-242.

Rosier J, Veulemans R, Masschelein R, Vanhoorne M, Van Peteghem C. 1987b Experimental human exposure to carbon disulphide. II. Urinary excretion of 2-thiothiazolidine-4-carboxylic acid (TTCA) during and after exercise. *Int Arch Occup Environ Health* 59:243-250.

Rosenman KD. 1984 Cardiovascular disease and workplace exposures. *Arch Environ Health* 39:218-224.

Ruijten MWMM, Sallé HJA, Verberk MM, Muijser H. 1990 Special nerve functions and colour discrimination in workers with long term low level exposure to carbon disulphide. *Br J Ind Med* 47:589-595.

Spyker DA, Gallanosa AG, Suratt PM. 1982 Health effects of acute carbon disulfide exposure. *J Toxicol Clin Toxicol* 19: 87-93.

Sugimoto K, Goto S, Hotta R. 1976a An epidemiological study on retinopathy due to carbon disulphide: CS_2 exposure level and development of retinopathy. *Int Arch Occup Environ Health* 37:1-8.

Sugimoto K, Goto S, Hotta R. 1976b Studies on chronic carbon disulphide poisoning: A 5 year follow-up study on retinopathy due to carbon disulphide. *Int Arch Occup Environ Health* 37:233-248.

Sweetnam PM, Taylor SWC, Elwood PC. 1987 Exposure to carbon disulphide and ischaemic heart disease in a viscose rayon factory. *Br J Ind Med* 44:220-227.

Tabacova S, Hinkova L. 1976 Further observations on the effect of carbon disulphide inhalation in the rat embryo [abstract]. *Teratology* 14:375.

Teisinger K, Soucek B. 1949 Absorption and elimination of carbon disulphide in man. *J Ind Hyg* 31:67.

Tiller JR, Schilling RSF, Morris JN. 1968 Occupational toxic factor in mortality from coronary heart disease. *Br J Med* 4:407-411.

Tolonen M. 1974 Chronic sub-clinical carbon disulphide poisoning. *Work Environ Health* 11:154-161.

Tolonen M, Hernberg S, Nurminen M, Tiitola K.1975 A follow-up study of coronary heart disease in viscose rayon workers exposed to carbon disulphide. *Br J Ind Med* 75 (32):1-10.

Van Doorn R, Delbressine LPC, Leijdekkers C-M, Vertin PG, Henderson PT. 1981 Identification and determination of 2-thiothiazolidine-4-carboxylic acid in urine of workers exposed to carbon disulfide. *Arch Toxicol* 47:51-58.

Vanhoorne M, De Bacquer D, Barbier F. 1992 Epidemiological study of gastrointestinal and liver effects of carbon disulfide. *Int Arch Occup Environ Health* 63:517-523.

Vanhoorne M, Comhaire F, De Baquer D. 1994 Epidemiological study of the effects of carbon disulfide on male sexuality and reproduction. *Arch Environ Health* 49 (4):273-278.

Vanhoorne M, De Rouck A, Bacquer D. 1996 Epidemiological study of the systemic ophthalmological effects of carbon disulfide. *Arch Environ Health* 51 (3):181-188.

Vasilescu C, Florescu A. 1980 Clinical and electrophysiological studies of carbon disulphide polyneuropathy. *J Neurol* 224:59-70.

Vigliani EC. 1954 Carbon disulphide poisonings in viscose rayon factories. *Br J Ind Med* 11:235-241.

WHO. 1979 *Environmental Health Criteria 10. Carbon disulfide.* World Health Organization, Geneva.

Yamada Y. 1977 A case of acute carbon disulphide by accidental ingestion. *Jpn J Ind Health*; 19: 140-141 (in Japanese). Cited in: Gehring PJ, Nolan PG, Watanabe PG, Schumann AM. 1991 Solvents, Fumigants, and Related Products. In: *Handbook of Pesticide Toxicology*. Volume 2. Hayes WJ, Laws ER (editors). Academic Press, London.

Zenk H. 1970 Schwefelkohlenstoff-Einwirkungen auf die rhino-otologischen Funktionen der Beschäftigten in der Kunstfaser-Industrie [CS_2-effects upon olfactory and auditory functions of employees in the synthetic-fiber industry]. *Int Arch Arbeitsmed* 27:210-220 (English abstract).

4 Carbon Tetrachloride

Maeve McParland

SUMMARY

- Toxicity is due to metabolites rather than carbon tetrachloride itself
- Acute exposure may result in rapid central nervous system depression
- Carbon tetrachloride is a potent hepatotoxin which can produce potentially fatal hepatorenal damage following ingestion, inhalation or dermal exposure
- Symptoms of hepatic and/or renal toxicity may be delayed in onset for several days
- Sensitisation of the myocardium to catecholamines can occur and at high concentrations sudden death can occur from cardiac arrest
- Administration of acetylcysteine may reduce complications of severe carbon tetrachloride exposure
- Carbon tetrachloride is considered a possible human carcinogen

DESCRIPTION

Carbon tetrachloride is a chlorinated hydrocarbon. It is a volatile colourless mobile liquid with a characteristic non-irritating, mild, sweet odour.

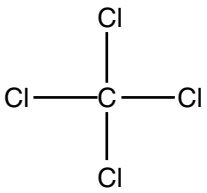
Synonyms

CCl_4, carbon tet., Freon 10, Halon 104, methane tetrachloride, perchloromethane, R10, tetrachlorocarbon, tetrachloromethane, tetraform.

Identification numbers

CAS	56-23-5
UN	1846
RTECS	FG 4900000
EINECS	2002628

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	CCl_4
molecular formula	

molecular mass	153.8
physical form	colourless liquid
relative vapour density	5.32
flash point (°C, closed cup)	nonflammable
boiling point (°C)	76.75
autoignition temperature (°C)	>1000
refractive index	1.4607
explosive limits (%v/v)	none

Odour threshold

96 ppm (Amoore and Hautala, 1983); 9.4-20 ppm (Ruth, 1986); >10ppm (IPCS, 1999); 50 ppm (Baselt, 2000).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK): 2 ppm (12.8 mg/m^3)
TWA (ACGIH): 5 ppm (32 mg/m^3)

Conversion factors

1 ppm = 6.41 mg/m^3
1 mg/l = 159 ppm
1 mg /m^3 = 0.156 ppm

Biomonitoring

A BEI has not been established for carbon tetrachloride by the ACGIH. Measurement of carbon tetrachloride and its metabolites in expired air has been the most convenient way to determine exposure (ATSDR, 1994). Carbon tetrachloride can also be detected by gas chromatography in blood and serum, which may also be used as an indicator of exposure. Any detectable blood concentration indicates exposure, but concentrations do not correlate well with adverse health effects (ATSDR, 1992b).

TOXICITY

Carbon tetrachloride has been studied extensively and most of the present understanding of metabolism by the liver and toxic effects on the liver by other agents has resulted from these studies. For a comprehensive view of the hepatic mechanisms and effects see Plaa (1986). Carbon tetrachloride is a CNS depressant and a mild anaesthetic agent. It can cause fatal damage to the liver and/or kidneys in both acute and chronic exposure. After acute exposure hepatic and/or renal dysfunction, may be delayed in onset for several days. CNS depression does not always precede the onset of nephrotoxicity or hepatotoxicity. Diverse effects on other organs are likely to be secondary to CNS, liver or kidney damage (ATSDR, 1992a). Carbon tetrachloride is no longer used as a solvent because of awareness of the risk of hepatorenal toxicity and the ready availability of less hazardous solvents. It is used primarily as a chemical intermediate (Reid, 2001).

Carbon tetrachloride causes fatty degeneration of the liver and centrilobular necrosis (Recknagel *et al*., 1989, Chyker *et al.,* 2000). Biochemical evidence of hepatic injury often includes greatly elevated activities of transaminases and a variety of other hepatic enzymes in plasma. The main histological abnormalities include hepatic steatosis and hepatic centrilobular necrosis. As hepatic injury develops, signs of renal damage may also be observed and may dominate the clinical picture; renal failure is the most frequent cause of death.

However, if the victim survives the first two weeks, the prognosis is good for complete recovery, or for only mildly compromised liver and kidney function (ATSDR, 1992a).

Carbon tetrachloride toxicity has been reported after accidental inhalation (Alswang, 1979), occupational inhalation (Barnes and Jones, 1967; Folland *et al*., 1976), accidental ingestion (Alston, 1970), intentional ingestion (Bagnasco *et al*., 1978; Fogel *et al.,* 1983; Mathieson *et al*., 1985) and dermal exposure (Javier Perez *et al.,* 1987). In a case series of nineteen carbon tetrachloride poisoned patients (age range 3-79 years) 4 cases of inhalation and 15 cases by ingestion symptoms evident on presentation to hospital included nausea, vomiting, diarrhoea, abdominal pain, headache, hypotonia, confusion, agitation, drowsiness and coma. Initial liver function changes included raised AST, bilirubin, and prothrombin time ratios. The length of stay in hospital ranged from 2 to 28 days, in some cases haemodialysis was required and some patients received acetylcysteine. One patient was lost to follow-up and one died; 17 patients recovered completely, however one of these had residual abnormal LFTs (Ruprah *et al.,* 1985).

There is a marked variation in individual susceptibility to carbon tetrachloride (Mathieson *et al.,* 1985). Fatal cases of carbon tetrachloride ingestion have occurred from as little as 1.5 ml (Bagnasco *et al*., 1978), and the fatal dose from inhalation or ingestion is often quoted as 3-5 ml (Mathieson *et al.,* 1985, Ruprah *et al.,* 1985; Driesbach and Robertson, 1987). However, much larger doses have been survived (Mathieson *et al*., 1985). Survival depends, to a large extent, on the victim's nutritional status and underlying hepatorenal function. Although, there are numerous reports of injury and death from both acute and chronic exposure to carbon tetrachloride in humans, there are few epidemiological studies on occupational exposure. There are no laboratory studies of long-term exposure (IPCS, 1999).

Absorption

Carbon tetrachloride is very lipid soluble and readily enters the body by inhalation, ingestion and dermal absorption. Inhalation is the primary route of exposure, with pulmonary absorption in humans estimated to be 60% (ATSDR, 1992a). It is readily absorbed from the gastrointestinal tract, and dermal absorption of the liquid or vapour can also occur but absorption by this route is slow.

Four hours after ingestion of approximately 250 ml of carbon tetrachloride whole blood concentrations were 31.5 mg/l and remained detectable for eight days (Mathieson *et al*., 1985).

Carbon tetrachloride was detected in alveolar air within ten minutes of immersion of the thumb in the solvent. The concentration continued to rise throughout a 30 minute exposure period and for the following 10-30 minute period. It then decreased exponentially. A mean peak breath concentration of 0.64 ppm after 30 minutes exposure was measured, and this dropped to 0.31 ppm two hours after cessation of exposure (Stewart and Dodd, 1964).

Distribution

There is no information available regarding distribution in humans from ingestion, inhalation or dermal exposure.

Animal studies reveal that the highest carbon tetrachloride concentrations occur in fat and in organs with a high fat content such as the liver, brain, kidney and bone marrow (ATSDR, 1994).

Carbon tetrachloride crosses the placenta producing levels in cord blood similar to that in maternal blood (Dowty *et al.,* 1976).

Metabolism

The metabolism of carbon tetrachloride has not been studied in man (Baselt, 2000). Metabolism of carbon tetrachloride is primarily in the liver but many other organs have been shown to metabolise it. In the liver the route is thought to be NADPH-dependent cytochrome P450 isoenzyme reductive dehalogenation with

formation of a trichloromethyl free radical, and a number of other reactions to form products such as carbon dioxide, carbon monoxide, hexachloroethane, chloroform and phosgene. Metabolism is thought to be dose-dependent and saturable, and to involve destruction of the cytochrome P450 during the metabolism process (Reid, 2001).

Elimination

Using the data of Stewart *et al.* (1965) it was calculated that the carbon tetrachloride concentration in expired air appeared to decline exponentially in a biphasic manner, with an initial half-life of less than one hour, and a second phase half-life of about 40 hours (ATSDR, 1994).

In a 61 year old man who intentionally ingested approximately 250 ml of carbon tetrachloride, whole blood concentrations fell in a bi-exponential fashion. The half-life of the first phase was 10.7 hours and of the second phase 42.6 hours. Carbon tetrachloride remained detectable for eight days (Mathieson *et al.*, 1985).

In rats, faecal elimination of unchanged carbon tetrachloride, did not significantly contribute to the overall elimination of carbon tetrachloride, either after acute treatment (intravenous or intraperitoneal) or after repeated inhalation exposures (Page and Carlson, 1994).

In monkeys, at least 51% of the absorbed dose was eliminated in the expired air as carbon tetrachloride (40%) and carbon dioxide (11%) in 29 days after exposure. Significant amounts were excreted in urine and faeces as metabolic products, including urea and carbonates (McCollister *et al.,* 1951).

Mode of action

The toxicity of carbon tetrachloride has been extensively studied and is widely recognised to be due to the reductive halogenation of carbon tetrachloride catalysed by cytochrome P450 in the liver. This leads to free radical formation and lipid peroxidation (Recknagel *et al.*, 1989; IPCS, 1999), which results in hepatic and renal toxicity. A cascade of secondary reactions then occurs resulting in plasma membrane disruption and cell death. However the exact nature and relative importance of these interactions with various tissues has not been fully elucidated (Dianzani, 1984).

Cleavage of the CCl_3-Cl bond occurs after binding of carbon tetrachloride to cytochrome P450 apoprotein in the mixed function oxidase system. This results in the formation of the reactive trichloromethyl radical ($\bullet CCl_3$), which may be further oxidised to form the trichloromethylperoxy free radical ($Cl_3COO\bullet$). The trimethylperoxy free radical species is considered to be much more reactive than the trichloromethyl radical (Slater, 1985; Recknagel *et al.,* 1989).

Cytochrome P450 is encased in lipid and the free radicals formed by the cleavage initiate peroxidative decomposition of the polyenoic lipids of the endoplasmic reticulum and generation of secondary free radicals (Recknagel, 1983; IPCS, 1999). This destructive lipid peroxidation leads to breakdown of membrane structure and function, and, if a sufficient quantity of carbon tetrachloride has been absorbed, the intracellular cytoplasmic calcium concentration increases, causing disruption of intracellular calcium homeostasis, resulting in cell death (Recknagel, 1983; Kalf *et al.,* 1987; Recknagel *et al.*, 1989). Lipid peroxidation produces a variety of substances that have high biological activities, including effects on cell division (Slater *et al.,* 1985). Coincidental with structural disorganisation of the endoplasmic reticulum, there is loss of microsomal enzyme function, including the cytochrome P450 monooxygenase system and glucose-6-phosphatase (Recknagel *et al.,* 1989).

The trichloromethyl radical can undergo anaerobic reactions resulting in the formation of a variety of toxins including chloroform and carbon monoxide (Ahr *et al.*, 1980), and under aerobic conditions may react to form trichloromethanol, a precursor of phosgene (Kalf *et al.*, 1987; ATSDR, 1992a). Phosgene may play a role in carbon tetrachloride-induced hepatotoxicity (Kubic and Anders, 1980; Kalf *et al.*, 1987).

An alternative hypothesis involves covalent binding of carbon tetrachloride metabolites to critical macromolecules leading to cell damage. Binding of carbon tetrachloride metabolites to hepatic nuclear DNA, proteins and lipids has been demonstrated and this could be relevant to carbon tetrachloride induced liver tumours and hepatotoxic effects (Diaz Gomez and Castro, 1980a,b). It appears that aerobic covalent binding and hepatotoxicity may be accounted for by the trichloromethyl free radical or the trichloromethylperoxy free radical, whereas carbenes (R3C:) may play a more important role when oxygen tension is low (Slater, 1982).

The fatty changes that are characteristic of carbon tetrachloride hepatotoxicity are due to the accumulation of triglycerides, but the mechanism is not yet clear. The mechanism is not the same as that producing liver necrosis, but metabolism of carbon tetrachloride is definitely required and lipid peroxidation may play a role (Reid, 2001).

Metabolic interactions

The metabolism of carbon tetrachloride is catalysed by cytochrome P450-dependent monooxygenases. Agents which induce such enzymes will enhance the toxicity of carbon tetrachloride. Conversely, agents inhibiting the drug-metabolising activity of the cytochrome P450 enzyme system will diminish the hepatotoxic effects of carbon tetrachloride.

Alcohols

The toxicity of carbon tetrachloride is enhanced by concomitant ingestion of alcohol (Alswang, 1979). Low molecular weight aliphatic alcohols can induce production of mixed-function oxidase enzymes, thereby potentiating the formation of carbon tetrachloride toxic intermediates and metabolites (Cornish and Adefuin, 1967; Traiger and Plaa, 1971; ATSDR, 1992a). The potentiating effect of these alcohols appears to be most effective when administered 18 to 24 hours prior to carbon tetrachloride exposure (Traiger and Plaa, 1971).

- **Ethanol**

  The consumption of ethanol prior to or during exposure to carbon tetrachloride vapours may increase the toxicity of carbon tetrachloride (Cornish and Adefuin, 1966, 1967; Cornish *et al.,* 1977; Sturbelt *et al.,* 1978). Studies in mice have shown an increased incidence of hepatotoxic effects in animals receiving ethanol prior to exposure to carbon tetrachloride, compared to those exposed to carbon tetrachloride alone (Cornish *et al.,* 1977). This additive effect may result from ethanol-induced induction of CYP2E1, the main enzyme involved in the metabolism of carbon tetrachloride (Cornish and Adefuin, 1967; Allis *et al*., 1996). Initially, there is a synergistic depression of the CNS. In some cases this is followed by pulmonary oedema, kidney and liver lesions. Sturbelt *et al.* (1978), extrapolating from studies on rats, concluded that the moderate amounts of ethanol commonly ingested by many individuals, may be enough to increase the hepatotoxic effects of halogenated hydrocarbons such as carbon tetrachloride. Consequently, chronic ethanol ingestion may put workers more at risk of toxicity if subsequently exposed to carbon tetrachloride. Manno *et al.* (1996) reported that in a group of workers exposed to a carbon tetrachloride containing fire extinguisher, signs of toxicity only developed in those with a previous history of high ethanol intake.

- **Isopropanol**

  Isopropanol has an even greater ability than ethanol to potentiate the hepatotoxic effects of carbon tetrachloride (Louria and Bogden, 1980). This interaction is highlighted in several reports of industrial accidents involving isopropanol and carbon tetrachloride (Folland *et al.,* 1976; Deng *et al.,* 1987). Three workers in a colour printing factory were admitted to community hospitals with acute hepatitis, one worker also developed acute renal failure and pulmonary oedema. An investigation was carried out to determine the aetiology of the outbreak. Seventeen of 25 workers at the plant had abnormal liver function tests (LFTs) 10 days after the outbreak. It was found that there was a strong correlation between abnormal LFTs and the combined use of carbon tetrachloride and isopropanol in a cleaning process (Deng *et al.,*

1987). A similar incident was reported by Folland *et al.* (1976). Fourteen of 43 workers developed non-specific illness when carbon tetrachloride was used to clean equipment close to an isopropanol packaging line. They developed symptoms of nausea, vomiting, headache, weakness and abdominal pain. Dizziness, blurred vision and diarrhoea were also reported. The illness lasted an average of 7 days. Two workers had signs of liver and renal toxicity. The onset and prevalence of illness was related to proximity to the area where the agents were being used. The potentiating interaction in these cases may also be related to the presence of acetone, the main metabolite of isopropanol. Acetone is known to induce the CYP2E1 enzyme (Morgott, 2001), and induction of this pathway contributes to the increased toxicity in a combined carbon tetrachloride and isopropanol exposure.

- **Methanol**

  Methanol exposure induces cytochrome P450 CYP2E1, which leads to increased metabolism and hence increased hepatotoxicity of carbon tetrachloride (Allis *et al.,* 1996). Methanol is thought to be a more effective potentiating agent that ethanol (Cornish and Adefuin, 1967; Traiger and Plaa, 1971).

Other interactions

- **Acetone**

  Acetone is considered a major potentiator of carbon tetrachloride toxicity (Folland *et al.*, 1976; IPCS, 1999). This may be related to acetone induced enzyme induction, increasing the production of the reactive metabolites of carbon tetrachloride.

- **Carbon disulphide**

  Exposure to carbon disulphide decreases the toxicity of carbon tetrachloride. Rats dosed simultaneously with carbon disulphide and carbon tetrachloride displayed hepatic effects resembling those due to carbon disulphide alone, rather than to effects caused by carbon tetrachloride alone (ATSDR, 1994). This is thought to be due to the destruction of the hepatic P450 metabolic system by carbon disulphide, such that activation of carbon tetrachloride to toxic metabolites is much reduced. Similar results have been reported in workers exposed to an 80:20 mixture of carbon tetrachloride and carbon disulphide used to fumigate grain (Peters *et al.,* 1986). The neurological effects observed in these individuals resembled those caused by carbon disulphide alone, and there was no evidence of carbon tetrachloride induced hepatotoxicity (Peters *et al.,* 1986; ATSDR, 1994).

- **Diet and nutritional status**

  It is suggested that diets sufficiently low in protein to reduce mixed function oxidase activity will have a protective effect, as there will be a reduced ability to bioactivate carbon tetrachloride to its toxic metabolites. However, more prolonged protein deprivation, in the presence of residual mixed function oxidase activity, may lead to more severe liver damage because of the loss of protective sulphydryl compounds such as glutathione (Plaa, 1986). Diabetes and certain nutritional deficiencies have been implicated in enhanced toxic effects from carbon tetrachloride (Capurro, 1973; ATSDR, 1992a; Torkelson, 1994).

- **Drugs**

  Drugs that are known to induce the cytochrome P450 enzymes will lead to greater metabolism of carbon tetrachloride and hence potentiate its toxic effects, e.g., phenobarbital (Mahieu *et al.*, 1983).

- **Trichloroethylene**

  Carbon tetrachloride induced hepatotoxicity in rats is enhanced by the simultaneous administration of trichloroethylene and this response is potentiated by pre-treatment with acetone (Charbonneau *et al.*, 1988). This may be relevant for people who work with a mixture of solvents.

CASE REPORTS

Accidental occupational exposure

A 36 year old boiler cleaner was working on the removal of sludge from a carbon tetrachloride tank. On the first day he acted as watchman for two other workers who were inside the tank, who were using full-face respirators. On the second day he entered the tank and washed it out several times with a high pressure hose. As the tank had been washed the previous day he did not anticipate any risk and did not wear a respirator. He worked in the tank for three hours, finishing at noon, and left to meet some friends. On the way he became nauseated and developed a severe headache, and decided, instead, to go home to bed. Over the next two days he became very drowsy, nauseated, vomited several times and passed very little urine. On the third day he was admitted to hospital where he complained of loin pain, nausea, vomiting and severe headache. On examination he was jaundiced, delirious and had extensive subconjunctival haemorrhages. He was anuric and laboratory investigations revealed high urea, AST and bilirubin. A week later urea and AST were even higher and he had thrombocytopenia. An electrocardiogram at this time showed evidence of myocarditis. The urinary output gradually improved, and three weeks after admission the blood urea and AST had fallen and platelet count was normal. At this stage, liver biopsy showed toxic hepatic injury, with a histology consistent with carbon tetrachloride toxicity. The patient failed to return for follow up liver function tests and biopsy but as far as was known, he was well (Barnes and Jones, 1967).

Ingestion of carbon tetrachloride treated with acetylcysteine

A 61 year old man was admitted to hospital three hours after ingestion of approximately 250 ml of carbon tetrachloride, which he had purchased from a high street pharmacy. The patient had a chronic psychiatric history and had previously taken several drug overdoses. He had been physically fit, did not drink alcohol, and five days previously had stopped his medication (diazepam and lofepramine). On admission he was alert and orientated and although he had not had nausea or vomiting, he had complained of severe diarrhoea for the previous hour. Physical examination was normal with no notable smell of solvent. Urine microscopy showed many granular casts. A plain abdominal radiograph showed radiopaque material consistent with carbon tetrachloride throughout the bowel. Initial biochemical, haematological and coagulation tests were normal except for an increased serum activity of alkaline phosphatase (noted previously and attributed to Paget's disease) and a slightly raised AST.

Gastric lavage was performed and, on the advice of a Poisons Unit, an acetylcysteine infusion was started approximately four hours post ingestion at the standard rate used to treat paracetamol poisoning. The whole blood concentration of carbon tetrachloride at four hours post ingestion was 41.5 mg/l; it remained detectable for eight days. The only substances detected at this stage were low concentrations of diazepam and nordiazepam. The carbon tetrachloride concentrations fell in bi-exponential fashion, the half-life of the first and second phase being 10.7 hours and 42.6 hours, respectively. Despite the very high blood concentrations of carbon tetrachloride the patient remained clinically well, except for diarrhoea which persisted for 24 hours. He became mildly dehydrated and was transiently oliguric, but responded well to intravenous fluid replacement. Plasma urea and creatinine concentrations remained normal throughout. His liver function deteriorated progressively over the first four days, but subsequently recovered (apart from the pre-existing elevated alkaline phosphatase), and was normal on discharge 20 days after admission (Mathieson *et al.,* 1985).

CLINICAL EFFECTS

Acute effects

Inhalation

Systemic effects are common from acute inhalation of carbon tetrachloride, see below.

Fourteen workers became unwell after exposure to carbon tetrachloride, eight had developed symptoms within 12 hours of exposure and a further six had symptoms within 48 hours. Symptoms reported by the workers were nausea (93%), vomiting (86%), headache (79%), abdominal pain (71%), dizziness (36%), diarrhoea (28%) and blurred vision (21%). The illness lasted an average of seven days (range 2-21 days) and four workers were hospitalised. Of these four, one had only renal damage, one had only elevated LFTs and the other two had both renal and liver involvement. All the workers had concurrent exposure to isopropanol, which potentiates the toxicity of carbon tetrachloride (Folland *et al*., 1976).

Barnes and Jones (1967) report three cases of acute carbon tetrachloride toxicity from occupational inhalation exposure. There was one case of myocarditis and all three developed liver damage, however, only one developed additional renal damage.

Manno *et al*. (1996) described cases of toxicity from exposure to carbon tetrachloride fire extinguishing liquid during two separate fire accidents. In the first incident five men were exposed for two hours, and in the second two men were exposed for approximately six hours. Symptoms including vomiting, diarrhoea, fever and liver and kidney impairment, only developed in two of the seven men with histories of heavy alcohol consumption. In a similar case, a 59 year old man with a history of moderate alcohol consumption developed nausea, vomiting and diarrhoea five days after exposure, followed by jaundice and acute renal failure. He recovered uneventfully and liver functions returned to normal (Tracey and Sherlock, 1968).

Dermal

Carbon tetrachloride is a skin irritant and can cause a defatting dermatitis with erythema and vesiculation. Systemic effects can occur from dermal exposure (Javier Perez *et al*., 1987), see below.

In a study investigating human dermal absorption of carbon tetrachloride, in volunteers, by means of thumb immersion, one subject experienced a mild burning sensation around the hair follicles after six minutes, and after 10 minutes a cooling sensation was experienced. At 20 to 30 minutes the burning sensation was described as moderately intense. The two other subjects experienced only the mild burning sensation and cooling sensation commencing after 10 minutes, and in all three this sensation subsided within 10 minutes of exposure. After removal from the solvent the skin of all three volunteers showed mild erythema that resolved within 10 minutes (Stewart and Dodd, 1964).

Three cases of acute renal failure were reported after topical self-administration of a scabies treatment that contained 67% carbon tetrachloride as an excipient. Between the third and seventh day all three patients had developed acute renal failure, necessitating peritoneal dialysis in two cases. After seven days, liver function was normal, and renal function recovered fully in all cases after 2.5-4 weeks. Renal biopsy in one case revealed acute tubular necrosis (Javier Perez *et al*., 1987).

Eye

Carbon tetrachloride vapour is slightly irritating to the eyes and the liquid or vapour may cause a burning sensation with lacrimation (Grant and Schuman, 1993). Restricted peripheral vision has been reported widely in the literature as an early sign of systemic poisoning but this has not been firmly established (Grant and Schumann, 1993).

Ingestion

Systemic effects are common from ingestion of carbon tetrachloride, see below. Ingestion of even a small quantity may cause toxicity.

Accidental ingestion of about half a mouthful in a 34 year old man caused persistent vomiting and diarrhoea with constant epigastric pain for the first 24 hours. He went on to develop hepatic and renal damage but gradually recovered. Hepatic function was restored completely by day 129 and renal function by day 139 (Alston, 1970).

Intentional ingestion of 100 ml by a 29 year old man caused acute tubular necrosis. Vomiting and elevated serum liver enzymes were noted within the first 24 hours and oliguria developed on the second day. Haemodialysis was started and the patient underwent dialysis for three hours each day on 11 of the following 15 days and also received total parenteral nutrition (TPN). All medication including TPN was withdrawn on day 12, when the diuretic phase of acute tubular necrosis started, and haemodialysis was stopped on day 15. The patient went home on day 23 and had complete recovery of hepatic and renal function on follow up, two weeks after discharge (Fogel *et al*., 1983).

Bagnasco *et al.* (1978) reported a case of intentional ingestion of 300-350 ml of carbon tetrachloride in a 22 year old man. His liver function deteriorated over the first 24 hours but gradually within the next 3 to 4 days the patient improved.

Postmortem examination in fatal cases of carbon tetrachloride ingestion revealed evidence of massive hepatic and renal necrosis (Ruprah *et al.,* 1985).

Systemic effects

Systemic effects from carbon tetrachloride may occur from inhalation, ingestion or dermal exposure. Carbon tetrachloride poisoning is characterised by initial gastrointestinal and neurological effects. Milder effects include nausea, vomiting (Capurro, 1973), dizziness, and headache (Folland *et al*, 1976; Ruprah *et al*., 1985). Nausea, vomiting, abdominal pain and diarrhoea are possibly due to initial effects of carbon tetrachloride on the autonomic nervous system (ATSDR, 1992a). At higher concentrations, symptoms may include convulsions, coma, and death from respiratory depression or circulatory collapse. Death may also occur as a result of ventricular arrhythmia.

On recovery from the narcotic effects of carbon tetrachloride, delayed effects involving damage to the kidneys, liver and lungs can occur. Exposure to lower concentrations, insufficient to cause loss of consciousness, usually results in severe gastrointestinal effects and can progress to serious kidney and hepatic damage. Acute hepatic necrosis and renal impairment can occur up to two weeks after carbon tetrachloride exposure. Other secondary effects reported include coagulation disorders, cardiac dysrhythmias, and pulmonary oedema; these effects are unlikely to resolve without improvement of any kidney and liver disorders.

A decrease in clotting factors, resulting from acute liver damage, may predispose the patient to haemorrhage. Changes in blood pressure or heart rate are probably secondary to renal effects on fluid and electrolyte retention or to CNS effects on the heart or blood vessels. In addition, carbon tetrachloride can decrease the myocardial threshold to the arrhythmogenic effects of endogenous epinephrine and this can result in sudden death from ventricular fibrillation.

Immunotoxicity

A rapidly and spontaneously reversible Goodpasture's syndrome was observed in a 43 year old man after acute inhalation of carbon tetrachloride. Diagnosis was based on the presence of circulating anti-glomerular basement membrane (GBM) and anti-alveolar basement membrane antibodies (Carlier *et al*., 1980).

Chronic effects

Inhalation

Symptoms from chronic carbon tetrachloride exposure are similar to those seen in acute exposure (see above). With long-term chronic exposure to low concentrations of carbon tetrachloride, both kidney and liver injury occur. However the milder the exposure, the greater the tendency for predominantly liver effects (Reid, 2001). Toxic hepatitis and cirrhosis have been reported after chronic exposure to high concentrations of carbon tetrachloride (ATSDR, 1992a). Persistent nausea should prompt an evaluation of liver function for toxic hepatitis.

Dermal

Dermatitis can occur following long or repeated skin contact with carbon tetrachloride liquid. It causes defatting and removal of the surface oils from the skin, leading to dryness, cracking and dermatitis.

Stewart and Dodd (1964) and Stewart *et al.* (1961) have conducted experimental human exposure studies with volunteer subjects. These reports indicate that absorption of the liquid through the skin may be significant, particularly in chronic exposure (Reid, 2001).

Eye

Two cases of conjunctival haemorrhage have been reported after dermal absorption of carbon tetrachloride (Javier Perez *et al*., 1987).

On critical examination of the relevant literature, Grant and Schumann (1993) concluded that chronic exposure to carbon tetrachloride was strongly suspected of causing retrobulbar neuritis, optic neuritis and optic atrophy. However, despite numerous claims in the literature, the link has not been firmly established (Grant and Schumann, 1993).

Ingestion

No information available.

Carcinogenicity

There is inadequate evidence in humans but sufficient evidence in experimental animals for the carcinogenicity of carbon tetrachloride. Consequently, carbon tetrachloride is in IARC group 2B and considered possibly carcinogenic to humans (IARC, 1999).

Tracey and Sherlock (1968), described a 59 year old man with an episode of carbon tetrachloride related acute renal failure, accompanied by evidence of acute liver damage. He recovered uneventfully and his liver function tests returned to normal. Seven years later he died from hepatocellular carcinoma and the authors concluded that carbon tetrachloride, which is a potent hepatocarcinogen in experimental animals, may have been carcinogenic in this individual.

Cantor *et al.* (1995) used mortality records from a five year period (1984-1989), coded for occupation and industry, and assessed them with regards to workplace exposures and possible breast cancer risk. Suggestive associations for probability and level of exposure were found for several organic solvents including carbon tetrachloride.

In a review of the studies of leukaemia and solvent exposures in the rubber industry, Checkoway *et al.* (1985) reported that the risk association of carbon tetrachloride exposure and lymphocytic leukaemia was greater than that for benzene.

Genotoxicity

On the basis of the available data carbon tetrachloride is not considered to be genotoxic (IPCS, 1999).

Reproductive toxicity

In their review of data on the reproductive effects of carbon tetrachloride, Barlow and Sullivan (1982) concluded that the lack of human reproductive toxicity data makes evaluation impossible.

There is evidence that testicular and ovarian damage may be induced at toxic doses. From the limited evidence, carbon tetrachloride is not thought to be teratogenic or embryolethal in rats, but fetotoxicity may occur at

maternally toxic doses (Barlow and Sullivan, 1982). Although carbon tetrachloride is lipophilic and may readily pass through the placenta to the fetus after maternal exposure (Dowty *et al.,* 1976; ATSDR, 1992a), it does not appear to be teratogenic in either animals or humans in the early stages of pregnancy. The human fetus typically develops the mixed function oxidase enzyme system necessary for the toxic metabolism of carbon tetrachloride in the latter months of pregnancy, thus susceptibility to the adverse effects of carbon tetrachloride may depend on the developmental stage and on the duration and concentration of the exposure (ATSDR, 1992a).

RISK GROUPS

The individuals at greater risk from carbon tetrachloride toxicity are those with induced liver enzymes or depleted glutathione stores. Alcohols greatly enhance the hepatotoxicity of carbon tetrachloride (see Metabolic interactions) and most cases of fatal carbon tetrachloride induced hepatotoxicity involve individuals with a history of heavy ethanol abuse or concomitant alcohol ingestion. Diabetes and certain nutritional deficiencies have also been implicated in enhanced toxic effects from carbon tetrachloride (Capurro, 1973; ATSDR, 1992a; Torkelson, 1994).

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Carbon tetrachloride is radiopaque and ingestion may be confirmed by abdominal X-ray (Bagnasco *et al.*, 1978; Mathieson *et al.,* 1985; Dally *et al.,* 1987). Gastric lavage may be considered if ingestion was recent, however, because of the risk of aspiration a cuffed endotracheal tube must be used to protect the airway. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive. See below for management of systemic effects.

Systemic effects

Monitor ECG, vital signs, and fluid and electrolyte status. Baseline liver function tests and renal function should be determined. Although the presenting signs and symptoms may be associated with functional impairment of the liver, renal function should be observed closely and oliguria or anuria anticipated. Monitoring of liver and kidney function should occur for up to two weeks (ATSDR, 1992a). Cardiac and pulmonary

systems and coagulation should also be evaluated periodically, since abnormalities can occur secondary to hepatic and renal damage. Antidotal therapy should be considered, see below.

Haemodialysis has been used in patients exposed to carbon tetrachloride, but its success in reversing the pathology of carbon tetrachloride has not been proven (ATSDR, 1992a). Fogel *et al.* (1983) suggest that with carbon tetrachloride toxicity, haemodialysis should be started at the onset of renal failure and that total parenteral nutrition (TPN) can be useful in avoiding protein catabolism and may aid hepatic regeneration.

Antidotes

- **Acetylcysteine**

  The mechanism of action of acetylcysteine in the treatment of carbon tetrachloride poisoning is unclear, but it may serve as a free radical scavenger or may maintain intracellular glutathione stores (Chyka *et al.,* 2000) and its early use may protect against carbon tetrachloride toxicity (Mathieson *et al.,* 1985; ATSDR, 1992a). Acetylcysteine is relatively safe and easily available and should be considered for serious carbon tetrachloride poisoning.

  In a study of 19 patients with acute carbon tetrachloride poisoning (confirmed by laboratory analysis), 13 were treated with acetylcysteine and had evidence of milder hepatic damage than the 6 patients who did not receive this treatment (Ruprah *et al.,* 1985). In another case successfully treated with acetylcysteine, this patient's serum carbon tetrachloride concentrations remained elevated for several days post ingestion (probably due to re-entry into the circulation from adipose tissue). Consequently it is recommended that acetylcysteine is given for longer than the regimen (20 hours) used in paracetamol poisoning (Mathieson *et al.,* 1985).

- **Hyperbaric oxygen**

  It is thought that elevated hepatic oxygen tensions may potentially alter the metabolism of carbon tetrachloride. In theory, oxygen may inhibit the NADPH-dependent reducing enzyme system resulting in formation of less $\bullet CCl_3$ free radical, by shifting the conversion of $\bullet CCl_3$ towards the $CCl_3OO\bullet$ pathway. It is proposed that the highly reactive $CCl_3OO\bullet$ (compared with $\bullet CCl_3$), may destroy the enzyme system thereby preventing production of further free radical intermediates (Kubic and Anders, 1980; Truss and Killenberg, 1982; Burkhart *et al.,* 1991). Hyperbaric oxygen therapy has been recommended for potentially lethal doses of carbon tetrachloride (Burkhart *et al.,* 1991). However, other authors have stated that, due to the free radical nature of the toxic intermediates in carbon tetrachloride metabolism, hyperbaric oxygen is contraindicated (ATSDR, 1992a)

- **Free radical scavengers**

  Treatment of carbon tetrachloride poisoning with free radical scavengers such as ascorbic acid or vitamin E, has been shown to be effective only if administered before or simultaneously with exposure to carbon tetrachloride (Truss and Killenberg, 1982). Consequently, these are unlikely to be of benefit in the clinical situation.

- **Cholestyramine**

  Carbon tetrachloride liver cirrhosis results from the accumulation of bile acids that are not being detoxified in the enterohepatic circulation. In rat studies, administration of cholestyramine, which has a strong affinity for bile acids in the intestine, decreases the induction of cirrhosis (De Heer *et al.*, 1980). This is only an experimental therapy and human case data are lacking.

Chronic exposure

With chronic carbon tetrachloride toxicity, removal from the source of exposure and avoidance of other hepatotoxins is the only management.

REFERENCES

Ahr HJ, King LJ, Nastainczyk W, Ullrich V. 1980 The mechanism of chloroform and carbon monoxide formation from carbon tetrachloride by microsomal cytochrome P-450. *Biochem Pharmacol* 29:2855-2861.

ATSDR (Agency for Toxic Substances and Disease Registry). 1992a Carbon tetrachloride toxicity. *Am Fam Physician* 46 (4):1199-1207.

ATSDR (Agency for Toxic Substances and Disease Registry). 1992b *Case studies in environmental medicine. No. 18 Carbon tetrachloride toxicity*. US Department of Health and Human Services.

ATSDR 1994 *Toxicological profile for carbon tetrachloride*. Agency for Toxic Substances and Disease Registry. US Department of Health and Human Services.

Allis JW, Brown BL, Simmons JE, Hatch GE, McDonald A, House DE. 1996 Methanol potentiation of carbon tetrachloride toxicity: the central role of cytochrome P450. *Toxicology* 12:131-140.

Alston WC. 1970 Hepatic and renal complications arising from accidental carbon tetrachloride poisoning in the human subject. *J Clin Pathol* 23: 249-253.

Alswang D. 1979 The case of Gerrity vs Carbona (Carbon tetrachloride the insidious killer). *J Environ Pathol Toxicol* 3 (1-2): 565-570.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Bagnasco FM, Stringer B, Muslim AF. 1978 Carbon tetrachloride poisoning: radiographic findings. *NY State J Med* 78:646-647.

Barlow SM, Sullivan FM. 1982 *Reproductive Hazards of Industrial Chemicals. An evaluation of animal and human data*. Academic Press, London.

Baselt RC. 2000 *Disposition of Toxic Drugs and Chemicals in Man*, fifth edition. Chemical Toxicology Institute, Foster City, California.

Barnes R, Jones RC. 1967 Carbon tetrachloride poisoning. *Am Ind Hyg Assoc J* 28 (6):557-560.

Burkhart KK, Hall AH, Gerace R, Rumack BH. 1991 Hyperbaric oxygen treatment for carbon tetrachloride poisoning. *Drug Saf* 6 (5):332-33.

Cantor KP, Stewart PA, Brinton LA, Dosemeci M. 1995 Occupational exposures and female breast cancer mortality in the United States. *J Occup Environ Med* 37 (3):336-348.

Capurro PU. 1973 Effects of exposure to solvents caused by air pollution with special reference to CCl4 and its distribution in air. *Clin Toxicol* 6 (1):109-124.

Carlier B, Schroeder E, Mahieu P. 1980 A rapidly and spontaneously reversible Goodpasture's syndrome after carbon tetrachloride inhalation. *Acta Clin Belg* 35 (3):193-198.

Charbonneau M, Perreault F, Greselin E, Brodeur J, Plaa GL. 1988 Assessment of the minimal effective dose of acetone for potentiation of the hepatotoxicity induced by trichloroethylene-carbon tetrachloride mixtures. *Fundam Appl Toxicol* 10 (3):431-438.

Checkoway H, Wilcosky T, Wolf P, Tyroler H. 1984 An evaluation of the associations of leukaemia and rubber industry solvent exposures. *Am J Ind Med* 5:239-249.

Chyka PA, Butler AY, Holliman BJ, Herman MI. 2000 Utility of acetylcysteine in treating poisonings and adverse drug reactions. *Drug Saf* 22 (2):123-148.

Cornish HH, Adefuin J. 1966 Ethanol potentiation of halogenated aliphatic solvent toxicity. *Am Ind Hyg Assoc J* 27 (1):57-61.

Cornish HH, Adefuin J. 1967 Potentiation of carbon tetrachloride by aliphatic alcohols. *Arch Environ Health* 14:447-449.

Cornish HH, Barth ML, Ling B. 1977 Influence of aliphatic alcohol on the hepatic response to halogenated olefins. *Environ Health Perspect* 21:149-152.

Dally S, Garnier R, Bismuth C. 1987 Diagnosis of chlorinated hydrocarbon poisoning by x ray examination. *Br J Ind Med* 44:424-425.

De Heer K, Sauer HD, Werner B, Kloeppel G. 1980 Protective effects of cholestyramine on liver cirrhosis induced by carbon tetrachloride in the rat. *Gut* 21:860-865.

Deng JF, Wang JD, Shih TS, Lan FL. 1987 Outbreak of carbon tetrachloride poisoning in a color printing factory related to the use of isopropyl alcohol and an air conditioning system in Taiwan. *Am J Ind Med* 12:11-19.

Dianzani MU. 1984 Lipid peroxidation and haloalkylation: two distinct mechanisms for CCl_4-induced liver damage. *Int Congr Ser Excerpta Med* 632:39-50.

Diaz Gomez MI, Castro JA. 1980a Nuclear activation of carbon tetrachloride and chloroform. *Res Commun Chem Pathol Pharmacol* 27 (1):191-194.

Diaz Gomez MI, Castro JA. 1980b Covalent binding of carbon tetrachloride metabolites to liver nuclear DNA, proteins, and lipids. *Toxicol Appl Pharmacol* 56:199-206.

Dowty BJ, Laseter JL, Storer J. 1976 The transplacental migration and accumulation in blood of volatile organic constituents. *Pediatr Res* 10:696-701.

Driesbach RH, Robertson WO. 1987 *Handbook of Poisoning: Prevention, Diagnosis and Treatment,* twelfth edition. Appleton and Lange, Connecticut.

Folland DS, Schaffner W, Ginn HE, Crofford OB, McMurray DR. 1976 Carbon tetrachloride toxicity potentiated by isopropyl alcohol. Investigation of an industrial outbreak. *J Am Med Assoc* 236:1853-1856.

Fogel RP, Davidman M, Poleski MH, Spanier AH. 1983 Carbon tetrachloride overdose responds to hemodialysis and parenteral nutrition [abstract]. *Can Med J Assoc* 128:561.

Grant WM, Schuman JS. 1993 *Toxicology of the Eye,* fourth edition. Charles C Thomas, Springfield, Illinois.

IARC (International Agency for Research on Cancer). 1999 *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*. IARC Monograph 71.

IPCS. 1999 *Environmental Health Criteria 208. Carbon Tetrachloride*. World Health Organization, International Programme on Chemical Safety, Geneva.

Javier Perez A, Courel M, Sobrado J, Gonzalez L. 1987 Acute renal failure after topical application of carbon tetrachloride [letter]. *Lancet* 1:515-516.

Kalf GF, Post GB, Snyder R. 1987 Solvent toxicology: Recent advances in the toxicology of benzene, the glycol ethers, and carbon tetrachloride. *Ann Rev Pharmacol Toxicol* 27:399-427.

Kubic VL, Anders MW 1980 Metabolism of carbon tetrachloride to phosgene. *Life Sci* 26 (25): 2151-2155.

Louria DB, Bogden JB. 1980 The dangers from limited exposure to carbon tetrachloride. *Crit Rev Toxicol* 7 (2):177-188.

Mahieu P, Geubel A, Rahier J, Scailteur V, Dieryck JP, Lauwerys R. 1983 Potentiation of carbon tetrachloride hepato-nephrotoxicity by phenobarbital in a man, a case report. *Int J Clin Pharmacol Res* 3 (6):427-430.

Manno M, Rezzadore M, Grossi M, Sbrana C. 1996 Potentiation of occupational carbon tetrachloride toxicity by ethanol abuse. *Hum Exp Toxicol* 15 (4):294-300.

Mathieson PW, Williams G, MacSweeney JE. 1985 Survival after massive ingestion of carbon tetrachloride treated by intravenous infusion of acetylcysteine. *Hum Toxicol* 4 (6):627-631.

McCollister DD, Beamer WH, Atchison GJ, Spencer HC. 1951 The absorption, distribution and elimination of radioactive carbon tetrachloride by monkeys upon exposure to low vapour concentrations. *J Pharm Exp Ther* 102: 112-124. Cited in: Baselt RC. 2000 *Disposition of Toxic Drugs and Chemicals in Man*, fifth edition. Chemical Toxicology Institute, Foster City, California.

Morgott DA. 2001 Acetone. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Page DA, Carlson GP. 1994 The role of the intestinal tract in the elimination of carbon tetrachloride. *Toxicol Appl Pharmacol* 124:268-274.

Peters HA, Levine RL, Matthews CG, Sauter S, Chapman L. 1986 Synergistic neurotoxicity of carbon tetrachloride/disulfide (80/20 fumigants) and other pesticides in grain storage workers. *Acta Pharmacol Toxicol* 57 (Suppl 7):535-546.

Plaa GH. 1986 Toxic responses of the liver. In: *Casarett and Doull's Toxicology: The Basic Science of Poisons*, third edition. Klassen CD, Amdur MO, Doull J (editors). Macmillan Publishing Company, New York.

Recknagel RO. 1983 A new direction in the study of carbon tetrachloride toxicity. *Life Sci* 33:410-408.

Recknagel RO, Glende EA, Dolak JA, Waller RL. 1989 Mechanisms of carbon tetrachloride toxicity. *Pharmacol Ther* 43:139-154.

Reid JB. 2001 Saturated methyl halogenated aliphatic hydrocarbons. In: *Patty's Toxicology,* fifth edition, Volume 5. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Ruprah M, Mant TG, Flanagan RJ. 1985 Acute carbon tetrachloride poisoning in 19 patients: implication for diagnosis and treatment. *Lancet* 1:1027-1029.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Slater TF, Cheeseman KH, Ingold KU. 1985 Carbon tetrachloride toxicity as a model for studying free radical mediated liver injury. *Philos Trans R Soc Lond B Biol Sci* 311:633-645.

Stewart RD, Dodd HC. 1964 Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride and 1,1,1-trichloroethane through the human skin. *Am Ind Hyg Assoc J* 25:439-446.

Stewart RD, Dodd HC, Erley DS, Holder BB. 1965 Diagnosis of solvent poisoning. *J Am Med Assoc* 193 (13):115-118.

Sturbelt O, Obermeier F, Siegers CP, Völpel M. 1978 Increased carbon tetrachloride toxicity after low level ethanol consumption. *Toxicology* 10:261-270.

Torkelson TR. 1994 Halogenated aliphatic hydrocarbons containing chlorine, bromine and iodine. In: *Patty's Industrial Hygiene and Toxicology,* fourth edition, Volume 2, Part E. Clayton GD and Clayton FE (editors). John Wiley & Sons Inc., New York.

Tracey JP, Sherlock P. 1968 Hepatoma following carbon tetrachloride poisoning. *NY State J Med* 68 (16):2202-2204.

Traiger GJ, Plaa GL. 1971 Differences in the potentiation of carbon tetrachloride in rats by ethanol and isopropanol pre-treatment. *Toxicol Appl Pharmacol* 20:105-112.

Truss CD, Killenberg PG. 1982 Treatment of carbon tetrachloride poisoning with hyperbaric oxygen. *Gastroenterology* 82:767-769.

5 Chloroform

Nicola Bates

SUMMARY

- Chloroform is absorbed through the gastrointestinal tract and lungs
- Dermal absorption is only likely to be significant following contact with the liquid rather than the vapour
- Chloroform causes CNS depression and delayed liver and renal damage
- The metabolites of chloroform, particularly phosgene, are responsible for toxicity
- Acetylcysteine may be used as an antidote
- Chloroform is a potential mutagen
- There is insufficient evidence for carcinogenicity in humans
- Chloroform may be teratogenic in humans

DESCRIPTION

Synonyms

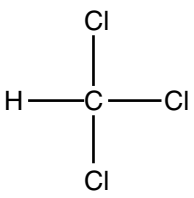
Trichloromethane, Freon 20, R20, methane trichloride, trichloroform, methyl trichloride, methenyl trichloride, methyl trichloride, 'formyl trichloride'.

Pure chloroform is light sensitive and is oxidised to phosgene and chlorine. Reagent grade chloroform usually contains 0.5-2% ethanol as a stabiliser. Ethanol scavenges the phosgene to form ethyl chloroformate.

Identification numbers

CAS	67-66-3
UN	1888
RTECS	FS 9100000
EINECS	2006638

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	$CHCl_3$
molecular formula	

molecular mass	119.38
physical form	clear, colourless, non-flammable highly volatile liquid, with a sweet odour
relative vapour density (air =1)	4.12
flash point (°C closed cup)	no data
boiling point (°C)	61.62
autoignition temperature (°C)	>1000
refractive index	1.4459
explosive limits in air (%v/v)	no data

Odour threshold

85 ppm (Amoore and Hautala, 1983), 50-200 ppm (Ruth, 1986), 205-307 ppm (Winslow and Gerstner, 1978).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK): 2 ppm (9 mg/m^3)
TWA (ACGIH): 10 ppm (50 mg/m^3)

Conversion factors

1 ppm = 4.89 mg/m^3
1 mg/l = 204 ppm
1 mg/l = 0.00838 mmol/l

Biomonitoring

The ACGIH has no biological exposure index for chloroform exposure (ACGIH, 2000).

TOXICITY

Chloroform was discovered in 1831, although it was not until 1834 that it was correctly analysed and named. It was first used as an anaesthetic in November 1847, the first death was reported in January 1848 in a 15 year old girl (Challen *et al*., 1958; Payne, 1981).

Toxicity may occur through ingestion, inhalation, injection or prolonged skin contact. The initial effects of chloroform toxicity are those of CNS depression. These effects come on rapidly following ingestion or inhalation. Hepatotoxicity occurs 10-48 hours post exposure with the liver function tests peaking 3–4 days post exposure. They usually return to normal within 6-8 weeks. Renal failure is usually evident within 24-48 hours. Death may occur early from arrhythmias or 4 to 5 days later due to severe liver damage.

Chloroform poisoning has occurred following

- Occupational exposure (Challen *et al*., 1958; Bomski *et al*., 1967; Phoon *et al.,* 1983; Li *et al.,* 1993)
- Intentional inhalation for suicide (Giusti and Chiarotti, 1981; Meichsner *et al*., 1998; Nadjem and Logemann, 1998) and abuse (Heilbrunn *et al*., 1945; Hutchens and Kung, 1985; Harada *et al*., 1997)
- Intentional ingestion for suicide (Waterston and Robinson, 1898; Kohr, 1990; Boyer *et al*., 1998) and abuse (Conlon, 1963)

- Accidental ingestion (Board, 1866; Storms, 1973) and inhalation (Allan *et al*., 1988)
- Intravenous injection (Timm and Moser, 1975; Rao *et al*., 1993)
- Clinical anaesthesia (Payne 1981; Thorpe and Spence, 1997)
- Criminal use, e.g., robbery, assault, homicide (McGee *et al*., 1987; McIntyre, 1988; Nashelsky *et al*., 1995; Vendura *et al*., 1996).

Ingestion of as little as 10 ml may cause CNS depression and death (Baselt, 2000). A 17 year old male survived ingestion of 4 ounces (114 ml) of chloroform (Schroeder, 1965), but the same quantity was fatal in a 42 year old (Board, 1866). Three ounces (84 ml) was survived by a 19 year old female (Waterston and Robinson, 1898). In a more recent case an adult survived ingestion of 230 ml of chloroform after treatment with acetylcysteine (Boyer *et al*., 1998). Intravenous injection of 0.5 ml of chloroform in a 21 year old man caused hepatotoxicity and lung changes, but he recovered within 3 days (Timm and Moser, 1975).

There has been concern over the risk of delayed chloroform poisoning (onset usually 2 days) after anaesthesia. This is usually attributed to liver damage and clinical effects include vomiting, jaundice, restlessness, delirium, coma and death. However, after reviewing the literature on 'delayed chloroform poisoning' from the mid-19th century onwards, Thorpe and Spence (1997) concluded that the risk was not as great as originally thought. Many reported cases did not stand up to scrutiny and the clinical features were not consistent with liver failure. Nine studies comparing the toxicity of various anaesthetics did not show a clinically significant difference in liver damage with chloroform. However, the numbers were small in most studies. Other causes of liver damage in these patients may have included hypoxia and hypercapnia. There may also have been predisposing factors such as dehydration, acidosis and alcoholism.

Absorption

Chloroform is rapidly absorbed. Inhalation is the main route of exposure owing to the high vapour pressure and high blood/air partition coefficient (Davidson *et al*., 1982).

In a study of the uptake of chloroform in 16 patients under general anaesthesia (eight ventilated patients, eight breathing spontaneously), uptake was rapid with a plateau being achieved after 45-50 minutes. In spontaneously breathing patients the arterial concentration reached 25% of the inspired concentration after 1 hour, and in ventilated patients the concentration reached 20% of the inspired concentration in 10 minutes and 40% after 1 hour (Poobalasingham and Payne, 1978).

About 80% of chloroform was absorbed after a single inhalation exposure of approximately 5 mg (^{38}Cl-labelled) chloroform in a volunteer (Morgan *et al*., 1970).

Chiou (1975) reanalysed the data of Fry *et al*. (1972) and calculated an apparent volume of distribution of 160 l for chloroform. The hepatic first-pass metabolism was estimated to be 32% and the pulmonary first-pass effect to be about 16%. So, after a single oral dose of 0.5g of chloroform, approximately 52% is available for absorption (IPCS, 1994).

Ingestion of 500 mg of chloroform in volunteers produced a maximum blood concentration exceeding 1 mg/l at about 1 hour (Fry *et al*., 1972). Inhalation of chloroform from an open container for 7 seconds (until the volunteer felt faint) produced a peak blood concentration of 4 mg/l at 20 minutes (Allan *et al*., 1988).

In a survey of 40 individuals with no known occupational exposure, all had non-detectable blood concentrations (<0.10 µg/l) of chloroform. However, 127 subjects using indoor swimming pools had an average blood chloroform concentration of 0.94 µg/l with a range of 0.10-3.1 µg/l (Aggazzotti *et al*., 1990). In another study, competitive swimmers using indoor pools had an average blood chloroform concentration of 0.89 µg/l, whereas none of the controls or those using outdoor pools had chloroform concentrations above the detection limit of 0.5 µg/l (Aiking *et al*., 1994). Chloroform is one of the trihalomethanes produced as a by-product of water chlorination.

In the industrial situation, chloroform absorption through the skin is only likely to be a problem following contact with the liquid rather than the vapour. Dick *et al*. (1995) examined dermal absorption of chloroform in volunteers. Chloroform in water or ethanol was applied to the ventral forearm and left on for eight hours. Absorption of chloroform was 7.8% when water was used and 1.6% when ethanol was used as the vehicle.

Distribution

There is limited information on the distribution of chloroform in humans. In an individual who died after inhalation of chloroform, the postmortem concentrations of chloroform were 47 mg/l in blood, 188 mg/l in liver, 144 mg/l in kidney, 74 mg/l in brain and 2 mg/l in urine (Meichsner *et al*., 1998). In a similar case the chloroform concentrations were: brain 113 µg/g, lung 72 µg/g, liver 178 µg/g, kidney 58 µg/g, urine 5 µg/g and stomach contents 63 µg/g (Nadjem and Logemann, 1998). In a murder victim where chloroform was used to facilitate robbery, the chloroform concentrations were heart blood (left) 280 mg/l, heart blood (right) 200 mg/l, urine 1.4 mg/l, stomach contents 21 mg/l, liver 800 µg/g, kidney 250 µg/g, lung 190 µg/g and brain 770 µg/g (Vendura *et al*., 1996).

Chloroform distribution was studied in mice using ^{14}C-labelled chloroform. Following inhalation of ^{14}C-chloroform the highest concentration of radioactivity was found in the body fat, particularly brown fat. Radioactivity was also high in the liver with lesser amounts in the blood, brain, lung, kidney and muscle. After 15 minutes there was a further increase in radioactivity in the fat. By 120 minutes, total radioactivity in the animals decreased and was essentially confined to the liver, duodenum and fat (Cohen and Hood, 1969).

This study also measured the concentration of volatile and non-volatile radioactivity in the liver. In animals killed immediately after anaesthesia the proportion of non-volatile radioactivity in the liver was 13.5%. At 15 minutes it was 43.7% and by 120 minutes the proportion was 85.6%. A similar increase in non-volatile radioactivity was also found in the duodenum (Cohen and Hood, 1969).

Metabolism

There is a large amount of data concerning the metabolism of chloroform some of which is contradictory, but this is probably because metabolism varies between species (Brown *et al.,* 1974; Charlesworth, 1976; Winslow and Gerstner, 1978).

Chloroform is metabolised in the liver by the microsomal cytochrome P450-dependent monoxygenase system to trichloromethanol, which spontaneously dechlorinates to produce phosgene. This process is dependent on reduced nicotinamide adenine nucleotide phosphate (NADPH) and requires oxygen. However, chloroform metabolism may also occur in the absence of oxygen (Testai and Vittozzi, 1984). Phosgene reacts with water to form carbonate (which is eliminated as carbon dioxide) and hydrochloric acid (chloride ion). This explains the formation of carbon dioxide without the formation of methylene chloride. The relative importance of this pathway depends on the dose of chloroform, suggesting that it may become saturated (Pohl, 1979).

The trichloromethyl radical has been suggested as a hepatotoxic metabolite, but this is not supported by evidence (see Mode of action). Dichloromethyl carbene has also been suggested as a metabolite of chloroform. This is a highly reactive species that reacts with water to form formyl chloride, which spontaneously decomposes to carbon monoxide and hydrochloric acid, or hydrolyses to formic acid. Small amounts of carbon monoxide and formic acid are found after the incubation of chloroform with liver microsomes and homogenate, respectively. This indicates that dichloromethyl carbene may be formed, however, it is not likely to be an important metabolite (Pohl, 1979).

When a known dose of ^{14}C-labelled chloroform was given intravenously to mice, about 4% of the dose was found in the liver and duodenum as non-volatile radioactivity. This suggests that metabolites other than chloride ions and carbon dioxide are formed, accumulate in the liver and are excreted into the duodenum in the bile (Cohen and Hood, 1969). Similar results were found in squirrel monkeys where a high concentration of radioactivity was found in the gall bladder (Brown *et al*., 1974).

Elimination

Chloroform is excreted mainly via the lungs as chloroform and carbon dioxide. In one study, volunteers were given 500 mg of chloroform in capsule form. Between 17.8% and 66.6% of the dose was exhaled as chloroform in 8 hours post ingestion. Maximum pulmonary excretion occurred between 40-120 minutes after ingestion.

Females eliminated less, probably due to uptake by adipose tissue of which females have a greater proportion. Chloroform was detectable in the breath of some subjects for up to 24 hours but at concentrations below measurable limits. Up to 68.3% of the dose was exhaled as chloroform and up to 50.6% as carbon dioxide. Maximum concentrations of carbon dioxide were obtained 75-210 minutes after ingestion of 500 mg ^{13}C-labelled chloroform in olive oil (Fry *et al.*, 1972).

The first half-life in subjects administered 500 mg of chloroform in capsule form was 9-21 minutes; the second phase had a half-life of 86-96 minutes (Fry *et al.*, 1972).

Urinary excretion of chloroform was low (<1%) following dermal exposure. Of the absorbed dose, more than 95% was excreted via the lungs and over 88% of this was carbon dioxide. The maximum pulmonary excretion occurred between 15 minutes and 2 hours after dosing (Dick *et al.*, 1995).

Mode of action

It is the metabolites of chloroform, not the solvent itself, which cause toxicity. Inhibition of microsomal enzymes has been shown to protect against chloroform induced hepatotoxicity in animals (Scholler, 1970).

Phosgene is the major metabolite responsible for chloroform toxicity, it is highly electrophilic and binds to tissue macromolecules. The trichloromethyl radical is also suggested as the agent responsible for chloroform induced hepatotoxicity, since this is the species thought to be involved in carbon tetrachloride hepatotoxicity. However, there are a number of observations which do not support this theory:

- Chloroform depletes glutathione, but carbon tetrachloride does not, so the trichloromethyl radical cannot be responsible for this effect.
- A larger proportion of a dose of ^{14}C-labelled carbon tetrachloride binds to lipids than with ^{14}C-labelled chloroform. This suggests that the chemical intermediates differ in their properties.
- In a study of deuterium-labelled chloroform no exchange of deuteriums occurred. This would be expected if the trichloromethyl radical was formed, i.e., a mixture of chloroform and deuterium-labelled chloroform would result (Pohl, 1979).

Chloroform depletes liver glutathione stores in animals. This process appears to involve a metabolite of chloroform, since pretreatment of rats with an enzyme inducer, such as phenobarbital, increases the amount of depletion (Masuda *et al.*, 1980). No depletion of glutathione in the kidney or blood occurs in the rat (Docks and Krishna, 1976).

Nephrotoxicity is probably due to prolonged hypoxia rather than a direct toxic effect. Well oxygenated patients do not develop nephrotoxicity.

Metabolic interactions

- **Enzyme inducers**

  Animal studies have shown that phenobarbital (an enzyme inducer) enhances the liver toxicity of chloroform. Pretreatment with ethanol did not influence the potentiating effect of phenobarbital (Cornish *et al.*, 1977).

- **Ethanol**

  Animal studies have shown that ethanol potentiates the liver toxicity of chloroform (Klassen *et al.*, 1966; Klassen *et al.*, 1967). Another study found no potentiation but this may have been because the doses of ethanol used were too small (Cornish *et al.*, 1977).

- ***n*-Hexane**

  n-Hexane can potentiate the hepato- and nephrotoxicity of chloroform in animals (Hewitt *et al.*, 1980).

- **Methyl ethyl ketone**

  Methyl ethyl ketone has been show to potentiate the hepatotoxicity and nephrotoxicity of chloroform in rats. The extent of liver and renal injury was dose related, but at the highest dose there was a reduction in the degree of potentiation. The mechanism of potentiation is unknown, but at high doses ketones may reduce the metabolism of chloroform and so reduce toxicity. Alternatively, high doses of ketones may damage the cells in such a way as to reduce the toxicity of chloroform (Brown and Hewitt, 1984).

CASE REPORTS

Two outbreaks of liver toxicity in two factories

Chloroform poisoning has been reported in two factories in Singapore. Thirteen workers from a factory manufacturing electrical household goods were diagnosed with viral hepatitis between October 1973 and July 1974. They all had jaundice and all but two had anorexia, nausea and vomiting. The occupational nurse noticed that all the victims worked in the same part of the factory. An open container of a degreaser containing 99.5% chloroform and 0.5% ethanol was found in this area. The air concentration of chloroform was more than 400 ppm. Blood concentrations in nine workers, five with jaundice and four others were 1.0-2.9 mg/l (Phoon *et al.*, 1975).

Another 11 cases of infectious hepatitis were diagnosed between May and August 1980, with a further five between November 1980 and October 1981 in workers at a factory making cassette recorders and digital clock radios. Again all the cases were from the same department where chloroform was applied to plastic casings. The plastic melted and the components became stuck together. On further investigation two more cases of hepatotoxicity were found. The chloroform concentration was measured on two occasions in December 1981. On the first it was 14.4-33.3 ppm and on the second 19.6-50.4 ppm. Blood samples taken in January were all negative for chloroform, but the company had reduced the number of workers using chloroform because of decreased production demands (Phoon *et al.*, 1983).

Acute inhalational abuse

A 23 year old male was found in bed unresponsive and gasping for air six hours after having been drinking with friends. Mouth-to-mouth resuscitation was given and a strong odour of chloroform was detected on the breath. Next to the bed was a bottle of laboratory grade chloroform and a chloroform soaked towel. A short run of ventricular tachycardia was observed which reverted to sinus rhythm without treatment. He was intubated and ventilated. On admission he was responsive only to painful stimuli, with constricted pupils and absent deep tendon reflexes. Diffuse rhonchi and wheezes were heard over both lung fields. Metabolic acidosis improved with sodium bicarbonate. He had an episode of bradycardia and arterial hypotension which resolved with sodium chloride infusion. He remained unconscious with arterial hypoxaemia and required positive expiratory end pressure (PEEP) ventilation. He became increasingly alert and his condition improved. He was weaned off the ventilator on the 2nd hospital day. He admitted intentionally inhaling an unknown amount of chloroform 'to see what would happen'. During the next few days he complained of nausea and poor appetite. By the 6th day he had jaundice of the skin and sclerae without liver or spleen enlargement. This resolved rapidly and he was discharged on the 12th day. The hypoxaemia and lung changes were thought to be due to aspiration of gastric contents before or during oro-tracheal intubation. A liver biopsy on day 11 revealed resolving centrilobular necrosis with fatty droplets within the mid-zonal surviving cells, dropout of hepatocytes and dilated sinusoids lined by Kupffer cells (Hutchens and Kung, 1985).

Acute accidental ingestion

A 19 year old male who had been drinking alcohol, accidentally ingested an unknown amount of chloroform. He collapsed and was taken to hospital. On admission he was found to be stuporous. He was transferred to an intensive therapy unit (ITU) and was by then unconscious with laboured breathing, cyanosis and reduced deep tendon reflexes. He was intubated and ventilated. Hypoxia could only be corrected with PEEP ventilation. LFTs were elevated but started to decrease after 4-6 days and were normal by eight weeks. The chloroform

concentration 10 hours after admission was 200 mg/l. Three days after admission he began to respond and he was extubated. He had ataxia and slight tremor on finger to nose testing. These resolved in two weeks (Storms, 1973).

CLINICAL EFFECTS

Acute exposure

Inhalation

Acute effects from occupational exposure to chloroform are uncommon (Harbison and Sleeman, 1998) and are most likely to occur following an industrial accident. Chloroform does not appear to cause respiratory irritation but the breath usually has a chloroform odour. Systemic effects are likely – see below.

Table 5.1 describes the physiological response to varying concentrations (in air) of chloroform in humans.

Table 5.1 Physiological response to varying concentrations (in air) of chloroform in man (Reid, 2001)

mg/l	ppm	Response
70-80	14,336-16,384	Narcotic limiting concentration
20	4,096	Vomiting, sensation of fainting
7.2	1,475	Dizziness, salivation
5	1,024	Dizziness, nausea, with definite after effects, fatigue and headache still felt later
1.9	389	Endured for 30 minutes without effects
1-1.5	205-307	Lowest amount that can be detected by smell

Dermal

Chloroform is irritant to the skin causing urticaria, erythema, blistering and burns. Dermal absorption may occur but is probably only significant following prolonged contact. Chemical burns to the face have been observed in victims forced to inhale chloroform from a pad held over the mouth and nose (McGee *et al*., 1987; McIntyre, 1988). This was also observed in a suicide case where the victim was found lying face down on a towel soaked in chloroform (Nadjem and Logemann, 1998).

Eye

Chloroform in the eye produces a stinging sensation, pain and hyperaemia of the conjunctiva. The epithelium may be damaged but recovery is rapid and usually complete within 1-3 days (Grant and Schuman, 1993).

Ingestion

There may be irritation of the throat, oesophagus and stomach following ingestion of chloroform, and haematemesis may occur (Piersol *et al*., 1933). Retrosternal soreness, pain on swallowing and gastric discomfort have also been reported (Schroeder, 1965). Muscular relaxation of the jaw resulting in upper respiratory obstruction has been reported (Schroeder, 1965). Systemic effects are likely, see below.

Systemic effects (from inhalation or ingestion)

Nausea and vomiting are common. Dizziness, headache, disorientation and anorexia may occur. CNS depression is rapid in onset (Piersol *et al*., 1933). There may be drowsiness followed by coma which may last for many hours. In patients with deep coma the gag reflex may be reduced or absent (Piersol *et al*., 1933). Hyporeflexia, respiratory depression, cyanosis, chemical pneumonitis and pulmonary oedema may occur. Respiratory arrest may occur rarely. The breath usually has a chloroform odour. Sweating (Board, 1866; Schroeder, 1965) and metabolic acidosis (Schroeder, 1965) have also been reported.

Dilated (Board, 1866; Waterston and Robinson, 1898) or constricted pupils (Hutchens and Kung, 1985) may be seen after inhalation of chloroform.

Cardiac effects

Chloroform causes depression of the cardiovascular system with hypotension and arrhythmias, including extrasystole, atrial block, SA block, bradycardia, bundle branch block, ventricular tachycardia, atrial fibrillation and cardiac arrest. Chloroform sensitises the myocardium to endogenous catecholamines.

Hepatic effects

Fatty degeneration of the liver, hepatomegaly and splenomegaly may occur. Central hepatic necrosis may occur 10-48 hours post exposure. LFTs peak 3-4 days post exposure and return to normal within 6-8 weeks. Permanent sequelae are rare. Prothrombin time and aminotransferases tend to rise more than the bilirubin and alkaline phosphatase levels. Jaundice from chloroform poisoning may be mistaken for viral hepatitis (Phoon *et al*., 1975; Phoon *et al*., 1983).

In postmortem studies of patients who have died following chloroform poisoning, the liver is grossly enlarged and pale with necrosis, particularly around the central veins. Often necrotic areas extend into the peripheral zones. Necrotic cells show increased eosinophilia and loss of nuclear and cytosolic detail. Border zones of healthy and necrotic areas show scattered and ballooned vacuolated cells which have undergone fatty degeneration. The kidney and heart show minor fatty degeneration (Pohl, 1979).

Renal effects

Kidney damage becomes evident within 24-48 hours of exposure. There may be proteinuria, haematuria, albuminuria, glucosuria, ketonuria and red cells and granular casts in urine (Schroeder, 1965).

Other routes

Ototoxicity has been reported in animals following direct ear contact with chloroform (Hu and Schwarz, 1987).

Drowsiness, mild liver damage, chemical pneumonitis and evidence of acute haemolysis occurred following an intravenous (IV) injection of 5 ml of chloroform (Timms and Moser, 1975). IV injection of 0.5 ml of chloroform has caused coma (Rao *et al*., 1993).

Chronic exposure

Inhalation

Lassitude, dry mouth, thirst, gastrointestinal discomfort, loss of appetite, ataxia, urinary frequency, inability to concentrate and dizziness have been reported in workers exposed to chloroform (77-237 ppm). Liver function tests were normal in all workers, but no biopsies were performed (Challen *et al*., 1958). Nausea and vomiting has also been reported (Phoon *et al.,* 1975).

Li *et al*. (1993) reported dizziness, fatigue, drowsiness, hypomnesia (memory impairment), increased dreams, anorexia and palpitations in chronically exposed workers (average 4.4 ppm, range 0.9-30 ppm).

Neurobehavioural testing revealed dose related negative changes and increased scores in passive mood states. There was decreased ability to concentrate, memory, perception and reaction time.

Adverse effects have been reported in individuals who chronically abuse chloroform. See below.

Hepatic effects

Hepatomegaly was found in 17 out of 68 workers exposed to chloroform (2-205 ppm) for 1-4 years. Three of these workers had toxic hepatitis and the frequency of hepatitis was higher in these workers than in the control group (Bomski *et al*., 1967).

Thirteen workers with jaundice were originally diagnosed as having viral hepatitis, but air concentrations of chloroform were found to be more than 400 ppm. The exposure time was less than six months. Five of these individuals and four other colleagues had blood chloroform concentrations of 1.0-2.9 mg/l (Phoon *et al*., 1975). In another factory 18 cases of toxic hepatitis were reported following a constant exposure to chloroform of 16.4-32.7 ppm for less than four months (Phoon *et al*., 1983).

There was evidence of mild liver damage, indicated by higher concentrations of serum prealbumin and transferrin in workers chronically exposed to chloroform (average 4.4 ppm, range 0.9-30 ppm) (Li *et al*., 1993).

Acute heart failure was the cause of death in an adult (39 years old) who died from acute chloroform intoxication after years of regular abuse. There was evidence of chronic chloroform toxicity with lipofuscin pigmentation of the heart and liver, and vacuolar degeneration of the endocardium (Harada *et al*., 1997).

Competitive swimmers using indoor pools had an average blood chloroform concentration of 0.89 µg/l but no evidence of liver damage (Aiking *et al*., 1994).

Renal effects

There was no evidence of renal toxicity in workers chronically exposed to chloroform (average 4.4 ppm, range 0.9-30 ppm) (Li *et al*., 1993).

Competitive swimmers using indoor pools (average chloroform water concentration 24 µg/l) had elevated β-2-microglobulin concentrations compared to controls and those who used outdoor pools (average chloroform water concentration 18.4 µg/l). This suggests that there was some degree of renal damage in those exposed to higher chloroform concentrations (Aiking *et al*., 1994).

Haematological effects

The haematological system is not a target for chloroform toxicity (ATSDR, 1997). Mild haemolysis has been reported after inhalational abuse of chloroform (Hutchens and Kung, 1985). Decreased erythrocytes and haemoglobin were observed in a subject who abused chloroform by ingestion for 10 years (Wallace, 1950).

Immunotoxicity

There are no studies on the immunotoxicity of chloroform in humans (ATSDR, 1997). In one study of 68 workers exposed to chloroform (2-205 ppm) for 1-4 years, splenomegaly was reported in 10 individuals (Bomski *et al*., 1967).

Dermal

The stratum corneum was completely destroyed in two young volunteers after the skin was exposed to chloroform for 15 minutes on 6 consecutive days. Milder changes occurred in two older subjects (Malten *et al*., 1968).

Eye

No information available.

Ingestion

Adverse effects have been reported in individuals who chronically abuse chloroform, see below.

Systemic effects from abuse of chloroform

Abuse of chloroform by ingestion or inhalation can cause irritability, anxiety, depression, delusions, delirium and paraesthesiae (Heilbrunn *et al.,* 1945). Hallucinations (Heilbrunn *et al.,* 1945; Conlon, 1963), tremor (Heilbrunn *et al.,* 1945; Conlon, 1963) and dysarthria (Conlon, 1963) have also been reported. Chronic abuse of chloroform may cause psychotic behaviour (Conlon, 1963).

One patient who ingested 1.6-2.6 g of chloroform daily for 10 years in a cough mixture developed hepatitis and nephrosis (Wallace, 1950). In another patient who ingested 21-28 ml of chloroform daily (in a pharmaceutical preparation also containing morphine, ether and alcohol) for an undetermined period, a liver biopsy revealed severe cellular damage (Conlon, 1963). Peripheral neuropathy was observed in three patients who abused chloroform in a pharmaceutical preparation also containing morphine, ether and alcohol (Conlon, 1963).

Carcinogenicity

There is insufficient evidence for the carcinogenicity of chloroform in humans, but sufficient evidence for its carcinogenicity in animals (reviewed in Chiu *et al*., 1996, IARC, 1999). On the basis of these data, chloroform may reasonably be anticipated to be a human carcinogen (Davidson *et al*., 1982). The International Agency for Research on Cancer classifies chloroform as Group 2B, possibly carcinogenic in humans (IARC, 1999). The mode of action of chloroform carcinogenesis is unknown (Chiu *et al*., 1996).

Several studies suggest an association between ingestion of chlorinated water and cancer in humans (reviewed in ATSDR, 1997). However, the results are not conclusive. These studies usually measure trihalomethanes, of which chloroform is present in the greatest quantity, but there are many other by-products of water chlorination that may be confounding factors (see Boorman *et al.*, 1999 for a review of toxicity evaluations of drinking water disinfection by-products; or IPCS, 2000).

Genotoxicity

The available data on the genotoxicity of chloroform is conflicting, and unequivocal evaluation of the genotoxic potential of chloroform cannot be made (Rosenthal, 1987; Chiu *et al*., 1996). Chloroform is considered a potential mutagen (Davidson *et al*., 1982).

Reproductive toxicity

Some animals studies have shown teratogenic effects following exposure to chloroform (as reviewed in Barlow and Sullivan, 1982; BUA, 1993), but results are conflicting. Chloroform may reasonably be anticipated to be teratogenic in humans (Davidson *et al.,* 1982), although human data are limited.

A retrospective review of female laboratory workers found a weak association between working with chloroform and spontaneous abortion (Wennborg *et al.*, 2000). Chloroform crosses the placenta and is present in cord blood in concentrations equal to or greater than that of maternal blood (Dowty *et al*., 1976).

Chloroform is found in water. It is one of the many by-products produced by the reaction of chlorine (in the chlorination of water) with naturally occurring organic material in source waters. A study of adverse reproductive outcomes and the concentrations of trihalomethanes in drinking water in Iowa, USA, found an increased risk of intrauterine growth retardation, associated with chloroform concentrations equal to, or

above, 10 µg/l. Compounding factors including maternal age, parity, prenatal care, marital status, education and maternal smoking were taken into consideration. However, the study has limitations including difficulty in ascertaining fluctuations in the trihalomethane concentrations and individual exposure concentrations (Kramer *et al*., 1992). Unknown contaminants may also have been compounding factors (IPCS, 1994).

RISK GROUPS

Animals pretreated with enzyme inducers (e.g., phenobarbital) have increased hepatotoxicity following chloroform exposure (Scholler, 1970; Docks and Krishna, 1976). Therefore patients on enzyme inducing drugs, alcoholics and those who are malnourished may be more at risk of hepatotoxicity from chloroform.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Chloroform is radiopaque and an X-ray may confirm ingestion (Dally *et al*., 1987). Gastric lavage may be considered if ingestion was recent, however, because of the risk of aspiration a cuffed endotracheal tube must be used to protect the airway. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive. See below for management of systemic effects.

Systemic effects

All patients initially require at least 24 hours observation with ECG monitoring. Blood concentrations of chloroform may be determined. Patients should be kept at complete bedrest, the use of stimulants, including epinephrine (adrenaline) and norepinephrine (noradrenaline), is best avoided because of the risk of sensitisation. In symptomatic patients hepatic and renal functions should be monitored for at least three days post exposure. Chest X-rays will be necessary to monitor the development of any respiratory complications.

Antidotes

Chloroform is known to deplete glutathione stores and acetylcysteine has been suggested as a possible antidote for hepatotoxic organic solvents (Laurenzi *et al*., 1987). Glutathione precursors such as cysteine have been shown to provide protection against liver toxicity in animals. Cysteine may also act as a nucleophilic agent.

This is supported by the observation that cysteamine, which is not a glutathione precursor, is also protective (Docks and Krishna, 1976).

There is limited data on the use of acetylcysteine in chloroform poisoning. However, it is relatively safe and easily available and should be considered for chloroform poisoning to minimise hepatic damage. Acetylcysteine has been used with success in patients with carbon tetrachloride poisoning. The regimen is the same as that for paracetamol poisoning but a longer duration of therapy is recommended (Ruprah *et al*., 1985). An adult who ingested 230 ml of chloroform survived with minimal hepatic damage after treatment with acetylcysteine for 4 days (Boyer *et al*., 1998).

Chronic exposure

In most cases of chronic poisoning clinical effects resolve gradually once exposure has ceased. Symptomatic and supportive care.

REFERENCES

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Aggazzotti G, Fantuzzi G, Tartoni PL, Predieri G. 1990 Plasma chloroform concentration in swimmers using indoor swimming pools. *Arch Environ Health* 45 (3):175-179.

Aiking H, van Acker MB, Scholten RJPM, Feenstra JF, Valkenburg HA. 1994 Swimming pool chlorination: a health hazard? *Toxicol Lett* 72 (1-3):375-380.

Allan AR, Blackmore RC, Toseland PA. 1988 A chloroform inhalation fatality - an unusual asphyxiation. *Med Sci Law* 28 (2):120-122.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997 *Toxicology Profile for Chloroform* (update). US Department of Heath and Human Services.

Barlow SM, Sullivan FM. 1982 *Reproductive Hazards of Industrial Chemicals. An evaluation of animal and human data*. Academic Press, London.

Baselt RC. 2000 *Disposition of Toxic Drugs and Chemicals in Man,* fifth edition. Chemical Toxicology Institute, California.

Board EC. 1866 Death from the imbibition of chloroform. *Br J Med* 1:541.

Bomski H, Sobolewska A, Strakowski A. 1967 Toxische Schädigung der Leber durch Chloroform bei Chemiebetriebswerken [Toxic damage of the liver by chloroform in chemical industry workers]. *Int Arch Gewerbepath Gewerbehyg* 24 (2):127-134.

Boorman GA, Dellarco V, Dunnick JK, Chapin RE, Hunter S, Hauchman F, Gardner H, Cox M, Sills RC. 1999 Drinking water disinfection byproducts: review and approach to toxicity evaluation. *Environ Health Perspect* 107 (Suppl 1):207-217.

Boyer E, Larson SC, Perrone J De Roos F. 1998 Limited hepatotoxicity following massive chloroform ingestion treated with oral *N*-acetylcysteine [abstract]. *Clin Toxicol* 36 (5):440.

Brown DM, Langley PF, Smith D, Taylor DC. 1974 Metabolism of chloroform - the metabolism of [14C]chloroform by different species. *Xenobiotica* 4:151-163.

Brown EM, Hewitt WR. 1984 Dose-response relationships in ketone-induced potentiation of chloroform hepato- and nephrotoxicity. *Toxicol Appl Pharmacol* 76:437-453.

BUA (Beratergremium für Umweltrelevante Altstoffe). 1993 *Chloroform*. BUA Report 1 (October 1985). S Hirzel, Stuttgart.

Challen PJR, Hickish DE, Bedford J. 1958 Chronic chloroform intoxication. *Br J Ind Med* 15:243-249.

Charlesworth FA. 1976 Patterns of chloroform metabolism. *Fd Cosmet Toxicol* 14:59-61.

Chiou WL. 1975 Quantitation of hepatic and pulmonary first-pass effect and its implications in pharmacokinetic study. I. Pharmacokinetics of chloroform in man. *J Pharmacokin Biopharm* 3 (3):193-201.

Chiu N, Orme-Zavaleta J, Chiu A, Chen C, DeAngelo A, Brattin W, Blancato J. 1996 Characterisation of cancer risk associated with exposure to chloroform. *Environ Carcino Ecotox Rev* C14 (2):81-104.

Cohen EN, Hood N. 1969 Application of low-temperature autoradiography to studies of the uptake and metabolism of volatile anesthetics in the mouse. I. Chloroform. *J Anesth* 30:257.

Conlon MF. 1963 Addiction to chlorodyne. *Br Med J* 2:1177.

Cornish HH, Barth ML, Ling B. 1977 Influence of aliphatic alcohols on the hepatic response to halogenated olefins. *Environ Health Perspect* 21:149-152.

Dally S, Garnier R, Bismuth C. 1987 Diagnosis of chlorinated hydrocarbon poisoning by x ray examination. *Br J Ind Med* 44:424-425.

Davidson IWF, Sumner DD, Parker JC. 1982 Chloroform: a review of its metabolism, teratogenic, mutagenic and carcinogenic potential. *Drug Chem Toxicol* 5 (1):1-87.

Dick D, Ng KME, Sauder DN, Chu I. 1995 In vitro and in vivo percutaneous absorption of ^{14}C-chloroform in humans. *Hum Exp Toxicol* 14:260-265.

Docks EL, Krishna G. 1976 The role of glutathione in chloroform-induced hepatotoxicity. *Exp Mol Pathol* 24:13-22.

Dowty BJ, Laseter JL, Storer J. 1976 The transplacental migration and accumulation in blood of volatile organic constituents. *Pediatr Res* 10:696-701.

Fry BJ, Taylor T, Hathaway DE. 1972 Pulmonary elimination of chloroform and its metabolite in man. *Arch Int Pharmacodyn* 196:98-111.

Giusti GV, Chiarotti M. 1981 Double 'suicide' by chloroform in a pair of twins. *Med Sci Law* 21 (1):2-3.

Grant WM, Schuman, JH. 1993 *Toxicology of the Eye,* fourth edition. Charles C Thomas, Springfield, Illinois.

Hakim A, Jain AK, Jain R. 1992 Chloroform ingestion causing toxic hepatitis. *J Assoc Physicians India* 40 (7):477.

Harada K, Ichiyama T, Ikeda H, Ishihara T, Yoshida K. 1997 An autopsy case of acute chloroform intoxication after intermittent inhalation for years. *Jap J Leg Med* 51:319-23.

Harbison RD, Sleeman RZ. 1998 Chlorinated hydrocarbons. In: *Hamilton and Hardy's Industrial Toxicology*, fifth edition. Harbison RD (editor). Mosby, St Louis.

Heilbrunn G, Liebert E, Szanto PB. 1945 Chronic chloroform poisoning. Clinical and pathological report of a case. *Arch Neurol Psychiatry* 53:68-72.

Hewitt WR, Miyajima H, Côté MG, Plaa GL. 1980 Acute alternation of chloroform-induced hepato- and nephrotoxicity by *n*-hexane, methyl *n*-butyl ketone, and 2-5-hexanedione. *Toxicol Appl Pharmacol* 53:230-248.

Hu K, Schwarz DWF. 1987 Electrophysical evaluation of chloroform-induced inner ear damage. *Arch Otorhinolaryngol* 244:222-228.

Hutchens KS, Kung M. 1985 "Experimentation" with chloroform. *Am J Med* 78:715-718.

IARC (International Agency for Research on Cancer). 1999 *Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents, and some other Substances*. IARC Monograph 73.

IPCS. 1994 *Environmental Health Criteria 163. Chloroform*. World Health Organization, International Programme on Chemical Safety, Geneva.

IPCS. 2000 *Environmental Health Criteria 216. Disinfections and disinfectant by-products*. World Health Organization, International Programme on Chemical Safety, Geneva.

Klassen CD, Plaa GL. 1966 Relative effects of various chlorinated hydrocarbons on liver and kidney function in mice. *Toxicol Appl Pharmacol* 9:139-151.

Klassen CD, Plaa GL. 1967 Relative effects of various chlorinated hydrocarbons on liver and kidney function in dogs. *Toxicol Appl Pharmacol* 10:119-131.

Kohr RM. 1990 Suicide by chloroform ingestion following self-mutilation. *Am J Forensic Med Path* 11 (4):324-328.

Kramer MD, Lynch CF, Isacson P, Hanson JW. 1992 The association of waterborne chloroform with intrauterine growth retardation. *Epidemiology* 3 (5):407-413.

Laurenzi RG, Locatelli C, Brucato A, Maccarini D. 1987 *N*-acetylcystein: a proposal for therapy in acute poisoning due to highly hepatotoxic organic solvents [abstract]. *Vet Hum Toxicol* 29 (Suppl 2):95.

Li L-H, Jiang X-Z, Liang Y-X, Chen Z-Q, Zhou Y-F, Wang Y-L. 1993 Studies on the toxicity and maximum allowable concentration of chloroform. *Biomed Environ Sci* 6:179-186.

Malten KE, Spruit D, Boemaars HG, de Keizer MJM. 1968 Horny layer injury by solvents. *Berufsdermatosen* 16 (3):135-47.

Masuda Y, Yano I, Murano T. 1980 Comparative studies on the hepatotoxic actions of chloroform and related halogenomethanes in normal and phenobarbital-pretreated animal. *J Pharm Dyn* 3:53-64.

McGee MB, Jejurikar SG and VanBerkom LC. 1987 A double homicide as a result of chloroform poisoning. *J Forensic Sci* 32 (5):1453-1459.

McIntyre JWR. 1988 The criminal use of chloroform administered by inhalation. *Med Law* 7:195-202.

Meichsner K, Lessig R, Müller K, Wehran HJ. 1998 Suizidale Chloroformintoxikation [Suicidal chloroform poisoning]. *Arch Kriminol* 201 (2-1):21-23.

Morgan A, Black A, Belcher DR. 1970 The excretion in breath of some aliphatic halogenated hydrocarbons following administration by inhalation. *Ann Occup Med* 13:219-233.

Nadjem H, Logemann E. 1998 Zur Kasuistik der suizidalen Chloroformintoxikation [A case of suicidal chloroform poisoning]. *Arch Kriminol* 202 (1-2):29-37.

Nashelsky MB, Dix JD, Adelstein EH. 1995 Homicide facilitated by inhalation of chloroform. *J Forensic Sci* 40 (1):134-138.

Payne JP. 1981 Chloroform in clinical anaesthesia. *Brit J Anaesth* 53:11-15.

Piersol GM, Tutmen HJ, Kau LS. 1933 Fatal poisoning following the ingestion of chloroform. *Med Clin N Am* 17:587-601.

Phoon WH, Liang OK, Kee CP. 1975 An epidemiological study of an outbreak of jaundice in a factory. *Ann Acad Med Singap* 4 (4):396-399.

Phoon WH, Goh KT, Lee LT, Tan KT, Kwok SF. 1983 Toxic jaundice from occupational exposure to chloroform. *Med J Malaysia* 38 (1):31-34.

Pohl LR. 1979 Biochemical toxicology of chloroform. In: *Reviews in Biochemical Toxicology*. Hodgson E, Bend JR, Philpol RM (editors). Elsevier North Holland Inc.

Poobalasingham N, Payne JP. 1978 The uptake and elimination of chloroform in man. *Br J Anaesth* 50:325-329.

Rao KN, Virji MA, Moraca MA, Diven WF, Martin TG, Schneider SM. 1993 Role of serum markers for liver function and liver regeneration in the management of chloroform poisoning. *J Anal Toxicol* 17:99-102.

Reid JB. 1994 Saturated methyl halogenated aliphatic hydrocarbons. In: *Patty's Toxicology,* fifth edition, Volume 5. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Rosenthal SL. 1987 A review of the mutagenicity of chloroform. *Environ Mol Mutagen* 10:2111-226.

Ruprah M, Mant TG, Flanagan RJ. 1985 Acute carbon tetrachloride poisoning in 19 patients: implication for diagnosis and treatment. *Lancet* 1:1027-1029.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Scholler KL. 1970 Modification of the effects of chloroform on the rat liver. *Br J Anaesth* 42:603-605.

Schroeder HG. 1965 Acute and delayed chloroform poisoning. A case report. *Br J Anaesth* 37:972-975.

Storms WW. 1973 Chloroform parties. *J Am Med Assoc* 225 (2):160.

Testai E, Vittozzi L. 1984 Different pathways of chloroform metabolism. *Arch Toxicol Suppl* 7:278-281.

Thorpe CM, Spence AA. 1997 Clinical evidence for delayed chloroform poisoning. *Br J Anaesth* 79:402-409.

Timms RM, Moser KM. 1975 Toxicity secondary to intravenous administered chloroform in humans. *Arch Intern Med* 135:1601-1603.

Vendura K, Strauch H, Pragst F, Prügel M. 1996 Tödliche Chloroformvergiftung mit Anschlussstraftat [Fatal chloroform poisoning with subsequent crime]. *Arch Kriminol* 198 (3-4):83-84.

Wallace CJ. 1950 Hepatitis and nephrosis due to cough syrup containing chloroform. *Calif Med* 73:442.

Waterston J, Robinson W. 1898 Poisoning by swallowing three ounces of chloroform. *Br Med J* 1:144-145.

Weenborg H, Bodin L, Vainio H, Axelsson G. 2000 Pregnancy outcome of personnel in Swedish biomedical research laboratories. *J Occup Environ Med* 42 (4):438-446.

Winslow SG, Gerstner HB. 1978 Health aspects of chloroform - a review. *Drug Chem Toxicol* 1 (3):259-275.

6 Diacetone Alcohol

Grainne Cullen

SUMMARY

- Diacetone alcohol is slightly toxic by ingestion
- It is irritating to skin and eyes
- Dermal absorption may lead to toxicity
- Eye, nose and throat irritation may occur on contact with diacetone alcohol vapour and these effects occur at concentrations well below those sufficient to cause systemic toxicity
- High concentrations of diacetone alcohol vapour may cause respiratory irritation, pulmonary discomfort, narcosis and systemic injury which includes renal and hepatic injury
- There is no information on the carcinogenicity or reproductive risk of diacetone alcohol
- There is little information on the genotoxic hazards of diacetone alcohol

DESCRIPTION

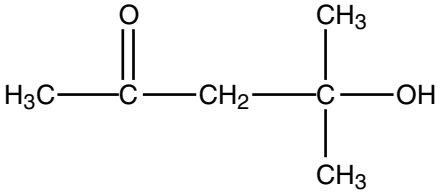
Synonyms

4-hydroxy-4-methyl-2-pentanone, 2-methyl-2-pentanol-4-one, diacetonyl alcohol, diacetone, dimethylacetonyl carbinol

Identification numbers

CAS	123-42-2
UN	1148
RTECS	SA 9100000
EINECS	2046267

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	$C_6H_{12}O_2$
molecular formula	
molecular mass	116.16

physical form	colourless, liquid that yellows with age; it has a mild odour
relative vapour density (air =1)	4.0
flash point (°C)	58
boiling point (°C)	169.2
autoignition temperature (°C)	603
refractive index	1.4242
explosive limits in air (%v/v)	1.8-6.9

Odour threshold

0.28 ppm in air (Amoore and Hautala 1983).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK and ACGIH): 50 ppm (241 mg/m^3)

Conversion factors

1ppm = 4.74 mg/m^3

1mg/l = 211 ppm

1mg/m^3 = 0.211 ppm

Biomonitoring

There is no biological exposure index for diacetone alcohol.

TOXICITY

Diacetone alcohol is used as a solvent for pigments, cellulose, resins, oils, fats and hydrocarbons. It is also used as a solvent in hydraulic brake fluid (Hathaway *et al*., 1996). There is scant information on the toxicity of diacetone alcohol in experimental animals and even less in humans. Most of the information on toxicity comes from animal experiments, the majority of which were carried out over 50 years ago.

There is no information on the absorption, distribution, metabolism, elimination or mode of action of diacetone alcohol in animals or humans (Topping *et al*., 2001).

Metabolic interactions

- **Chloroform**

  Diacetone alcohol (or 4-hydroxy-4-methyl-2-pentanone) is a metabolite of methyl isobutyl ketone (MIBK). MIBK and its metabolites (including diacetone alcohol) can potentiate the hepatotoxicity of chloroform in animals. This is probably due to induction of cytochrome P450 enzymes (Vézina *et al*., 1990). It is possible that exposure to a mixture of diacetone alcohol and chloroform may result in greater hepatotoxicity than exposure to chloroform alone.

CASE REPORT

Glomerulonephritis after occupational exposure to diacetone alcohol and ethanol in paint

A 59 year old man spent 3 days painting a floor using 30 l of paint containing a mixture of diacetone alcohol and ethanol as solvents. He first noticed oedema of the legs a month later. Despite initial improvement with diuretic therapy, his oedema could not be controlled and he had gained 12 kg in weight. He was admitted to hospital where nephrotic syndrome was suspected and a renal biopsy revealed a subacute proliferative glomerulonephritis. A lasting remission was obtained with immunosuppressive therapy (Von Scheele *et al*., 1976). This is an isolated case report and the role of diacetone alcohol is unclear.

CLINICAL EFFECTS

Acute exposure

Inhalation

Inhalation of high concentrations of diacetone alcohol vapour may lead to narcosis and systemic injury (Topping *et al.,* 2001). Eye, nose and throat irritation may occur at concentrations well below those necessary to cause significant systemic injury (Topping *et al.,* 2001). In a study of human volunteers, eye irritation appeared in the majority of subjects at 100 ppm and at this concentration practically all subjects complained of irritation to nose or throat (Silverman *et al*., 1946). Renal and hepatic injury has been reported in experimental animals and following prolonged or severe exposures in humans, there may be a risk of renal and hepatic damage (Keith, 1932). There is one report of subacute glomerulonephritis, which was diagnosed 40 days after occupational exposure to diacetone alcohol and ethanol paint solvents, although the causal relationship is unclear (Von Scheele 1976).

Dermal

Diacetone alcohol is irritating to the skin and following prolonged exposure there may be erythema and defatting. Diacetone alcohol may be absorbed through the skin leading to mild systemic effects following severe skin exposures (Topping *et al.,* 2001).

Eye

Exposure to diacetone alcohol vapour may cause eye irritation. In rabbit eyes undiluted diacetone alcohol caused severe corneal injury (Carpenter and Smyth, 1948).

Ingestion

Diacetone alcohol has a low degree of oral toxicity (Topping *et al.,* 2001) although human data are lacking. Hypotension and narcosis have been described in experimental animals.

In experiments, rats injected with diacetone alcohol developed narcosis (Von Oettingen, 1943). In rabbits, injection of diacetone alcohol had a marked depressant action on respiration and caused narcosis. The time of onset, depth and duration of effects was dependent on the dose and route of administration. Intravenous injection of diacetone alcohol in rabbits caused hypotension (thought to be due to a reduction in the cardiac output, rather than vasodilatation). Hypotension and respiratory depression were also noted in anaesthetised dogs injected with diacetone alcohol (Walton *et al*., 1923).

Hepatic effects

Liver damage has been described in experimental animals. Rats fed diacetone alcohol via stomach tube developed temporary cloudy swelling, vacuolisation and granulation of the hepatic cells. These effects developed

six hours post dose reaching a maximum intensity at 24 hours. Recovery was practically complete in seven days (Keith, 1932).

Renal effects

Renal injury (indicated by the presence of albumin and sugar in the urine) has been demonstrated in experimental animals following the repeated (12 times a day for an unspecified period) subcutaneous injection of diacetone alcohol (Von Oettingen, 1943).

Haematological effects

Haemolysis has been described in experimental animals. Destruction of erythrocytes and a reduction of haemoglobin was demonstrated in rats fed diacetone alcohol via stomach tube. These changes reverted to normal after a few days (Keith, 1932).

Chronic exposure

Inhalation

No information available.

Dermal

Chronic skin exposure may lead to defatting of the skin with drying and cracking (Hathaway *et al*., 1996).

Eye

No information available.

Ingestion

No information available.

Carcinogenicity

There is no information on the potential risk of carcinogenicity of diacetone alcohol (Topping *et al*., 2001). It has not been evaluated by the IARC.

Genotoxicity

Diacetone alcohol was reported to be apparently clastogenic (producing structural chromosome changes) in one series of experiments. This effect is unlikely to be due to interaction with DNA since diacetone alcohol does not possess any strongly electrophilic groups. An anti-mitotic effect may be due to the length of treatment and/or changes in osmolality (Brooks *et al*., 1988).

Diacetone alcohol did not induce reverse gene mutation in bacteria or mitotic gene conversion in yeast. However, in the rat liver chromosome assay, in the concentration range 2,000-4,000 μg/ml a small increase in chromatid damage was seen (4,000 μg/ml caused >60% growth inhibition of the cells). This effect was not dose related but was seen in two experiments. In the first, concentrations of 3,000, 1,500 and 750 μg/ml diacetone alcohol were used and a small number of chromatid exchanges, breaks and acentric fragments were seen in cultures exposed to the highest concentration. The second experiment examined the effects of concentrations of 4,000, 3,000 and 2,000 μg/ml diacetone alcohol. Chromatid breaks, exchanges and acentric

fragments were seen at the lowest level but similar effects were absent at 3,000 μg/ml and only a single chromatid break and two fragments were seen at 4,000 μg/ml. In both experiments a small increase in the incidence of chromatid gaps was seen in cultures exposed to diacetone alcohol (Brooks *et al.*, 1988).

Reproductive toxicity

Diacetone alcohol has not been tested for its ability to affect reproduction (REPROTEXT® Document, 2001; Topping *et al.*, 2001).

RISK GROUPS

None identified.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. Give oxygen as necessary. Monitor blood pressure and respiration. In symptomatic patients, monitor renal and hepatic function and check for haemolysis.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Oral fluids may be given. Monitor blood pressure and respiration and in severe cases, liver and renal function and check for haemolysis.

Systemic effects

In severe cases, monitor liver and renal function and check for haemolysis.

Antidotes

There is no specific antidote for diacetone alcohol.

Chronic exposure

In severe cases, monitor liver and renal function, and monitor for haemolysis. Treatment is supportive.

REFERENCES

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6): 272-290.

Brooks TM, Meyer AL, Hutson DH. 1988 The genetic toxicology of some hydrocarbon and oxygenated solvents. *Mutagenesis* 3: 227-232.

Carpenter CP, Smyth HF. 1948 Chemical burns of the rabbit cornea. *Am J Ophthalmol* 29:1363-1372.

Hathaway GJ, Proctor NH, Hughes JP. 1996 *Proctor & Hughes' Chemical Hazards of the Workplace,* fourth edition. John Wiley & Sons Inc, New York.

Keith HM. 1932 Effect of diacetone alcohol on the liver of the rat. *Arch Pathol Lab Med* 13:707-712.

REPROTEXT® Document. 2001 *Diacetone alcohol*. In: Heitland G & Hurlbut KM (editors): REPROTEXT® Database (electronic version) MICROMEDEX, Greenwood Village, Colorado, USA. Available at www.tomescps.com/DATA/RE/RE1405.HTM (site visited 24/07/01).

Silverman L, Schulte HF, First MW. 1946 Further studies on sensory response to certain industrial solvent vapors. *J Ind Hyg Toxicol* 28:262-266.

Smyth HF, Carpenter CP. 1948 Further experiences with the range finding test in the industrial toxicology laboratory. *J Ind Hyg Toxicol* 30:63-68.

Topping DC, Morgott DA, O'Donoghue JL. 2001 Ketones of six to thirteen carbons. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Vézina M, Kobusch AB, du Souich P, Greselin E, Plaa GL. 1990 Potentiation of chloroform-induced hepatotoxicity by methyl isobutyl ketone and two metabolites. *Can J Physiol Pharmacol* 68 (8):1055-1061.

Von Oettingen WF. 1943 Aliphatic alcohols. *Public Health Bull* 281:138.

Von Scheele C, Althoff P, Kempi V, Schelin U. 1976 Nephrotic syndrome due to subacute glomerulonephritis – association with hydrocarbon exposure? *Acta Med Scand* 200:427-429.

Walton DC, Kehr EF, Loevenhart AS. 1928 A comparison of the pharmacological action of diacetone alcohol and acetone. *J Pharmacol Exp Ther* 33:175-183.

7 Diisobutyl Ketone

Nicola Bates

SUMMARY

- There is limited information available on the toxicity of diisobutyl ketone; it is of low toxicity
- Diisobutyl ketone is irritant
- It is not considered to be genotoxic
- Diisobutyl ketone has not been evaluated for reproductive toxicity or carcinogenicity

DESCRIPTION

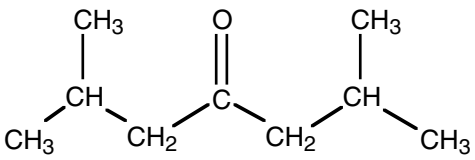
Synonyms

Diisobutyl ketone, diisopropyl acetone, isovalerone, 2,6-dimethyl-4-heptanone, DBK, DiBK, sym-diisopropyl acetone, valerone

Identification numbers

CAS	108-83-8
UN	1157
RTECS	MJ5775000
EINECS	2036201

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	$C_9H_{18}O$
molecular formula	
molecular mass	142.3
physical form	colourless liquid with a mild sweet odour
relative vapour density (air=1)	4.9
flash point (°C)	60
boiling point (°C)	168.1
autoignition temperature (°C)	396
refractive index	1.4210
explosive limits (%v/v)	0.8-7.1

Odour threshold

0.11 ppm (Amoore and Hautala, 1983; Ruth, 1986).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK and USA): 25 ppm (148 mg/m^3).

Conversion factors

1 ppm = 5.82 mg/m^3
1 mg/m^3 = 0.17 ppm
1 mg/l = 172 ppm

Biomonitoring

There is no biological exposure index for diisobutyl ketone.

TOXICITY

There is limited information on the toxicity of diisobutyl ketone and much of the data is from the older literature. Animal studies have shown diisobutyl ketone to be of relatively low toxicity (Carpenter *et al*., 1949; McOmie and Anderson, 1949; Smyth *et al*., 1949; Carpenter *et al*., 1953; Dodd *et al*., 1987).

There is no information on the absorption, distribution, metabolism, elimination or mode of action of diisobutyl ketone in experimental animals or humans (Topping, 2001). There is no information on metabolic interactions of diisobutyl ketone.

CASE REPORTS

A 60 year old man was exposed to diisobutyl ketone in his job as a laboratory technician. The solvent was heated to 367 °C and used under pressure. After about one month (May to June 1985) he developed severe headaches and vision loss. He was referred for neurological and neuropsychological evaluation on several occasions for headaches. Neurological evaluation revealed peripheral neuropathy. A CT scan in November 1985 was normal. An MRI was performed in January 1986 and showed numerous small, discrete focal lesions scattered throughout the white matter and bilaterally in the upper pons. In August 1986 MRI showed multiple focal areas of high signal intensity in the white matter, some in the periventricular white matter and other areas midway between the ventricles and cortex. In May 1987 there were multiple small focal lesions deep in the white matter of both cerebral hemispheres and the pons. There appeared to be some improvement compared to the previous results. In a battery of neuropsychological tests he was normal for tests on attention and executive function but was below expectation for verbal, language and memory tests. His wife reported that he was irritable and apathetic, but he denied changes in mood. Results suggested some affective changes with deficits in manual motor speed, verbal fluency, visuospatial organisation and short-term memory (White et al., 1993). However, there was no measurement of exposure concentrations of diisobutyl ketone or evaluation of exposure to any other chemicals in the workplace. Consequently, the cause of the neurological effects is unclear.

CLINICAL EFFECTS

Acute exposure

Inhalation

Diisobutyl ketone is irritant to the eyes and mucous membranes. Most subjects exposed to concentrations above 25 ppm developed eye irritation, with nose and throat irritation at concentrations above 50 ppm (Silverman *et al*., 1946). Humans exposed to 100 ppm for 3 hours developed mild lacrimation and throat irritation, slight headache and dizziness. Pulse rate and blood pressure remained normal, and tests for urine sugar and albumin were also normal. The performance of simple co-ordination tests was not affected by the exposure (Carpenter *et al.,* 1953).

Exposure to a high concentration of diisobutyl ketone causes CNS depression in animals (McOmie and Anderson, 1949; Carpenter *et al.,* 1953) and is expected to have the same effect in humans (Hathaway *et al*., 1996).

Dermal

Diisobutyl ketone may cause skin irritation (Hathaway *et al.,* 1996). On rabbit skin diisobutyl ketone produces only mild irritation (McOmie and Anderson, 1949; Smyth *et al*., 1949). However, the conditions of exposure may be important. In the study by Potokar *et al.* (1985) diisobutyl ketone was irritant to rabbit skin when occluded but non-irritant when semi-occluded.

Eye

Eye irritation is usually noted at concentrations above 25 ppm (Silverman *et al*., 1946). In a volunteer study subjects complained of slight transient eye irritation at the beginning of exposure to 50 ppm and 100 ppm (Carpenter *et al*., 1953). In rabbit eyes, diisobutyl ketone causes minimal irritation (Carpenter and Smyth, 1948; McOmie and Anderson, 1949; Smyth *et al*., 1949).

Ingestion

A number of ketones are an aspiration hazard (Panson and Winek, 1980). There is no information on diisobutyl ketone but it should be considered a potential hazard. Aspiration into the lungs may cause chemical pneumonitis and pulmonary oedema.

Chronic exposure

Inhalation

There is limited information on the chronic effects of diisobutyl ketone. Headache, vision loss and peripheral neuropathy have been reported in a worker exposed to fumes of heated diisobutyl ketone. Results of neurological and neuropsychological evaluation suggested some affective changes with deficits in manual motor speed, verbal fluency, visuospatial organisation and short-term memory (White *et al*., 1993). However, there was no measurement of exposure concentrations of diisobutyl ketone or evaluation of exposure to any other chemicals in the workplace. Consequently, the cause of the neurological effects is unclear.

In rats exposed to 905 ppm for 6 hours on nine occasions there was evidence of toxicity only in males. There was an increase in kidney weights, increased urine volume, hyaline droplets in the renal tubules and increased serum proteins and liver weights. Similar, but less pronounced effects were observed at 300 ppm. The effects resolved or decreased over a 2 week recovery period. The significance of these findings to human exposure is unknown (Dodd *et al*., 1987).

Dermal

Chronic exposure to diisobutyl ketone on the skin may cause drying and cracking. Dermatitis may occur due to its defatting action (Hathaway *et al.*, 1996).

Eye

No information available.

Ingestion

No information available.

Carcinogenicity

There is no information on the potential risk of carcinogenicity of diisobutyl ketone (Topping *et al.*, 2001). It has not been evaluated by the IARC.

Genotoxicity

Diisobutyl ketone has been found to give negative results in tests for genotoxicity (Brooks *et al.*, 1988; Topping *et al.*, 2001).

Reproductive toxicity

There is no information on the reproductive toxicity of diisobutyl ketone in animals or humans.

RISK GROUPS

None identified.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Diisobutyl ketone is of low acute toxicity and gastric decontamination is unlikely to be required unless a very large quantity has been ingested. However, because of the potential risk of aspiration a cuffed endotracheal tube must be used to protect the airway, since diisobutyl ketone may be an aspiration hazard. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive.

Antidote

There is no specific antidote for diisobutyl ketone.

Chronic exposure

Symptomatic and supportive care.

REFERENCES

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Brooks TM, Meyer AL, Hutson DH. 1988 The genetic toxicology of some hydrocarbon and oxygenated solvents. *Mutagenesis* 3 930:227-232.

Carpenter CP, Smyth HF. 1948 Chemical burns of the rabbit cornea. *Am J Ophthalmol* 29:1363-1372.

Carpenter CP, Smyth HF, Pozzani UC. 1949 The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. *J Ind Hyg Toxicol* 31:343-346.

Carpenter CP, Pozzani UC, Weil CS. 1953 Toxicity and hazard of diisobutyl ketone vapors. *AMA Arch Ind Hyg Occup Med* 8:377-381.

Dodd DE, Losco PE, Troup CM, Pritts IM, Tyler TE. 1987 Hyalin droplet nephrosis in male Fischer-344 rats following inhalation of diisobutyl ketone. *Toxicol Ind Health* 3 (4):433-457.

Hathaway GJ, Proctor NH, Hughes JP. 1996 *Proctor and Hughes' Chemical Hazards of the Workplace,* fourth edition. John Wiley & Sons Inc, New York.

McOmie WA, Anderson HH. 1949 Comparative toxicologic effects of some isobutyl carbinols and ketones. *Univ Calif Publ Pharmacol* 2:217-230.

Panson RD, Winek CL. 1980 Aspiration toxicity of ketones. *Clin Toxicol* 17 (2):271-317.

Potokar M, Grundler OJ, Herusener A, Jung R, Mürmann P, Schöbel C, Suberg H, Zechel HJ. 1985 Studies on the design of animal tests for the corrosiveness of industrial chemicals. *Fd Chem Toxicol* 23 (6):615-517.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Silverman L, Schulte HF, First MW. 1946 Further studies on sensory response to certain industrial solvent vapors. *J Ind Hyg Toxicol* 28:262-266.

Smyth HF, Carpenter CP, Weil CS. 1949 Range-finding toxicity data, list III. *J Ind Hyg Toxicol* 31:60-62.

Topping DC, Morgott DA, O'Donoghue JL. 2001 Ketones of six to thirteen carbons. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

White RF, Feldman RG, Moss MB, Proctor SP. 1993 Magnetic resonance imaging (MRI), neurobehavioral testing, and toxic encephalopathy: two cases. *Environ Res* 61 (1):117-123.

8 *N,N*-Dimethylformamide (DMF)

Nicola Bates

SUMMARY

- Dimethylformamide (DMF) is absorbed by inhalation, ingestion, injection and dermal exposure
- Toxicity is thought to be due to a metabolite of DMF
- DMF is a mild to moderate skin and irritant
- The target organ of toxicity, from both acute and chronic exposure, is the liver
- Ingestion of alcohol after exposure to DMF may cause facial flushing, nausea, dizziness and tightness of the chest
- DMF is possibly genotoxic
- It is not classifiable as to its carcinogenicity in humans
- There is limited information on the reproductive toxicity of DMF

DESCRIPTION

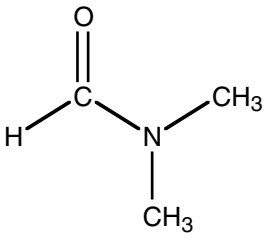
Synonyms

Formic acid dimethyl amide, formyl dimethylamide, *N,N*-dimethyl formic acid amide, DMF, DMFA.

Identification numbers

CAS	68-12-2
UN	2265
RTECS	LQ 2100000
EINECS	200-679-5

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	C_3H_7NO
molecular formula	
molecular mass	73.09

physical form	colourless liquid with a pungent fishy odour
relative vapour density (air=1)	2.51
flash point (°C)	67 (open cup); 58 (closed cup)
boiling point (°C)	152.5
autoignition temperature (°C)	445
refractive index	1.4305
explosive limits in air (%v/v)	2.2-15.2

Odour threshold

2.2 ppm (Amoore and Hautala, 1983), 99 ppm (Ruth, 1986).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK and ACGIH): 10 ppm (30 mg/m^3).

Conversion factors

1 ppm = 3.038 mg/m^3
1 mg/m^3 = 0.329 ppm
1 mg/l = 329 ppm

Biomonitoring

The biological exposure index (BEI) set by the ACGIH has recently been changed from 40 mg mono-*N*-methylformamide (NMF)/l in urine to 15 mg/l (ACGIH, 2000). Also, a new BEI for urinary *N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine (AMCC) of 40 mg/l is now recommended, although this test is not routinely available (Käfferlein and Angerer, 1999). Methods for simultaneous analysis of NMF and AMCC are currently being developed (Käfferlein and Angerer, 1999).

NMF in urine represents an index of daily exposure and AMCC represents an index of the average exposure over the preceding working days. AMCC is considered a better biological exposure index because it has a longer half-life and its formation is more closely related to DMF toxicity (Käfferlein *et al*., 2000).

TOXICITY

Dimethylformamide is a widely used synthetic organic solvent, first synthesised in 1893 (Kennedy, 1986). It is used mainly in the manufacture of films, fibres, coatings, adhesives and polyurethane lacquers. It is particularly useful as a solvent for polar polymers such as polyvinyl chloride (PVC) and polyacrylonitrile which have strong intermolecular forces (Kennedy, 1986). Most cases of occupational exposure involve inhalation or dermal absorption. Gastric irritation and liver toxicity may occur from exposure, but the risk of hepatotoxicity is low (Gescher, 1993).

Absorption

Dimethylformamide is absorbed by inhalation, ingestion, injection and dermal exposure. In a study of volunteers exposed to 20 ppm for eight hours the mean quantity of dimethylformamide absorbed via the lungs was 49.3 µmol/kg (Mráz *et al*., 1989). Pulmonary retention of DMF in volunteers was 90% (Mráz and Nohova, 1992b).

Dermal absorption of DMF may be significant (Lauwerys *et al*., 1980; Mráz and Nohova, 1992a); consequently the airborne concentration of DMF may not necessarily reflect the risk of exposure (Lauwerys *et al*., 1980). Liquid DMF is absorbed through the skin at a rate of 9.4 mg/cm^2/hour. The rate of absorption of DMF vapour varies depending on the ambient temperature and humidity. The yield of metabolites in volunteers exposed dermally to DMF was only half that of those exposed by inhalation, but the ratio was the same. Skin exposure to DMF is characterised by rapid absorption, extensive accumulation and slow elimination. Volunteers exposed to 10 ppm of DMF for 8 hours excreted 300 µmol of *N*-(hydroxymethyl)-*N*-methylformamide (HMMF) in urine in 24 hours. Immersion of one hand in liquid DMF for 10 minutes resulted in excretion of the same quantity of HMMF. In volunteers exposed to DMF vapour, percutaneous absorption was calculated to account for 13-36% of the total uptake (Mráz and Nohova, 1992a).

The use of impermeable gloves is more effective than silicone or glycerol barrier creams at reducing dermal absorption of DMF (Lauwerys *et al*., 1980).

Distribution

There is no information available on the distribution of dimethylformamide.

Metabolism

The metabolism of dimethylformamide is complex and has not been fully elucidated. It is metabolised by cytochrome P450-dependent mixed function oxidases in the liver. There are two primary metabolites: *N*-(hydroxymethyl)-*N*-methylformamide (HMMF) and mono-*N*-methylformamide (NMF, also abbreviated to MMF). The principal urinary metabolite was thought to be mono-*N*-methylformamide (Barnes and Ranta, 1972) but this is not the case. The main urinary metabolite of dimethylformamide in humans is actually HMMF (Mráz *et al*., 1989). However, this compound is unstable to gas chromatography conditions and undergoes thermal degradation on the column producing NMF. Without degradation of HMMF, NMF is present in urine in only a small concentration, either because it is reabsorbed or metabolised further (Gescher, 1993). Formamide was thought to be an important urinary metabolite of DMF (Lundberg *et al*., 1981) but this also undergoes degradation during analysis (Mráz *et al*., 1991). It is probably produced by thermal decomposition of *N*-(hydroxymethyl)formamide (HMF) which is generated by enzymatic *N*-methyl oxidation of NMF (Gescher, 1993).

Both primary metabolites, HMMF and NMF, undergo further metabolism. Oxidation of the formyl group of HMMF, and particularly NMF, ultimately produces the mercapturic acid, *N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine (AMCC) and this has been identified as an important urinary metabolite in man (Mráz and Turecek, 1987), but much less so in rodents (Mráz *et al*., 1989; Mráz *et al*., 1991). AMCC is degraded to ethyl-*N*-methylcarbamate (EMC) during preparation of specimens for analysis (Käfferlein and Angerer, 1999).

Oxidation of the formyl groups of the metabolites produces a short-lived intermediate. This intermediate reacts with reduced glutathione to produce a compound, *S*-(*N*-methylcarbamoyl)glutathione (SMG, also abbreviated to NMG) which is ultimately excreted as AMCC. The intermediate may be methyl isocyanate. AMCC is known to be a metabolite of methyl isocyanate (this is the chemical involved in the mass poisoning incident in Bhopal, India in 1984), and it is assumed that methyl isocyanate is an intermediate in DMF metabolism. It may be this compound or its conjugate compound, SMG, which is responsible for the hepatotoxicity of DMF (Gescher, 1993).

A study in rats demonstrated that HMMF formation occurred 12 hours after intraperitoneal administration of DMF and that NMF could only be detected in serum after 20-24 hours (Van den Bulcke *et al*., 1994). DMF appeared to be less toxic than HMMF or NMF but, when viewed over a period of several days, it was found that DMF was more toxic than the other two chemicals. Also, with HMMF and NMF the hepatotoxicity occurred earlier than with DMF. The time course (maximal 20-24 hours) and level of toxicity were similar with HMMF and NMF suggesting a similar mode of action. DMF toxicity was maximal at 48 hours after administration (Van den Bulcke *et al*., 1994).

Elimination

Käfferlein and Angerer (1999) estimate the quantities of the different metabolites as follows: DMF 5-15%, NMF 5%, formamide 5%, AMCC 15% and HMMF 50-80%. In a study of 92 workers exposed to DMF the mean NMF pre-shift urine concentration was 2.05 mg/l; post-shift 13.08 mg/l. For AMCC the pre-shift urine concentration was 21.44 and post-shift 30.31 mg/l (Käfferlein and Angerer, 1999).

HMMF is rapidly excreted and does not accumulate in the body (Gescher, 1993). In volunteers exposed to DMF for 8 hours the peak DMF and HMMF concentrations were reached in 6-8 hours and the peak AMCC concentration in 24-36 hours. The excretion half lives for DMF, HMMF and AMCC were approximately 2, 4 and 23 hours respectively. After exposure for five consecutive days there was accumulation of AMCC. After ingestion of AMCC it was rapidly eliminated with a half-life of about 1 hour. This difference in elimination times for AMCC (as the chemical itself or as a metabolite of DMF) may be due to reversible protein binding of a reactive intermediate (Mráz and Nohova, 1992b).

Urinary concentrations of AMCC in workers exposed to DMF varied from 10-590 μM (mean 109 μM). Concentrations of HMMF were 14-112 μM (mean 45 μM) (Mráz *et al.*, 1989). In a study of volunteers exposed to 20 ppm DMF for 8 hours the quantity of the different metabolites in the urine (a mean, expressed as a percentage of the amount absorbed) was as follows: DMF 0.7%, HMMF (as NMF) 25.9%, HMF (as formamide) 23.9% and AMCC 14.5% (Mráz *et al.*, 1989).

Mode of action

A short-lived intermediate metabolite, possibly methyl isocyanate or its conjugate, SMG, is thought to be responsible for the hepatotoxicity of DMF (Gescher, 1993).

Hepatotoxicity is observed later when a high dose of DMF is given compared to the onset when a low dose is administered (Lundberg *et al.*, 1981; Van den Bulcke *et al.*, 1994). DMF has been shown to inhibit its own metabolism (Mráz *et al.*, 1993). It is a competitive inhibitor of the generation of the toxic metabolite and thus SMG from NMF (Gescher, 1993). This accounts for the long-half life of AMCC and the delay in the onset of toxicity (Gescher, 1993).

When several formamide analogues were administered to mice only those forming mercapturic acids caused hepatotoxicity (Kestell *et al.*, 1987).

Metabolic interactions

- **Ethanol**

Ingestion of alcohol, even a small quantity, after exposure to DMF (by ingestion or inhalation) may cause flushing (always of the face and sometimes the neck, arms, hands and chest), nausea, dizziness and tightness of the chest (a disulfiram-like reaction). The effects may occur up to four days after exposure (Lyle *et al.*, 1979) and usually resolve in about 2 hours (Chivers, 1978; Lyle *et al.*, 1979). Flushing episodes may be associated with periorbital swelling, dysgeusia (impairment of the sense of taste) and wheezing (Cox and Mustchin, 1991). In one study 19 of 102 workers (18.6%) were affected (Lyle *et al.*, 1979).

Ethanol is a competitive inhibitor of the enzyme involved in DMF metabolism (P450 CYP2E1) and exposure to DMF after ingestion of ethanol delays the appearance of HMMF and AMCC in the urine (Mráz *et al.*, 1992b). The mechanism of action of the disulfiram-like reaction may be due to the inhibition of alcohol dehydrogenase, probably by a metabolite of DMF, resulting in increased concentrations of acetaldehyde after ingestion of alcohol (Cox and Mustchin, 1991). Animal studies have shown that DMF affects both ethanol and acetaldehyde concentrations (Hanasono *et al.*, 1977).

CASE REPORTS

Occupational exposure

A 40 year old man presented to hospital with abdominal pain, nausea and headache two weeks after starting work as a fabric coating machine operator. He stated that other workers suffered similar effects. Liver function tests showed an elevated AST. Alkaline phosphatase and bilirubin concentrations at this time were normal. Tests for hepatitis A IgM antibody and hepatitis B surface antigen were negative. An abdominal ultrasound was normal. He was thought to have toxic hepatitis and was removed from his work; his symptoms resolved. The ALT was elevated at three times normal 3.5 months later. A liver biopsy showed changes consistent with resolving toxic injury, including evidence of diffuse regeneration, binucleated hepatocytes and variation in nuclear size. There was also spotty unicellular necrosis, enlarged Kupffer cells within the sinusoids and diffuse steatosis. There was no evidence of chronic disease. Transaminase concentrations returned to normal 6 months after removal from exposure. Workplace evaluation found that large quantities of DMF and several other solvents in lesser quantities, were used in poorly ventilated areas without appropriate skin protection. A survey of the other workers found that 33 (62%) have elevated AST or ALT concentrations. Of these 19 (33%) had elevations greater than twice normal. These 19 workers were moved from direct exposure to DMF and transaminase concentrations returned to normal within 1-5 months (Redlich *et al.*, 1988).

Acute dermal and inhalation exposure

A 52 year old man who worked in a fabric coating plant was splashed over approximately 20% of his body surface with DMF when a machine malfunctioned. He washed the DMF from his skin put on the same clothes and drove home. He noticed that the odour of DMF was strong in the car. He had dermal irritation and hyperaemia as the only immediate effects. Then, 62 hours after the incident, he developed epigastric pain of increasing severity and vomiting. On examination, he was hypertensive. Despite severe abdominal pain there was no tenderness or rigidity. He complained of weakness and inco-ordination but there were no objective neurological changes. Liver function tests showed that bilirubin, AST and ALT were elevated. These had been normal on routine testing less than 2 months earlier. Prothrombin time, amylase, lipase and alkaline phosphatase, chest X-ray and urine analyses were normal. He had leucocytosis. His symptoms resolved within 4 days. A liver biopsy 11 days after the incident revealed minimal septal fibrosis and accumulations of mononuclear cells (Potter, 1973).

CLINICAL EFFECTS

Acute exposure

Inhalation

Acute inhalation of DMF may cause nausea, vomiting, progressive epigastric or abdominal pain with upper right quadrant tenderness, headache, anorexia, fatigue, dizziness and agitation. Mild respiratory irritation may occur. Laboratory analysis may reveal leucocytosis and abnormal LFTs. Recovery usually occurs in 2-3 weeks (IPCS, 1991).

Dermal

DMF is a mild to moderate skin irritant and is absorbed through the skin. It also enhances dermal absorption of some other substances.

Eye

DMF is a moderate eye irritant and corneal injury heals slowly (Kennedy and Sherman, 1986). When applied to rabbit eyes a 25% solution of DMF had no effect; 50% was slightly irritant and 75-100% caused a more severe inflammation (Massmann, 1956). A more detailed study using 0.1 ml of undiluted DMF placed in the

conjunctival sac, gave rise to moderate corneal damage from 1-3 days after administration to rabbit eyes. A microscopic sheen was apparent on the surface of the eye between 7 and 14 days. Conjunctival redness progressed to moderate involvement at 2 days with copious discharge; this resolved within 14 days. There were no effects on the iris. Washing of the eye 20 seconds after administration produced more severe effects. Severe penetrating damage was observed in the cornea from 2 to 7 days with gross opacity and very dense subsurface vascularisation. Mild iritis occurred at 2 days. The corneal response resolved in 2-4 weeks (Kennedy and Sherman, 1986).

Ingestion

There are few cases of ingestion of DMF reported, most involve T-61® (see below). Ingestion of DMF is likely to cause gastric irritation and liver damage.

Other routes

Ingestion or injection of T-61®, a veterinary euthanasia drug

Intentional ingestion or injection of T-61® a veterinary euthanasia drug containing DMF as a solvent (0.6 ml/ml) has caused hepatic dysfunction and fulminant hepatic failure. The preparation contains embutramide (a general anaesthetic), tetracaine (a local anaesthetic) and mebezonium (a neuromuscular blocking agent) and these cause coma and respiratory failure. Patients who survive the initial CNS depression may develop DMF induced hepatic damage. Liver toxicity may occur following ingestion (Cordell *et al*., 1986; Nicolas *et al*., 1990; Trevisani *et al*., 1993) or injection of the preparation (Kingston and Saxena, 1979; Buylaert *et al*., 1996). In reported cases the liver enzymes have become abnormal 2 (Trevisani *et al*., 1993), 4 (Nicolas *et al*., 1990) and 6 days later (Buylaert *et al*., 1996). In one case they were normal until 14 days after exposure (Kingston and Saxena, 1979). In cases where derangement of liver function has been early, the hepatotoxicity has been severe. There appears to be a relationship between the degree of liver toxicity and the dose of DMF ingested or injected: 0.11 ml/kg (Cordell *et al*., 1986) and 0.13 ml/kg (assuming a body weight of 55 kg; Cavaliere *et al*., 1982) caused only mild liver damage; 0.45 ml/kg caused severe hepatotoxicity (Trevisani *et al*., 1993); 0.6 ml/kg resulted in fatal fulminant hepatic failure (Nicolas *et al*., 1990). This drug preparation is available in Canada, most of Europe (but not the UK), Nigeria and New Zealand (Giorgi and Bertini, 2000).

Contaminant of sodium fluorescein

DMF, present as a contaminant of sodium fluorescein, was thought to be responsible for an increase in adverse effects reported from the use of sodium fluorescein in angiograms. Fluorescein is given intravenously for the assessment of many retinal disorders. Following an increase in the number and severity of adverse effects, analysis of one batch of sodium fluorescein revealed the presence of DMF. There was a marked increase in the frequency of nausea and the severity of vomiting. The incidence of adverse effects returned to background levels when fluorescein from a different source was used (Jacob *et al*., 1982).

Chronic exposure

Inhalation

The effects of chronic inhalation of DMF resemble those of acute exposure. Nausea, vomiting, epigastric or abdominal pain, headache, anorexia, fatigue, dizziness and agitation may occur. Mild respiratory irritation may occur. Laboratory analysis may reveal leucocytosis and abnormal LFTs (IPCS, 1991). Thrombocytopenia and prolonged prothrombin time has been reported in exposed workers (Imbriani *et al*., 1986). Individuals with long-term exposure may have relatively few symptoms, but that may be because of tolerance or because those that feel unwell have moved from exposure (Redlich *et al*., 1990).

Exposure to a high concentration of DMF is associated with abnormal liver function (Wang *et al*., 1991). In one study, elevated liver enzyme concentrations were found in 76% of workers, but most of them had minimal symptoms (Redlich *et al*., 1988). A study of workers exposed to DMF (up to 7.0 ppm) or DMF (up to 2.1

ppm) and toluene (4.2 ppm) found no difference in haematological or biochemical parameters compared with controls. However, there was a dose dependent increase in subjective symptoms, particularly gastrointestinal effects such as nausea and abdominal pain (Cai *et al.*, 1992).

Liver biopsy of individuals with short exposure (less than two months) may show focal hepatocellular disturbance (hepatocyte pleomorphism, anisokaryosis, acidophil bodies, mitoses, binucleate cells, periodic acid-Schiff (PAS)-positive Kupffer cell inclusions and microvesicular steatosis and no inflammation). In those with more long-term exposure there may be macrovesicular steatosis without inflammation or fibrosis (Redlich *et al.*, 1990). Urine may be positive for porphobilinogen (Potter, 1973) and elevated creatine phosphokinase concentrations have been reported (Wang *et al.*, 1991).

Subchronic studies in monkeys showed no adverse effects when exposed for 6 hours/day for 5 days/week for 13 weeks to concentrations of up to 500 ppm (Hurtt *et al.*, 1989).

Dermal

Contact dermatitis has been reported (Camarasa, 1987). Prolonged exposure may cause irritation, oedema and scaling (Klavis, 1970).

Eye

No information available.

Ingestion

No information available.

Carcinogenicity

There is inadequate evidence in humans for the carcinogenicity of DMF and evidence suggests a lack of carcinogenicity in animals. Consequently, DMF is in IARC Group 3 and is not classifiable as to its carcinogenicity in humans (IARC, 1999).

Several reports have suggested that exposure to DMF may be associated with an increased risk of various cancers (Ducatman *et al.*, 1986; Levin *et al.*, 1987). A cluster of testicular germ cell cancers in aircraft repairmen may have been due to exposure to DMF (Ducatman *et al.*, 1986). Workers exposed to DMF had a higher incidence of cancers of the buccal cavity and pharynx and malignant melanoma. A significant excess of prostate cancer was observed in those exposed to DMF and acrylonitrile (Chen *et al.*, 1988). However, in another study there was no significant association between exposure to DMF and cancers of the buccal cavity and pharynx, liver, malignant melanoma, prostate and testis (Walrath *et al.*, 1989).

Genotoxicity

DMF has been well studied and appears to have no mutagenic activity (Antoine *et al.*, 1983; Kennedy, 1986). There is limited evidence of genotoxicity in workers exposed to DMF. *In vitro* and *in vivo* tests for genotoxicity have shown that DMF does not induce damage in genetic material (IPCS, 1991; BUA, 1994). However, there are several reports of chromosome aberrations in the lymphocytes of exposed workers (Koudela and Spazier, 1979; Major *et al.*, 1998) and this has not been adequately explained (BUA, 1994).

Reproductive toxicity

There is only limited information on the reproductive effects of DMF. Miscarriage was reported in three out of nine women exposed to a number of chemicals including DMF (Farquharson *et al.*, 1983). Disturbances in menstruation were noted in 26 of 70 (37%) women exposed to DMF. There are no data available for controls.

From an analysis of company statistics, general morbidity associated with gynaecological problems was higher in women exposed to DMF (Aldyreva and Gafurov, 1980). Another study reported 14% miscarriages in women exposed to DMF compared to 10% in controls (Schottek, 1972). There were no statistical analyses of these data (IPCS, 1991).

Subchronic studies in monkeys showed no reproductive effects (e.g., semen analyses, testicular pathology, menses cycling) when exposed for 6 hours/day for 5 days/week for 13 weeks to concentrations of up to 500 ppm (Hurtt *et al*., 1989).

DMF is only slightly embryotoxic or teratogenic in animal studies (Kennedy, 1986). Effects are only seen with high doses that produce maternal toxicity. In the case of gavage or intraperitoneal administration (neither of which reflect industrial exposure), an increase in malformations may occur in the absence of maternal toxicity. This is also true for dermal exposure but with a smaller incidence (IPCS, 1991).

RISK GROUPS

Individuals with pre-existing liver damage may be more at risk of hepatotoxicity if exposed to DMF.

Cytochrome P450 CYP2E1 is involved in the biotransformation of many chemicals, including DMF. Several polymorphisms of CYP2E1 have been identified. In a study of DMF metabolism investigating the effect of the *Pst*I/*Rsa*I polymorphism, there was no difference in the urinary concentration of NMF in c1 homozygotes (*Rsa*I/*Rsa*I), c2 heterozygotes (*Pst*I/*Rsa*I) or c2 homozygotes (*Pst*I/*Pst*I). The urinary half-life of NMF after respiratory exposure was slightly longer in the single c2 homozygote subject than in the other two groups. This may have been due to individual variation or a lower CYP2E1 expression. In view of the wide variation in the other groups, the former explanation is more likely (Nomiyama *et al*., 2001).

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Monitor liver function. Further treatment is symptomatic and supportive.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein. Despite apparent worsening of effects in rabbit eyes when washed with water following DMF exposure, the magnitude of the response is not great enough to contraindicate irrigation. Copious irrigation can prevent serious lasting injury to the eye (Kennedy and Sherman, 1986).

Ingestion

Gastric decontamination should be considered following ingestion of DMF. It is not known whether activated charcoal would be of any benefit. The white blood cell count and LFTs should be monitored. A ratio of AST to ALT of less than one will distinguish toxic liver disease from alcoholic hepatitis (Redlich *et al*., 1988; Fleming *et al*., 1990). Treatment is symptomatic and supportive. Antidotal therapy may be considered (see below).

Antidotes

Antidotal therapy has been used in two cases of intentional exposure to T61® where reduced glutathione (Trevisani *et al*., 1993) and acetylcysteine (Buylaert *et al*., 1996) were given. However, it is not clear from these cases whether it was of any benefit in protecting the liver.

Experiments in rats measuring the effect of acetylcysteine on the concentration of the liver enzyme sorbitol dehydrogenase (SDH) (the most specific indicator of hepatotoxicity in rats) demonstrated a lower rise in SDH in acetylcysteine treated animals. However, this difference was only significant when the data of four series were pooled. This suggests a small or non-existent protective effect of acetylcysteine but may have been due to large inter-individual variations in the effects of dimethylformamide. It should be noted, however, that in these experiments acetylcysteine was given prior to exposure to DMF which does not reflect the clinical situation (Buylaert *et al*., 1996).

From these data it is unclear whether acetylcysteine has a protective effect in DMF poisoning. However, it is relatively safe and easily available and should be considered for serious DMF poisoning.

Chronic exposure

Symptomatic and supportive care.

REFERENCES

Antoine JL, Arany J, Léonard A, Henrotte J, Jenar-Dubuisson G, Decat G. 1983 Lack of mutagenic activity of dimethylformamide. *Toxicology* 26:207-212.

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Aldyreva MV, Gafurov SA. 1980 [*Labour protection in the production of artificial leather*.] Moscow, Medizina (in Russian). Cited in: IPCS. 1991 *Environmental Health Criteria 114. Dimethylformamide*. World Health Organization, International Programme on Chemical Safety, Geneva.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Barnes JR, Ranta KE. 1972 The metabolism of dimethylformamide and dimethylacetamide. *Toxicol Appl Pharmacol* 23:271-276.

BUA (Beratergremium für Umweltrelevante Altstoffe). 1994 *N,N-Dimethylformamide*. BUA Report 84 (December 1991). S Hirzel, Stuttgart.

Buylaert W, Calle P, De Paepe P, Verstraete A, Samyn N, Vogelaers D, Vandenbulcke M, Belpaire F. 1996 Hepatotoxicity of *N*,*N*-dimethylformamide (DMF) in acute poisoning with veterinary euthanasia drug T-61. *Hum Exp Toxicol* 15:607-611.

Cai S-X, Huang M-Y, Xi L-Q, Li Y-L, Qu J-B, Kawai T, Yusagi T, Mizunuma K, Watanabe T, Ikeda M. 1992 Occupational dimethylformamide exposure 3. Health effects of dimethylformamide after occupational exposure at low concentrations. *Int Arch Occup Environ Health* 63:461-468.

Camarasa JG. 1987 Contact dermatitis from dimethylformamide. *Contact Dermatitis* 16:234.

Cavaliere U, Andreano C, Raducci G, Andreoni C, Iacovella A. 1982 Intossicazione da T61 (Tanax). [T61 intoxication]. *Min Anest* 48:861-864.

Chen JL, Fayerweather WF, Pell S. 1988 Cancer incidence of workers exposure to dimethylformamide and/or acrylonitrile. *J Occup Med* 30 (10):813-818.

Chivers CP. 1978 Disulfiram effects from inhalation of dimethylformamide [letter]. *Lancet* 1:331.

Cordell WH, Curry SC, Furbee RB, Mitchell-Flynn DL. 1986 Veterinary euthanasia drugs as suicide agents. *Ann Emerg Med* 15:939-943.

Cox NH, Mustchin CP. 1991 Prolonged spontaneous and alcohol-induced flushing due to the solvent dimethylformamide. *Contact Dermatitis* 24:69-70.

Ducatman AM, Conwill DE, Crawl J. 1986 Germ cell tumors of the testicle among aircraft repairmen. *J Urol* 136:834-836.

Farquharson RO, Hall MA, Fullerton WT. 1983 Poor obstetric outcome in three quality control laboratory workers. *Lancet* 30:983-984.

Fleming LE, Shalat SL, Redlich CA. 1990 Liver injury in workers exposed to dimethylformamide. *Scand J Work Environ Health* 16:289-292.

Gescher A. 1993 Metabolism of *N,N*-dimethylformamide: key to understanding its toxicity. *Chem Res Toxicol* 6 (3):245-251.

Giorgi M, Bertini S. 2000 Tanax® (T-61): an overview. *Pharmacol Res* 41 (4):379-383.

Hanasono GK, Fuller RW, Broddle WD, Gibson WR. 1977 Studies on the effects of *N,N*-dimethylformamide on ethanol disposition and on monoamine oxidase activity in rats. *Toxicol Appl Pharmacol* 39:461-472.

Hurtt ME, Placke ME, Killinger JM, Singer AW, Kennedy GL Jr. 1992 13-Week inhalation toxicity study of dimethylformamide (DMF) in cynomolgus monkeys. *Fund Appl Toxicol* 18:596-601.

IARC (International Agency for Research on Cancer). 1999 *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*. IARC Monograph 71.

Imbriani M, Ghittori S, Prestinoni A, Longoni P, Cascone G, Gamba G. 1986 Effects of dimethylformamide (DMF) on coagulation and platelet activity. *Arch Environ Health* 41:90-93.

IPCS. 1991 *Environmental Health Criteria 114. Dimethylformamide*. World Health Organization, International Programme on Chemical Safety, Geneva.

Jacob JSH, Rosen ES, Young E. 1982 Report on the presence of a toxic substance, dimethylformamide, in sodium flurorescein used for fluorescein angiography. *Br J Ophthalmol* 66:567-568.

Käfferlein HU, Angerer J. 1999 Simultaneous determination of two human urinary metabolites of *N,N*-dimethylformamide using gas chromatography-thermionic sensitive detection with mass spectrometric confirmation. *J Chromatog B* 734:285-298.

Käfferlein HU, Göen T, Müller J, Wrbitzky R, Angerer J. 2000 Biological monitoring of workers exposed to *N,N*-dimethylformamide in the synthetic fibre industry. *Int Arch Occup Environ Health* 73:113-120.

Kennedy GL Jr. 1986 Biological effects of acetamide, formamide and their monomethyl and dimethyl derivatives. *CRC Crit Rev Toxicol* 17:129-182.

Kennedy GL Jr, Sherman H. 1986 Acute and subchronic toxicity of dimethylformamide and dimethylacetamide following various routes of administration. *Drug Chem Toxicol* 9 (2):147-170.

Kestell P, Threadgill MD, Gescher A, Gledhill AP, Shaw AJ, Farmer PB. 1987 An investigation of the relationship between the hepatotoxicity and the metabolism of *N*-alkylformamides. *J Pharmacol Exp Ther* 240 (1):265-270.

Kingston RL, Saxena K. 1979 Intentional poisoning by injection of veterinary euthanasia drug [abstract]. *Clin Toxicol* 15:492.

Klavis G. 1970 Leberfunktionsstörungen nach Dimethylformamid [Liver dysfunction after dimethylformamide]. *Arbeitsmed Sozialmed Arbeitshyg* 5:251 (in German). Cited in: BUA (Beratergremium für Umweltrelevante Altstoffe). 1994 *N,N-Dimethylformamide*. BUA Report 84 (December 1991). S Hirzel, Stuttgart.

Koudela K, Spazier K. 1979 [Effects of dimethylformamide on human peripheral lymphocytes.] *Cesk Hyg* 24:432-436 (in Czech). Cited in: IPCS. 1991 *Environmental Health Criteria 114. Dimethylformamide*. World Health Organization, International Programme on Chemical Safety, Geneva.

Lauwerys R, Kivits S, Lhoir M, Rigolet P, Houbeau D, Buchet JP, Roels HA. 1980 Biological surveillance of workers exposed to dimethylformamide and the influence of skin protection on its percutaneous absorption. *Int Arch Occup Environ Health* 45:189-203.

Levin SM, Baker DB, Landrigan PJ, Monaghan SV, Frumin E, Braithwaite M, Towne W. 1987 Testicular cancer in leather tanners exposed to dimethylformamide [letter]. *Lancet* 2:1153.

Lundberg I, Lundberg S, Kronevi T. 1981 Some observations on dimethylformamide hepatotoxicity. *Toxicology* 22:1-7.

Lyle WH, Spence TWM, McKinneley WM, Duckers K. 1979 Dimethylformamide and alcohol intolerance. *Br J Ind Med* 36:63-66.

Major J, Hudák A, Kiss G, Jakab MG, Szaniszló J, Náray M, Nagy I, Tampa A. 1998 Follow-up biological and genotoxicological monitoring of acrylonitrile- and dimethylformamide-exposed viscose rayon plant workers. *Environ Mol Mutagen* 31:301-310.

Massmann W. 1956 Toxicological investigations on dimethylformamide. *Br J Ind Med* 13:51-54.

Mráz J, Cross H, Gescher A, Threadgill MD, Flek J. 1989 Differences between rodents and humans in the metabolic toxification of *N,N*-dimethylformamide. *Toxicol Appl Pharmacol* 98:507-516.

Mráz J, Gescher A, Cross H, Shaw AJ, Flek J. 1991 New findings in the metabolism of *N,N*-dimethylformamide - consequences for evaluation of occupational risk. *Sci Total Environ* 101:131-134.

Mráz J, Nohova H. 1992a Percutaneous absorption of *N,N*-dimethylformamide in humans. *Int Arch Occup Environ Health* 64:79-83.

Mráz J, Nohova H. 1992b Absorption, metabolism and elimination of *N,N*-dimethylformamide in humans. *Int Arch Occup Environ Health* 64:85-92.

Mráz J, Jheeta P, Gescher A, Hyland R, Thummel K, Threadgill MD. 1993 Investigation of the mechanistic basis of *N,N*-dimethylformamide toxicity. Metabolism of *N,N*-dimethylformamide and its deutered isotopomers by cytochrome P450 E1. *Chem Res Toxicol* 6:197-207.

Mráz J, Turacek F. 1987 Identification of *N*-acetyl-*S*-(*n*-methylcarbamoyl) cysteine, a human metabolite of *N,N*-dimethylforamide and *N*-methylformamide. *J Chromatog* 414:399-404.

Nicolas F, Rodineau P, Rouzioux J-M, Tack I, Chabac S, Meram D. 1990 Fulminant hepatic failure in poisoning due to ingestion of T61, a veterinary euthanasia drug. *Crit Care Med* 18 (5):573-575.

Nomiyama T, Nakashima H, Sano Y, Chen LL, Tanaka S, Miyauchi H, Yamauchi T, Sakurai H, Omae K. 2001 Does the polymorphism of cytochrome P-450 2E1 affect the metabolism of *N,N*-dimethylformamide? Comparison of the half-lives of urinary *N*-methylformamide. *Arch Toxicol* 74:755-759.

Potter HP. 1973 Dimethylformamide-induced abdominal pain and liver injury. *Arch Environ Health* 27:340-341.

Redlich CA, Beckett WS, Sparer J, Barwick KW, Riely CA, Miller H, Sigal SL, Shalat SL, Cullen MR. 1988 Liver disease associated with occupational exposure to solvent dimethylformamide. *Ann Intern Med* 108:68-686.

Redlich CA, West AB, Fleming L, True LD, Cullen MR, Riely CA. 1990 Clinical and pathological characteristics of hepatotoxicity associated with occupational exposure to dimethylformamide. *Gastroenterology* 99:748-757.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Schottek W. 1972 [Towards the problem of hygiene standardization of chemicals having embryotoxic action.] In: Sanotsky IV, editor. [*Hygiene standardisation in study of remote effects of industrial substances*.] Moscow, Medizina (in Russian). Cited in IPCS. 1991 *Environmental Health Criteria 114. Dimethylformamide*. World Health Organization, International Programme on Chemical Safety, Geneva.

Trevisani F, Tamé MR, Bernardi M, Tovoli C, Gasbarrini A, Panarelli M, Gasbarrini G. 1993 Severe hepatic failure occurring with T61 ingestion in an attempted suicide. *Dig Dis Sci* 38 (4):752-756.

Van den Bulcke M, Rossle MT, Wijnants P, Buylaert W, Belpaire FM. 1994 Metabolism and hepatotoxicity of *N*,*N*-dimethylformamide, *N*-hydroxymethyl-*N*-methylformamide and *N*-methylformamide in the rat. *Arch Toxicol* 68:291-295.

Walrath J, Fayerweather WE, Gilby PG, Bell S. 1989 A case-control study of cancer among Du Pont employees with potential for exposure to dimethylformamide. *J Occup Med* 31 (5):432-438.

Wang J-D, Lai M-Y, Chen J-S, Lin J-M, Chiang J-R, Shiau S-J, Chang W-S. 1991 Dimethylformamide-induced liver damage among synthetic leather workers. *Arch Environ Health* 46 (3):161-166.

9 Ethanol

Jennifer Butler

SUMMARY

- Ethanol is a colourless liquid with a pleasant odour and a burning taste
- It is well absorbed orally and may be absorbed via the respiratory tract and dermally
- Dose-related CNS depression occurs, ranging from inebriation to anaesthesia, coma, respiratory failure and death
- Ethanol vapours can produce eye and upper respiratory tract irritation
- Ethanol is known to be co-factor in the development of certain cancers
- No reproductive toxicity has been reported following *occupational* exposure to ethanol by any route

DESCRIPTION

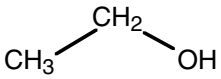
Synonyms

Absolute ethanol, alcohol, algrain, anhydrol, anhydrous alcohol, cologne spirit, dehydrated alcohol, denatured alcohol, ethyl alcohol, ethyl hydroxide, EtOH, fermentation alcohol, grain alcohol, methylcarbinol, molasses alcohol, potato alcohol, spirits of wine.

Identification numbers

CAS	64-17-5
UN	1170
RTECS	KQ 6300000
EINECS	2005786

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	C_2H_6O
molecular formula	
molecular mass	46.07
physical form	clear, colourless, mobile liquid with a pleasant odour
relative vapour density (air=1)	1.59
flash point (°C)	13
boiling point (°C)	78.5

autoignition temperature (°C)	363
refractive index	1.361
explosive limits in air (%v/v)	3.3-9.0

Odour threshold

84 ppm (Amoore and Hautala, 1983).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK and ACGIH): 1,000 ppm

Conversion factors

1 ppm = 1.88 mg/m^3

1 mg/l = 532 ppm

1 mg/m^3 = 0.532 ppm

Biomonitoring

A biological exposure index for ethanol has not been established by the ACGIH (ACGIH, 2000).

TOXICITY

Ethanol is a chemical with an enormous range of uses and applications in industry, cosmetics and food. Industrial ethanol is synthesised from ethylene, but beverage alcohol is derived mainly from the fermentation of carbohydrates and supply for this purpose is not augmented by industrial ethanol. Ethanol is used in the synthesis of a huge variety of organic compounds, and is second only to water as an industrial solvent.

There are very few reports of adverse effects following occupational ethanol exposure by any route. Although exposure in the occupational setting is common, ethanol is not considered to be of great importance as an industrial hazard. Reports of chronic exposures to ethanol in the workplace have not shown an association with adverse health effects. In addition, specific links to ethanol exposure are hard to establish owing to the wide exposure to ethanol in the general population. The majority of adverse effects are reported following recreational and chronic ingestion of ethanol. These effects are outside the remit of this chapter, and will not be discussed further. However, it is important to note that recreational ingestion of ethanol can have implications for the workplace; ethanol can interact and alter the metabolism of other chemicals used in the occupational setting (Juntunen, 1982).

Absorption

Ethanol is highly soluble in water and is rapidly absorbed via the gastrointestinal tract. Peak ethanol concentrations are seen after 30 to 120 minutes. The presence of food in the stomach or ingestion of a large quantity of ethanol may delay the absorption (Gibson *et al.,* 1985; Baselt, 2000).

Lester and Greenberg (1951) found that in human volunteers exposed to ethanol, 62% of ethanol in the inspired air was absorbed. In the same study the authors calculated the absorption via the respiratory tract that would be necessary to cause a continuous increase in blood ethanol concentration. They concluded that a worker exposed to the occupational standard (in this study: 1.8 mg/l ethanol (958 ppm)) would have to breathe at a rate greater than 117 l/min. As a ventilation rate of 30 l/min is associated with hard work, the

likelihood of systemic effects from airborne ethanol is extremely low. This conclusion is supported by a human volunteer study carried out by Campbell and Wilson (1986).

Subjects exposed to 6,900-8,500 ppm for three hours, achieved blood ethanol concentrations in the range 10-75 mg/l. Initially they complained of minimal irritation of the eyes and nose, which did not persist for more than 10 minutes. No systemic effects were reported (Lester and Greenberg, 1951).

The dermal toxicity of a solvent is determined by two factors (a) the rate of permeation of the solvent and (b) the toxicity of the permeating solvent. The permeability constant for ethanol for human skin has been calculated as 11.3 g/m^2/h (Ursin *et al.,* 1995). An average 70 kg, 175 cm tall man with a body surface area of 1.85 m^2 would absorb approximately 21 g of ethanol per hour. Systemic effects following dermal exposure to ethanol in the workplace are unlikely.

Distribution

As ethanol is water soluble, it does not bind to plasma proteins and is distributed in body water. It has a volume of distribution of 0.49-0.59 l/kg, which is roughly equivalent to total body water (Baselt, 2000).

Metabolism

Most (at least 90%) of the absorbed ethanol is oxidised in the liver to acetaldehyde by the action of alcohol dehydrogenase (ADH) and the transfer of hydrogen to nicotinamide adenine dinucleotide (NAD) which forms NADH. The NADH must then be re-oxidised back to NAD before the ethanol can be oxidised. The resulting increase in NADH affects the NADH/NAD ratio, which produces changes in the ratio of all NADH/NAD-dependent metabolites leading to altered biochemical pathways and a metabolic imbalance in the liver. This imbalance is easily established when ethanol is present as it is the preferred substrate for ADH, and can displace up to 90% of all other substances normally utilised by the liver and dominate liver metabolism (Hills and Venable, 1982).

The next stage of ethanol metabolism is the conversion of acetaldehyde to acetate by aldehyde dehydrogenase. Normally acetaldehyde concentrations in the blood are moderately elevated after the ingestion of ethanol.

The average adult metabolises 7-10 g ethanol per hour (Osborn, 1998), with blood ethanol concentrations falling at a rate of 120–250 mg/l/h. The rate is largely independent of the blood ethanol concentration (Gibson *et al.*, 1985; Baselt, 2000)

Elimination

A very small percentage of absorbed ethanol is excreted unchanged in the breath, urine, sweat and faeces, the remaining 90-95% is metabolised via liver enzymes to acetaldehyde and acetate (Hills and Venable, 1982; Baselt, 2000).

Nomiyama and Nomiyama (1974) studied the elimination of seven organic solvents via the respiratory tract. Ethanol was found to have a large rate constant as compared to other organic solvents in the study. This large rate constant was thought to reflect the rapid decrease in ethanol blood concentrations. The authors also calculated that the ratio of retained versus eliminated solvent was 20% for ethanol, which implies that the lungs are not a main route of elimination.

Blood ethanol concentrations fall at a rate of 120–250 mg/l/h. This rate is largely independent of the absolute blood ethanol concentration (Gibson *et al.*, 1985; Baselt, 2000).

Mode of action

Although the toxic effects of ethanol are well recognised, its mechanism of toxicity is not completely understood and has been subject to debate. Ethanol toxicity may be multi-factorial, affecting many processes but leading to one classic syndrome of intoxication. Ethanol depresses the CNS, possibly by dissolving in the lipid membrane of cells and disordering the lipid matrix (Goldstein, 1984). This membrane disordering effect is only measurable

at concentrations of ethanol well above the pharmacological range, and these changes can be produced by minor differences in temperature that produce no signs of intoxication. Therefore, the membrane fluidity mechanism of ethanol intoxication is rivalled by the interaction of ethanol with various proteins such as neurotransmitter-gated ion channels (Goldstein, 1984; Lovinger *et al.*, 1989; Osborn, 1994).

Owing to the similarity between the behavioural effects of ethanol and those of sedative hypnotic agents such as benzodiazepines and barbiturates, it has been suggested that ethanol acts by enhancing gamma aminobutyric acid (GABA)-nergic functions. Ethanol does augment GABA mediated synaptic transmission by interacting with $GABA_A$ receptors and their associated chloride channels (Charness *et al.*, 1989).

Metabolic interactions

Metabolic interactions involving ethanol can be divided into two groups:

Interference with ethanol metabolism

Ethanol is metabolised via liver ADH to acetaldehyde and then via aldehyde dehydrogenase (ALDH) to acetate. Interference with aldehyde dehydrogenase by various factors can lead to an accumulation of acetaldehyde which leads to tachycardia, hypertension and hyperventilation. In the workplace, agents such as amides (e.g., dimethylformamide), oximes, thiurams, carbamates and others, have proven to be effective inhibitors of aldehyde dehydrogenase (Hills and Venable, 1982).

Ethanol altering the metabolism of other workplace chemicals

Ethanol is an effective inducer of the enzyme systems cytochrome P450 CYP2E1 and microsomal mixed function oxidase system (Cornish *et al.,* 1977; ATSDR, 1997). As these enzymes are involved in the metabolism of several important and commonly used industrial chemicals, induction of these pathways can lead to increased toxicity of these agents.

Recreational ethanol use may also put workers more at risk from those solvents associated with long-term neurotoxicological effects (Juntunen, 1982). Geller *et al.* (1979) have suggested a mechanism of 'co-solvency', which may be particularly significant for nervous system tissue, where there are barriers between the circulation and the nerve cells. Membranes with a high fat content such a myelin, preferentially take up hydrophobic molecules, whereas penetration to the cytoplasm of the nerve cell bodies is facilitated by a hydrophilic molecule. Ethanol in combination with certain workplace solvents can have a synergistic effect.

- **Benzene**

  Ethanol enhances the metabolism and the toxicity of benzene in animals (Baarson *et al.*, 1982; Nakajima *et al.*, 1985). Increased severity of benzene induced anaemia, lymphopenia and bone marrow aplasia were observed in benzene treated mice given ethanol (Baarson *et al.*, 1982). Both ethanol and benzene are inducers of P450 CYP2E1. The enhancement of benzene induced haematotoxicity is of particular concern for benzene exposed workers who consume ethanol, since benzene can interfere with the elimination of ethanol and co-exposure may result in CNS depression (ATSDR, 1997).

- **Carbon disulphide**

  Carbon disulphide has been shown to inhibit the activity of the enzyme aldehyde dehydrogenase; thus concurrent exposure to carbon disulphide and ethanol can increase the blood acetaldehyde concentration. It is thought that workers exposed to carbon disulphide may experience a disulfiram-like reaction when subsequently exposed to ethanol (Rainey, 1977).

- **Carbon tetrachloride**

  The consumption of ethanol prior to or during exposure to carbon tetrachloride vapours may increase the toxicity of carbon tetrachloride (Cornish and Adefuin, 1966, 1967; Cornish *et al.,* 1977; Sturbelt *et*

al., 1978). Studies in mice have shown an increased incidence of hepatotoxic effects recorded in animals receiving ethanol prior to exposure to carbon tetrachloride, compared to those exposed to carbon tetrachloride alone (Cornish *et al.,* 1977). This additive effect may result from ethanol induced induction of P450 CYP2E1, the main enzyme involved in the metabolism of carbon tetrachloride (Cornish and Adefuin, 1967; Allis *et al*., 1996). Initially, there is a synergistic depression of the CNS. In some cases this is followed by pulmonary oedema, kidney and liver lesions. Sturbelt *et al.* (1978), extrapolating from studies on rats, concluded that the moderate amounts of ethanol commonly ingested by many individuals, may be enough to increase the hepatotoxic effects of halogenated hydrocarbons such as carbon tetrachloride. Consequently, chronic ethanol ingestion may put workers more at risk of toxicity if subsequently exposed to carbon tetrachloride. Manno *et al.* (1996) reported that in a group of workers exposed to a carbon tetrachloride containing fire extinguisher, signs of toxicity only developed in those with a previous history of high ethanol intake.

- **Chloroform**

  Animal studies have shown that ethanol potentiates the liver toxicity of chloroform (Klassen *et al*., 1966; Klassen *et al*., 1967). Another study found no potentiation but this may have been because the doses of ethanol used were too small (Cornish *et al*., 1977).

- **Dimethylformamide (DMF)**

  Ingestion of alcohol, even a small quantity, after exposure to DMF (by ingestion or inhalation) may cause flushing (always of the face and sometimes the neck, arms, hands and chest), nausea, dizziness and tightness of the chest (a disulfiram-like reaction). The effects may occur up to 4 days after exposure (Lyle *et al*., 1979) and usually resolve in about 2 hours (Chivers, 1978; Lyle *et al*., 1979). Flushing episodes may be associated with periorbital swelling, dysgeusia (impairment of sense of taste) and wheezing (Cox and Mustchin, 1991). In one study 19 of 102 workers (18.6%) were affected (Lyle *et al*., 1979).

  Ethanol is a competitive inhibitor of the enzyme involved in DMF metabolism (P450 CYP2E1) and exposure to DMF after ingestion of ethanol delays the appearance of the metabolites, *N*-(hydroxymethyl)-*N*-methylformamide and *N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine, in the urine (Mráz *et al*., 1992). The mechanism of action of the disulfiram-like reaction may be the inhibition of alcohol dehydrogenase, probably by a metabolite, resulting in increased concentrations of acetaldehyde after ingestion of ethanol (Cox and Mustchin, 1991). Animal studies have shown that DMF affects both ethanol and acetaldehyde concentrations (Hanasono *et al*., 1977).

- **Glycol ethers**

  As ethanol is the preferred substrate of alcohol dehydrogenase (ADH), it blocks the metabolism of glycol ethers, and the production of their toxic metabolites. As a result of this interaction, ethanol is used as an antidote in glycol ether poisoning. It is only useful in the immediate phase after exposure, as administration of ethanol is of very little benefit once the glycol ether has been metabolised.

- **Methanol**

  Methanol, like ethanol, is metabolised by ADH to formaldehyde, which is further metabolised to formic acid. These metabolites are highly toxic resulting in serious CNS and ocular toxicity (Bennett *et al.,* 1953). As ethanol is the preferred substrate of ADH, it can be used as a competitive inhibitor of methanol metabolism, allowing the methanol to be eliminated unchanged. Ethanol is widely used as the antidote of choice for methanol toxicity (Jacobsen and McMartin, 1997).

- **Methyl *n*-butyl ketone (MnBK)**

  Exposure to ethanol and methyl *n*-butyl ketone has been shown to have an additive acute CNS depressant effect in mice. This is probably due to competition between ethanol and 2-hexanol for alcohol dehydrogenase (Sharkawi *et al*., 1994).

- **Methylene chloride**

  Methylene chloride and ethanol appear to have an antagonistic effect rather than an additive or synergistic interaction following acute short-term exposures. However, animal studies have shown that following chronic exposure to both agents, ethanol appears to enhance the hepatotoxic effects of methylene chloride (Balmer *et al.,* 1976).

- **Methyl ethyl ketone (MEK)**

  Ethanol appears to inhibit microsomal oxidation of MEK. In a volunteer study, ingestion of ethanol and inhalation of MEK resulted in increased MEK concentrations in the blood, suggesting that ethanol inhibited MEK metabolism. When the ethanol was ingested before exposure to MEK the blood concentration of MEK remained high throughout the exposure. When ethanol was given after cessation of MEK exposure the same effect was seen in the elimination phase. The concentration of the metabolite 2-butanol was increased almost 10 times in the presence of ethanol. The higher blood concentration of MEK in the presence of ethanol was reflected in increased exhalation and urinary excretion of MEK. The elimination of MEK through the lungs was 8% in the presence of ethanol compared to 3% without ethanol. The elimination of MEK in the urine doubled with co-exposure to ethanol but was still less than 1% of the absorbed dose (Liira *et al*., 1990).

  Animal studies have also demonstrated that concomitant MEK exposure slows the metabolism of ethanol (Cunningham *et al*., 1989), and other studies have shown that MEK increases microsomal activity (Couri *et al*., 1977) and inhibits alcohol dehydrogenase (Cunningham *et al*., 1989).

- **Tetrachloroethylene**

  In a volunteer study, ethanol blood concentrations of 300-1,000 mg/l had no effect on tetrachloroethylene blood or breath concentrations during exposure to 100 ppm. There were no interactive effects of ethanol and tetrachloroethylene on neurobehavioural or neurophysiological tests (Hake and Stewart, 1977). However, in another study, exposure to tetrachloroethylene (25 ppm) and ethanol (doses of 0.75 and 1.5 ml 100°-proof vodka/kg body weight, to achieve blood concentrations of 400 and 800 mg/l) significantly increased blood tetrachloroethylene concentrations. In contrast, blood tetrachloroethylene concentrations were not increased at 100 ppm, as tetrachloroethylene metabolism was saturated at this dose. Performance in behavioural tests was unaffected by simultaneous exposure and it was concluded that low doses of ethanol in tetrachloroethylene exposed workers did not pose a hazard (Stewart *et al.,* 1977). Animal studies have shown that ethanol does not potentiate the liver toxicity of tetrachloroethylene (Cornish and Adefuin, 1966; Klassen *et al*., 1966).

- **Thiuram disulphides**

  A widely known interaction involving ethanol is the disulfiram reaction. It is observed in workers involved in the manufacture of chemical accelerators for the rubber vulcanisation process. Workers using tetramethyl thiuram monosulphide (disulfiram) developed flushing of the face and hands, rapid pulse, hypotension, difficulty in breathing and nausea after drinking beer (Hills and Venable, 1982). It is thought that the thiuram disulphides inhibit aldehyde dehydrogenase, allowing the accumulation of acetaldehyde.

- **Toluene**

  Ethanol also affects toluene metabolism. Even a low blood ethanol concentration can decrease toluene metabolism (Baelum *et al*., 1993). Inhalation of toluene (80 ppm for four hours) and ingestion of ethanol (1.5 ml/kg of vodka after three hours of toluene exposure) resulted in a 42.5% increase in the blood toluene concentration. However, workers who regularly drank ethanol had lower blood toluene concentrations than those who seldom drank. This suggests that toluene may induce liver enzymes (Waldron *et al*., 1983). In another survey, workers with the highest exposure to toluene and ethanol had lower liver enzyme concentrations compared to controls with high ethanol but low toluene exposure (Boewer *et al.,* 1988). The reason for this is unclear.

- **Trichloroethylene**

  Alcohol dehydrogenase is thought to be one of the main enzymes involved in the metabolism of trichloroethylene. Concurrent exposure to ethanol appears to greatly alter the metabolism of trichloroethylene, increasing the concentration of trichloroethylene, and its metabolites chloral hydrate and trichloroethanol. There may also be an increase in ethanol and acetaldehyde concentrations (Hills and Venable, 1982; Koppel *et al.,* 1988). Human volunteers who inhaled trichloroethylene at 50 ppm for six hours daily for five days and simultaneously ingested ethanol (blood concentration 600 mg/l) showed a 2.5-fold increase in blood trichloroethylene concentration (Müller *et al.,* 1975). As a result of this interaction there may be an additive and increased depressive effect on the CNS and mental function.

  Ingestion of ethanol before or during work (but not after work), produced increases in the blood trichloroethylene concentration and decreases in the urinary excretion rates of trichloroethylene metabolites. This effect lasted until the next day. These effects were smaller with increased exposure concentrations of trichloroethylene. Induction of trichloroethylene metabolism by consumption of ethanol the evening before work caused small changes in trichloroethylene metabolism at 50 ppm, but greater changes at 500 ppm (Sato *et al*., 1991).

  Ethanol may also enhance the hepatotoxic effects of trichloroethylene. Studies in rats found that ethanol potentiated trichloroethylene hepatotoxicity at trichloroethylene concentrations as low as 500 ppm (Nakajima *et al.,* 1988). In another animal study, rats receiving ethanol prior to trichloroethylene exposure had AST levels approximately 75% higher than trichloroethylene exposed animals without ethanol pre-treatment (Cornish and Adefuin, 1966).

  One effect of the combination of ethanol and trichloroethylene has been termed 'degreasers flush'. Workers exposed to 200 ppm of trichloroethylene daily for three weeks reported extreme dermal flushing and red blotches on the face, neck and shoulders after consumption of as little as one-half pint of beer (Stewart *et al.,* 1974).

- **Xylene**

  The metabolism of both ethanol and xylene involves the enzymes alcohol dehydrogenase and aldehyde dehydrogenase. In an experimental study of the metabolic interaction of ethanol and *m*-xylene, ingestion of a moderate dose of ethanol (800 mg/kg) before exposure to xylene (6 or 11.5 mmol/m^3 (145 or 280 ppm) for 4 hours) raised the blood xylene concentration by 1.5-2-fold. The urinary concentration of methylhippuric acid decreased by about 50%, whereas the excretion of the minor metabolite 2,4-xylenol was unchanged or increased. Some individuals had a transiently raised acetaldehyde concentration and this may be the cause of their dizziness and nausea (Riihimäki *et al*., 1982). Another volunteer study found that ethanol is only likely to affect *m*-xylene kinetics at high concentrations, i.e., above the occupational exposure limit. Ingestion of ethanol (the night before) and then inhalation of *m*-xylene at 400 ppm for two hours, resulted in lower *m*-xylene concentrations in blood and alveolar air compared to 100 ppm. Urinary excretion of *m*-methylhippuric acid was increased at 400 ppm. This study showed that ingestion of ethanol for 2 days prior to xylene exposure was enough to alter the kinetics of xylene, but only at a high xylene concentration (Tardif *et al*., 1994). Ethanol exposure has also been shown to modify xylene kinetics in animal studies (Savolainen *et al.,* 1978).

CASE REPORTS

There are no relevant case reports of occupational exposure to ethanol.

CLINICAL EFFECTS

Acute exposure

Inhalation

Human volunteers exposed to concentrations of 10-20 mg/l (approximately 5,000-10,000 ppm) complained of coughing, and 'smarting' of the eyes and nose. At 30 mg/l (15,960 ppm) there was continuous lacrimation, and marked coughing which could be tolerated but with much discomfort. The atmosphere became 'intolerable and suffocating' at 40 mg/l (21,280 ppm). With an increase in the ventilation rate, simulating work activity, the adverse effects became noticeable at lower concentrations (Lester and Greenberg, 1951).

Dermal

Human volunteers exposed to ethanol using a modified Draize test reported little or no irritation. A 21-day continuous patch test did not show any adverse effects until day 13. Erythema, and hardening were the worst effects reported over the 21-day test period (Phillips *et al.,* 1972). It may be concluded that no adverse effects are expected on acute dermal exposure to ethanol.

Eye

Splash contact with ethanol causes an immediate burning sensation with reflex closure of the eyelids. The eye may be painful but this is transient with a residual foreign body sensation. Ethanol contact may cause corneal injury and loosening of the epithelium, however, recovery is rapid and complete (Grant and Schuman, 1993).

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Ingestion

Ethanol is predominantly a CNS depressant. At first it depresses the areas of the brain associated with highly integrated functions, leading to animated behaviour and disinhibition (Osborn, 1998). As the blood ethanol concentration increases there is successive impairment of neural activity and sedation. At high blood concentrations there is loss of protective reflexes, coma, and risk of death from respiratory depression.

The clinical effects following exposure to ethanol correlate well with blood concentration as outlined below. However, as the toxicity of ethanol is also related to the route and rate of absorption and the tolerance of the individual, the blood ethanol concentration should be interpreted with care. Death has occurred at relatively low blood ethanol concentrations, following aspiration of stomach contents.

- Mild intoxication (associated with blood ethanol concentrations <1,500 mg/l): Altered mood, disinhibition and slight incoordination.

- Moderate intoxication (associated with blood ethanol concentrations 1,500-3,000 mg/l): Nystagmus, diplopia, dysarthria and ataxia. Involvement of the autonomic nervous system may also lead to hypotension and hypothermia. Hypoglycaemia and lactic acidosis can occur. There may be flushing, tachycardia, sweating and incontinence. Increasing CNS depression occurs with drowsiness, progressing to stupor and coma. Sedation with loss of the gag reflex leaves the patient at risk of aspirating the stomach contents. Rhabdomyolysis (skeletal muscle breakdown) has been reported in a patient immobilised by ethanol for four hours (Hewitt and Winter, 1995).

- Serious intoxication (associated with blood ethanol concentrations of >3,000 mg/l): Coma, convulsions, respiratory depression and cardiovascular collapse. Concentrations in the range 5-7 g/l are associated with fatalities, usually leading to death from respiratory depression (Gibson *et al.,* 1985; Charness *et al.*, 1989; Osborn, 1998; Bevan, 2001). A concentration as high as 11,270 mg/l has been survived with aggressive supportive management (Berild and Hasselbalch, 1981).

As a result of inter-individual variation, and differences in route of exposure, rate of absorption, degree of tolerance of the individual, and medical predispositions, the blood ethanol concentration may not always correlate with toxicity. A group of patients presenting to a detoxification centre with massively elevated ethanol levels (range 3,000-5,000 mg/l), were reported to be conscious and able to respond appropriately (Redmond, 1983; Redmond, 1986). However, these cases are considered exceptional. The fatal oral dose for ethanol is quoted at 5,000 mg/kg in a non-ethanol tolerant adult (Osborn, 1998).

Chronic exposure

Inhalation

Chronic inhalation of ethanol is not thought to be significant in the occupational setting.

Dermal

A 21-day continuous patch test on human volunteers did not show any adverse effects until day 13. Erythema, and hardening were the worst effects reported over the 21-day test period (Phillips *et al.,* 1972). Therefore, prolonged dermal contact with ethanol may cause erythema, drying and hardening of the skin.

Eye

No information available.

Ingestion

The effects of chronic ingestion of ethanol are widely known and well documented. Alcohol abuse may reslt in physical dependence, malnutrition, neurological effects including amnesia and dementia, cardiac myopathy, hepatoxicity, pancreatitis, gastrointestinal bleeding and oesophageal varices. Chronic ethanol ingestion is not an occupational route of exposure. For more information see Charness *et al.* (1989); Regan (1990); Weatherall *et al.* (1996) and Ashworth and Gerada (1997).

Immunotoxicity

Allergic responses to ethanol are rare. Przybilla and Ring (1983) report a case of anaphylaxis following exposure to beverage ethanol. Provocation tests determined that the patient was allergic to acetic acid, a metabolite of ethanol.

Carcinogenicity

Ingestion of beverage alcohol is associated with a multitude of cancers including those of the oral cavity, gastrointestinal tract, liver, pancreas and breast (reviewed in IARC, 1988 and Garro and Lieber, 1990). However, there is very little information or evidence of ethanol exposure in the workplace as a cause for cancer. Teta *et al.* (1992) studied a population of workers in an ethanol production facility. Although a small excess of some cancers of the larynx, buccal cavity and pharynx were noted, the strong-acid method of production may have been a contributing or even causative factor. Ethanol has been found to be a co-factor in the development of cancers (IARC, 1988); this may be of importance in workers exposed to other workplace carcinogens.

In various experiments in mice involving administration of carcinogens in an ethanol vehicle, ethanol enhanced the incidence of nasal cavity tumours induced by *N*-nitrosodimethylamine and enhanced the incidence of oesophageal and lung tumours in mice exposed to *N*-nitrosodiethylamine. There is also evidence for the carcinogenicity of acetaldehyde, the metabolite of ethanol (IARC, 1988; 1999).

Genotoxicity

Ethanol was not found to be mutagenic in various tests on *S. typhimurium* strains (reviewed in Obe and Anderson, 1987 and Bevan, 2001). Increased incidences of chromosomal aberrations, sister chromatid exchanges and aneuploidy (deviation in chromosome numbers) were found in the peripheral lymphocytes of patients with excessive ethanol ingestion (Obe and Anderson, 1987), but there is no information on occupational ethanol exposures.

Reproductive toxicity

Ingestion of excess alcohol during pregnancy leads to a range of congenital defects termed 'fetal alcohol syndrome'. This syndrome is associated with pre-natal exposure in alcoholic mothers. There have been no reports of this syndrome as a result of occupational and industrial exposures to ethanol by any route (Charness *et al.,* 1989; Bevan, 2001).

RISK GROUPS

The enzyme aldehyde dehydrogenase (ALDH) is involved in the metabolism of ethanol; it converts acetaldehyde to acetate. Genetic polymorphisms may result in deficiency of this enzyme in some populations (e.g., Japanese and Native Americans). Complete deficiency of this enzyme, which is also involved in ethanol metabolism, results in intolerance to alcohol. As a result acetaldehyde may accumulate, leading to toxicity (Harbison, 1998).

Recreational ingestion of ethanol may put workers at increased risk of adverse effects following ethanol interaction with other workplace agents, see 'Metabolic interactions'.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Gastric lavage is not necessary following ingestion of ethanol. Activated charcoal is not of benefit. If there has been any vomiting, coughing or wheezing in a patient with altered mental status, then the

patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive. See below for management of systemic effects.

Systemic effects

Treatment is essentially supportive. If the patient is symptomatic, determination of a blood ethanol concentration should be considered. It is important to ensure the patient is adequately hydrated. Hypotension usually responds to intravenous fluids. In severe cases the electrolytes, blood gases and blood sugar should be monitored. Hypoglycaemia should be corrected with intravenous glucose/dextrose. Acidosis usually responds to correction of the hypoglycaemia and hypovolaemia but additional sodium bicarbonate may be required. Convulsions usually respond to the correction of hypoglycaemia, but diazepam may be used if required. Ventilate for respiratory depression. Haemodialysis should only be considered in life threatening cases (e.g., if the blood ethanol concentration is >5,000 mg/l or the arterial pH is less than 7), however, in practice this is rarely used.

Antidotes

There is no specific antidote for ethanol.

Chronic exposure

Not applicable.

REFERENCES

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Allis JW, Brown BL, Simmons JE, Hatch GE, McDonald A, House DE. 1996 Methanol potentiation of carbon tetrachloride hepatotoxicity: the central role of cytochrome P450. *Toxicology* 112:131-140

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatiles for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290

Ashworth M, Gerada C. 1997 Addiction and dependence II: Alcohol. Br Med J 315: 358-60

ATSDR. 1997 *Toxicological Profile for Benzene (update)*. Agency for Toxic Substances and Disease Registry. US Department of Health and Human Services.

Baarson KA, Snyder CA, Green JD, Sellakumar A, Goldstein BD, Albert RE. 1982 The hematological effects of inhaled benzene on peripheral blood, bone marrow, and spleen cells are increased by ingested ethanol. *Toxicol Appl Pharmacol* 64:393-404.

Baelum J, Mølhave L, Hansen ST, Døssing M. 1993 Hepatic metabolism of toluene after gastrointestinal uptake in humans. *Scand J Work Environ Health* 19:55-62.

Balmer MF, Smith FA, Leach LJ, Yuile CL. 1976 Effects in the liver of methylene chloride inhaled alone and with ethyl alcohol. *Am Ind Hyg Assoc J* 37:345-352

Baselt RC. 2000 *Disposition of Toxic Drugs and Chemicals in Man,* fifth edition. Chemical Toxicology Institute, California.

Bennett IL, Cary FH, Mitchell GL, Cooper MN. 1953 Acute methyl alcohol poisoning: A review based on experiences in an outbreak of 323 cases. *Medicine* 32:431-463.

Berild D, Hasselbalch H. 1981 Survival after a blood alcohol of 1127 mg/dl. *Lancet* 2 (8242):363.

Bevan C. 2001 Monohydric alcohols – C_1-C_6. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Boewer C, Enderlain G, Wollgast U, Mawka S, Palowski H, Bliber R. 1988 Epidemiological study on the hepatotoxicity of occupational toluene exposure. *Int Arch Occup Environ Health* 60:181-186.

Campbell L, Wilson HK. 1986 Blood alcohol concentrations following the inhalation of ethanol vapour under controlled conditions. *J Forensic Sci Soc* 26:129-135.

Charness ME, Simon RP, Greenberg DA. 1989 Ethanol and the nervous system. *N Engl J Med* 321:442-454.

Chivers CP. 1978 Disulfiram effects from inhalation of dimethylformamide [letter]. *Lancet* 1:331.

Cornish HH, Adefuin J. 1966 Ethanol potentiation of halogenated aliphatic solvent toxicity. *Am Ind Hyg Assoc J* 27 (1):57-61.

Cornish HH, Adefuin J. 1967 Potentiation of carbon tetrachloride by aliphatic alcohols. *Arch Environ Health* 14:447-449

Cornish HH, Barth ML, Ling B. 1977 Influence of aliphatic alcohol on the hepatic response to halogenated olefins. *Environ Health Perspect* 21:149-152.

Couri D, Hetland LB, Abdel-Rahman MS, Weiss H. 1977 The influence of inhaled ketone solvent vapors on hepatic microsomal biotransformation activities. *Toxicol Appl Pharmacol* 41:285-289.

Cox NH, Mustchin CP. 1991 Prolonged spontaneous and alcohol-induced flushing due to the solvent dimethylformamide. *Contact Dermatitis* 24:69-70.

Cunningham J, Sharkawi M, Plaa GL. 1989 Pharmacological and metabolic interactions between ethanol and methyl *n*-butyl ketone, methyl isobutyl ketone, methyl ethyl ketone, or acetone in mice. *Fundam Appl Toxicol* 13:102-109.

Garro AJ, Leiber CS. 1990 Alcohol and cancer. *Ann Rev Pharmacol Toxicol* 30:219-249.

Geller I, Gause E, Kaplan H, Hartmann RJ. 1979 Effects of acetone, methyl ethyl ketone and methyl isobutyl ketone on a match-to-sample task in the baboon. *Pharmcol Biochem Behav* 11 (4):401-406.

Gibson PJ, Cant AJ, Mant TGK. 1985 Ethanol poisoning. *Acta Paediatr Scand* 74:977-978.

Goldstein DB. 1984 The effects of drugs on membrane fluidity. *Ann Rev Pharmacol Toxicol* 24:43-64.

Grant WM, Schuman JS. 1993 *Toxicology of the Eye,* fourth edition. Charles C Thomas, Springfield, Illinois.

Hake CL, Stewart RD. 1977 Human exposure to tetrachloroethylene: inhalation and skin contact. *Environ Health Perspect* 21:231-238.

Hanasono GK, Fuller RW, Broddle WD, Gibson WR. 1977 Studies on the effects of *N′N*-dimethylformamide on ethanol disposition and on monoamine oxidase activity in rats. *Toxicol Appl Pharmacol* 39:461-472.

Harbison RD. 1998 Alcohols and glycols. In: *Hamilton and Hardy's Industrial Toxicology*, fifth edition. Harbison RD (editor). Mosby, St Louis.

Hewitt SM, Winter RJ. 1995 Rhabdomyolysis following acute alcohol intoxication. *J Accid Emerg Med* 12:143-144.

Hills BW, Venable HL. 1982 The interaction of ethyl alcohol and industrial chemicals. *Am J Ind Med* 3:321-333.

IARC (International Agency for Research on Cancer). 1988 *Alcohol Drinking*. IARC Monograph 44.

IARC (International Agency for Research on Cancer). 1999 *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*. IARC Monograph 71.

Jacobsen D, McMartin KE. 1997 Antidotes for methanol and ethylene glycol poisoning. *Clin Toxicol* 35:127-143.

Juntunen J. 1982 Alcoholism in the occupational neurology: diagnostic difficulties with special reference to the neurological syndromes caused by organic solvents. *Acta Neurol Scand* 92 (Suppl):89-108.

Klassen CD, Plaa GL. 1966 Relative effects of various chlorinated hydrocarbons on liver and kidney function in mice. *Toxicol Appl Pharmacol* 9:139-151.

Klassen CD, Plaa GL. 1967 Relative effects of various chlorinated hydrocarbons on liver and kidney function in dogs. *Toxicol Appl Pharmacol* 10:119-131.

Koppel C, Lanz HJ, Ibe K. 1988 Acute trichloroethylene poisoning with additional ingestion of ethanol - concentrations of trichloroethylene and its metabolites during hyperventilation therapy. *Intensive Care Med* 14:74-76.

Lester D, Greenberg LA. 1951 The inhalation of ethyl alcohol by man. I. Industrial hygiene and medicolegal aspects. II. Individuals treated with tetraethylthiuram disulfide. *Q J Stud Alcohol* 12:167-178.

Liira J, Riihimäki V, Engström K. 1990 Effects of ethanol on the kinetics of methyl ethyl ketone in man. *Br J Ind Med* 47:325-330.

Lovinger DM, White G, Weight FF. 1989 Ethanol inhibits NMDA-activated ion current in hippocampal neurons. *Science* 243:1721.

Lyle WH, Spence TWM, McKinneley WM, Duckers K. 1979 Dimethylformamide and alcohol intolerance. *Br J Ind Med* 36:63-66.

Manno M, Rezzadore M, Grossi M, Sbrana C. 1996 Potentiation of occupational carbon tetrachloride toxicity by ethanol abuse. *Hum Exp Toxicol* 15:294-300.

Mráz J, Nohova H. 1992 Absorption, metabolism and elimination of *N*,*N*-dimethylformamide in humans. *Int Arch Occup Environ Health* 64:85-92.

Müller G, Spassowski M, Henschler D. 1975 Metabolism of trichloroethylene in man. III. Interaction of trichloroethylene and ethanol. *Arch Toxicol* 33:173-189.

Nakajima T, Okuyama O, Yonekura I, Sato A. 1985 Effects of ethanol and phenobarbital administration on the metabolism and toxicity of benzene. *Chem Biol Interact* 55:23-38.

Nakajima T, Okino T, Ohuyama S, Kaneko T, Yonekura I, Sato A. 1988 Ethanol-induced enhancement of trichloroethylene metabolism and hepatotoxicity: difference from the effect of phenobarbital. *Toxicol Appl Pharmacol* 94:227-237.

Nomiyama K, Nomiyama H. 1974 Respiratory elimination of organic solvents in man. Benzene, toluene, *n*-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. *Int Arch Arbeitsmed* 32:85-91.

Obe G, Anderson D. 1987 Genetic effects of ethanol. ICPEMC working paper No. 15/1. *Mutat Res* 186 177-200.

Osborn HH. 1998 Ethanol. In: *Goldfrank's Toxicologic Emergencies*, sixth edition. Goldfrank LR, Flomenblum NE, Lewin NA, Weisman RS, Howland MA, Hoffman RS (editors). Appleton and Lange, Stamford, Connecticut.

Phillips L II, Steinberg M, Maibach HI, Akers WA. 1972 A comparison of rabbit and human skin response to certain irritants. *Toxicol Appl Pharmacol* 21:369-382.

Przybilla B, Ring J. 1983 Anaphylaxis to ethanol and sensitisation to acetic acid [letter]. *Lancet* 1 (8322):483.

Rainey JM. 1977 Disulfiram toxicity and carbon disulphide toxicity. *Am J Psychiatry* 134 (4):371-378.

Redmond AD. 1983 Blood alcohol concentration and conscious level [letter]. *Alcohol Alcoholism* 18 (1):89-91.

Redmond AD. 1986 Central nervous system depression and high blood ethanol levels [letter]. *Lancet* 1 (8484):805.

Regan TJ. 1990 Alcohol and the cardiovascular system. J Am Med Assoc 264: 377-81

Riihimäki V, Savolainen K, Pfäffli P, Pekari K, Sippel HW, Laine A. 1982 Metabolic interaction between *m*-xylene and ethanol. *Arch Toxicol* 49:253-263.

Sato A, Endoh K, Kaneko T, Johanson G. 1991 Effects of consumption of ethanol on the biological monitoring of exposure to organic solvent vapours: a simulation study with trichloroethylene. *Br J Ind Med* 48:548-556.

Savolainen K, Vainio H, Helojoki M, Elovaara E. 1978 Biochemical and toxicological effects of short-term, intermittent *m*-xylene inhalation exposure and combined ethanol intake. *Arch Toxicol* 41:195-205.

Sharkawi M, Granvil C, Faci A, Plaa GL. 1994 Pharmacodynamic and metabolic interactions between ethanol and two industrial solvents (methyl *n*-butyl ketone and methyl isobutyl ketone) and the principal metabolite in mice. *Toxicology* 94:187-195.

Stewart RD, Hake CL, Peterson JE. 1974 "Degreaser's Flush": Dermal response to trichloroethylene and ethanol. *Arch Environ Health* 29:1-5.

Stewart RD, Hake CL, Wu A, Kalbfleisch J, Newton PE, Marlow SK, Vucicevic-Salama M. 1977 Effects of perchloroethylene/drug interaction on behavior and neurological function. Final report. *NIOSH PB83-17460*.

Sturbelt O, Obermeier F, Siegers CP, Völpel M. 1978 Increased carbon tetrachloride hepatotoxicity after low-level ethanol consumption. *Toxicology* 10:261-270.

Tardif R, Sato A, Laparé S, Brodeur J. 1994 Ethanol induced modification of *m*-xylene toxicokinetics in humans. *Occup Environ Med* 51:187-191.

Teta MJ, Perlman GD, Ott MG. 1992 Mortality study of ethanol and isopropanol production workers at two facilities. *Scand J Work Environ Health* 18:90-96.

Ursin C, Hansen CM, Van Dyk JW, Jensen PO, Christensen IJ, Ebbehoej J. 1995 Permeability of commercial solvents through living human skin. *Am Ind Hyg Assoc J* 56:651-660.

Waldron HA, Cherry N, Johnston JD. 1983 The effects of ethanol on blood toluene concentrations. *Int Arch Occup Environ Health* 51:365-369.

Weatherall DJ, Ledingham JGC, Warrell DA (editors). 1996 Alcohol and drug related problems. In: *Oxford Textbook of Medicine*, third edition, Volume 3. Oxford University Press, Oxford.

10 Ethyl *sec*-Amyl Ketone

Nicola Bates

SUMMARY

- There is limited information available on the toxicity of ethyl *sec*-amyl ketone; it is of low toxicity
- It is irritant to eyes and mucous membranes
- Ethyl *sec*-amyl ketone has not been evaluated for genotoxicity, carcinogenicity or reproductive toxicity

DESCRIPTION

Synonyms

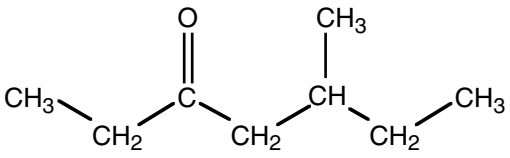
Ethyl amyl ketone, ethyl *sec*-amyl ketone, ethyl isoamyl ketone, 5-methyl-3-heptanone, methyl heptanone.

Ethyl sec-amyl ketone is not to be confused with ethyl *n*-amyl-ketone (3-octanone, ethyl pentyl ketone, ethyl amyl ketone, EAK, amyl ethyl ketone) CAS number 106-68-3.

Identification numbers

CAS	541-85-5
UN	2271
RTECS	MJ 7350000
EINECS	2087937

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	$C_8H_{16}O$
molecular formula	
molecular mass	128.2
physical form	clear liquid with a pungent fruity odour
relative vapour density (air=1)	data not available
flash point (closed cup °C)	43
boiling point (°C)	160.5
autoignition temperature (°C)	data not available
refractive index	1.4160
explosive limits (%v/v)	0.9

Odour threshold

6 ppm (Amoore and Hautala, 1983; Ruth, 1986).

Conversion factors

1 ppm = 5.24 mg/m^3
1 mg/m^3 = 0.19 ppm
1 mg/l = 190 ppm

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK and AICGH): 25 ppm (130 mg/m^3).

Biomonitoring

There is no biological exposure index for ethyl *sec*-amyl ketone.

TOXICITY

There is very limited information of the toxicity of ethyl *sec*-amyl ketone. This solvent has good warning properties and this should prevent over exposure (Topping *et al.,* 2001).

There is no information on the absorption, distribution, metabolism, elimination or mode of action of ethyl *sec*-amyl ketone in experimental animals or humans. There is no information on metabolic interactions of ethyl *sec*-amyl ketone.

CASE REPORTS

There are no well documented cases of occupational exposure to ethyl *sec*-amyl ketone.

CLINICAL EFFECTS

Acute exposure

Inhalation

Ethyl *sec*-amyl ketone is irritant to mucous membranes. Exposure to 25 ppm produced a strong odour and mild irritation of the nasal passages. Doses of 50-100 ppm caused headache, nausea and moderate irritation of the eyes, nose and throat (unpublished data, Shell Chemical Company).

Exposure to a high concentration of ethyl *sec*-amyl ketone causes CNS depression in animals (unpublished data, Shell Chemical Company) and is expected to have the same effect in humans (Hathaway *et al*., 1996).

Dermal

Ethyl *sec*-amyl ketone may cause moderate skin irritation (unpublished data, Shell Chemical Company).

Eye

Ethyl *sec*-amyl ketone has caused eye irritation and transient corneal damage in experimental animals (unpublished data, Shell Chemical Company).

Ingestion

A number of ketones are an aspiration hazard (Panson and Winek, 1980). There is no information on ethyl *sec*-amyl ketone but it should be considered a potential hazard. Aspiration into the lungs may cause chemical pneumonitis and pulmonary oedema.

Chronic exposure

Inhalation

There is no information on the effects of chronic exposure to ethyl *sec*-amyl ketone in humans. Rats given 82, 410 or 820 mg/kg orally 5 days/week for 13 weeks developed depressed activity and reduced weight gain in the latter two groups. Those receiving 820 mg/kg developed reduced hind limb grip strength. There was histological evidence of a γ-diketone neuropathy in the sciatic and tibial nerves at the highest doses, but the effect at 410 mg/kg was minimal (see Hexane, Chapter 12, for more information on γ-diketone neuropathy). There were no behavioural or neurotoxic effects at the lowest dose (Salocks *et al.,* 1990). There are no reports of neurotoxicity in humans.

Dermal

Chronic exposure to ethyl *sec*-amyl ketone on the skin may cause drying and cracking (Hathaway et al., 1996). Dermatitis may occur due to its defatting action (unpublished data, Shell Chemical Company).

Eye

No information available.

Ingestion

No information available.

Carcinogenicity

There is no information on the potential risk of carcinogenicity of ethyl *sec*-amyl ketone (Topping *et al.*, 2001). It has not been evaluated by the IARC.

Genotoxicity

There is no information on the potential risk of genotoxicity of ethyl *sec*-amyl ketone (Topping *et al.*, 2001).

Reproductive toxicity

There is no information on the reproductive toxicity of ethyl *sec*-amyl ketone in animals or humans (Topping *et al.*, 2001).

RISK GROUPS

None identified.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Ethyl *sec*-amyl ketone is of low acute toxicity and gastric decontamination is unlikely to be required unless a very large quantity has been ingested. However, because of the potential risk of aspiration a cuffed endotracheal tube must be used to protect the airway, since ethyl *sec*-amyl ketone may be an aspiration hazard. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive.

Antidote

There is no specific antidote for ethyl *sec*-amyl ketone.

Chronic exposure

Symptomatic and supportive care.

REFERENCES

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Hathaway GJ, Proctor NH, Hughes JP. 1996 *Proctor and Hughes' Chemical Hazards of the Workplace*, fourth edition. John Wiley & Sons Inc, New York.

Panson RD, Winek CL. 1980 Aspiration toxicity of ketones. *Clin Toxicol* 17 (2):271-317.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Salocks CB, Topping DC, Vlaovic, Burrell AD, O'Donoghue J. 1990 Subchronic neurotoxicity of 5-methyl-3-heptanone in rats: correlation of behavioural symptoms and neuropathology [abstract]. *Toxicologist* 10:121.

Shell Chemical Company, unpublished data. Houston, Texas. Cited in: Topping DC, Morgott DA, David RM, O'Donoghue JL. 2001 Ketones of six to thirteen carbons. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Topping DC, Morgott DA, O'Donoghue JL. 2001 Ketones of six to thirteen carbons. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

11 Glycol Ethers and Esters

Nicola Bates

SUMMARY

- The glycol ethers and esters are a large group of compounds which are similar in their toxicity
- They are absorbed orally, dermally and by inhalation
- The alkoxyacetic acid metabolites are responsible for toxicity not the parent compounds
- Glycol ethers cause neurotoxicity, renal and haematological (bone marrow depression) damage
- Effects usually resolve once removed from exposure
- There is limited information on the carcinogenicity and genotoxicity of glycol ethers
- There is a risk of adverse reproductive effects

DESCRIPTION

Synonyms

See **Table 11.1**.

Note: Owing to the relatively long chemical names of the glycol ethers they are usually referred to in an abbreviated form (see **Table 11.1**). For example, ethylene glycol (mono)ethyl ether is often referred to as EGEE. The ester, ethylene glycol monoethyl ether acetate is then referred to as EGEEA, EGEEAc or EEAc (for ethoxyethyl acetate). The former system is used here. The alkoxyacetic acid metabolites are also abbreviated, for example, methoxyacetic acid (MAA), ethoxyacetic acid (EEA) and butoxyacetic acid (BAA).

Identification numbers

See **Table 11.1**.

PHYSICAL AND CHEMICAL PROPERTIES

See **Table 11.2**.

Table 11.1 Some glycol ethers and their acetates (ECETOC, 1995)

Name	Synonyms	CAS	RTECS	UN	EINECS
ethylene glycol (mono) methyl ether	EGME, 2-methoxyethanol, methyl cellosolve	109-86-4	KL 5775000	1188	203-713-7
ethylene glycol (mono) methyl ether acetate	EGMEA, 2-methoxyethyl acetate, methyl cellosolve acetate	110-49-6	KL 5950000	1189	203-772-9
methoxyacetic acid	MAA	625-45-6	AI 8650000	-	210-894-6
ethylene glycol (mono) ethyl ether	EGEE, 2-ethoxyethanol	110-80-5	KK 8050000	1171	203-804-1
ethylene glycol (mono) ethyl ether acetate	EGEEA, 2-ethoxyethyl acetate	111-15-9	KK 8225000	1172	203-839-2
ethylene glycol (mono) *n*-propyl ether	EGnPE, *n*-propylethanol	2807-30-9	KM 2800000	-	220-548-6
ethylene glycol (mono) *n*-propyl ether acetate	EGnPEA, 2-propoxyethyl acetate	20706-25-6	AJ 3345000	-	-
ethylene glycol (mono) iso-propyl ether	EGiPE, 2-isopropoxyethanol	109-59-1	KL 5075000	-	203-685-6
ethylene glycol (mono) *n*-butyl ether	EGBE, butyl cellusolve, 2-butoxyethanol, butyl glycol	111-76-2	KJ 8575000	2369	203-905-0
ethylene glycol *n*-butyl ether acetate	EGBEA, 2-*n*-butoxyethyl acetate	112-07-2	KJ 8925000	-	203-933-3
ethylene glycol (mono) phenyl ether	EGPhE, 2-phenoxyethanol	122-99-6	KM 0350000	-	204-589-7
ethylene glycol dimethyl ether	EGDME, 1,2-dimethoxyethane	110-71-4	KI 1451000	2252	203-794-9
ethylene glycol diethyl ether	EGDEE, 1,2-diethoxyethanol	629-14-1	KI 1225000	1153	211-076-1
diethylene glycol (mono) methyl ether	DEGME, 2-(2-methoxyethoxy)ethanol	111-77-3	KL 6125000	-	203-906-6
diethylene glycol (mono) ethyl ether	DEGEE, 2-(2-ethoxyethoxy)ethanol	111-90-0	KK 8750000	-	203-919-7
diethylene glycol (mono) ethyl ether acetate	DEGEEA, 2-(2-ethoxyethoxy)ethanol acetate	112-15-2	KK 8925000	-	203-940-1
diethylene glycol (mono) butyl ether	DEGBE, 2-(2-*n*-butoxyethoxy)ethanol	112-34-5	KJ 9100000	-	203-961-6
diethylene glycol butyl ether acetate	DEGBEA, 2-(2-butoxyethoxy)ethyl acetate	124-17-4	KJ 9275000	-	204-685-9
diethylene glycol dimethyl ether	DEGDME, bis (2-methoxyethyl)ether	111-96-6	KN 3339000	-	203-924-4
diethylene glycol diethyl ether	DEGDEE, bis (2-ethoxyethyl)ether	112-36-7	KN 3160000	-	203-963-7
triethylene glycol (mono) methyl ether	TEGME, 2-[2-(methoxyethoxy)ethoxy]ethanol	112-35-6	KL 6390000	-	203-962-1
triethylene glycol (mono) ethyl ether	TEGEE, 2-[2-(2-ethoxyethoxy)ethoxy)ethanol	112-50-5	KK 8950000	-	203-978-9
triethylene glycol (mono) *n*-butyl ether	TEGBE, 2-[2-(2-butoxyethoxy)ethoxy]ethanol	143-22-6	KJ 9450000	-	205-592-6

Table 11.1 Some glycol ethers and their acetates (ECETOC, 1995) *continued*

Name	Synonyms	CAS	RTECS	UN	EINECS
triethylene glycol dimethyl ether	TEGDME, 2,5,8,11-tetraoxadodecane	112-49-2	XF 0665000	-	203-977-3
2-propylene glycol 1-methyl ether	2PG1ME, 1-methoxy-2-propanol	107-98-2	UB 7700000	3092	203-539-1
2-propylene glycol 1-methyl ether 2-acetate	2PG1MEA, 1-methoxy-2-acetoxypropane	108-65-6	AI 8925000	-	203-603-9
2-propylene glycol 1-ethyl ether	2PG1EE, 1-ethoxy-2-propanol	1569-02-4	UB 5250000	-	216-374-5
2-propylene glycol 1-ethyl ether 2-acetate	2PG1EEA, 1-ethoxy-2-acetoxypropanol	54839-24-6	-	-	259-370-9
2-propylene glycol 1-*n*-butyl ether	2PG1BE, 1-butoxy-2-propanol	5131-66-8	UA 7700000	-	225-878-4
2-propylene glycol 1-phenyl ether	2PG1PhE, 1-phenoxy-2-propanol	770-35-4	UB 8886500	-	212-222-7
1-propylene glycol 2-methyl ether	1PG2ME, 2-methoxypropanol-1	1589-47-5	UB 7645000	-	216-455-5
1-propylene glycol 2-methyl ether 1-acetate	1PG2MEA, 2-methoxy-1-acetoxypropane	70657-70-4	AI 8967450	-	274-724-2
dipropylene glycol (mono)methyl ether	DPGME	34590-94-8	JM 1575000	-	252-104-2
dipropylene glycol (mono)ethyl ether	DPGEE, 2-ethoxymethoxyethoxypropanol	15764-24-6	JM 1225000	-	-
tripropylene glycol (mono)methyl ether	TPGME	25498-49-1	UB 8070000	-	247-045-4

Table 11.2 Physical and chemical properties of the glycol ethers and their esters (ECETOC, 1995)

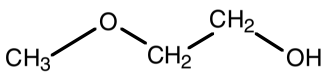
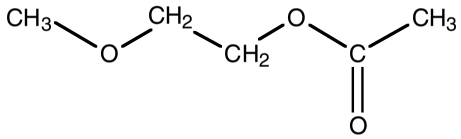
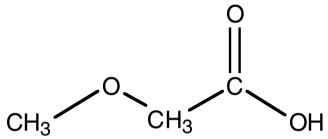
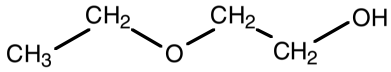
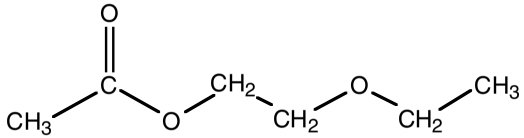
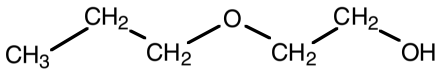
Glycol ether	Molecular formula	Structural formula	Molecular mass	Melting point (°C)	Boiling point (°C at 1013 hPa)	Vapour pressure (hPa @ 20 °C (25 °C))
EGME	$C_3H_8O_2$		76.09	-85.1	124	6.2 (9.7)
EGMEA	$C_5H_{10}O_3$		118.1	-65	145	9.3
MAA	$C_3H_6O_3$		90.09	approx. 7	202	1.8
EGEE	$C_4H_{10}O_2$		90.1	<-80	135-137	5
EGEEA	$C_6H_{12}O_3$		132.2	-62	153-159	2
EGnPE	$C_5H_{12}O_2$		104.2	approx. -60	150-152	1.3

Table 11.2 Physical and chemical properties of the glycol ethers and their esters (ECETOC, 1995) *continued*

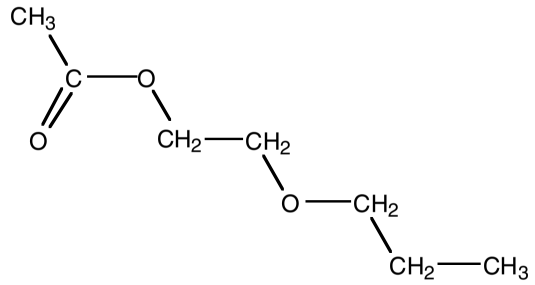
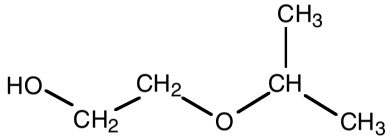
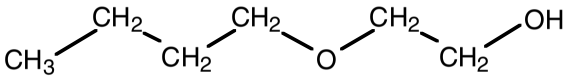
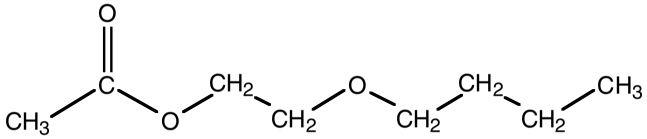
Glycol ether	Molecular formula	Structural formula	Molecular mass	Melting point (°C)	Boiling point (°C at 1013 hPa)	Vapour pressure (hPa @ 20 °C (25 °C))
EGnPEA	$C_7H_{14}O_3$		146.2	nk	173	0.67
EGiPE	$C_5H_{12}0_2$		104.2	< -60	144	(6.9)
EGBE	$C_6H_{14}O_2$		118.2	-77	171	(1.17)
EGBEA	$C_8H_{16}O_3$		160.2	-64	192	0.4

Table 11.2 Physical and chemical properties of the glycol ethers and their esters (ECETOC, 1995) *continued*

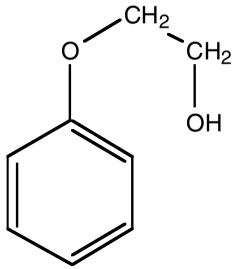
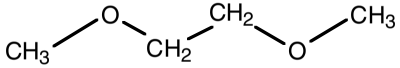
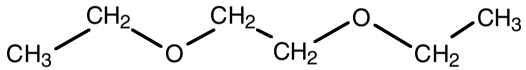
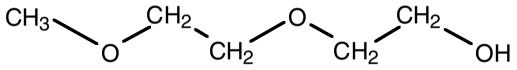
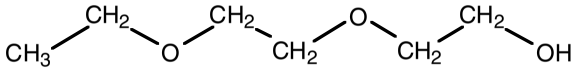
Glycol ether	Molecular formula	Structural formula	Molecular mass	Melting point (°C)	Boiling point (°C at 1013 hPa)	Vapour pressure (hPa @ 20 °C (25 °C))
EGPhE	$C_8H_{10}O_2$		138.2	13	246	0.04
EGDME	$C_4H_{10}O_2$		90.1	-58 to -71	84	64
EGDEE	$C_6H_{14}O_2$		118.2	-74	121	12.5 (16.5)
DEGME	$C_5H_{12}O_3$		120.1	-85	190-196	(0.24)
DEGEE	$C_6H_{14}O_3$		134.2	-76	197-205	(0.19)

Table 11.2 Physical and chemical properties of the glycol ethers and their esters (ECETOC, 1995) *continued*

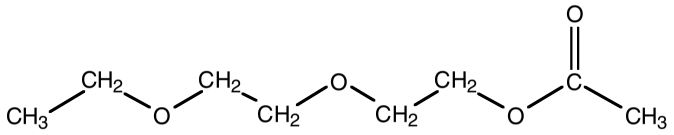
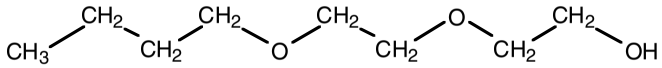
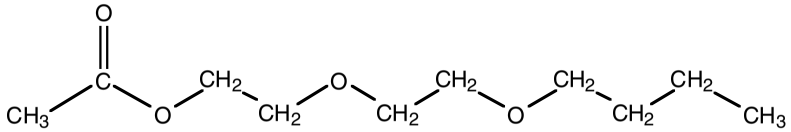
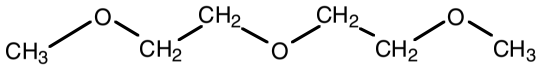
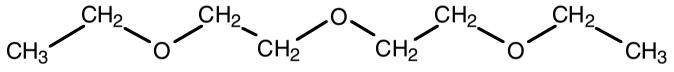
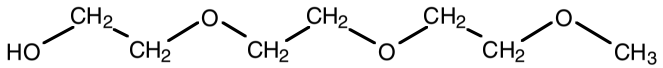
Glycol ether	Molecular formula	Structural formula	Molecular mass	Melting point (°C)	Boiling point (°C at 1013 hPa)	Vapour pressure (hPa @ 20 °C (25 °C))
DEGEEA	$C_8H_{15}O_4$		176.2	-25	210-220	0.13
DEGBE	$C_8H_{18}O_3$		162.2	-68	230	(0.057)
DEGBEA	$C_{10}H_{20}O_4$		204.3	nk	247	<0.013
DEGDME	$C_6H_{14}O_3$		134.2	-68	162	2.27
DEGDEE	$C_8H_{18}O_3$		162.2	nk	189	(0.67)
TEGME	$C_7H_{16}O_4$		164.2	-44	249.2	<0.013

Table 11.2 Physical and chemical properties of the glycol ethers and their esters (ECETOC, 1995) *continued*

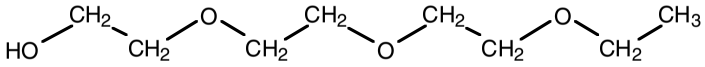
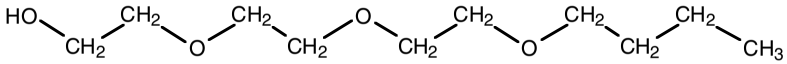
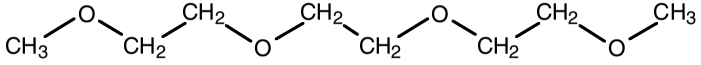
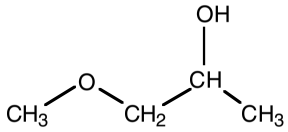
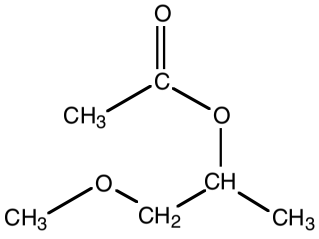
Glycol ether	Molecular formula	Structural formula	Molecular mass	Melting point (°C)	Boiling point (°C at 1013 hPa)	Vapour pressure (hPa @ 20 °C (25 °C))
TEGEE	$C_8H_{18}O_4$		178.2	-30	235-280	<0.01
TEGBE	$C_{10}H_{22}O_4$		206.3	-35	255-295	<0.01
TEGDME	$C_8H_{18}O_4$		178.2	-40	210-230	1.2
2PG1ME	$C_4H_{10}O_2$		90.1	-96	120	12
2PG1MEA	$C_6H_{12}O_3$		132.2	< -67	145.8	4.9

Table 11.2 Physical and chemical properties of the glycol ethers and their esters (ECETOC, 1995) *continued*

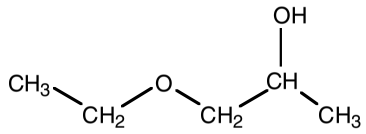
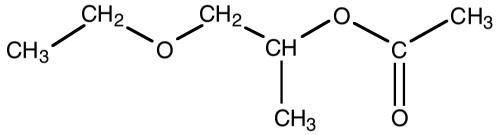
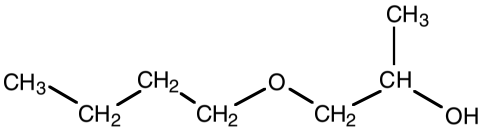
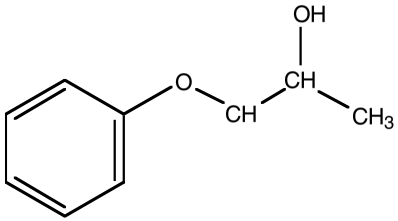
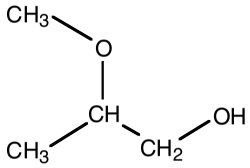
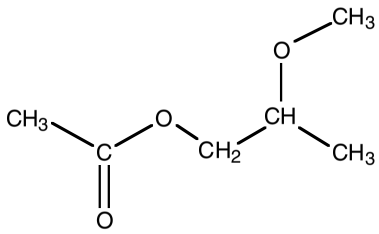
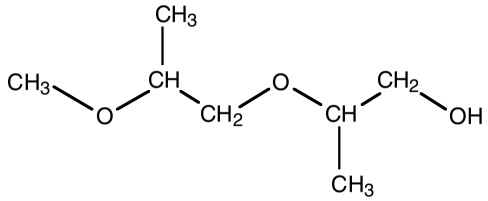
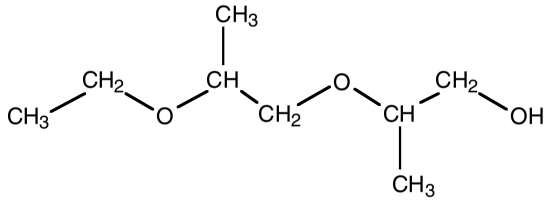
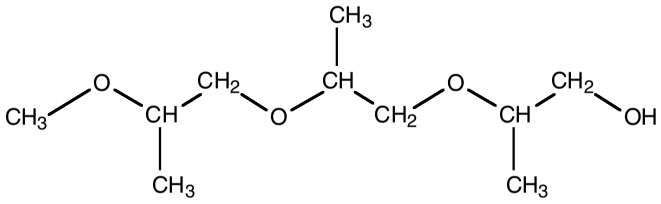
Glycol ether	Molecular formula	Structural formula	Molecular mass	Melting point (°C)	Boiling point (°C at 1013 hPa)	Vapour pressure (hPa @ 20 °C (25 °C))
2PG1EE	$C_5H_{12}O_2$		104.2	-90	132	10
2PG1EEA	$C_7H_{14}O_3$		146.2	-89	158	2.026
2PG1BE	$C_7H_{16}O_2$		132.2	< -75	170.2	0.8
2PG1PhE	$C_9H_{12}O_2$		152.2	approx. 13	242.7	(0.05)
1PG2ME	$C_4H_{10}O_2$		90.1	< -50	130-133	5.5

Table 11.2 Physical and chemical properties of the glycol ethers and their esters (ECETOC, 1995) *continued*

Glycol ether	Molecular formula	Structural formula	Molecular mass	Melting point (°C)	Boiling point (°C at 1013 hPa)	Vapour pressure (hPa @ 20 °C (25 °C))
1PG2MEA	$C_6H_{12}O_3$		132.2	approx. <20	150-151	2.9
DPGME	$C_7H_{16}O_3$		148.2	-83	184-197	1
DPGEE	$C_8H_{18}O_3$		162.2	< -50	188.3	56.67
TPGME	$C_{10}H_{22}O_4$		206.3	-78	242.2	0.03

Odour thresholds

See **Table 11.3**

Table 11.3 Odour thresholds of glycol ethers (Ruth, 1986)	
Glycol ether	**Odour threshold**
DPGME	34-968 ppm
EGME	0.9-93 ppm
EGMEA	0.33-49 ppm
EGBE	0.1-59 ppm
EGBEA	0.12-0.20 ppm

OCCUPATIONAL EXPOSURE

Exposure limits

See **Table 11.4.**

Table 11.4 Occupational exposure limits (ECETOC, 1995)				
Glycol ether	**TWA (UK)**		**TWA (ACGIH)**	
	ppm	**mg/m³**	**ppm**	**mg/m³**
EGME	5	16	5	16
EGMEA	5	25	5	24
EGEE	10	37	5	18
EGEEA	10	55	5	27
EGiPE	-	-	25	106
EGBE	25	120	20	98
EGBEA	25	120	-	-
2PG1ME	100	360	100	360
DPGME	-	-	100	600

Conversion factors

See **Table 11.5.**

Biomonitoring

Urinary concentrations of the alkoxyacetic acid metabolites are used for biomonitoring. See **Table 11.6.**

Table 11.5 Conversion factors for glycol ethers and their acetates at 20 °C and 1013 hPa (except those marked [a] for which 25 °C applies) (ECETOC, 1995)

Glycol ether	1 ppm equals (in mg/m³)	1 mg/m³ equals (in ppm)
EGME	3.11	0.322
EGMEA	4.90	0.2
MAA	1.74	0.58
EGEE	3.73	0.27
EGEEA	5.47	0.183
EGnPE[a]	4.25	0.24
EGnPEA[a]	5.98	0.17
EGiPE	4.25	0.24
EGBE	4.91	0.204
EGBEA	6.65	0.15
EGPhE	5.74	0.17
EGDME[a]	3.74	0.267
EGDEE[a]	4.83	0.21
DEGME	4.99	0.20
DEGEE	5.57	0.179
DEGEEA	7.3	0.14
DEGBE	6.75	0.15
DEGBEA	8.48	0.12
DEGDME	5.57	0.18
DEGDEE[a]	6.64	0.15
TEGME	6.72	0.15
TEGEE	8.66	0.12
TEGBE	10	0.1
TEGDME	7.3	0.14
2PG1ME	3.75	0.267
2PG1MEA	5.4	0.185
2PG1EE	4.25	0.235
2PG1EEA	6.09	0.16
2PG1BE	5.49	0.182
2PG1PhE	6.33	0.158
1PG2ME	3.74	0.267
1PG2MEA	5.49	0.182
DPGME	6.2	0.016
DPGEE	4.25	0.235
TPGME	8.62	0.116

Table 11.6 Biological exposure indices (ACGIH, 2000)			
Glycol ether	**Determinant**	**Sampling time**	**BEI**
EGEE	EAA	end of shift at end of working week	100 mg/g creatinine
EGEEA	EAA	end of shift at end of working week	100 mg/g creatinine
EGME	MAA	end of shift at end of working week	Non-quantitative. Biological monitoring should be considered, but a specific BEI could not be determined due to insufficient data.
EGMEA	MAA	end of shift at end of working week	

TOXICITY

Most information on the toxicity of glycol ethers concerns EGME, EGEE and EGBE. There is only limited information on the other glycol ethers and even less on their acetates. However, it is clear that these compounds, although apparently similar in the effects they may cause, differ in the severity. Generally:

- The diethylene glycol ethers are less toxic than the ethylene glycol ethers (Harbison, 1998). They are less irritant to the skin with less percutaneous toxicity than the ethylene glycol ethers (Ballantyne and Myers, 1987).
- The triethylene glycols are less toxic than the diethylene glycols (NIOSH, 1980).
- The toxicity of the glycol ether acetates is similar to the parent compound as the ester linkage is rapidly hydrolysed.
- Some glycol ethers (e.g., propylene glycol monomethyl ether (PGME) and its acetate) appear to be metabolised differently compared to ethylene glycol ethers and, since it is the metabolites which are responsible for toxicity, may, as a result, be less toxic than the ethylene glycol ethers (Miller *et al*., 1981; 1983; 1984a; 1984b).

Toxicity from exposure to glycol ethers was first observed in the 1930s when EGME was used for the manufacture of stiffened or 'fused' shirt collars (Donley, 1936; Greenberg *et al*., 1938; Parsons and Parsons, 1938). The reports described workers with encephalopathy and bone marrow depression.

Absorption

Glycol ethers are readily absorbed by inhalation, ingestion and dermally (Browning and Curry, 1994). The rate of dermal absorption is inversely proportional to the molecular mass of the glycol ether. Generally, dermal absorption decreases with increasing molecular mass or decreasing volatility. This is true for both the ethylene glycol and diethylene glycol series. EGME is absorbed three times more readily than EGEE and EGEEA and ten times more readily than EGBE (Dugard *et al*., 1984). An *in vitro* study of isolated human epidermis demonstrated that rates of dermal absorption were slower for the diethylene glycols compared to their ethylene glycol equivalents (Dugard *et al*., 1984). In another study using several glycol ethers (EGEE, PGME, PGMEAc, 2PG1BE, EGDME, EGDEE, DEGDME) all were rapidly absorbed with a lag time of less than 1 hour and in most cases less than 30 minutes (Larese *et al.,* 1999). Toxicity following skin absorption has occurred in animals (Carpenter *et al*., 1956; Duprat and Gradiski, 1979) and humans (Ohi and Wegman, 1978; Morton, 1990).

In a volunteer study comparing exposure by mouth (via a respirator) and dermal absorption (while only wearing shorts and breathing air through a respirator) it was found that the average blood concentrations of EGBE were 3-4 times higher after dermal exposure. The results of this study suggested that absorption through the skin may account for about 75% of the total uptake of EGBE (Johanson and Boman, 1991). However, this measure of dermal uptake is thought to be an overestimate. The sample collection technique used in this study probably affected the results; local absorption of EGBE near the sampling site may have lead to a falsely high blood concentration. A more recent study using a different method has shown that dermal absorption accounts for no more than 15-27% of the total uptake of EGBE in humans (Corley *et al*., 1997).

During exposure of only 25% of the body surface (more realistic in terms of the working environment), dermal absorption only accounted for 4.4-48.4% of the total (Corley *et al*., 1997). In another study it was estimated that when the whole body surface is exposed to vapour, dermal uptake could account for 55% of the total uptake of EGME and 42% of EGEE (Kežeć *et al*., 1997). Rates of absorption of EGBE in a volunteer study were between 7 and 96 nmol/min/cm^2 (Johanson *et al*., 1988).

The rate of absorption via the lungs depends on the concentration of the glycol ether and the respiration rate. In human volunteers, 76% of the inhaled dose of EGME was absorbed (Groeseneken *et al*., 1989). This figure was 64% for EGEE when at rest but the rate of uptake increased as the exposure concentration or the ventilation rate increased (Groeseneken *et al*., 1986a). Pulmonary uptake of EGBE in volunteers was 10 μmol/min or 57% of the inspired amount (Johanson *et al*., 1986).

It should be noted however, that many of these studies on rates of absorption have used almost pure glycol ethers. This does not reflect the situation in industry where solvent mixtures are used. The effect on absorption rates of other components in industrial mixtures is unknown. In an experimental study, the use of acetone as a vehicle decreased the lag time and increased the percutaneous absorption of the glycol ethers tested (Larese *et al.,* 1999).

Distribution

The distribution of glycol ethers has not been well studied in humans (Browning and Curry, 1994). The volume of distribution of EGBE was 0.7 l/kg in individuals exposed to 20 ppm for 2 hours (Johanson *et al*., 1986).

Distribution has been measured in animals given radiolabelled EGME and PGME. At 48 hours after ingestion of EGME the blood had the greatest quantity per gram of tissue. There was less in the target organs of toxicity (the testes, thymus and spleen). In the case of PGME the liver had the greatest quantity per gram of tissue, however rats exposed to PGME had increased liver weight so the significance of a high concentration of radioactivity in the liver is unknown (Miller *et al*, 1983; Miller *et al*, 1984b). Following ingestion of PGMEA the liver had the highest dose per gram of tissue at 48 hours (Miller *et al*, 1984a).

Metabolism

Monoalkyl ethers are metabolised via alcohol dehydrogenase to their respective alkoxyacetic acids, e.g., methoxyacetic acid (MAA) from EGME, ethoxyacetic acid (EAA) from EGEE and butoxyacetic acid (BAA) from EGBE. Glycol ether acetates are believed to be metabolised by the same mechanisms as the glycol ethers after hydrolysis of the ester moiety (Groeseneken *et al*., 1987). Treatment with alcohol dehydrogenase inhibitors, such as pyrazole, blocks conversion of the glycol ether to the alkoxyacetic acid metabolite (Moss *et al*., 1985; Ghanayem *et al*., 1987).

Although the majority of the work on urinary metabolites has been carried out in exposed workers, the same compounds (i.e., the alkoxyacetic acids) have also been found in the urine (Rambourg-Schepens *et al.,* 1988; Gijsenbergh *et al*., 1989) and blood (Gualtieri *et al*., 1995) of individuals who have ingested large quantities of glycol ether-containing products.

There may be a minor metabolic pathway (Laitinen *et al*., 1996) through ethylene glycol, glycoaldehyde, glycolic acid and glyoxylic acid to oxalic acid, although this has been disputed (Browning and Curry, 1994). Oxalate crystals have been found in the urine in some cases of acute glycol ether ingestion (Nitter-Hauge, 1970; Rambourg-Schepens *et al*., 1988) and in the kidneys at biopsy (Nisse *et al*., 1998). However, oxalate has not been detected in most cases of glycol ether poisoning (Nitter-Hauge, 1970; Gijsenbergh *et al*., 1989; McKinney *et al*., 2000), nor has it been demonstrated in animal studies (Truhaut *et al.,*1979). Methanol is another possible product of metabolism if there is cleavage of the ether linkage (Browning and Curry, 1994). Ethylene glycol and methanol are not usually detected after ingestion of glycol ether (Young and Woolner, 1946; Nitter-Hauge, 1970; Gualtieri *et al*., 1995; Wermuth and Furbee, 1997; McKinney *et al*., 2000). However, there are a small number of cases where ethylene glycol has been detected following ingestion of a large quantity of a glycol ether. The ethylene glycol concentrations reported were 1.1 g/l (Litowitz *et al*., 1991) and 0.31 g/l (Nisse *et al*., 1998). Serious toxicity may occur with ethylene glycol concentrations above 200 mg/l. The primary metabolic pathway (to alkoxyacetic acids) may become saturated following ingestion of a large quantity of glycol ether (Rambourg-Schepens *et al*., 1988) and this may account for the presence of ethylene glycol and oxalate in some cases.

Elimination

In human volunteers less than 0.4% of absorbed EGEE was excreted via the lungs (Groeseneken *et al.*, 1986a). Less than 0.03% of inhaled EGBE is excreted unchanged in the urine (Johanson *et al.*, 1986). Urinary excretion of the alkoxyacetic acid metabolites of glycol ethers is very variable (Johanson *et al.*, 1986; Johanson and Johnsson, 1991).

EAA is detected in urine within one hour of exposure to EGEE. The rate of excretion of EAA increased to a maximum 3-4 hours after cessation of exposure in human volunteers. The excretion rate of EAA had not returned to pre-exposure levels after 42 hours. On average 23% of absorbed EGEE was excreted as EAA in 42 hours (Groeseneken *et al.*, 1986b). Similarly, 22% of absorbed EGEEA was excreted as EAA in 42 hours (Groeseneken *et al.*, 1987). In another study only 12% of a dose of EGME and 14% of a dose of EGEE were excreted as MAA and EAA within 48 hours (Kežeć *et al.*, 1997). The total amount of MAA excreted was estimated (by extrapolation) to be 85.8% of an inhaled dose of EGME (Groeseneken *et al.*, 1989). After inhalation of EGBE, 17-55% was excreted in the urine as BAA (Johanson *et al.*, 1986).

The elimination half-life of the alkoxyacetic acid metabolites increases as the length of the alkyl chain decreases; so the elimination half-life increases in the order of butoxyacetic acid, ethoxyacetic acid and methoxyacetic acid. See **Table 11.7**.

Table 11.7 Elimination half-lives of glycol ethers and their metabolites in humans

Exposed to:	Route	Chemical measured	Mean urinary half-life (range)	Mean blood half-life (range)	Reference
EGBE	dermal	EGBE	-	0.66 hours (0.6-0.72)	Corley *et al.*, 1997
EGBE	inhalation	EGBE	-	0.66 hours	Johanson and Johnsson, 1991
EGBE	inhalation	EGBE	-	39.5 minutes (21.2-63.4)	Johanson *et al.*, 1986
EGBE	dermal	EGBE	-	36 minutes (19-53)	Johanson and Boman, 1991
EGBE	ingestion	EGBE	-	210 minutes *	Gijsenbergh *et al.*, 1989
EGBE	dermal	BAA	-	3.27 hours (2.35-4.38)	Corley *et al.*, 1997
EGBE	inhalation	BAA	-	4.3 hours	Johanson and Johnsson, 1991
EGME	inhalation	MAA	77 hours (66.1-89.7)	-	Groeseneken *et al.*, 1989
EGME	inhalation or dermal	MAA	72 hours	-	*Kězić et al.*, 1997
EGEE	inhalation or dermal	EAA	42 hours	-	*Kězić et al.*, 1997
EGEE	inhalation	EAA	21-24 hours	-	Groeseneken *et al.*, 1986b
EGEEA	inhalation	EAA	23.6 hours	-	Groeseneken *et al.*, 1987
EGBE	inhalation	BAA	5.77 hours	-	Johanson *et al.*, 1986
EGBE	ingestion	BAA	5.3 hours	-	Gijsenbergh *et al.*, 1989

**The product ingested in this case also contained ethanol, which may have inhibited metabolism and so prolonged the half-life.*

Mode of action

Glycol ethers have a wide spectrum of toxicity and for the most part the mechanisms are unclear. The alkoxyacetic acid metabolites are thought to be responsible for toxicity. There is strong evidence that these metabolites are responsible for testicular (Gray *et al*., 1985; Moss *et al*., 1985) and haematological (Ghanayem *et al*., 1987) toxicity. Cell culture testing has shown that while the glycol ethers themselves have no discernible toxic effect, toxicity occurs with their metabolites at much lower concentrations (Gray *et al*., 1985). The parent compounds vary in the severity of testicular toxicity but it is not clear whether this reflects differences in metabolism or in the inherent toxicity of the metabolites (Gray *et al*., 1985). MAA causes the most severe testicular changes; EAA is less toxic and *n*-propoxyacetic acid (PAA) and BAA produced no effects. However toxicity may occur at high doses with these compounds (Gray *et al*., 1985). It is suggested that the free carboxyl group on MAA may be important in toxicity, when conjugated with glycine the toxicity of MAA *in vitro* was abolished (Gray *et al*., 1985). It has been reported that MAA but not EGME inhibits the production of lactate by Sertoli cells in culture (Beattie *et al*., 1984). Lactate is an important energy substrate for developing spermatocytes and this may be a mechanism of toxicity. However, in cell cultures supplementation with lactate did not reduce toxicity, even though it has been shown that spermatocytes can utilise exogenous lactate (Gray *et al*., 1985).

Further evidence for the role of the alkoxyacetic acid metabolites in the toxicity of glycol ethers is the observation that treatment with substances which block the enzyme alcohol dehydrogenase (responsible for metabolism) reduces toxicity. Animal studies have demonstrated that pre-treatment with pyrazole provides protection against testicular damage (Moss *et al*., 1985) and haematological toxicity (Ghanayem *et al*., 1987).

Haemolysis in rat erythrocytes exposed *in vitro* to BAA is preceded by swelling and adenosine triphosphate (ATP) depletion, suggesting that the target is the erythrocyte membrane. Incubation of cells with EGBE found that blood was capable of metabolising it *in vitro* and that EGBE was essentially devoid of haemolytic activity (Ghanayem, 1989). The osmotic fragility of erythrocytes is increased by exposure to glycol ethers rendering them more sensitive to osmotic lysis (Carpenter *et al*., 1956).

The severe metabolic acidosis observed with acute ingestion of glycol ethers is due to the presence of the alkoxyacetic acid metabolite.

Metabolic interactions

- **Ethanol**

As ethanol is the preferred substrate of alcohol dehydrogenase (ADH), it blocks the metabolism of glycol ether, and the production of the toxic metabolites. As a result of this interaction, ethanol is used as an antidote in glycol ether poisoning. It is only useful in the immediate phase after exposure, as administration of ethanol is of very little benefit once the glycol ether has been metabolised. The drug, fomepizole, has a similar action to ethanol, and has been used as a substitute for ethanol in glycol ether intoxication (Nisse *et al*., 1998).

CASE REPORTS

Chronic occupational exposure

A sudden outbreak of illness in the industrial setting may occur because of a change in practice. An example of this is reported by Ohi and Wegman (1978). Acetone was used as a solvent for cleaning equipment in a textile printing plant. When this became temporarily unavailable, EGME was used instead. This was used for cleaning by hand without gloves, and, although air flow in the wash area was reduced, the air concentration of EGME was 8 ppm which did not exceed the TLV (25 ppm). Absorption was thought to be primarily through the skin.

The first patient, a 48 year old male had worked for a number of years in the plant and was admitted to hospital because of confusion. Over the previous three months he had noticed lethargy with unusual sleepiness, decreased hearing, anorexia and weight loss. His family noted that he was agitated. On examination he was

found to be grossly disorientated and lapsing in and out of sleep. He responded appropriately to commands and examination was otherwise normal. His haemoglobin and platelet count were low. A white cell count was also low at 2,600 with 27% mature neutrophils, 1% metamyelocytes, 68% lymphocytes, 1% monocytes and 2% eosinophils. Bone marrow aspiration revealed marrow depression with some signs of recovery. The initial diagnosis was encephalopathy due to alcoholism (he was a moderate to heavy drinker) or industrial toxic exposure. He was managed with vitamins and mineral supplements and made a slow recovery over the following weeks.

The second patient, a 45 year old male was admitted because of cough, shortness of breath, pyrexia, lethargy, staggering gait, blurred vision, slurred speech, poor memory, headache, confusion, anorexia, nausea, vomiting and nocturia. These effects had developed over the previous month after he had started working on the same operation as the first patient. Examination revealed only abnormal neurological signs with poor concentration, orientation, reasoning and recent memory. His haemoglobin and haemacrit were low. So was the white cell count at 5,100 with 30% neutrophils, 1% metamyelocytes, 58% lymphocytes, 8% monocytes and 2% eosinophils. A bone marrow aspirate showed marrow damage compatible with a marrow toxin. He recovered within a week without treatment (Ohi and Wegman, 1978).

Acute intentional ingestion

A 19 year old male ingested up to 840 ml of a product containing 20-35% EGBE and 15-25% propylene glycol. Gastric lavage was performed and he was given activated charcoal. He rapidly developed coma and required ventilation. He had convulsions, severe hypotension and aspirated, which resulted in hypoxia. Symptoms included acidosis, disseminated intravascular coagulation (DIC), thrombocytopenia and a reduced haematocrit. He began to improve over 24 hours, but acidosis continued and he was haemodialysed 29-33 hours after ingestion. He recovered but required prolong neurorehabilitation (Burkhart and Donovan, 1998).

CLINICAL EFFECTS

Acute exposure

Inhalation

Glycol ethers are irritant to the skin, eyes and respiratory tract. They may cause lacrimation, rhinorrhoea, cough, dyspnoea and nausea. A high concentration may cause CNS depression.

Cherry angiomas were reported in 6 out of 7 workers exposed to EGBE which had been applied to the floor of one of the rooms at work. Cherry angiomas are red/purple smooth lesions due to permanent dilatation of blood vessels and are usually found on the trunk and proximal extremities. The workers had developed immediate symptoms of irritation with dyspnoea and nausea at the time of the incident and had removed themselves from exposure. However, some of them had to enter the treated room during the course of their work. Some of the workers had been sent home because of their symptoms, but all were well enough to return to work the next day. Cherry angiomas began to develop 4-22 weeks after the incident. When examined 8 months after the incident 6 workers complained of recurrent eye and tracheobronchial irritation and retro-orbital headache. Four of them had a dry cough. Five years after the exposure cherry angiomas continued to appear (Raymond *et al.*, 1998).

Dermal

Glycol ethers are irritant to the skin; however, the severity depends on the particular ether (see **Table 11.8**). In a volunteer study where the fingers were immersed in neat EGBE for 2 hours the skin became wrinkled and less elastic. There was a decrease in finger volume and skin thickness. These effects reached a maximum 2-4 hours after cessation of exposure and then resolved. This was thought to be due to delipidisation and dehydration of the skin. In some cases there was slight erythema which resolved in 1-2 days (Johanson *et al.*, 1988).

Table 11.8 Comparative acute irritation effects of glycol ethers in animal studies (Ballantyne and Myers, 1987)

Ether	Skin irritation	Eye irritation
Ethylene		
methyl	minor	moderate
ethyl	moderate	severe
propyl	moderate	severe
butyl	moderate	severe
hepyl	moderate	severe
hexyl	severe	severe
Diethylene		
methyl	minor	moderate
ethyl	minor	moderate
butyl	minor	severe
heptyl	minor	severe
hexyl	minor	severe

In rabbit studies, exposure to ethylene glycol hexyl ether for 4 hours caused mild to moderate erythema and oedema. There was some necrosis and desquamation. Diethylene glycol hexyl ether was less irritant (Ballantyne and Myers, 1987). In an animal study comparing EGEEA and EGBEA, both were found to be practically non-irritant (Truhaut *et al.*, 1979).

Eye

Glycol ethers are irritant to eyes; however, the severity depends on the particular ether (Grant and Schuman, 1993), see **Table 11.8**. In rats, ethylene glycol hexyl ether and diethylene glycol hexyl ether caused severe conjunctivitis with hyperaemia, iritis, chemosis and discharge. There was full recovery (Ballantyne and Myers, 1987).

Ingestion

Ingestion of a large quantity of glycol ether (usually in a suicide attempt) results in coma, respiratory depression, convulsions and severe hypotension. Restlessness, weakness, confusion and disorientation, agitation, cyanosis and hyperventilation have been reported. Transient non-cardiogenic pulmonary oedema has been reported (Bauer *et al.*, 1992). The onset of effects is usually rapid, i.e., within 2 hours (Gijsenbergh *et al.*, 1989; McKinney *et al.,* 2000), but there may be a delay in presentation because initial effects may be non-specific (8 and 18 hours: Nitter-Hauge, 1970; 12 hours: Rambourg-Schepens *et al.*, 1988; 10 hours: Bauer et al., 1992).

Laboratory analyses may reveal severe metabolic acidosis, DIC, hepatotoxicity (abnormal LFTs and INR), reduced haemocrit and haemoglobin and evidence of renal impairment. Urine analysis may reveal proteinuria and oxalate crystals may be present. Hypocalcaemia (Nitter-Hauge, 1970), hypokalaemia (Nitter-Hauge, 1970; Rambourg-Schepens *et al.*, 1988; Bauer et al., 1992), thrombocytopenia and non-haemolytic hypochromic anaemia (Bauer *et al.*, 1992) have occasionally been reported. Haemolytic anaemia and haematuria may occur (Rambourg-Schepens *et al.*, 1988; Gijsenbergh *et al.*, 1989). Cases of ingestion of glycol ether are summarised in **Table 11.9**.

Table 11.9 Cases of ingestion of glycol ether

Glycol ether	Quantity	Co-ingestants	Age/sex	Results of investigations	Treatment	Outcome	Reference
DGME	NK 20-30%	Mineral spirits (65-70%), xylene (2-4%)	59 F	Acidosis, osmolar gap 12 mOsm/kg H_2O Ethylene glycol and methanol not detected	Ethanol	Recovery	Wermuth and Furbee, 1997
EGBE	500 ml of 9.1% (45.5 g)	Ethanol 2.5%	53 M	Acidosis	Ethanol, haemodialysis	Recovery	Bauer *et al.*, 1992
EGBE	500 ml of 12.7% (63.5 g)	Ethanol 3.2%	23 F	Acidosis, no osmolar gap, oxalate excretion normal	Diuresis, haemodialysis	Recovery	Gijsenberg *et al.*, 1989
EGBE	360-480 ml of 22% (79-106 g) and 12 days later 480 ml of 22%	-	17 M	Acidosis, ethylene glycol not detected	Ethanol, haemodialysis on both occasions	Recovery	Gualtieri *et al.*, 1995
EGBE	NK 5.6%	-	87 F	Acidosis, ethylene glycol concentration 1.1 g/l	Ethanol, haemodialysis (stopped due to arrhythmias)	Death after 3 days	Litovitz *et al.*, 1991
EGBE	225 ml	Isopropanol	51 F	Acidosis, ethanol, ethylene glycol and methanol not detected, osmolar gap 1 mOsm/kg H_2O	Ethanol	Recovery	McKinney *et al.*, 2000
EGBE	250 ml of 9.1%	Ethanol 2.5% (23 g)	52 F	Acidosis, ethylene glycol concentration 0.31 g/l, oxalate crystals on biopsy	Ethanol, fomepizole,	Recovery	Nisse *et al.*, 1998
EGBE	250-500 ml of 12% (30-60 g)	-	50 F	Acidosis, oxalates in urine	Diuresis	Recovery	Rambourg- Schepens *et al.*, 1988
EGME	100 ml pure	-	41 M	Acidosis, oxalate in urine, methanol not detected	Ethanol	Recovery	Nitter-Hauge, 1970
EGME	100 ml pure	-	23 M	Acidosis, oxalate in urine, methanol not detected	Ethanol	Recovery	Nitter-Hauge, 1970
EGME	285 ml ? pure	-	44 M	No methanol detected	-	Death	Young and Woolner, 1946

NK = not known

Most cases reported involve EGBE (Rambourg-Schepens *et al*., 1988; Gijsenbergh *et al*., 1989; Litovitz *et al*., 1991; Bauer *et al*., 1992; Burkhart and Donovan, 1998; McKinney *et al*., 2000; Nisse *et al*., 1998), but cases of EGME (Nitter-Hauge, 1970) and dipropylene glycol monomethyl ether have also been reported (Wermuth and Furbee, 1997). Recovery from severe poisoning may be prolonged; residual neurological damage has been reported (Burkhart and Donovan, 1998), but this may have been a result of hypoxia following aspiration.

Renal biopsy in a patient with persistent renal impairment showed acute tubular necrosis, vascular lesions and oxalate crystal deposition in the renal parenchyma (Nisse *et al*., 1998). Findings in postmortem examination in two fatal cases included haemorrhagic gastritis, degenerative changes in the renal tubules and fatty degeneration of the liver (Young and Woolner, 1946).

Chronic exposure

Systemic effects from chronic exposure (dermal and/or inhalation)

Chronic exposure to glycol ethers may cause encephalopathy which is characterised by gradual onset of personality changes, confusion, headache, dizziness, lethargy, fatigue and abnormal sleepiness. There may also be staggering gait, blurred vision, slurred speech, nausea, vomiting, anorexia and weight loss, agitation, irritability and poor concentration, orientation, reasoning and memory (Parsons and Parsons, 1938; Zavon, 1963; Ohi and Wegman, 1978; Morton, 1990).

Cough and shortness of breath (Ohi and Wegman, 1978), hearing loss (Zavon, 1963), paraesthesia, weakness and diminished sensation and grip strength in the hands (with normal nerve conduction studies) and bilateral labyrinthine hypofunction have been reported (Morton, 1990). On examination there may be tremor, hyperreflexia, increased muscle tone, ataxia with positive Romberg's sign and dysarthria (Parsons and Parsons, 1938; Zavon, 1963). Pupils may be dilated and sluggish (Parsons and Parsons, 1938). Nocturia has been reported (Parsons and Parsons, 1938; Ohi and Wegman, 1978). Neurological effects usually resolve once the victim has been removed from exposure (Parsons and Parsons, 1938; Ohi and Wegman, 1978), but in some cases effects have persisted for years (Morton, 1990).

Haematological effects

Glycol ethers and their esters may cause haematological abnormalities, particularly bone marrow depression. Haematological effects have been reported in exposed humans (Donley, 1936; Greenburg *et al*., 1938; Parsons and Parsons, 1938; Zavon, 1963; Ohi and Wegman, 1978; Cohen, 1984; Welch and Cullen, 1988; Larese *et al*., 1992; Kim *et al*., 1999) and animals (Truhaut *et al*., 1979).

Macrocytic anaemia and leucopenia (Greenburg, 1938; Larese *et al*., 1992), thrombocytopenia (Greenburg *et al*., 1938), granulocytopenia (Parsons and Parsons, 1938; Zavon, 1963; Welch and Cullen, 1988) and pancytopenia (Ohi and Wegman, 1978) have been reported in exposed workers. These haematological effects may be observed on routine medical examination in workers who are asymptomatic. Haematological parameters return to normal on cessation of exposure (Greenburg, 1938; Cohen, 1984; Larese *et al*., 1992).

Most of the reports mentioned above concern individual workers, but there are also studies looking at effects on groups of workers. In a study of two groups exposed to EGEEA (high exposure group mean concentration 3.03 ppm and low exposure group mean concentration 1.76 ppm), the mean white blood cell counts were significantly lower in the high exposure group compared to the controls, and a significant number of workers were leucopenic. Bone marrow aspiration of workers with leucopenia revealed bone marrow hypoplasia. Other haematological parameters were normal. None of the controls were affected (Kim *et al*., 1999).

A study of printers exposed to a variety of organic solvents including EGEE and dipropylene glycol monomethyl ether demonstrated bone marrow changes (e.g., myeloid hypoplasia) despite normal peripheral blood pictures. These changes could not be explained by known risk factors (Cullen *et al*., 1983). However, there were no measures of individual exposure to any one solvent and it is impossible to draw any conclusions from this study (ECETOC, 1995).

Workers exposed to EGME showed no clinically meaningful differences in haematological or fertility indices compared to controls. Tests included white blood cell count (WBC), red blood cell count (RBC), haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, luteinising hormone (LH), follicle stimulating hormone (FSH), testosterone levels and semen analysis (Cook *et al*., 1982). Workers exposed to EGBE (0.59 ppm) had no significant changes in red blood cell numeration, haemoglobin, mean corpuscular volume or haemoglobin, haptoglobin, reticulocyte numeration and osmotic resistance and hepatic or renal parameters. However, there was a significant decrease in haemocrit and a significant increase in mean corpuscular haemoglobin concentration, which suggests membrane damage of red blood cells (Haufroid *et al*., 1997).

Depression of red cell pyruvate kinase was found in exposed workers without obvious haematological effects (Cullen *et al*., 1992). (Low pyruvate kinase activity is a consistent finding in acquired haematological disorders.)

In animals, glycol ethers have been shown to cause decreased RBC count and haemoglobin, haemolytic anaemia, lymphocytopenia, neutropenia (Dodd *et al*., 1983; Grant *et al*., 1985) and leucopenia (Nagano *et al*., 1981). These changes are usually reversible (Dodd *et al*., 1983; Grant *et al*., 1985). There are variations in species' response to the haemolytic effects of BAA. In a study comparing different species, rats, mice, rabbits, hamsters and baboons were classified as sensitive, and humans, pigs, dogs, cats and guinea pigs as insensitive (Ghanayem and Sullivan, 1993). An *in vitro* study on rat and human erythrocytes confirmed this with minimal haemolysis in human cells compared to the rat (Ghanayem, 1989). In an animal study using EGEEA and EGBEA only renal damage was found, there were no haematological changes (Truhaut *et al*., 1979).

Various studies suggest that blood concentrations of glycol ethers resulting in the severe haematological changes observed in animal studies are unlikely to be achieved through inhalation and/or dermal exposure (Corley *et al*., 1997). However, it may be possible to achieve a toxic concentration following intentional ingestion of a large quantity of glycol ether.

Renal effects

Chronic occupational exposure to glycol ethers is associated with changes in renal function. A study of silk-screen printers found a higher risk of urinary stones compared to controls. Some of the renal changes noted were typical of chronic metabolic acidosis (Laitinen *et al*., 1996).

Immunotoxicity

Only limited data are available on the immunotoxicity of glycol ethers. No information on humans is available. Some animal studies have demonstrated thymic atrophy and immunosuppression (reviewed in ECETOC, 1995).

Eye

Glycol ethers are irritant to eyes. Two workers exposed to EGME with typical signs and symptoms of toxic encephalopathy developed eye irritation with hyperaemia, watering and a smarting, burning sensation. These effects increased as exposure continued (Parsons and Parsons, 1938).

Ingestion

There are no data on chronic ingestion of glycol ethers. An 18 year old male who ingested a large quantity of EGBE on two separate occasions 12 days apart developed typical signs and symptoms of toxicity (see acute ingestion). The first episode was characterised by metabolic acidosis and hepatotoxicity; renal and haematological effects did not occur on either occasion (Gualtieri *et al*., 1995).

Carcinogenicity

There is no information available on the carcinogenicity of glycol ethers or glycol ether acetates (ECETOC, 1995). They have not been evaluated by the IARC.

Genotoxicity

Not all the glycol ethers have been tested for genotoxicity, but for those that have the results were mostly negative (reviewed in ECETOC, 1995).

Reproductive toxicity

A number of studies have demonstrated reproductive toxicity for glycol ethers in animals, both males and females (reviewed in Hardin, 1983; Paustenbach, 1988; IPCS, 1990; ECETOC, 1995). In an assessment of developmental risks from occupational exposure to glycol ethers in the semiconductor industry, Paustenbach (1988) concluded that employees should not be at risk of adverse developmental, reproductive and other effects provided that the airborne concentrations of these chemicals were maintained below safety limits and that dermal exposure was minimal.

Testicular changes

There is limited information in humans and much of the available data are inconclusive. Exposed workers have been shown to have an increased prevalence of oligospermia and azoospermia compared to controls (Welch *et al*., 1988). A study of workers exposed to EGME possibly showed a smaller testicular size in 6 exposed subjects compared to 9 controls (Cook *et al*., 1982). A study of semen quality in workers concluded that exposure to EGEE may have an effect on sperm counts, but not on other parameters of morphology and function. The average sperm count per ejaculate was significantly lower in workers than in the controls when other factors were taken into account. However, the mean sperm concentration of the two groups did not differ. Also, no effect of exposure to EGEE was detected in semen volume, sperm viability, motility, velocity, morphology or testicular volume (Ratcliffe *et al*., 1989).

A study comparing male patients diagnosed as infertile or subfertile attending a clinic for reproductive disorders, found ethoxyacetic acid in the urine of 39 patients and 6 controls. Methoxyacetic acid was found in 1 patient and 2 controls. Urinary concentrations of ethoxyacetic acid did not correlate with various measures of sperm quality (Veulemans *et al*., 1993).

Studies in animals have demonstrated degenerative changes in germinal epithelium (Miller *et al*., 1981; Foster *et al*., 1983), testicular atrophy (Beattie *et al*., 1984; Grant *et al*., 1985; Horimoto *et al*., 2000) and decreased sperm count and motion (Horimoto *et al*., 2000). These changes are usually reversible, but very high doses may prevent complete recovery (Foster *et al*., 1983). Testicular changes are characterised by degeneration and depletion of the primary spermatocyte population at the pachytene stage of the meiotic prophase and in division (Foster *et al*., 1983; Moss *et al*., 1985).

Fetotoxicity/embryotoxicity and teratogenicity

Potential exposure to mixtures containing glycol ethers have been associated with an increased risk of subfertility and spontaneous abortion among female workers (Pastides *et al*., 1988; Correa *et al*., 1996). A dose-response effect with subfertility and spontaneous abortion has been demonstrated. Among the spouses of exposed male workers there was no increased risk of spontaneous abortion (Correa *et al*., 1996). In another study of female workers there was an increased risk of miscarriage in workers using glycol ethers (Pastides *et al*., 1988).

There is limited information on the reproductive effects of the glycol ether acetates. A woman exposed to EGMEA during both pregnancies gave birth to two boys with hypospadia (failure of closure of the urethral groove) and bifid scrotum. The first boy also had micropenis. Dermal absorption was thought to be important in this case (Bolt and Golka, 1990).

Animal studies have shown malformations involving numerous organ systems (Nagano *et al*., 1981; Hanley *et al*., 1984; Horton *et al*., 1985), an increased incidence of resorptions (Hanley *et al*., 1984; Horton *et al*., 1985) and decreased fetal weight (Nagano *et al*., 1981; Doe *et al*., 1983; Hanley *et al*., 1984; Horton *et al*., 1985). Teratogenic effects appear to be similar among the species tested, but there is variation in susceptibility, with rabbits being the most susceptible (Hanley *et al*., 1984). Prolongation of gestation has also been observed (Hardin, 1983).

RISK GROUPS

Exposure to glycol ethers has been shown to be associated with adverse haematological effects. Consequently, individuals predisposed to haematological anaemia by disorders such as hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency and sickle cell anaemia, may be at greater risk of haematological toxicity if exposed to these chemicals (Ghanayem, 1989). In addition, Cullen *et al*. (1992) found an association between ethnic group and haematological effects in exposed workers. Black workers, in particular, were found to have marginally low haemoglobin concentrations and total granulocyte counts. Although the study numbers were small, the difference was large and the association very strong.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Gastric decontamination should be considered following ingestion of a large quantity. Most cases reported involved intentional suicidal ingestion or accidental ingestion in mistake for alcohol. Cases reported in the literature are summarised in **Table 11.9**. Activated charcoal is unlikely to be of any benefit (Browning and Curry, 1994). The blood gases, haemoglobin, liver function and osmolality (but see note below) should be monitored. Urinalysis including the presence of oxalate crystals is also recommended.

The airway must be protected. Aspiration has been reported in glycol ether poisoning (Buckhart and Donovan, 1998). Ventilation will be required in patients with severe CNS depression. Hypotension should be managed with IV fluids and dopamine or dobutamine if necessary.

Acidosis should be treated with sodium bicarbonate. If acidosis is refractory then haemodialysis should be considered. Antidotal therapy should be considered.

Glycol ethers and their alkoxyacetic acid metabolites produce a linear increase in plasma osmolality with increasing plasma concentration. However, the change in osmolality is small, only 3-12 mOsm/kg H_2O in one

study (Browning and Curry, 1992) and may not be clinically useful in cases of acute poisoning with glycol ethers (Lund *et al.,* 1983; Browning and Curry, 1992). The normal osmolar gap is variable and may be 1-34 mOsm/kg H_2O (Dorwart and Chalmers, 1975). In cases of acute poisoning where the osmolality has been measured it has been found to be 12 mOsm/kg H_2O (Wermuth and Furbee, 1997), 1 mOsm/kg H_2O (McKinney *et al*., 2000) and absent (Gijsenbergh *et al*., 1989).

Antidotes

As the metabolites are responsible for the toxicity, competitive inhibitors of alcohol dehydrogenase should be considered for severe cases of acute ingestion of glycol ethers. If they are to be used they should be administered as soon as possible, because metabolites are usually detectable in the urine very quickly after ingestion of glycol ethers. Ethanol is readily available and been used in a number of cases (Nitter-Hauge, 1970; Litovitz *et al*., 1991; Bauer *et al*., 1992; Gualtieri *et al*., 1995; Wermuth and Furbee, 1997; Nisse *et al*., 1998; McKinney *et al*., 2000). Fomepizole is an alternative competitive inhibitor which may be used. There is only limited experience with its use in glycol ether poisoning (Nisse *et al*., 1998). It is newer, less readily available and expensive. However, ethanol therapy usually necessitates intensive care facilities because a high blood ethanol concentration (which must be regularly monitored) is required and this results in CNS depression. Fomepizole has the advantage of not producing CNS depression and has few side effects; intensive care facilities are therefore not required.

Chronic exposure

Treatment of chronic glycol ether toxicity is symptomatic and supportive. Antidotal therapy is of no benefit. Vitamin and mineral supplementation may be given in those with bone marrow depression.

REFERENCES

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Ballantyne B, Myers RC. 1987 The comparative acute toxicity and primary irritancy of the monohexyl ethers of ethylene and diethylene glycol. *Vet Hum Toxicol* 29 (5):361-366.

Bauer P, Weber M, Mur JM, Protois JC, Bollaert PE, Condi A, Larcan A, Lambert H. 1992 Transient non-cardiogenic pulmonary edema following massive ingestion of ethylene glycol butyl ether. *Intensive Care Med* 18:250-251.

Beattie PJ, Welsh MJ, Brabec MJ. 1984 The effect of 2-methoxyethanol and methoxyacetic acid on Sertoli cell lactate production and protein synthesis *in vitro*. *Toxicol Appl Pharmacol* 76:56-61.

Bolt HM, Golka K. 1990 Maternal exposure to ethylene glycol monomethyl ether acetate and hypospadia in offspring: a case report. *Br J Ind Med* 47:352-353.

Browning RG, Curry SC. 1992 Effect of glycol ethers on plasma osmolality. *Hum Exp Toxicol* 11:488-490.

Browning RG, Curry SC. 1994 Clinical toxicology of ethylene glycol monoalkyl ethers. *Hum Exp Toxicol* 13:325-335.

Burkhart K, Donovan JW. 1998 Butoxyethanol intoxication and hemodialysis [abstract]. *Clin Toxicol* 36 (5):517.

Carpenter CP, Pozzani UC, Weil CS, Nair JH III, Keck GA, Smyth HF. 1956 The toxicity of butyl cellosolve solvent. *AMA Arch Ind Health* 14:114-131.

Cohen R. 1984 Reversible subacute ethylene glycol monomethyl ether toxicity associated with microfilm production: a case report. *Am J Ind Med* 6:441-446.

Cook RR, VanPeenen PFD, Bodner KM, Dickson GS, Kolesar RC, Flanagan K, Uhlmann CS. 1982 A cross-sectional study of ethylene glycol monomethyl ether process employees. *Arch Environ Health* 37 (6):346-351.

Corley RA, Markham DA, Banks C, Delorme P, Masterman A, Houle JM. 1997 Physiologically based pharmacokinetics and the dermal absorption of 2-butoxyethanol vapor by humans. *Fund Appl Toxicol* 39:120-130.

Correa A, Gray RH, Cohen R, Rothman N, Shah F, Seacat H, Corn M. 1996 Ethylene glycol ethers and risks of spontaneous abortion. *Am J Epidem* 143 (7):707-717.

Cullen MR, Rado T, Waldron JA, Sparer J, Welch LS. 1983 Bone marrow injury in lithographers exposed to glycol ether and organic solvents used in multicolor offset and ultraviolet curing printing processes. *Arch Environ Health* 38 (6):347-354.

Cullen MR, Solomon LR, Pace PE, Buckley P, Duffy TP, McPhedran P, Kelsey KT, Redlich CA. 1992 Morphologic, biochemical and cytogenetic studies of bone marrow and circulating blood cells in painters exposed to ethylene glycol ethers. *Environ Res* 59:250-264.

Dodd DE, Snellings WM, Maronpot RR, Ballantyne B. 1983 Ethylene glycol monobutyl ether: acute, 9-day and 90-day vapor inhalation studies in Fischer 344 rats. *Toxicol Appl Pharmacol* 68:405-414.

Doe JE, Samuels DM, Tinston DJ, DeSilva Wickramaratne GA. 1983 Comparative aspects of the reproductive toxicology by inhalation in rats of ethylene glycol monomethyl ether and propylene glycol monomethyl ether. *Toxicol Appl Pharmacol* 69:43-47.

Donley DE. 1936 Toxic encephalopathy and volatile solvents in industry. Report of a case. *J Ind Hyg Toxicol* 18:571-577.

Dorwart WV, Chalmers L. 1975 Comparison of methods for calculating serum osmolality from chemical concentrations, and the prognostic value of such calculations. *Clin Chem* 21 (2):190-194.

Dugard PH, Walker M, Mawdsley SJ, Scott RC. 1984 Absorption of some glycol ethers through human skin *in vitro*. *Environ Health Perspect* 57:193-197.

Duprat P, Gradiski D. 1979 Percutaneous toxicity of butyl cellosolve (ethylene glycol monobutyl ether). *IRCS Med Sci* 7:26.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 1995 The toxicology of glycol ethers and its relevance to man. *Technical Report* No.64.

Foster PMD, Creasy DM, Foster JR, Thomas LV, Cook MW, Gangolli SD. 1983 Testicular toxicity of ethylene glycol monomethyl and monoethyl ethers in the rat. *Toxicol Appl Pharmacol* 69:385-399.

Ghanayem BI. 1989 Metabolic and cellular basis of 2-butoxyethanol-induced hemolytic anemia in rats and assessment of human risk in vitro. *Biochem Pharmacol* 38 (10):1679-1684.

Ghanayem BI, Burka LT, Matthews HB. 1987 Metabolic basis of ethylene glycol monobutyl ether (2-butoxyethanol) toxicity: role of alcohol and aldehyde dehydrogenases. *J Pharmacol Exp Therap* 242 (1):222-231.

Ghanayem BI, Sullivan CA. 1993 Assessment of the haemolytic activity of 2-butoxyethanol and its major metabolite, butoxyacetic acid, in various mammals including man. *Hum Exp Toxicol* 12:305-311.

Gijsenbergh FP, Jenco M, Veulemans H, Groeseneken D, Verberckmoes R, Delooz HH. 1989 Acute butylglycol intoxication: a case report. *Hum Toxicol* 8:243-245.

Grant D, Sulsh S, Jones HB, Gangolli SD, Butler WH. 1985 Acute toxicity and recovery in the hemopoietic system of rats after treatment with ethylene glycol monomethyl and monobutyl ethers. *Toxicol Appl Pharmacol* 77:187-200.

Grant WM, Schuman, JH. 1993 *Toxicology of the Eye*, fourth edition. Charles C Thomas, Springfield.

Gray TJB, Moss EJ, Creasy DM, Gangolli SD. 1985 Studies on the toxicity of some glycol ethers and alkoxyacetic acids in primary testicular cell cultures. *Toxicol Appl Pharmacol* 79:490-501.

Greenburg L, Mayers MR, Goldwater LJ, Burke WJ, Moskowitz S. 1938 Health hazards in the manufacture of 'fused collars'. 1. Exposure to ethylene glycol monomethyl ether. *J Ind Hyg Toxicol* 20:134-147.

Groeseneken D, Veulemans H, Masschelein R. 1986a Respiratory uptake and elimination of ethylene glycol monoethyl ether in experimental human exposure. *Br J Ind Med* 43:544-549.

Groeseneken D, Veulemans H, Masschelein R. 1986b Urinary excretion of ethoxyacetic acid after experimental exposure to ethylene glycol monoethyl ether. *Br J Ind Med* 43:615-619.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E. 1987 Ethoxyacetic acid: a metabolite of ethylene glycol monoethyl ether acetate in man. *Br J Ind Med* 44:488-493.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E. 1989 Experimental human exposure to ethylene glycol monomethyl ether. *Int Arch Occup Environ Health* 61:243-247.

Gualtieri J, Harris C, Roy R, Corley R, Manderield C. 1995 Multiple 2-butoxyethanol intoxications in the same patient: clinical findings, pharmacokinetics and therapy [abstract]. *Clin Toxicol* 33 (*5*):550-551.

Hanley TR, Yano BL, Nitschke KD, John JA. 1984 Comparison of the teratogenic potential of inhaled ethylene glycol ether in rats, mice and rabbits. *Toxicol Appl Pharmacol* 75:409-422.

Harbison RD. 1998 Alcohols and glycols. In: *Hamilton and Hardy's Industrial Toxicology*, fifth edition. Harbison RD (editor). Mosby, St Louis.

Hardin BD. 1983 Reproductive toxicity of the glycol ethers. *Toxicology* 27:91-102.

Haufroid V, Thirion F, Mertens P, Buchet J-P, Lison D. 1997 Biological monitoring of workers exposed to 2-butoxyethanol. *Int Arch Occup Environ Health* 70:232-236.

Horimoto M, Isobe Y, Isogai Y, Tachibana M. 2000 Rat epididymal sperm motion changes induced by ethylene glycol monoethyl ether, sulfasalazine and 2,5-hexanedione. *Reprod Toxicol* 14 (1):55-63.

Horton VL, Sleet RB, John-Greene JA, Welsch F. 1985 Developmental phase-specific and dose-related teratogenic effects of ethylene glycol monomethyl ether in CD-1 mice. *Toxicol Appl Pharmacol* 80:108-118.

IPCS. 1990 *Environmental Health Criteria 115. 2-Methoxyethanol, 2-ethoxyethanol and their acetates*. World Health Organization, International Programme on Chemical Safety, Geneva.

Johanson G, Kronberg H, Näslund PH, Byfält Nordqvist M. 1986 Toxicokinetics of inhaled 2-butoxyethanol (ethylene glycol monobutyl ether) in man. *Scand J Work Environ Health* 12:594-602.

Johanson G, Boman A Dynénsius B. 1988 Percutaneous absorption of 2-butoxyethanol in man. *Scand J Work Environ Health* 14:101-109.

Johanson G, Boman A. 1991 Percutaneous absorption of 2-butoxyethanol vapour in human subjects. *Br J Ind Med* 48:788-792.

Johanson G, Johnsson S. 1991 Gas chromatographic determination of butoxyacetic acid in human blood after exposure to 2-butoxyethanol. *Arch Toxicol* 65:433-435.

Kežeć S, Mahieu K, Monster AC, de Wolff FA. 1997 Dermal absorption of vaporous and liquid 2-methoxyethanol and 2-ethoxyethanol in volunteers. *Occup Environ Med* 54:38-43.

Kim Y, Lee N, Sakai T, Kim K-S, Yang JS, Park S, Lee CR, Cheong H-K, Moon Y. 1999 Evaluation of exposure to ethylene glycol monoethyl ether acetates and their possible haematological effects on shipyard painters. *Occup Environ Med* 56:378-382.

Laitinen J, Liesivuori J, Savolainen H. 1996 Urinary alkoxyacetic acids and renal effects of exposure to ethylene glycol ethers. *Occup Environ Med* 53:595-600.

Larese F, Fiorito A, De Zotti R. 1992 The possible haematological effects of glycol monomethyl ether in a frame factory. *Br J Ind Med* 49:131-133.

Larese Filon F, Fiorito A, Adami G, Barbieri P, Coceani N, Bussani R, Reisenhofer E. 1999 Skin absorption *in vitro* of glycol ethers. *Int Arch Occup Environ Health* 72:480-484.

Litovitz TL, Bailey KM, Schmitz BF, Holm KC, Klein-Schwartz W. 1991 1990 Annual report of the American Association of Poison Control Centers national data collection system. *Am J Emerg Med* 9 (5):461-509.

Lund ME, Banner W, Finley PR, Burnham L, Dye JA. 1983 Effect of alcohols and selected solvents on serum osmolality measurements. *J Toxicol-Clin Toxicol* 20 (2):115-132.

McKinney P, Palmer RB, Blackwell W, Benson BE. 2000 Butoxyethanol ingestion with prolonged hyperchloremic metabolic acidosis treated with ethanol therapy. *Clin Toxicol* 38 (7):787-793.

Miller RR, Ayres JA, Calhoun LL, Young JT, McKenna MJ. 1981 Comparative short-term inhalation toxicity of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in rats and mice. *Toxicol Appl Pharmacol* 61:368-377.

Miller RR, Hermann EA, Langvardt PW, McKenna MJ, Schwetz BA. 1983 Comparative metabolism and disposition of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in male rats. *Toxicol Appl Pharmacol* 67:229-237.

Miller RR, Hermann EA, Young JT, Calhoun LL, Kastl PE. 1984a Propylene glycol monomethyl ether acetate (PGMEA) metabolism, disposition and short-term vapor inhalation toxicity studies. *Toxicol Appl Pharmacol* 75:521-530.

Miller RR, Hermann EA, Young JT, Landry TD, Calhoun LL. 1984b Ethylene glycol monomethyl ether and propylene glycol monomethyl ether: metabolism, disposition and subchronic inhalation toxicity studies. *Environ Health Perspect* 57:233-239.

Morton WE. 1990 Occupational phenoxyethanol neurotoxicity: a report of three cases. *J Occup Med* 32 (1):42-45.

Moss EJ, Thomas LV, Cook MV, Walters DG, Foster PMD, Creasy DM, Gray TJB. 1985 The role of metabolism in 2-methoxyethanol-induced testicular toxicity. *Toxicol Appl Pharmacol* 79:480-489.

Nagano K, Nakayama E, Oobayashi H, Yamada T, Adachi H, Nishizawa T, Ozawa H, Nakaichi M, Okuda H, Minami K, Yamazaki K. 1981 Embryotoxic effects of ethylene glycol monomethyl ether in mice. *Toxicology* 20:335-343.

NIOSH. 1980 *Registry of Toxic Effects of Chemical Substances*, DHHS (NIOSH) Publication No. 81-116. Cincinnati, US Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health. Cited in: Hardin BD. 1983 Reproductive toxicity of the glycol ethers. *Toxicology* 27:91-102.

Nisse P, Coquelle-Couplet V, Forceveille X, Mathieu-Nolf M. 1998 Renal failure after suicidal ingestion of window cleaner. *Vet Hum Toxicol* 40 (3):173.

Nitter-Hauge S. 1970 Poisoning with ethylene glycol monomethyl ether. Report of cases. *Acta Med Scand* 188:277-280.

Ohi G, Wegman DH. 1978 Transcutaneous ethylene glycol monomethyl ether poisoning in the work setting. *J Occup Med* 20 (10):675-676.

Parsons CE, Parson MEM. 1938 Toxic encephalopathy and 'granulopenic anemia' due to volatile solvents in industry: report of two cases. *J Ind Hyg Toxicol* 20 (2):124-133.

Pastides H, Calabrese EJ, Hosmer DW, Harris DR. 1988 Spontaneous abortion and general illness symptoms among semiconductor manufacturers. *J Occup Med* 30 (7):543-551.

Paustenbach DJ. 1988 Assessment of developmental risks resulting from occupational exposure to select glycol ethers within the semiconductor industry. *J Toxicol Environ Health* 23:29-75.

Rambourg-Schepens MO, Buffet M, Bertault R, Jaussaud M, Journe B, Fay R, Lamiable D. 1988 Severe ethylene glycol butyl ether poisoning. Kinetic and metabolic pattern. *Hum Toxicol* 7:187-189.

Ratcliffe JM, Schrader SM, Clapp DE, Haslperin WE, Turner TW, Hornung RW. 1989 Semen quality in workers exposed to 2-ethoxyethanol. *Br J Ind Med* 46:399-402.

Raymond LW, Williford LS, Burke WA. 1998 Eruptive cherry angiomas and irritant symptoms after one acute exposure to the glycol ether solvent 2-butoxyethanol. *J Occup Environ Med* 40 (12):1059-1064.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Truhaut R, Dutertre-Catella H, Phu-Lich N, Huyen VN. 1979 Comparative toxicological study of ethylglycol acetate and butylglycol acetate. *Toxicol Appl Pharmacol* 51:117-127.

Veulemans H, Steeno O, Masschelein R, Groeseneken D. 1993 Exposure to ethylene glycol ethers and spermatogenic disorders in man: a case-control study. *Br J Ind Med* 50:71-78.

Welch LS, Cullen MR. 1988 Effects of exposure to ethylene glycol ethers on shipyard painters: I. Hematologic effects. *Am J Ind Med* 14:527-536.

Welch LS, Schrader SM, Turner TW, Cullen MR. 1988 Effects of exposure to ethylene glycol ethers on shipyard painters: II. Male reproduction. *Am J Ind Med* 14:509-526.

Wermuth M, Furbee B. 1997 Dipropylene glycol monomethyl ether (DPGME) ingestion [abstract]. *Clin Toxicol* 35 (5):512.

Young EG, Woolner LB. 1946 A case of fatal poisoning from 2-methoxy-ethanol. *J Ind Hyg* 28:267-268.

Zavon MR. 1963 Methyl cellusolve intoxication. *Am Ind Hyg Assoc J* 24:36-41.

12 Hexane/*n*-Hexane

Nicola Bates

SUMMARY

- Hexane is absorbed orally and by inhalation; there is limited information on dermal absorption
- Relatively low acute toxicity; causes mild irritation and CNS depression
- Chronic exposure may result in peripheral polyneuropathy, characteristically a distal, symmetrical sensiomotor polyneuropathy
- Neurotoxicity is due to the main metabolite (2,5-hexanedione, a γ-diketone compound) and not *n*-hexane itself
- Insidious onset of clinical effects; there is deterioration after removal from exposure before gradual improvement
- Depending on the severity of exposure, neurotoxicity usually has a good outcome, but recovery may be slow
- Co-exposure to other solvents (e.g., methyl ethyl ketone) potentiates the toxicity of *n*-hexane
- Urinary concentrations of 2,5-hexanedione may be used for biomonitoring
- There is limited information on the carcinogenicity, genotoxicity and reproductive toxicity of *n*-hexane

DESCRIPTION

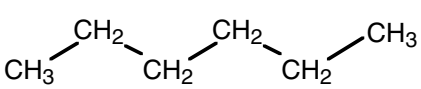
Synonyms

Hexyl hydride, hexane, normal hexane. 'Commercial hexane' is a mixture of hexane isomers (*n*-hexane, 2-methylpentane, 3-methylpentane, 2,3-dimethylbutane), cyclohexane, methyl cyclopentane and small quantities of pentane and heptane isomers, acetone, methyl ethyl ketone, dichloromethane and trichloroethylene (Perbellini 1981a; 1981b).

Identification numbers

CAS	110-54-3
UN	1208 (hexanes)
RTECS	MN 9275000
EINECS	2037776

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	C_6H_{14}
molecular formula	

molecular mass	86.13
physical form	colourless, highly volatile and flammable liquid
relative vapour density (air=1)	0.66
flash point (°C)	-21.7
boiling point (°C)	68.74
autoignition temperature (°C)	225
refractive index	1.342
explosive limits in air (%v/v)	1.1-7.5

Odour threshold

130 ppm (Amoore and Hautala, 1983).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK): 20 ppm (72 mg/m^3)
TWA (ACGIH): 50 ppm (176 mg/m^3)

Conversion factors

1 ppm = 3.52 mg/m^3
1 mg/m^3 = 0.284 ppm
1 mg/l = 284 ppm

Biomonitoring

Many studies have shown that the urine concentration of 2,5-hexanedione can be correlated to *n*-hexane exposure (Perbellini *et al*., 1981a; Iwata *et al*., 1983; Mutti *et al*., 1984; Saito *et al*., 1991; Cardona *et al*., 1993; Periago *et al*., 1993).

However, there are some problems with the methods used for 2,5-hexanedione determination (Saito *et al*., 1991; Soriano *et al*., 1996) and there have been various attempts to refine them (Perbellini *et al*., 1990). The most common method (Perbellini et al., 1981) is time consuming and there may be loss of 2,5-hexanedione from the urine sample during the concentration procedure. Another simpler method (Fedtke and Bolt, 1987) is less sensitive and in addition there may be conversion of other metabolites to 2,5-hexanedione. It has been shown that strong acid hydrolysis, converts 4,5-dihydroxy-2-hexanone to 2,5-hexanedione, whereas weak acid hydrolysis converts it to 2,5-dimethylfuran (Fedtke and Bolt, 1987). Simultaneous analysis of several different metabolites in urine, including 4,5-dihydroxy-2-hexanone, may be a better indicator of exposure than 2,5-hexanedione alone (Soriano *et al*., 1996). However, research on this subject using human subjects is lacking. In addition, a biological limit has been established for 2,5-hexanedione only.

The biological exposure limit (BEI) set by the ACGIH for *n*-hexane is 2,5-hexanedione 5 mg/g of creatinine in urine (ACGIH, 2000). However, since this involves acid hydrolysis this concentration of 2,5-hexanedione must in fact be a total of 2,5-hexanedione itself and 4,5-dihydroxy-2-hexanone which has been converted into 2,5-hexanedione (Fedtke and Bolt, 1987).

A post-shift urine concentration of 2,5-hexanedione greater than 7.5 mg/l is associated with significant electromyographic abnormalities. However, this same study found three workers with significant electromyographic changes who had 2,5-hexanedione urine concentrations of between 3 and 4.5 mg/l (Governa *et al*., 1987). In another study of exposed workers without signs or symptoms of polyneuropathy but with high urinary concentrations of 2,5-hexanedione (mean 11 mg/l; range 5.3-24.2 mg/l) there were no significant

changes in sensory nerve conduction velocities (SNCV) or motor nerve conduction velocities (MNCV). However, the mean amplitude of the sensory nerve action potentials (SNAP) was significantly decreased below normal (Pastore *et al.*, 1994).

In animal studies it was noted that there was a sudden decrease in the urine concentration of metabolites when dosing was interrupted at weekends (Soriano *et al.*, 1996) and this has implications for the timing of samples taken for biological monitoring. Similarly, a study of workers exposed to *n*-hexane demonstrated that the urinary concentration of 2,5-hexanedione was higher at the end of the working week (Cardona *et al.*, 1993).

Urine concentrations of 2,5-hexanedione are unchanged in samples stored at –20 °C or 4 °C for 30 days, but deteriorate rapidly when stored at 25 °C (Saito *et al.*, 1991).

Screening for evidence of polyneuropathy has also been recommended for exposed workers (Chang *et al.*, 1993). Nerve conduction studies have been shown to be reliable and sensitive; evoked potential studies may also be useful. The MNCVs and SNCVs were normal in asymptomatic workers exposed to *n*-hexane with urine 2,5-hexanedione concentrations greater than the recommended BEI. However, there were significant decreases in the mean amplitude of SNAPs and this has been suggested as a criterion for early diagnosis of neuropathy in patients without clinical signs (Pastore *et al.*, 1994).

TOXICITY

n-Hexane is of low acute toxicity (Couri and Milks, 1982; IPCS, 1991), but in chronic exposure it may be the most toxic of the alkanes (Carreón, 2001). Peripheral neuropathy following chronic exposure to *n*-hexane was recognised from the mid 1960s (Spencer *et al.*, 1980). The typical picture is insidious onset and slow progression (Spencer *et al.*, 1980). Adverse effects from *n*-hexane in an industrial environment are now relatively rare (Harbison, 1998). However, when *n*-hexane neuropathy occurs, more than one worker may be affected (Herskowitz *et al.*, 1971; Paulson and Waylonis, 1976; Scelsi *et al.*, 1981; Wang *et al.*, 1986; Huang *et al.*, 1991; Chang *et al.*, 1993). Cases of *n*-hexane-induced polyneuropathy reported in the older literature usually arose from ignorance of the hazards of a chemical originally thought to be non-hazardous. Now, an outbreak is usually associated with a change in working practice, e.g., a recent change to a product containing *n*-hexane (Huang *et al.*, 1991), reduced ventilation or a combination of such factors (Wang *et al.,* 1986). Polyneuropathy has occurred following exposure to *n*-hexane at a wide range of air concentrations (30-2,500 ppm); duration of exposure before onset has ranged from 2 months to 5 years (IPCS, 1991). However, long-term low level exposure may cause neuropathy (Barrgård *et al.*, 1991).

Reports of polyneuropathy from abuse of *n*-hexane-containing glues first appeared in the mid 1970s (Goto *et al.*, 1974; Shirabe *et al.*, 1974; Korobkin *et al.*, 1975; Towfighi *et al.*, 1976; Griffin, 1981); but there have been more recent reports (Smith and Albers, 1997).

It is important to note that the metabolism of *n*-hexane varies between species and it is suggested that humans have a greater susceptibility to *n*-hexane-induced polyneuropathy than the rat (Perbellini *et al.*, 1982). In many studies, it is unclear whether hexane or *n*-hexane was involved. Also, in industry many exposures are to solvent mixtures not to pure *n*-hexane.

Absorption

n-Hexane is rapidly absorbed. Steady-state concentrations of *n*-hexane in blood depend on the exposure concentration. The blood concentration of *n*-hexane has been shown to correlate with air concentrations and alveolar air concentration (Brugnone *et al.*, 1978). The pulmonary uptake of *n*-hexane in workers is 17% (Mutti *et al.*, 1984). In an experimental study near-plateau concentrations were reached after 15 minutes of exposure (Veulemans *et al.*, 1982).

There is limited information on dermal absorption of *n*-hexane. In a limited study, no *n*-hexane was detected in the blood or exhaled air in a volunteer who immersed one hand in *n*-hexane for 1 minute (Nomiyama and Nomiyama, 1975).

Distribution

Hexane is lipophilic. Tissue/air partition coefficients for *in vitro* tissue samples ranged from 2.8 to 5.2 for heart, muscle, brain, kidney and liver, whereas the fat/air partition coefficient was 104 (Perbellini *et al.,* 1985).

In a study in rats, tissue concentrations of 2,5-hexanedione were not proportional to the dose of *n*-hexane and the highest concentrations were found in the blood, kidneys and sciatic nerve (Baker and Rickert, 1981). *n*-Hexane is distributed in tissues in quantities proportional to their lipid content. The exception is the blood, which has a disproportionately high concentration (Böhlen *et al.*, 1973). Fetal concentrations of *n*-hexane and the metabolites methyl *n*-butyl ketone and 2-5-hexanedione were similar to maternal tissue concentrations (Bus *et al.*, 1979).

Metabolism

Hexane is metabolised by cytochrome P450-dependent monoxygenases and alcohol dehydrogenase in the liver to a number of metabolites including 2,5-hexanedione, 2-hexanol, 2,5-dimethylfuran, methyl *n*-butyl ketone (2-hexanone) and γ-valerolactone. 2,5-Hexanedione (a γ-diketone compound) is usually found in the greatest concentration (Perbellini *et al.*, 1980; Governa *et al.*, 1987) and is believed to be the substance responsible for neurotoxicity. The urinary concentration of 2,5-hexanedione has been shown to correlate with both hexane exposure (Perbellini *et al.*, 1981a; Iwata *et al.*, 1983; Mutti *et al.*, 1984; Saito *et al.*, 1991; Cardona *et al.*, 1993; Periago *et al.*, 1993) and the severity of electroneuromyographic changes in exposed workers (Governa *et al.*, 1987), and is used as a biological indicator of exposure.

Other metabolites, 5-hydroxy-2-hexanone and 2,5-hexanediol are also metabolised to 2,5-hexanedione. 2-Hexanol is the main metabolite in animals, but is of only limited importance in humans (Perbellini *et al.*, 1982; Fedtke and Bolt, 1987; Governa *et al.*, 1987).

Elimination

The concentration of exhaled *n*-hexane has been shown to correlate with the concentration of *n*-hexane in air and the urinary concentration of 2,5-hexanedione. Exposure to 176 mg/m^3 (50 ppm) resulted in a urinary 2,5-hexanedione concentration of 7.2 mg/l and an exhaled *n*-hexane concentration of 25.4 mg/m^3 (7.2 ppm) (Periago *et al.*, 1993). It is estimated that about 10% of absorbed *n*-hexane is exhaled unchanged (Mutti *et al.*, 1984). The elimination of *n*-hexane is rapid and biphasic with half-lives of 0.2 and 1.5-2 hours (Veulemans *et al.*, 1982).

In a study in rats the half-life of *n*-hexane was 1-2 hours in all tissues except the kidney where it was 5-6 hours (Baker and Rickert, 1981). In a comparative study in the rat, rabbit and monkey subjected to inhalation of *n*-hexane at 5,000 ppm for 6, 12 and 24 hours, 2,5-hexanedione was still detected in the urine 60 hours following exposure. It was also found that the maximum rate of excretion of 2,5-hexanedione occurred several hours after exposure had ceased (Perbellini *et al.*, 1982).

Mode of action

The peripheral, rather than the central, nervous system is the main target in *n*-hexane toxicity. Studies in rats exposed to *n*-hexane have demonstrated a decrease in nerve-specific marker proteins in the distal segment of the sciatic nerve, whereas the concentrations remained unchanged in the brain and proximal sciatic nerve (Huang *et al.*, 1992). The metabolites of *n*-hexane are more neurotoxic than the parent compound (Krasavage *et al.,* 1980; Abou-Donia *et al.*, 1982). In animals the relative neurotoxicity of these compounds in decreasing order of potency were 2,5-hexanedione, 5-hydroxy-2-hexanone, 2,5 hexanediol, methyl *n*-butyl ketone, 2-hexanol and *n*-hexane (Krasavage *et al.,* 1980; Abou-Donia *et al.*, 1982). In terms of neurotoxicity 2,5-hexanedione was 38 times more potent than *n*-hexane (Krasavage *et al.,* 1980). Neuropathy has been induced in animals administered 2,5-hexanedione (Spencer and Schaumburg, 1975).

2,5-Hexanedione is a γ-diketone compound with a 1,4 spacing of the carbonyl groups. Other γ-diketones (e.g., 2,5-heptanedione and 3,6-octanedione) are also neurotoxic whereas α- and β-diketone compounds (e.g., 2,3-hexanedione and 2,4-hexanedione) are not (Spencer *et al.*, 1978; O'Donoghue and Krasavage, 1979; DeCaprio *et al.*, 1982). The neurotoxic effect of 2,5-hexanedione is thought to be due to it binding

with axonal components (DeCaprio *et al*., 1982). 2,5-Hexanedione has been shown to bind to functional amino (NH_2) groups of axonal proteins forming substituted pyrrole groups (DeCaprio and O'Neill, 1985; Genter *et al*., 1987). Both neurotoxic and non-neurotoxic diketones bind to these amino groups, but only the neurotoxic compounds form pyrrole adducts (DeCaprio *et al*., 1982). Rats exposed to 2,5-hexanedione excreted less pyrroles when given zinc supplements compared to controls (Mateus *et al*., 2000). However, this was only a short-term study and the potential protective effect of zinc against 2,5-hexanedione-induced neurotoxicity was not investigated.

Neurofilament accumulation has been observed in *n*-hexane neuropathy (DeCaprio and O'Neill, 1985). There are 3 main hypotheses on the causes, these are as follows:

- Physicochemical changes triggered by the hydrophobic pyrrole adduct resulting in the disruption of function or transport of neurofilaments (DeCaprio and O'Neill, 1985).
- Auto-oxidation of pyrrole adducts resulting in crosslinking between the neurofilaments (Graham *et al*., 1982; Anthony *et al*., 1983; Graham *et al*., 1995).
- Disruption of the normal relationships between neurofilaments and cytoskeletal components, particularly microtubules (Griffin *et al*., 1983).

Whatever the cause of neurofilament accumulation, the ultimate effect of these changes is thought to be physical blockade of the axonal nutrient flow and subsequent nerve degeneration (DeCaprio and O'Neill, 1985).

In animal studies, the number of 'giant' axons was inversely related to the neurotoxic index of the compound and to the length of the clinical course required to produce paralysis. This suggests that axonal swelling may not be a pre-requisite for axonal dysfunction and is possibly a secondary phenomenon (Krasavage *et al*., 1980).

The acute CNS depressant effects of methyl *n*-butyl ketone are thought to be due to the metabolite 2-hexanol, an aliphatic alcohol with general anaesthetic properties (Feldman, 1999).

Metabolic interactions

Some substances can potentiate the neurotoxicity of *n*-hexane. Consequently, chronic exposure to *n*-hexane, even at low concentrations, with concurrent exposure to another solvent may result in neuropathy. When evaluating *n*-hexane exposure using urinary 2,5-hexanedione as a bio-indicator it is important to consider co-exposure to other solvents such as MEK (Shibata *et al*., 1990). Also, because other compounds such as methyl *n*-butyl ketone cause similar toxic effects to *n*-hexane, exposure to solvent mixtures containing any neurotoxic hexacarbon should be minimised (Spencer *et al*., 1980).

- **Acetone**

  The serum and nerve concentration of 2,5-hexanedione was significantly increased in rats treated with 2,5-hexanedione in combination with acetone, compared to 2,5-hexanedione alone. Methyl ethyl ketone and toluene were also tested with 2,5-hexanedione. The effect with acetone was weaker than that of methyl ethyl ketone but stronger than that of toluene (Zhao *et al*., 1998).

- **Chloroform**

  n-Hexane can potentiate the hepato- and nephrotoxicity of chloroform in animals (Hewitt *et al*., 1980).

- **Methyl *n*-butyl ketone (MnBK, 2-hexanone)**

  Metabolism of both *n*-hexane and methyl *n*-butyl ketone results in production of the same neurotoxic metabolite, 2,5-hexanedione. The toxic effects are therefore additive and workers exposed to both solvents are likely to be at greater risk of neurotoxicity (Feldman, 1999).

- **Methyl ethyl ketone (MEK, 2-butanone)**

  Methyl ethyl ketone potentiates the effects of *n*-hexane. MEK was first suspected of potentiating the neurotoxic effects of *n*-hexane after neuropathy was reported in 18 glue-sniffers following a formulation change. The glue had contained 31% *n*-hexane but neuropathy only developed after the concentration was reduced to 16% and MEK was added to the product. No further cases were reported after the MEK was removed (Altenkirch *et al*., 1978).

  MEK potentiation of hexane neuropathy has been demonstrated in animals (Altenkirch *et al*., 1979). Studies have shown that co-exposure to 2,5-hexanedione and methyl ethyl ketone results in more rapid onset of neurotoxicity than administration of 2,5-hexanedione alone (Ralston *et al*., 1985). Methyl ethyl ketone is not itself neurotoxic. The mechanism of this phenomenon is unclear, it is not thought to be due to 2,5-hexanedione alone (Shibata *et al*., 1990). In animals exposed to the same concentration of *n*-hexane the level of urinary *n*-hexane metabolites depended on the concentrations of MEK involved in the co-exposure. The concentration of the main *n*-hexane metabolites, 2,5-hexanedione and 2-hexanol decreased as the MEK concentration increased (Shibata *et al*., 1990). However, a more recent study demonstrated that although urinary concentrations of 2,5-hexanedione decreased in the short-term with co-exposure to MEK, the concentration of 2,5-hexanedione actually increased with more prolonged exposure (Ichihara *et al*., 1998).

  In a toxicokinetic study of human volunteers, co-exposure to methyl ethyl ketone had little effect on *n*-hexane toxicokinetics. However, there was a decrease in the rate of formation of 2,5-hexanedione suggesting inhibition of the metabolism of *n*-hexane (Van Engelen *et al*., 1997).

  The serum and nerve concentration of 2,5-hexanedione was significantly increased in rats treated with 2,5-hexanedione in combination with methyl ethyl ketone, compared to 2,5-hexanedione alone. The effect was strongest with methyl ethyl ketone compared to co-exposure with acetone or toluene (Zhao *et al*., 1998).

- **Toluene**

  The serum and nerve concentration of 2,5-hexanedione was significantly increased in rats treated with 2,5-hexanedione in combination with toluene compared to 2,5-hexanedione alone. The effect with toluene was weaker than that observed with acetone and methyl ethyl ketone (Zhao *et al*., 1998). Workers exposed simultaneous to methyl ethyl ketone and *n*-hexane had increased urinary excretion of 2,5-hexanedione, whereas simultaneous exposure to toluene and *n*-hexane reduced urinary excretion (Cardona et al., 1993).

- **Solvent mixtures**

  Workers exposed to mixtures of *n*-hexane and one or more of toluene, ethyl acetate and acetone below the occupational exposure limits did not give rise to increased urinary concentrations of 2,5-hexanedione. It was concluded that in these low concentrations the solvents did not alter *n*-hexane metabolism (Kawai *et al*., 2000).

CASE REPORTS

Peripheral neuropathy following chronic inhalation

A 60 year old male was admitted to hospital in 1979 with a five year history of progressive lower extremity weakness and sensory loss. He had worked as a janitor for an adhesive tape manufacturer. The company had used the solvents *n*-hexane and toluene from February to July 1971. Use of *n*-hexane was stopped after publication of the first report of *n*-hexane neuropathy in the United States (Herskowitz *et al*., 1971). However, the patient found that *n*-hexane was useful for removing glue stains and he had sequestered a container of it which he used to clean table tops in the laboratory. He used gloves during this process and spent less than two hours daily cleaning the laboratory area. He did not use *n*-hexane

anywhere else. In 1973 the safety manager discovered that he was using *n*-hexane and measured the solvent content of the air in the laboratory on five separate occasions. The average concentration was 325 ppm with a single peak of 450 ppm. He was permitted to continue using the solvent as the concentration never exceeded 500 ppm, which, at the time, was the TLV for *n*-hexane.

He first noticed weakness and numbness of the lower limbs in 1974 and over the next few years the numbness progressed up to the calves. In 1976 he began to have difficulty in walking and, on retirement in 1977, was unable to walk without assistance. On examination he had marked lower extremity weakness with distal upper and lower extremity sensory loss. Electromyography indicated denervation in distal lower extremity muscles. By 1979 he had moderate subjective improvement in lower extremity sensation but still had difficulty in walking. Sensory nerve responses were delayed in the upper and lower extremities. A sural nerve biopsy showed myelinated and unmyelinated enlarged axons. Normal axons were surrounded by a thin myelin sheath. The swollen axons were distended by massive accumulations of neurofilaments; some were surrounded only by a single basement membrane. The slow onset of this patient's illness was thought to be due to the relatively low level of exposure to *n*-hexane (Ruff *et al.*, 1981). A more recent anecdotal report has suggested that low level exposure to *n*-hexane (2.8-28 ppm) for 30 years may have caused neuropathy (Barrgård *et al.*, 1991).

Peripheral neuropathy following chronic inhalation

Six months after starting work in a printing factory, a 30 year old male developed numbness and painful paraesthesia in both legs. This was followed by weakness and muscle wasting. His worked involved regular cleaning of a rubber roller blanket with solvents including *n*-hexane. He did not wear gloves or respiratory protection. One month after the onset of symptoms, his upper limbs also became affected. He gave up work but continued to deteriorate over the next two months. Several of his work colleagues had also become unwell. On examination he had a typical sensorimotor peripheral neuropathy which was more severe in the lower limbs. There was hyporeflexia, severe distal and mild proximal muscle wasting and weakness. Sensory impairment was present in a glove and stocking distribution. Nerve conduction studies showed very small median, ulnar and sural sensory action potential amplitudes. Similarly the median, ulnar, posterior tibial and common peroneal motor action potential amplitudes were small and highly dispersed. Electromyography showed active denervation changes in distal muscles. Somatosensory, visual and brainstem auditory evoked potentials studies were normal. Sural nerve biopsy showed a normal number of myelinated and non-myelinated fibres. There was mild thickening of the perineurium and giant axonal swellings in many myelinated fibres. An electron micrograph showed the swollen axons had attenuated myelin sheaths and contained accumulated neurofilaments in the axoplasm and loss of neurotubules. Some axons had no myelin sheath. In other areas there was no axonal swelling, but paranodal myelin attenuation resulting in a widened nodal gap. He began to recover in the proximal limbs after four months of physiotherapy. At follow up after 12 months there was mild distal weakness in the legs with painful paraesthesia in the feet and poor exercise endurance (Chang *et al.*, 1993).

Parkinsonism following chronic inhalation

A 49 year old female worked for 20 years in a leather product company. After this time she continued to work at home for a further 11 years until the onset of illness. At home the working environment was unprotected and uncontrolled. She used two glues; one used daily (containing *n*-hexane 85.5%) and the other used twice weekly (containing *n*-hexane 49%, acetone 5%, ethyl acetate 9%, trichloroethylene 7% and 1,2-dichloropropane 5%). She first developed rapidly progressing disease with severe akinesia, moderate hypertonia, mild parkinsonism and tremor in May and stopped using *n*-hexane products in November. Fourteen months after this she was confined to a wheelchair. Treatment with levodopa initially gave a good response but became less effective after a few weeks and dyskinesias were evident. However, she responded well to apomorphine. Homovanillic acid in the cerebrospinal fluid (CSF) was reduced; this is consistent with findings in other Parkinsonian patients. Electromyelography revealed mild axonal neuropathy (Pezzoli *et al.*, 1989). The neuropathy improved after removal from *n*-hexane exposure, but there was rapid progression of parkinsonism and she died five years after the onset of symptoms (Pezzoli *et al.*, 1995).

CLINICAL EFFECTS

Acute exposure

Inhalation

Acute exposure to 500 ppm of *n*-hexane for 3-10 minutes causes no effect; brief exposure to 1,400-2,000 ppm results in headache, nausea and eye and throat irritation; 5,000 ppm for 10 minutes causes dizziness and mild CNS depression (reviewed in Schaumberg and Spencer, 1976; Cavender, 1994). Euphoria may occur which is why *n*-hexane is abused. Coma may occur after exposure to a high concentration. Polyneuropathy is not expected from an acute exposure to *n*-hexane.

Dermal

n-Hexane is a mild skin irritant. Dermal exposure to *n*-hexane may cause immediate irritation with a burning sensation and transient erythema (IPCS, 1991). A slight and transient erythema appeared after 10-20 minutes of exposure to 1.5 ml of analytical grade *n*-hexane confined to a 2 cm circle on the forearm (Wahlberg, 1984). More prolonged contact may result in itching and blisters. Studies using excised rat skin have shown that dermal absorption of *n*-hexane is low (Tsuruta, 1982). However, in a study of workers exposed to *n*-hexane, those who wore gloves had a mean urinary concentration of 2,5-hexanedione that was about half that of workers who did not protect their hands and arms. This suggests that dermal absorption may account for up to 50% of the total absorbed dose of *n*-hexane (Cardona *et al*., 1993).

Eye

There is limited information on the effects of *n*-hexane in contact with the eye (IPCS, 1991). However, since *n*-hexane is a mild skin irritant it is also likely to cause irritation to the eye.

Ingestion

Acute ingestion of *n*-hexane may cause nausea, vomiting, dizziness, CNS depression with drowsiness and possibly coma. There is a risk of aspiration of *n*-hexane into the lungs (Gerade, 1963), which may cause chemical pneumonitis and pulmonary oedema. Ingestion of 50 g is said to be fatal (Cavender, 1994) but this is anecdotal.

Chronic exposure

Inhalation

Neurological effects

n-Hexane-induced peripheral neuropathy is well described with a typical picture of sensory loss followed by motor signs and symptoms. There is usually numbness, which is insidious in onset and typically of hands and feet (a glove and stocking distribution) and rarely beyond the knees or wrists. Weakness usually appears first in the legs and then the arms with reduced or absent tendon reflexes. In severe cases there is marked distal atrophy and proximal weakness. Muscle cramping and weight loss commonly occur (Smith and Albers, 1997) and there may be general malaise, headache, dizziness and anorexia (Huang *et al*., 1989). Onset of effects often resembles Guillain-Barré syndrome. These neurological changes are also termed 'dying-back' neuropathy or central-peripheral distal axonopathy.

After cessation of exposure the clinical condition may deteriorate further; this is often termed 'coasting' and has been described frequently (Goto *et al*., 1974; Shirabe *et al*., 1974; Korobkin *et al*., 1975; Towfighi *et al*., 1976; Cianchetti *et al*., 1976; Griffin, 1981; Huang *et al*., 1989; Chang, 1990; Chang *et al*., 1993; Kuwabara *et al*., 1993). This phenomenon has also been described with other toxic neuropathies (Huang *et al*., 1989; Smith and Albers, 1997). In a review of four patients muscle strength, sensory deficit and nerve conduction deteriorated over a 2-5 month period (maximal within 1-2 months) before a slow recovery over the next 12

months. The sensory symptoms disappeared in 3-5 months and the tendon reflexes returned to normal within about a year (Huang *et al.*, 1989). Most severe toxicity is usually seen in individuals abusing *n*-hexane (Harbison, 1998) with a more rapid onset of clinical signs and symptoms of neuropathy.

Laboratory investigations (haematological, hepatic, renal) in *n*-hexane exposed individuals are usually normal (Spencer *et al.*, 1980).

In a long-term study of *n*-hexane-induced neuropathy patients, 50% of them had hyperreflexia and urination urgency as the most common effect two years after the onset of illness (Bravaccio *et al.*, 1981). Impotence has occasionally been reported with *n*-hexane neuropathy, but it is unclear whether this is related to nervous system dysfunction (Korobkin *et al.*, 1975). Autonomic disturbances, particularly excessive sweating of hands and feet, have been reported. This is more commonly seen in *n*-hexane abusers rather than occupationally exposed individuals (Spencer *et al.*, 1980).

Parkinsonism following occupational exposure to *n*-hexane has been reported (Pezzoli *et al.*, 1989; Pezzoli *et al.*, 1995; Vanacore *et al.,* 2000).

Pathologically, *n*-hexane neuropathy presents as loss of large myelinated fibres with focally enlarged 'giant' axons with massive accumulation of neurofilaments (10 nm) and associated thinning of the overlying myelin (Schaumberg and Spencer, 1976). There may also be paranodal myelin retraction and occasional segmental demyelination (Griffin, 1981). These effects have also been observed with other toxic neuropathies. It should be noted that Guillain-Barré syndrome is characterised by myelin pathology, whereas hexacarbon neuropathy is characterised by axonal pathology (Spencer *et al.*, 1980).

Electroneurophysiological studies reflect the severity of clinical features of neuropathy. There is usually a fall in nerve conduction velocities (NCV), profound amplitude reduction of compound muscle action potentials (CMAP) and sensory nerve action potentials (SNAP), and obvious prolongation of distal latencies (DL). Conduction block has also been reported (Kuwabara *et al.*, 1993). In evoked potential (EP) studies there is usually prolonged conduction time in visual, auditory and somatosensory pathways in the CNS (Chang, 1990).

Individuals without signs or symptoms of neuropathy may, however, have evidence of neurological damage. Workers exposed to 58 ppm of *n*-hexane (on average) did not show any signs or symptoms of polyneuropathy, but a series of peripheral nervous system function parameters showed statistically significant alterations compared to controls (Sanagi *et al.*, 1980). Workers without any signs or symptoms of neurotoxicity who were exposed to *n*-hexane, toluene and xylene were found to have evidence of neurological damage measured by the frequency of postural sway when compared to controls (Yokohama *et al.*, 1997). The frequency of sways with eyes open (vestibulocerebellar type of sway) was related positively to the urinary concentration of 2,5-hexanedione and inversely to the concentration of methylhippuric acid (xylene metabolite). This is compatible with histopathological changes in the vermis (containing the vestibulocerebellum) of *n*-hexane exposed animals (Schaumberg and Spencer, 1976). Exposed workers also had increased frequency of sway with eyes closed (spinocerebellar afferent type of sway), and this supports the observations of adverse effects on the spinocerebellar tract and peripheral nerves in *n*-hexane exposed animals (Schaumberg and Spencer, 1976).

Co-exposure to some other solvents may potentiate the neurotoxic effects of *n*-hexane. In these circumstances exposure to a relatively low concentration of *n*-hexane may cause neuropathy (see Metabolic interactions).

Immunotoxicity

Chronic exposure to *n*-hexane is associated with immunological changes (Jackson *et al.,* 1996; Karakaya *et al.*, 1996). In a study of 35 workers exposed to *n*-hexane it was found that they had a significant reduction in IgG, IgM and IgA concentrations. In addition, there was a correlation between the urine concentration of 2,5-hexanedione and serum immunoglobin concentrations. There was no difference between the white blood cell count in the exposed and the control groups. The nature and mechanism of these effects has not been clarified (Karakaya *et al.*, 1996).

There was a significant reduction in chemotaxis, but not respiratory burst, in polymorphonuclear leucocytes harvested from *n*-hexane exposed workers (Governa *et al.,* 1994).

Workers exposed to *n*-hexane (mean breathing air zone concentration 58 ppm; range 4.3-300 ppm), toluene (mean 27 ppm; range 5.37-115.2 ppm) and methyl ethyl ketone (mean 11 ppm; range 2.43-47 ppm) had no impairment of natural killer cell activity or changes in interleukin-2 or gamma-interferon concentrations (Yücesoy *et al.*, 1999).

Dermal

There is only limited information on chronic dermal exposure to *n*-hexane. Workers in a soybean hexane-extraction plant had a higher incidence of dry or irritated skin than maintenance workers (NIOSH, 1983).

Eye

Ocular effects may occur in individuals exposed *n*-hexane. Blurred vision, constriction of the visual field, optic nerve atrophy and retrobulbar neuritis have been reported. However, the ocular effects are usually mild and do not correlate with the severity of neuropathy (IPCS, 1991).

Macula changes, particularly macula oedema and changes in colour vision have also been reported in chronically exposed individuals. These workers did not have signs or symptoms of neuropathy (Raitta *et al.*, 1978). A subsequent study in these workers found a significant reduction in peak-to-peak amplitudes for several visual evoked potential components, possibly due to conduction block in intracerebral axons. There was also a significant increase in the latency of some components, which was attributed to partial axonal degeneration in the visual pathways. A significant decrease in the amplitude of the electroretinogram with a reduced latency in the 'b' wave was also noted (Seppäläinen *et al.*, 1979). In two patients with mild changes in colour vision, the abnormality was still present four years later (Chang, 1990).

Studies in rats administered 2,5-hexanedione have shown that 2,5-hexanedione reaches the aqueous humor and retina. This results in damage to the photoreceptor cells of the retina and is more pronounced in the presence of light (Bäckström *et al.*, 1998).

Ingestion

Peripheral neuropathy was reported in a 28 year old male who had chronically ingested benzin (a low boiling petroleum distillate) which contained *n*-hexane, because he believed it would cure gonorrhoea. He had ingested a cupful diluted in water once or twice daily for 5-6 weeks when he began to notice weakness in his arms and legs. The weakness in his legs progressed and he developed muscle atrophy despite discontinuation. He gradually improved over several months but was left with slight permanent weakness in his legs (Schwarz, 1933; Feldman, 1999).

Carcinogenicity

The carcinogenic potential of *n*-hexane has not been adequately studied (IPCS, 1991); it has not been evaluated by the IARC.

Genotoxicity

Only limited mutagenicity testing has been conducted on *n*-hexane (IPCS, 1991). *n*-Hexane has produced negative results in point mutation assays but there is some evidence that it can produce chromosomal aberrations *in vitro* (IPCS, 1991).

2,5-Hexanedione was a weak inducer of chromosome loss in yeast but very potent in the presence of propionitrile (Zimmerman *et al.*, 1989). However, this test may not be suitable as a predictor of genetic damage because no direct action on genetic material occurs (Topping *et al.*, 2001).

Reproductive toxicity

The reproductive toxicity of *n*-hexane has not been sufficiently investigated and many studies are inadequate (IPCS, 1991). There is no substantial evidence of embryotoxicity or teratogenicity in rats (Bus *et al.*, 1979; IPCS, 1991; Daughtrey *et al.*, 1994). Testicular atrophy was noted in rats given 2,5-hexanedione in drinking water. These changes were seen before the onset of clinical signs of neuropathy (O'Donoghue *et al.*, 1978). There are insufficient data to assess whether chronic *in utero* exposure can cause neuropathy (IPCS, 1991).

RISK GROUPS

There are no medical conditions which predispose individuals to hexacarbon neuropathy (Spencer *et al.*, 1980).

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

n-Hexane is of low acute toxicity and gastric decontamination is unlikely to be required unless a very large quantity has been ingested. However, because of the risk of aspiration a cuffed endotracheal tube must be used to protect the airway, since *n*-hexane is an aspiration hazard. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive.

Antidote

There is no specific antidote for *n*-hexane.

Chronic exposure

Referral to a neurologist for electroneurophysiological assessment is recommended for any individual with suspected neuropathy. The prognosis of *n*-hexane-induced polyneuropathy is usually good (Huang *et al.*, 1989; Chang, 1990), although it depends on the severity (Smith and Albers, 1997). Recovery may be slow. In a study of 11 patients with moderate to severe neuropathy, all were able to resume normal daily activities within 1-4 years. The sensory disturbance usually resolves much earlier than motor disturbances (Huang *et al.*, 1989; Chang, 1991).

REFERENCES

Abou-Donia MB, Makkawy H-AM, Graham DG. 1982 The relative neurotoxicities of *n*-hexane, methyl *n*-butyl ketone, 2,5-hexanediol and 2,5-hexanedione following oral or intraperitoneal administration in hens. *Toxicol Appl Pharmacol* 62:369-389.

Altenkirch H, Stoltenberg G, Wagner HM. 1978 Experimental studies on hydrocarbon neuropathies induced by methyl ethyl ketone. *J Neurol* 219:159-170.

Altenkirch H, Stoltenburg-Didinger G, Wagner HM. 1979 Experimental data on the neurotoxicity of methyl-ethyl-ketone (MEK). *Experimentia* 35 (4):503-504.

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Anthony DC, Boekelheide K, Anderson CW, Graham DG. 1983 The effects of 3,4-dimethyl substitution on the neurotoxicity of 2,5-hexanedione. II. Dimethyl substitution accelerates pyrrole formation and protein crosslinking. *Toxicol Appl Pharmacol* 71:372-382.

Bäckström B, Shibata E, Nylén P, Collins PV. 1998 2,5-Hexanedione concentrations and morphological changes within the eye of the albino rat. *Arch Toxicol* 72:597-600.

Baker TS, Rickert DE. 1981 Dose-dependent uptake, distribution and elimination of inhaled *n*-hexane in the Fischer-344 rat. *Toxicol Appl Pharmacol* 61:414-422.

Barrgård L, Sällsten G, Nordborg C, Gieth W. 1991 Polyneuropathy possibly caused by 30 years of low exposure to *n*-hexane. *Scand J Work Environ Health* 17:205-207.

Böhlen P, Schlunegger UP, Läuppi E. 1973 Uptake and distribution of hexane in rat tissue. *Toxicol Appl Pharmacol* 25:242-249.

Bravaccio F, Ammendola A, Barruffo L, Carlomagnio S. 1981 H-reflex behavior in glue (*n*-hexane) neuropathy. *Clin Toxicol* 18 (12):1369-1375.

Brugnone F, Perbellini L, Grigolini L, Apostoli P. 1978 Solvent exposure in a shoe upper factory. 1. *n*-Hexane and acetone concentration in alveolar and environmental air and in blood. *Int Arch Occup Environ Health* 42:51-62.

Bus JB, White EL, Tye RW, Barrow CS. 1979 Perinatal toxicity and metabolism of *n*-hexane in Fischer-344 rats after inhalation exposure during gestation. *Toxicol Appl Pharmacol* 51:295-302.

Cardona A, Marhuenda D, Marti J, Brugnone F, Roel J, Perbellini L. 1993 Biological monitoring of occupational exposure to *n*-hexane by measurement of urinary 2,5-hexanedione. *Int Arch Occup Environ Health* 65:71-74.

Carreón T. 2001 Aliphatic hydrocarbons. In: *Patty's Toxicology,* fifth edition, volume 4. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Cavender F. 1994 Aliphatic hydrocarbons. In: *Patty's Industrial Hygiene and Toxicology* fourth edition, Volume 2, Part B. Clayton GD and Clayton FE (editors). John Wiley & Sons, New York.

Chang CM, Yu CW, Fong KY, Leung SY, Tsin TW, Yu YL, Cheung TF, Chan SY. 1993 *n*-Hexane neuropathy in offset printers. *J Neurol Neurosurg Psychiatry* 56 (5):538-542.

Chang YC. 1990 Patients with *n*-hexane induced polyneuropathy: a clinical follow up. *Br J Ind Med* 47:485-489.

Chang YC. 1991 An electrophysical follow up of patients with *n*-hexane polyneuropathy. *Br J Ind Med* 48:12-17.

Cianchetti C, Abbritti G, Perticoni G, Siracusa A, Curradi F. 1976 Toxic polyneuropathy of shoe-industry workers. A study of 122 cases. *J Neurol Neurosurg Psychiatry* 39:1151-1161.

Couri D, Milks M. 1982 Toxicity and metabolism of the neurotoxic hexacarbons *n*-hexane, 2-hexanone and 2,5-hexanedione. *Ann Rev Pharmacol Toxicol* 22:145-166.

Daughtrey WC, Neeper-Bradley T, Duffy J, Haddock L, Keenan T, Kirwan C, Soiefer A. 1994 Two-generation reproductive study on commercial hexane solvent. *J App Toxicol* 14 (5):387-393.

DeCaprio AP, Olajos EJ, Weber P. 1982 Covalent binding of a neurotoxic *n*-hexane metabolite: conversion of primary amines to substituted pyrrole adducts by 2,5-hexanedione. *Toxicol Appl Pharmacol* 65:440-450.

DeCaprio AP, O'Neill EA. 1985 Alterations in rat axonal cytoskeleton proteins induced by *in vitro* and *in vivo* 2,5-hexanedione exposure. *Toxicol Appl Pharmacol* 78:235-247.

Fedtke N, Bolt HM. 1987 The relevance of 4,5-dihydroxy-2-hexanone in the excretion kinetics of *n*-hexane metabolites in rat and man. *Arch Toxicol* 61:131-137.

Feldman RG. 1999 *Occupational and Environmental Neurotoxicology*. Lippincott-Raven, Philadelphia.

Genter MB, Szakál-Quinn G, Anderson CW, Anthony DC, Graham DG. 1987 Evidence that pyrrole formation is a pathogenic step in γ-diketone neuropathy. *Toxicol Appl Pharmacol* 87:351-362.

Gerade H. 1963 Toxicological studies on hydrocarbons. *Arch Toxicol* 6:329-341.

Goto I, Matsumura M, Inoue N, Murai Y, Shida K, Santa T, Kuroiwa Y. 1974 Toxic neuropathy due to glue sniffing. *J Neurol Neurosurg Psychiatry* 37:848-853.

Governa M, Calisti R, Coppa G, Tagliavento G, Colombi A, Troni W. 1987 Urinary excretion of 2,5-hexanedione and peripheral polyneuropathies in workers exposed to hexane. *J Toxicol Environ Health* 20:219-228.

Governa M, Valentino M, Visonà I, Monaco F. 1994 Human polymorphonuclear leukocyte chemotaxis as a tool in detecting biological early effects in workers occupationally exposed to low levels of *n*-hexane. *Hum Exp Toxicol* 13:663-670.

Graham DG, Anthony DC, Boekelheide K, Maschmann NA, Richards RG, Wolfram JW, Shaw BR. 1982 Studies of the molecular pathogenesis of hexane neuropathy. II. Evidence that pyrrole derivatization of lysyl residues leads to protein crosslinking. *Toxicol Appl Pharmacol* 64:415-422.

Graham DG, Amarnath V, Valentine WM, Pyle SJ, Anthony DC. 1995 Pathogenetic studies of hexane and carbon disulfide neurotoxicity. *Crit Rev Toxicol* 25 (2):91-112.

Griffin JW. 1981 Hexacarbon neurotoxicity. *Neurobehav Toxicol Teratol* 3:437-444.

Griffin JW, Fahnestock KE, Price DL, Cork LC. 1983 Cytoskeleton disorganisation induced by local application of b,b'-iminodipropionitrile and 2,5-hexanedione. *Ann Neurol* 14:55-61.

Harbison RD. 1998 Aliphatic hydrocarbons. In: *Hamilton and Hardy's Industrial Toxicology*, fifth edition. Harbison RD (editor). Mosby, St Louis.

Herskowitz A, Ishi N, Schaumberg H. 1971 *n*-Hexane neuropathy. A syndrome occurring as a result of industrial exposure. *N Engl J Med* 285 (2):82-85.

Hewitt WR, Miyajima H, Côté MG, Plaa GL. 1980 Acute alternation of chloroform-induced hepato- and nephrotoxicity by *n*-hexane, methyl *n*-butyl ketone, and 2-5-hexanedione. *Toxicol Appl Pharmacol* 53:230-248.

Huang C-C, Chu N-S, Cheng S-Y, Shin T-S. 1989 Biphasic recovery in *n*-hexane polyneuropathy. A clinical and electrophysiological study. *Acta Neurol Scand* 80:610-615.

Huang C-C, Shih T-S, Cheng S-Y, Chen S-S, Tchen P-H. 1991 *n*-Hexane polyneuropathy in a ball-manufacturing factory. *J Occup Med* 33 (2):139-142.

Huang J, Shibata E, Kato K, Aseda N, Takeuchi Y. 1992 Chronic exposure to *n*-hexane induces changes in nerve-specific proteins in the distal peripheral nerve of the rat. *Hum Exp Toxicol* 11:323-327.

Ichihara G, Saito I, Kamijima M, Yu X, Shibata E, Toida M, Takeuchi Y. 1998 Urinary 2,5-hexanedione increases with potentiation of neurotoxicity in chronic coexposure to *n*-hexane and methyl ethyl ketone. *Int Arch Occup Environ Health* 71:100-104.

IPCS. 1991 *Environmental Health Criteria 122. n-Hexane*. World Health Organization, International Programme on Chemical Safety, Geneva.

Iwata M, Takeuchi Y, Hisanaga N, Ono Y. 1983 A study on biological monitoring of *n*-hexane exposure. *Int Arch Occup Environ Health* 51:253-260.

Jackson JR, de Kechove D, Karakay A. 1996 Changes in immunoglobulin concentrations and urinary 2,5-hexanedione concentrations [letter]. *Hum Exp Toxicol* 15:284-285.

Karakaya A, Yücesoy B, Burgaz S, Sabir HU, Karakaya AE. 1996 Some immunological parameters in workers occupationally exposed to *n*-hexane. *Hum Exp Toxicol* 15:56-58.

Kawai T, Miyama Y, Horiguchi S, Sakamoto K, Zhang Z-W, Higashikawa K, Ikeda M. 2000 Possible metabolic interaction between hexane and other solvents co-exposed at sub-occupational exposure limit levels. *Int Arch Occup Environ Health* 73:449-456.

Korobkin R, Asbury AK, Sumner AJ, Nielsen SL. 1975 Glue sniffing neuropathy. *Arch Neurol* 32:158-162.

Krasavage WJ, O'Donoghue JL, DiVincenzo GD, Terhaar CJ. 1980 The relative neurotoxicity of methyl-*n*-butyl ketone, *n*-hexane and their metabolites. *Toxicol Appl Pharmacol* 52:433-441.

Kuwabara S, Nakajima M, Tsuboi Y, Hirayama K. 1993 Multifocal conduction block in *n*-hexane neuropathy. *Muscle Nerve* 16 (2):1416-1417.

Mateus ML, dos Santos APM, Batoreu MC. 2000 Evidence for zinc protection against 2,5-hexanedione toxicity by co-exposure of rats to zinc chloride. *J Appl Toxicol* 20:211-214.

Mutti A, Falzoi M, Lucertini S, Arfini G, Zignani M, Lombardi S, Franchini I. 1984 *n*-Hexane metabolism in occupationally exposed workers. *Br J Ind Med* 41:533-538.

NIOSH. 1983 Health hazard evaluation report. Cincinnati, Ohio. National Institute for Occupational Safety and Health. HETA-80-256-1386. Cited in: IPCS. 1991 *Environmental Health Criteria 122. n-Hexane*. World Health Organization, International Programme on Chemical Safety, Geneva.

Nomiyama K, Nomiyama H. 1975 [Concerning the cutaneous absorption of *n*-hexane in humans]. *Jpn J Hyg* 30:140 (in Japanese). Cited in: IPCS. 1991 *Environmental Health Criteria 122. n-Hexane*. World Health Organization, International Programme on Chemical Safety, Geneva.

O'Donoghue JL, Krasavage WJ. 1979 Hexacarbon neuropathy: a γ-diketone neuropathy? *J Neuropathol Exp Neurol* 38:333.

O'Donoghue JL, Krasavage WJ, Terhaar CJ. 1978 Toxic effects of 2,5-hexanedione [abstract]. *Toxicol Appl Pharmacol* 45:269.

Pastore C, Marheunda D, Marti J, Cardona A. 1994 Early diagnosis of *n*-hexane-caused neuropathy. *Muscle Nerve* 17:981-986.

Paulson GW, Waylonis GW. 1976 Polyneuropathy due to *n*-hexane. *Arch Intern Med* 136:880-882.

Perbellini L, Brugnone F, Pavan I. 1980 Identification of the metabolites of *n*-hexane, cyclohexane and their isomers in men's urine. *Toxicol Appl Pharmacol* 53:220-229.

Perbellini L, Brugnone F, Faggionato G. 1981a Urinary excretion of the metabolites of *n*-hexane and its isomers during occupational exposure. *Br J Ind Med* 38:20-26.

Perbellini L, Brugnone F, Gaffuri E. 1981b Neurotoxic metabolites of 'commercial hexane' in the urine of shoe factory workers. *Clin Toxicol* 18 (12):1377-1385.

Perbellini L, Amantini MC, Brugnone F, Frontali N. 1982 Urinary excretion of *n*-hexane metabolites. A comparative study in rat, rabbit and monkey. *Arch Toxicol* 50:203-215.

Perbellini L, Brugnone F, Caretta D, Maranelli G. 1985 Partition coefficients of some industrial aliphatic hydrocarbons (C5-C7) in blood and human tissues. *Br J Ind Med* 42:162-167.

Perbellini L, Amoros DM, Llorens AC, Guiliari C, Brugnone F. 1990 An improved method of analysing 2,5-hexanedione in urine. *Br J Ind Med* 47:421-424.

Periago JF, Cardona A, Marhuenada D, Roel J, Villanueva M, Marti J, Luna A. 1993 Biological monitoring of occupational exposure to *n*-hexane by exhaled air analysis and urinalysis. *Int Arch Occup Environ Health* 65:275-278.

Pezzoli G, Barbieri S, Ferrante C, Zecchinelli A, Foa V. 1989 Parkinsonism due to *n*-hexane exposure [letter]. *Lancet* 2:874.

Pezzoli G, Antonini A, Barbieri S, Canesi M, Perbellini L, Zecchinelli A, Mariani CB, Bonetti A, Leenders KL. 1995 *n*-Hexane-induced parkinsonism: pathogenic hypotheses. *Mov Disord* 10 (3):279-282.

Raitta C, Seppäläinen A-M, Huuskonen MS. 1978 *n*-Hexane maculopathy in industrial workers. *Graefes Arch Ophthalmol* 209:99-110.

Ralston WH, Hilderbrand RL, Uddin D, Andersen ME, Gardier RW. 1985 Potentiation of 2,5-hexanedione neurotoxicity by methyl ethyl ketone. *Toxicol Appl Pharmacol* 81:319-729.

Ruff RL, Petito CK, Acheson LS. 1984 Neuropathy associated with chronic low level exposure to *n*-hexane. *Clin Toxicol* 18 (5):515-519.

Saito I, Shibata E, Huang J, Hisanaga N, Ono Y, Takeuchi Y. 1991 Determination of urinary 2,5-hexanedione concentration by an improved analytical method as an index of exposure to *n*-hexane. *Br J Ind Med* 48:568-574.

Sanagi S, Seki Y, Sugimoto K, Hirata M. 1980 Peripheral nervous system functions of workers exposed to *n*-hexane at low level. *Int Arch Occup Environ Health* 47:69-79.

Scelsi R, Poggi P, Fera L, Gonella G. 1981 Industrial neuropathy due to *n*-hexane. Clinical and morphological findings in three cases. *Clin Toxicol* 18 (12):1387-1393.

Schaumburg H, Spencer PS. 1976 Degeneration in central and peripheral nervous systems produced by pure *n*-hexane: an experimental study. *Brain* 99:183-192.

Schwarz HG. 1933 Benzin-Vergiftung chronische, medizinale [Chronic medicinal benzin poisoning]. *Samml Vergiftungsf* 4:247-248.

Seppäläinen A, Raitta C, Huuskonen M. 1979 *n*-Hexane-induced changes in visual evoked potentials and electroretinograms of industrial workers. *Electroencephalogr Clin Neurophysiol* 47:492-498.

Shibata E, Huang J, Ono Y, Hisanaga N, Iwata M, Saito I, Takeuchi Y. 1990 Changes in urinary *n*-hexane metabolites by co-exposure to various concentrations of methyl ethyl ketone and fixed *n*-hexane levels. *Arch Toxicol* 64:165-168.

Shirabe T, Tsuda T, Terao A, Araki S. 1974 Toxic polyneuropathy due to glue-sniffing. Report of two cases with a light and electro-microscopic study of the peripheral nerves and muscles. *J Neurol Sci* 21:101-113.

Smith AG, Albers JW. 1997 *n*-Hexane neuropathy due to rubber cement sniffing. *Muscle Nerve* 20:1445-1450.

Soriano T, Menéndez M, Sanz P, Repetto M. 1996 Method for the simultaneous quantification of *n*-hexane metabolites: application to *n*-hexane metabolism determination. *Hum Exp Toxicol* 15:497-503.

Spencer PS, Schaumberg HH, 1975 Experimental neuropathy produced by 2,5-hexanedione – a major metabolite of the neurotoxic industrial solvent methyl *n*-butyl ketone. *J Neurol Neurosurg Psychiat* 38:771-775.

Spencer PS, Bishoff MC, Schaumburg HH. 1978 On the specific molecular configuration of neurotoxic aliphatic hexacarbon compounds causing central-peripheral distal axonopathy. *Toxicol Appl Pharmacol* 44:17-28.

Spencer PS, Schaumburg HH, Sabri MI, Veronesi B. 1980 The enlarging view of hexacarbon neuropathy. *CRC Crit Rev Toxicol* 7 (4):279-356.

Topping DC, Morgott DA, O'Donoghue JL. 2001 Ketones of six to thirteen carbons. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Towfighi J, Gonatas NK, Pleasure D, Cooper HS, McCree L. 1976 Glue sniffer's neuropathy. *Neurology* 26:238-243.

Tsuruta H. 1982 Percutaneous absorption of organic solvents III. On the penetration rates of hydrophobic solvents through excised rat skin. *Ind Health* 20:335-345.

Vanacore N, Gasparini M, Brusa L, Meco G. 2000 A possible association between exposure to *n*-hexane and parkinsonism. *Neurol Sci* 21:49-52.

van Engelen JGM, Rebel-de Haan W, Opdam JJG, Mulder GJ. 1997 Effect of coexposure to methyl ethyl ketone (MEK) on *n*-hexane toxicokinetics in human volunteers. *Toxicol Appl Pharmacol* 144:385-395.

Veulemans H, Van Vlem E, Janssens H, Masschelein R, Leplat A. 1982 Experimental human exposure to *n*-hexane. Study of the respiratory uptake and elimination and of *n*-hexane concentration in peripheral venous blood. *Int Arch Occup Environ Health* 49:251-263.

Wahlberg JE. 1984 Erythema-inducing effects of solvents following epicutaneous administration to man - studied by laser Doppler flowmetry. *Scand J Work Environ Health* 10:159-162.

Wang J-D, Chang Y-C, Kao K-P, Huang C-C, Lin C-C, Yeh W-Y. 1986 An outbreak of *n*-hexane induced polyneuropathy among press proofing workers in Taipei. *Am J Ind Med* 10:111-118.

Yokoyama K, Araki S, Murata K, Nishikitani M, Nakaaki K, Yokota J, Ito A, Sakata E. 1997 Postural sway frequency analysis in workers exposed to *n*-hexane, xylene and toluene: assessment of subclinical cerebellar dysfunction. *Environ Res* 74:110-115.

Yücesoy B, Yücel A, Erdem O, Bergaz S, Imir T, Karakaya AE, Karakaya A. 1999 Effects of occupational chronic co-exposure to *n*-hexane, toluene, and methyl ethyl ketone on NK cell activity and some immunoregulatory cytokine levels in shoe workers. *Hum Exp Toxicol* 18:541-546.

Zhao W, Misumi J, Yasui T, Aoki K, Kimura T. 1998 Effects of methyl ethyl ketone, acetone, or toluene coadministration on 2,5-hexanedione concentration in the sciatic nerve, serum, and the urine of rats. *Int Arch Occup Environ Health* 71 (4):236-244.

Zimmerman FK, Scheel I, Resnick MA. 1989 Induction of chromosome loss by mixtures of organic solvents including neurotoxins. *Mutat Res* 224:287-303.

13 Isopropanol

Jennifer Butler

SUMMARY

- Isopropanol is absorbed by all routes; systemic effects are unlikely from acute dermal exposure
- It is mildly irritating to the skin, eyes, gastrointestinal tract and respiratory tract
- Systemic effects include CNS and respiratory depression, cardiac arrhythmias and renal damage
- Isopropanol has been linked with an increased incidence of nasal and laryngeal cancers in production workers
- There are no reports of reproductive effects following isopropanol exposure in humans

DESCRIPTION

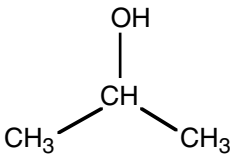
Synonyms

Dimethylcarbinol, 2-hydroxypropane, IPA, isohol, isopropanol, isopropyl alcohol, 1-methylethanol, 1-methylethyl alcohol, petrohol, propan-2-ol, *n*-propan-2-ol, 2-propanol, 2-propyl alcohol, I-propyl alcohol, *sec*-propyl alcohol, secondary propyl alcohol

Identification numbers

CAS	67-63-0
UN	1219
RTECS	NT 8050000
EINECS	2006617

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	C_3H_8O
molecular formula	
molecular mass	60.10
physical form	flammable liquid
relative vapour density (air = 1)	2.07
flash point (°C)	11.7
boiling point (or range) (°C)	83

autoignition temperature (°C)	455.6
refractive index (°C)	1.377
explosive limits in air (%v/v)	2.5-11.8

Odour threshold

22 ppm (Amoore and Hautala, 1983).

OCCUPATIONAL EXPOSURE

Exposure Limits

TWA (UK): 400 ppm (980 mg/m^3)
TWA (ACGIH): 200 ppm (490 mg/m^3)

Conversion factors

1 ppm = 2.45 mg/m^3
1 mg/l = 408 ppm
1 mg/m^3 = 0.41 ppm

Biomonitoring

A biological exposure index for isopropanol has not been established by the ACGIH (ACGIH, 2000). The biological exposure index for acetone, the metabolite of isopropanol, is an end of shift urinary acetone concentration of 50 mg/l (ACGIH, 2000).

TOXICITY

Isopropanol is a common industrial and laboratory solvent and is present in a wide range of domestic products and in some coolants and antifreezes. Historically, it was available as a 'rubbing alcohol' for the relief of rheumatic and muscular pain, and for cooling fevers in children (Garrison, 1953; Adelson, 1962). The medicinal uses of isopropanol are now limited owing to the potential for serious effects (Garrison, 1953; McFadden and Haddow, 1969). Despite the widespread use of isopropanol, there are very few reports of toxic effects following chronic or occupational exposures. It is considered to have a relatively low order of acute and chronic toxicity (Bevan, 2001). The majority of the information on toxicity, kinetics and clinical effects are known from acute cases including intentional ingestion as an ethanol substitute, intentional self-harm, excessive dermal application and therapeutic errors in administration (Garrison, 1953; Adelson, 1962; McFadden and Haddow, 1969; Alexander *et al.,* 1982; Vicas and Beck, 1993).

Isopropanol is predominantly a central nervous system (CNS) depressant. However, toxicity following exposure to isopropanol is also related to its metabolite acetone, which is also a CNS depressant. It is controversial whether it is the parent compound or its metabolite that is responsible for the major CNS effects observed following exposure to isopropanol. An intentional ingestion by an individual with reduced alcohol dehydrogenase activity did not result in the profound CNS depressant effects expected for the volume consumed. The lack of serious effects was probably related to the reduced production of acetone (Chan *et al.,* 1993). However, Gaudet and Fraser (1989) report a patient who was awake and conversant when his blood acetone concentration was at its peak (1,600 mg/l).

Following ingestion, isopropanol is rapidly absorbed, with signs and symptoms occurring within 30 minutes of ingestion (Lacouture *et al.,* 1983; Pappas *et al.,* 1991). In some cases absorption time is delayed, especially following ingestion of large volumes of isopropanol. Ingestion of as little as 20 ml can cause effects (Lacouture

et al., 1983). The lowest lethal oral dose has been reported as 250 ml (Lewis, 1992). Fatalities are associated with isopropanol blood concentrations in the range 1,500-2,000 mg/l (Adelson, 1962; Lacouture *et al.,* 1983). However, doses as high as 4,400-5,600 mg/l have been survived with supportive measures and haemodialysis (King *et al.,* 1970; Lacouture *et al.,* 1983).

Absorption

Isopropanol is rapidly absorbed by the oral route with signs and symptoms occurring within 30 minutes of ingestion (Lacouture *et al.*, 1983; Pappas *et al.*, 1991). In some cases absorption time is delayed especially following ingestion of a large quantity of isopropanol. In a study using dogs as a model, isopropanol was detected in the blood at a concentration of 919 mg/l, 15 minutes post dose (60 ml of a 70% solution via a nasogastric tube). Maximum blood concentrations were reported at 2-3 hours post dose (Jerrard, *et al.*, 1992).

Isopropanol is rapidly absorbed by inhalation. A neonate inadvertently administered 70% isopropanol via a ventilator had a peak blood isopropanol concentration of 1,860 mg/l at one hour post exposure (Vicas and Berk, 1993).

Distribution

Isopropanol has a volume of distribution of 0.6 l/kg with maximal distribution occurring within 2 hours of exposure (Lacouture *et al.,* 1983; Baselt, 2000). In experimental animals, isopropanol was detected not only in the blood but also in the spinal fluid, liver, kidneys and brain. Isopropanol appears to pass the blood brain barrier twice as effectively as ethanol (IPCS, 1990).

Metabolism

In the liver, the enzyme alcohol dehydrogenase metabolises isopropanol to acetone. Approximately 80% of an ingested dose is metabolised by this pathway. The remaining 20% is eliminated unchanged by the kidneys (Daniel *et al.*, 1981; Gaudet and Fraser, 1989). In dogs given isopropanol by nasogastric tube acetone was detected in the blood as quickly as 15 minutes post exposure, with significant concentrations detectable from 3-4 hours post exposure onwards (Jerrard *et al.*, 1992).

Elimination

The majority of absorbed isopropanol (80%) is metabolised to acetone, while the remaining 20% is excreted unchanged via the lungs, kidney, saliva and gastric secretions. Reabsorption may follow excretion via the last two routes. The metabolite, acetone, is eliminated predominately by the kidney and some via the lungs (Smith, 1983; Bevan, 2001).

Elimination of isopropanol follows first-order kinetics with a half-life ranging from 2.9-16.2 hours (Pappas *et al.,* 1991; Chan *et al.,* 1993; Baselt, 2000). Urinary elimination of isopropanol is approximately 540 mg per hour (calculated from Rosansky, 1982). The elimination of the metabolite, acetone, is longer at 18-27 hours (Natowicz *et al.,* 1985; Sakata *et al.,* 1989; Jones, 2000).

Isopropanol is rapidly eliminated via haemodialysis at a rate of 27,000 mg per hour, which is approximately fifty times the rate of removal by urinary elimination alone (Rosansky, 1982).

Mode of action

There is little information on the mode of activity of isopropanol. Many authors suggest that as it is a water-soluble alcohol, it may have the same mode of action as ethanol. However, the mode of action of ethanol is also a subject of debate. It may depress the CNS by dissolving in the cell lipid membrane and disordering the lipid matrix (Goldstein, 1984). The low molecular weight alcohols (those with 3-8 carbon

atoms) all appear to have this ability to disorder biological membranes. The sedative and hypnotic effects of ethanol, and other low weight alcohols, may also be related to their effects on the neurotransmitter gamma amino butyric acid (GABA) and glutamate activated ion channels (Goldstein, 1984; Charness *et al.*, 1989; Lovinger *et al.*, 1989).

Metabolic interactions

- **Carbon tetrachloride (CCl_4)**

  Isopropanol may potentiate the hepatic and renal toxicity of carbon tetrachloride. Three workers in a colour printing factory were admitted to community hospitals with acute hepatitis, one worker also developed acute renal failure and pulmonary oedema. An investigation was carried out to determine the aetiology of the outbreak. Seventeen of twenty-five workers at the plant had abnormal liver function tests (LFTs) 10 days after the outbreak. It was found that there was a strong correlation between abnormal LFTs and the combined use of CCl_4 and isopropanol in a cleaning process (Deng *et al.,* 1987). A similar incident was reported by Folland *et al.* (1976). Fourteen of 43 workers developed non-specific illness when CCl_4 was used to clean equipment close to an isopropanol packaging line. They developed symptoms of nausea, vomiting, headache, weakness and abdominal pain. Dizziness, blurred vision and diarrhoea were also reported. The illness lasted an average of 7 days. Two patients had signs of liver and renal toxicity. The onset and prevalence of illness was related to proximity to the area where the agents were being used. The potentiating interaction in these cases may also be related to the presence of acetone, the main metabolite of isopropanol. Acetone is known to induce the CYP2E1 enzyme (Morgott, 2001), and induction of this pathway contributes to the increased toxicity in a combined CCl_4/isopropanol exposure.

- **Ethanol**

  Many alcohols are metabolised by liver alcohol dehydrogenase (ADH). As ADH has a much higher affinity for its preferred substrate, ethanol, the metabolism of many other alcohols can be reduced or even completely blocked by the concurrent administration of, or exposure to, ethanol. The metabolism of isopropanol may be blocked in this way (Alexander *et al.,* 1982). The significance of this interaction for the occupational setting is unclear, but as there has been some suggestion that isopropanol is twice as potent a CNS depressant as ethanol (Lacouture *et al.,* 1983; Smith, 1983), concurrent exposure to these agents may prolong the depressant effects of isopropanol.

CASE REPORTS

There are no cases of toxicity relating to an occupational setting.

'Pseudo' renal failure after isopropanol intoxication

A 30 year old man presented to an emergency department complaining of abdominal pain. He admitted to drinking 500 ml of rubbing alcohol (isopropanol) sixteen hours earlier. The patient appeared inebriated, with a mild tachycardia. His breath smelt fruity. Physical examination was normal except for mild abdominal tenderness. Blood chemistry revealed mild hypernatraemia and hypokalaemia. The initial isopropanol blood concentrations was 220 mg/l, with an acetone concentration of 2,590 mg/l. Gastric lavage was performed in the emergency department and the patient was given IV fluids. By day four the patient appeared to have made a full recovery. However, just before discharge the serum creatinine rose to 15 mg/l, and a urine ketone test was strongly positive. The patient was found to have ingested more isopropanol in the toilets and left the hospital against advice. Initially the elevated creatinine was thought to be secondary to acute tubular necrosis caused by the isopropanol. However, his blood chemistry was not consistent with this diagnosis. It was concluded that acetone, the metabolite of isopropanol, had interfered with the determination of creatinine, giving a falsely elevated value (Hawley and Falko, 1982).

Acute isopropanol ingestion treated with haemodialysis

A 28 year old man was admitted to hospital 45 minutes after ingestion of approximately 1,000 ml of rubbing alcohol over a 10 minute period. The patient was hypotensive, with a rectal temperature of 36.1 °C. His respirations were 14 per minute and shallow. He was comatose and unresponsive to any stimuli, with absent corneal and deep tendon reflexes. Pupils were dilated. He was given IV fluids and the urine was positive for acetone. He underwent haemodialysis approximately 5 hours post ingestion. At this time the isopropanol concentration was 4,400 mg/l (acetone 400 mg/l). After 2 hours of dialysis he was agitated with a normal blood pressure. After a further 3 hours of dialysis he was calmer and responded to simple commands. The isopropanol concentration was 1,000 mg/l (acetone 100 mg/l) and dialysis was stopped at this point. He made an uneventful recovery (King *et al*., 1970).

CLINICAL EFFECTS

Acute exposure

Inhalation

Isopropanol is a mucous membrane irritant. Exposure to 400 ppm for three to five minutes caused mild irritation of the eyes nose and throat (Baselt, 2000). Systemic effects are possible by this route, but only in exceptional circumstances, see below.

Dermal

A review of studies using animal skin models found that isopropanol is only mildly irritant to skin. Only following prolonged contact were there reports of irritation (IPCS, 1990). These findings are supported by human volunteer studies where isopropanol produced little irritation. There are also isolated reports of sensitisation (reviewed in Bevan, 2001). Isopropanol is absorbed dermally although systemic effects are unlikely from acute exposure.

Marked CNS effects have been reported in febrile children receiving topical application of isopropanol as a cooling measure. However, inhalation as well as the dermal route was also thought to be of importance in these cases (Garrison, 1953; Senz and Goldfarb, 1958; McFadden and Haddow 1969).

Eye

Isopropanol is irritating to the eyes but injury is transient. Prolonged liquid contact or high vapour concentrations can cause patchy corneal epithelial loss with rapid recovery (Grant and Schuman, 1993).

Isopropanol (70%) has been used as a disinfectant on the eyelids in preparation for ocular surgery. On occasion during this procedure some of the wash solution entered the eyes. The patient usually complained of an immediate uncomfortable burning and stinging sensation. Damage was only observed if the contact was prolonged (Grant and Schuman, 1993).

Ingestion

Symptoms occur within 30-60 minutes after ingestion (Lacouture *et al.,* 1983; Smith, 1983). Initially there is a burning sensation in the mouth and throat, gastrointestinal irritation with abdominal pain, vomiting and haematemesis. As isopropanol is a potent CNS depressant, there is a risk of aspiration of the stomach contents (Adelson, 1962). Systemic effects may occur, see below.

Systemic effects

Systemic effects are usually only observed following ingestion of isopropanol. However, they may occur following inhalation or with prolonged dermal exposure but only in exceptional circumstances, for example, febrile children receiving topical application of isopropanol as a cooling measure (Garrison, 1953; Senz and Goldfarb, 1958; McFadden and Haddow 1969) and therapeutic error (Vicas and Beck, 1993).

The CNS effects include dizziness, disorientation, headache and confusion. As the dose and blood concentration increase, drowsiness can progress to coma. Tachycardia is commonly seen, although there may be bradycardia. Hypo- or hyperglycaemia may occur. In a review of five fatal cases of isopropanol ingestion, severe intoxication was associated with coma, hypothermia, hyporeflexia, respiratory depression and cardiac arrest (Adelson, 1962). Marked hypotension is a poor prognostic sign.

Renal toxicity may occur with oliguria, ketonuria and anuria. Acute tubular necrosis, rhabdomyolysis, acute myopathy, myoglobinuria, hepatic dysfunction and haemolytic anemia, have also been reported (Lacouture *et al.,* 1983), but may be due to hypotension, prolonged coma, or 'crush' injury in the sedated patient (Hawley and Falko, 1982) rather than a direct toxic effect. Acetone has been reported to cause renal toxicity in rats, but there are very few reports of nephrotoxicity in humans (IPCS, 1998).

Elevated serum creatinine in the absence of renal damage has been reported with isopropanol intoxication. It was attributed to high acetone concentrations, possibly interfering with the assay (Hawley and Falko, 1982).

Chronic exposure

Inhalation

There are no reports on the effects of chronic exposure to isopropanol.

Dermal

Repeated skin contact with isopropanol can cause defatting dermatitis with drying and cracking. Rare cases of allergic contact dermatitis have been reported (Bevan, 2001).

Eye

No information available.

Ingestion

Not applicable in the occupational setting.

Other effects

Immunotoxicity

In vitro studies involving concanavalin A-stimulated murine spleen cells, found that isopropanol and acetone enhanced the incorporation of labelled thymidine into the cells. Isopropanol also inhibited the killing of YAC-1 tumour by natural killer effector cells from mouse or rat spleens. A suggested explanation of these effects was multi-factorial, possibly involving the inhibition of the synthesis and/or the secretion and/or function of at least one monocyte-derived substance that inhibited cell proliferation (reviewed by IPCS, 1990).

Carcinogenicity

A study of 262 men working in an isopropanol plant, for an average of 15.5 years, found that there were 26 deaths, which is slightly above the expected number (23.6). There was also a non-significant increase in deaths from neoplasms (9 against an expected 6.19). Of the deaths from cancer, only the incidence of carcinoma of the nose and sinus was above the expected level compared to the general population (Alderson and Rattan, 1980). Teta *et al.* (1992) also found an increased incidence of laryngeal cancer among workers involved in the process of manufacturing isopropanol and ethanol by the strong acid process. However, it is unclear whether this increased incidence is due to the isopropanol itself, some intermediary in the process in this plant, or the strong acid method.

Genotoxicity

Studies investigating the genotoxicity of isopropanol have produced conflicting results. Examination of the bone marrow cells of rats exposed to varying concentrations of isopropanol vapours (1.03 to 10.2 mg/m^3 for 4 hours/day) for four months found that there were statistically significant increases in the percentage of mitotic aberrations. An increase in mitotic aberrations was also found in onion root tip cells exposed to isopropanol. Chinese hamster lung fibroblasts did not show an increase in sister chromatid exchange frequencies *in vitro,* when treated with isopropanol (range 3.3 to 100 mmol/l). Reverse mutation spot tests, with and without metabolic activation by S9 rat liver, were negative for various *Salmonella typhimurium* strains exposed to 0.18 mg isopropanol per plate (reviewed in IPCS, 1990).

Reproductive toxicity

There are no reports of human reproductive or fetal abnormalities following workplace exposure to isopropanol (reviewed in IPCS, 1990 and Shepard, 2001). Rodent studies investigating the reproductive and teratogenic effects of isopropanol have demonstrated that isopropanol reduced fertility, maternal weight gain and fetal body weights, and caused fetal abnormalities (most commonly skeletal defects). The rats in these studies were exposed to concentrations ranging from 3,500 to 10,000 ppm for 7 hours a day for 19 days. These concentrations far exceed the isopropanol concentrations experienced in the workplace (Nelson *et al.,* 1988).

RISK GROUPS

None identified.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Gastric lavage is not indicated following ingestion of isopropanol, as it is quickly absorbed by the gut. Activated charcoal is not of benefit. If there has been any vomiting, coughing or wheezing in a patient with altered mental status, then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive. See below for management of systemic effects.

Systemic effects

Close monitoring of the patient's respiration is required because of the risk of respiratory depression. In severe cases electrolytes, creatinine, glucose, full blood count, arterial blood gases, serum acetone and isopropanol, renal and liver function should be monitored. Hypotension should be treated with intravenous fluids and ionotropes if necessary. Deep coma and refractory hypotension are indications for haemodialysis or peritoneal dialysis; this should also be considered in patients with an isopropanol level greater than 4,000 mg/l (Lacouture *et al.,* 1983).

The presence of non-acidotic acetonaemia and acetonuria are key factors allowing the differentiation of isopropanol from ethanol intoxication, diabetes mellitus, starvation and cyanide poisoning (Agarwal, 1979; Lacouture *et al.,* 1983).

Antidotes

There is no specific antidote for isopropanol.

Chronic exposure

There is no specific management for chronic isopropanol exposure. Symptomatic and supportive care.

REFERENCES

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Adelson L. 1962 Fatal intoxication with isopropyl alcohol (rubbing alcohol). *Am J Clin Path* 38 (2):144-151.

Agarwal SK. 1979 Non-acidotic acetonemia: a syndrome due to isopropyl alcohol intoxication. *J Med Soc New Jersey* 76 (13):914-917.

Alderson MR, Rattan NS. 1980 Mortality of workers on an isopropyl alcohol plant and two MEK dewaxing plants. *Br J Ind Med* 37:85-89.

Alexander CB, McBay AJ, Hudson RP. 1982 Isopropanol and isopropanol deaths—ten years experience. *J Forens Sci* 27 (3):541-548.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6): 272-290.

Baselt RC. 2000 *Disposition of Toxic Drugs and Chemicals in Man*, fifth edition. Chemical Toxicology Institute, California.

Bevan C. 2001 Monhydric alcohols – C_1-C_6. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Chan KM, Wong, ET, Matthews WS. 1993 Severe isopropanolemia without acetonemia or clinical manifestations of isopropanol intoxication. *Clin Chem* 39 (9):1922-1925.

Charness ME, Simon RP, Greenberg DA. 1989 Ethanol and the nervous system. *N Engl J Med* 321:442-454.

Daniel DR, McAnalley BH, Garriott JC. 1981 Isopropyl alcohol metabolism after acute intoxication in humans. *J Anal Toxicol* 5:110-112.

Deng JF, Wang JD, Shih TS, Lan FL. 1987 Outbreak of carbon tetrachloride poisoning in a color printing factory related to the use of isopropyl alcohol and an air conditioning system in Taiwan. *Am J Ind Med* 12:11-19.

Folland DS, Schaffner W, Ginn HE, Crofford OB, McMurray DR. 1976 Carbon tetrachloride toxicity potentiated by isopropyl alcohol. Investigation of an industrial outbreak. *J Am Med Assoc* 236:1853-1856.

Garrison RF. 1953 Acute poisoning from the use of isopropyl alcohol in tepid sponging. *J Am Med Assoc* 152 (4):317-318.

Gaudet MP, Fraser GL. 1989 Isopropanol ingestion: case report with pharmacokinetic analysis. *Am J Emerg Med* 7 (3):297-299.

Goldstein DB. 1984 The effects of drugs on membrane fluidity. *Ann Rev Pharmacol Toxicol* 24:43-64.

Grant WM, Schuman JS. 1993 *Toxicology of the Eye*, fourth edition. Charles C Thomas, Springfield, Illinois.

Hawley PC, Falko JM. 1982 'Pseudo' renal failure after isopropyl alcohol intoxication. *S Med J* 75 (5):630-631.

IPCS. 1990 *Environmental Health Criteria 103. 2-Propanol*. World Health Organization, International Programme on Chemical Safety, Geneva.

IPCS. 1998 *Environmental Health Criteria 207. Acetone*. World Health Organization, International Programme on Chemical Safety, Geneva.

Jerrard D, Verdile V, Yealy D, Krenzelok E, Menegazzi J. 1992 Serum determinations in toxic isopropanol ingestion. *Am J Emerg Med* 10:200-202.

King LH, Bradley KP, Shires DL. 1970 Hemodialysis for isopropyl alcohol poisoning [letter]. *J Am Med Assoc* 211:1855.

Jones AW. 2000 Elimination half-life of acetone in humans: case reports and review of the literature. *J Anal Toxicol* 24:8-10.

Lacouture PG, Wason S, Abrams A, Lovejoy FH. 1983 Acute isopropyl alcohol intoxication: diagnosis and management. *Am J Med* 75:680–686.

Lewis RJ Sr. 1992 *Sax's Dangerous Properties of Industrial Materials*, eighth edition. Van Nostrand Reinhold, New York.

Lovinger DM, White G, Weight FF. 1989 Ethanol inhibits NMDA-activated ion current in hippocampal neurons. *Science* 243:1721.

McFadden SW, Haddow JE. 1969 Coma produced by topical application of isopropanol. *Pediatrics* 43:622-623.

Mecikalski MB, Depner TA. 1982 Peritoneal dialysis for isopropanol poisoning. *West J Med* 137:322-325.

Morgott DA. 2001 Acetone. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Natowicz M, Donahue J, Gorman L, Kane M, McKissick J, Shaw L. 1985 Pharmacokinetic analysis of a case of isopropanol intoxication. *Clin Chem* 31 (2):326-328.

Nelson KW, Ege JF Jr, Ross M, Woodman LE, Silverman L. 1943 Sensory response to certain industrial solvent vapors. *J Ind Hyg* 25:282-285

Nelson BK, Brightwell WS, MacKenzie-Taylor DR, Khan A, Burg JR, Weigel WW, Goad PT. 1988 Teratogenicity of *n*-propanol and isopropanol administered at high inhalation concentration to rats. *Fd Chem Toxicol* 26 (3):247-254.

Pappas AA, Ackerman BH, Olsen KM, Taylor EH. 1991 Isopropanol ingestion: A report of six episodes with isopropanol and acetone serum concentration time data. *Clin Toxicol* 29:11-21.

Rosansky SJ. 1982 Isopropyl alcohol poisoning treated with hemodialysis: kinetics of isopropyl alcohol and acetone removal. *Clin Toxicol* 19 (3):265-271.

Sakata M, Kikuchi J, Haga M. 1989 Disposition of acetone, methyl ethyl ketone and cyclohexanone in acute poisoning. *Clin Toxicol* 27 (1-2):67-77.

Senz EH, Goldfarb DL. 1958 Coma in a child following use of isopropyl alcohol in sponging. *J Pediatr* 53:322-323.

Shepard TH. 2001 Isopropyl alcohol. Shepard's Catalog of Teratogenic Agents (electronic version). MICROMEDEX, Greenwood Village, Colorado, USA. Available at: http://www.tomescps.com (site visited July 2001).

Smith MS. 1983 Solvent toxicity: isopropanol, methanol, and ethylene glycol. *Ear Nose Throat J* 62:11-26.

Teta MJ, Perlman G, Ott MG. 1992 Mortality study of ethanol and isopropanol production workers at two facilities. *Scand J Work Environ Health* 18:90-96.

Vicas IMO, Beck R. 1993 Fatal inhalational isopropyl alcohol poisoning in a neonate. *Clin Toxicol* 31 (3):473-481.

14 Methanol

Jennifer Butler

SUMMARY

- Methanol causes toxicity by ingestion, inhalation, and dermal exposure
- Initial clinical effects resemble alcohol (ethanol) intoxication
- Methanol itself is of a moderate order of toxicity; it is the metabolite, formic acid, that is responsible for its toxic effects
- Ethanol or fomepizole may be used as antidotes for methanol toxicity and act by blocking metabolism
- Methanol intoxication is characterised by CNS depression, metabolic acidosis and ocular toxicity
- There are no studies in the literature on the reproductive, carcinogenic or mutagenic effects of methanol in humans

DESCRIPTION

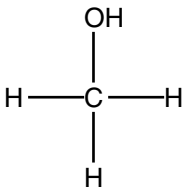
Synonyms

Carbinol, columbian spirits, methanol, methyl alcohol, methyl hydrate, methyl hydroxide, methylol, monohydroxymethane, pyroxylic spirits, wood alcohol, wood naphtha, wood spirit.

Identification numbers

CAS	67-56-1
UN	1230
RTECS	PC 1400000
EINECS	2006596

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	CH_4O
molecular formula	
molecular mass	32.04
physical form	colourless, flammable liquid with alcoholic odour

relative vapour density (air=1)	1.11
flash point (°C)	12
boiling point (°C)	65
autoignition temperature (°C)	470
refractive index	1.3292
explosive limits (%v/v)	6.0-36.5

Odour threshold

100 ppm (Amoore and Hautala, 1983).

OCCUPATIONAL EXPOSURE

Exposure Limits

TWA (UK and ACGIH): 200 ppm (266 mg/m^3).

Conversion factors

1 ppm = 1.31 mg/m^3
1 mg/l = 764 ppm
1 mg/m^3 = 0.764 ppm

Biomonitoring

The ACGIH biological exposure index for methanol is an end of shift urinary methanol concentration of 15 mg/l. Methanol may be present in the urine of individuals who have not been exposed and this may affect interpretation. Such background concentrations are incorporated in the BEI value (ACGIH, 2000).

TOXICITY

Methanol is produced from the distillation of wood and it is sometimes referred to as wood alcohol or wood naphtha. It is a colourless liquid with an alcoholic odour when pure. Crude methanol may have an unpleasant pungent odour. Methanol is used extensively as a solvent, chemical intermediate, in the production of glycol ethers, and in the manufacture of charcoal. It is also widely available in windshield washing and de-icing products, as well as in antifreeze and model engine fuels. The majority of toxic exposures to methanol have occurred following intentional ingestion. Inhalation and dermal absorption are the main routes of exposure in the occupational setting.

The degree of toxicity following exposure to methanol is related to many factors including the amount of methanol ingested, the extent of folate deficiency, the activity of alcohol dehydrogenase (ADH) and concurrent ingestion of ethanol. Severe intoxication can lead to metabolic acidosis, coma, convulsions and respiratory arrest. It also causes visual and neurological effects that may be permanent (McLean *et al.,* 1980; Anderson *et al.,* 1987).

The toxic dose of methanol reported in the literature varies widely. Bennett *et al.* (1953) reported an outbreak of 323 cases of methanol poisoning due to adulterated 'moonshine'. The lowest fatal dose was 15 ml of 40% methanol, however, in this outbreak survival was reported following ingestion of approximately 500 ml of methanol. In an outbreak in Papua New Guinea similar disparity between the ingested dose and the severity of the outcome was observed. Blindness and death followed consumption of 100 ml of methanol, while ingestion of 500 ml produced no apparent disability (Scrimgeour, 1980).

There is often a wide range variation in blood methanol concentrations compared with the severity of outcome. A concentration of 220 mg/l caused headache, nausea, vomiting and abdominal pain, these symptoms and retinal oedema were also seen in a patient with a methanol concentration of 300 mg/l (Bennett *et al.,* 1953). However, blood methanol concentrations as high as 9,200 mg/l have been survived without sequelae, as a result of prompt, aggressive treatment (Martens *et al.,* 1982). This difference between levels and outcome may be related to methanol's relatively low order of toxicity compared with its metabolite, formic acid. The severity of outcome appears to be related more to the formic acid concentration and the time to initiation of treatment. Therefore, formic acid concentrations are possibly more useful in estimating the potential toxicity. A high formic acid concentration with metabolic acidosis has been associated with a more severe outcome and the potential for development of neurological sequelae (Anderson *et al.,* 1987; Brent *et al.,* 2001).

Absorption

Methanol is absorbed by all routes. Inhalation and dermal absorption are the main routes of exposure in the occupational setting. In a study of 33 methanol exposed workers, the amount of methanol absorbed by inhalation correlated with the vapour concentration and the duration of exposure. The rate of absorption of inhaled methanol in this group was calculated as 173.5 ng/ppm/hour, or 0.1735 mg methanol after 15 minutes exposure at 4,000 ppm (Kawai *et al.,* 1991). Approximately 58% of the inhaled dose of methanol is retained by the lungs (Šedivec *et al.,* 1981).

The rate of dermal absorption in volunteers was found to be 0.192 mg/cm^2/min. Exposure of one hand to liquid methanol for only 2 minutes could lead to the absorption of as much methanol (170 mg) as would be taken up by the lungs from an 8 hour exposure to the maximum allowable concentration (MAC) of 50 mg/m^3 (38 ppm) (Dutkiewicz *et al.,* 1980).

On ingestion, peak methanol concentrations are seen at 30–60 minutes. Initial symptoms occur at 30 minutes to 2 hours post ingestion or inhalation. The onset of clinical effects may be delayed for several hours following dermal exposure (Downie *et al.,* 1992).

Distribution

The volume of distribution of methanol in humans is 0.6 l/kg (Baselt, 2000). In dogs, methanol was found to distribute readily to all organs and tissues in direct relation to their water content (Yant and Schrenk, 1937).

Metabolism

The first step of methanol metabolism is the oxidation to formaldehyde by alcohol dehydrogenase (ADH). Formaldehyde is then metabolised by the specific enzyme formaldehyde dehydrogenase. In this reaction formaldehyde combines with reduced glutathione to form s-formyl glutathione. This hydrolyses to produce formic acid and glutathione. Formaldehyde oxidation occurs in the erythrocytes and in liver mitochondria. Due to the numerous metabolic routes, all formaldehyde is metabolised to the toxic formic acid (Liesivuori and Savolainen, 1991) and it is not seen to accumulate in methanol intoxication.

Formaldehyde may also be metabolised to formic acid via a tetrahydrofolic acid-dependent one-carbon pool. Formic acid binds to tetrahydrofolic acid (THF) to form 10-formyl-THF. Various other enzymatic reactions direct 10-formyl-THF to other pathways. In rats, formic acid is metabolised at about twice the rate of monkeys (McMartin *et al.,* 1977). However, hepatic THF levels in humans and monkeys are about half that seen in rats, and formylated-THF derivatives are 2-fold higher in monkeys than rats. Consequently, low hepatic concentrations of THF in humans and monkeys may lead to an accumulation of formic acid.

Cases have been reported where ingestion of methanol has not resulted in acidosis, even in the absence of ethanol therapy. A 6 week old infant was accidentally fed a methanol containing windshield fluid mixed in infant formula. On discovery of the mistake the patient was immediately taken to hospital and a nasogastric lavage was performed. Apart from tachypnoea, which resolved within 3 hours of ingestion, there were no abnormal signs. A blood concentration taken 2 hours post ingestion showed a methanol concentration of 456 mg/l. A subsequent methanol concentration suggested a half-life of 28 hours and a clearance rate of 8.8 mg/l/hour. In this case, low alcohol dehydrogenase levels in infants may have slowed the rate of methanol metabolism and therefore slowed the generation of toxic metabolites, reducing the risk of sequelae (Brent *et al.,* 1991).

Elimination

In cases of human toxicity, the kinetics of methanol elimination have been difficult to determine, as the standard treatment with ethanol and haemodialysis alter the kinetics. Studies in monkeys suggest that the kinetics of methanol elimination are zero-order at blood concentrations in the range 1,000-2,000 mg/l, i.e., at levels normally reported in human toxicity (Noker *et al.,* 1980). However, McMartin *et al.* (1977) found that methanol elimination followed first-order kinetics in a monkey receiving large doses of methanol (3 g/kg). The mixed kinetics may be due to the greater contribution of first-order processes (urinary and pulmonary clearance) to the whole body clearance of methanol (Jacobsen *et al.*, 1988).

During haemodialysis of a patient who had ingested methanol, the average half-life of methanol and formic acid were 3.5 hours and 45 minutes, respectively. The half-life of methanol when not having dialysis was calculated at 15.1 hours (Barton-Burns *et al.*, 1998). In some studies, the methanol elimination half-life is long. Brent *et al.* (1991) found that the methanol elimination half-life in a 6 week old child was 28 hours, but this may be due to reduced alcohol dehydrogenase levels in neonates. The half-life of methanol appears to be variable in the range 2-54 hours (Barton-Burns *et al.,* 1998; Baselt, 2000; Brent *et al.,* 2001).

Formic acid, the metabolite responsible for the majority of toxic effects following methanol exposure, appears to be cleared less quickly from ocular tissue when compared with systemic clearance (Garner *et al.,* 1995).

Only a small quantity of methanol (<1%) is excreted unchanged in the urine (Dutkiewicz *et al.,* 1980; Kawai *et al.,* 1991).

Mode of action

Metabolism of methanol ultimately leads to the formation of formic acid. This acid inhibits mitochondrial cytochrome oxidase activity leading to hypoxia. Tissues with a high oxygen demand are affected: optic nerve, brain, heart and kidneys. Formic acid inhibits cytochrome oxidase activity by binding at the sixth coordination position of the ferric haem iron (Liesivuori and Savolainen, 1997).

The inhibition of cytochrome oxidase by formic acid increases with decreasing pH, suggesting that the active inhibitor is the undissociated acid. Thus acidosis may potentiate the inhibition of cellular respiration and hasten the onset of cellular injury. The progressive acidosis will induce circulatory failure, leading to tissue hypoxia and lactic acid production, which further increases the acid load, and in turn increases the concentration of undissociated formic acid (Garner *et al.,* 1995; Liesivuori and Savolainen, 1997).

The ocular toxicity from methanol poisoning is thought to be due to inhibition of retinal and optic cytochrome oxidase by the accumulated formic acid (Garner *et al.,* 1995). Correction of metabolic acidosis is associated with vision improvement (Herken and Rietbrock, 1968).

Metabolic interactions

- **Carbon tetrachloride**

Concurrent exposure to methanol vapours enhances the hepatotoxicity of carbon tetrachloride (Cornish and Adefuin, 1967; Allis *et al.*, 1996). Animal studies show that there is increased metabolism of carbon tetrachloride in the microsomes of methanol treated animals (Allis *et al.*, 1996). Methanol is an inducer of the CYP2E1 enzyme, which plays a large role in the metabolism of carbon tetrachloride.

- **Ethanol**

As ethanol is the preferred substrate of alcohol dehydrogenase (ADH), it blocks the metabolism of methanol, and the production of toxic formic acid. As a result of this interaction, ethanol is used as an antidote in methanol poisoning. It is only useful in the immediate phase after exposure, as administration of ethanol is of very little benefit once the methanol has been metabolised. The drug, fomepizole, has a similar action to ethanol, and could be used as a substitute for ethanol in methanol intoxication (Brent *et al.,* 2001).

- **Methyl ethyl ketone (MEK)**

MEK may have inhibited methanol metabolism following ingestion of approximately 240 ml of an ink cleaning solution thought to contain MEK 47% and methanol 45%. There was minimal metabolism of methanol to formate despite a high methanol concentration (2,020 mg/l; 63 mmol/l) and the anion gap remained normal. The MEK probably acted by inhibiting alcohol dehydrogenase (Price *et al*., 1994).

CASE REPORTS

Acute dermal methanol toxicity

Two workers were involved in washing a ship's tanks with methanol, prior to loading and transportation of a cargo of methanol from a port in Saudi Arabia. One worker wore full protective clothing; the other did not because he was sunburnt, and wore only a shirt, shorts and sandals. Both wore positive pressure breathing apparatus. The worker without the protective suit spent 2-3 hours spraying in the tank. His cotton shirt and shorts became soaked with methanol. After finishing the job, he went up on deck to work for about 1 hour where his clothes soon dried. He began to feel lethargic, which he thought might be due to too much sun or the onset of 'flu. The next day he awoke feeling ill. He had blurred vision with a halo round near objects. His eyes were painful and he had dizziness, ataxia and dyspepsia. His symptoms were recognised by a colleague as methanol toxicity and an occupational physician was summoned. This physician persuaded the port customs officer to allow them to use the ship's supply of whisky. However, because Saudi Arabia is an alcohol-free state this involved the patient and the whisky being accompanied by an armed customs guard to ensure that the whisky was used for medical purposes only. On admission to hospital the worker was found to be severely acidotic, and was treated with IV sodium bicarbonate and oral whisky. Later in the day he became semi-comatose and was transferred to another hospital. He still had severe acidosis. Funduscopy revealed red and blurred optic discs. No blood methanol concentrations were determined at either hospital. The patient was given more IV ethanol, sodium bicarbonate and oral folic acid. On day two his vision was improving, and on day three when his vision had returned to normal, ethanol therapy was stopped. He was discharged well on day 5 (Downie *et al.*, 1992).

Acute inhalational and dermal methanol toxicity

Two volunteer fire-fighters developed toxicity from inhalation and dermal exposure to vapourised methanol. The incident happened following derailment and overturning of at least five railroad cars used for transporting chemicals. Two of these contained methanol, two contained sodium hydroxide and one contained isobutane. A HAZMAT (hazardous materials) station was established adjacent to the scene of the accident and police began evacuating the area. The two fire-fighters arrived late at the scene, on the opposite side of the tracks to the HAZMAT station. They reported running approximately 150 yards from where they had parked their vehicle between the non-involved railroad cars to reach the station. They were wearing short-sleeved shirts and shorts, shoes but no socks. The total estimated time spent crossing the potential hazard area was less than two minutes. They did not notice an odour at the time of exposure but on questioning later, they remembered a small cloud developing over the wreckage. On reaching the station they disrobed and donned standard fire-fighting gear. However, after 10 minutes of work, both men began to feel dizzy and nauseated and one of them vomited. They appeared to be confused and were removed from the scene for treatment for suspected heat exhaustion. On arrival at the health facility, patient one appeared well but complained of headache; patient two complained of headache and light-headedness. Although the initial diagnosis was of heat exhaustion, the methanol concentrations were determined and found to be 190 mg/l and 130 mg/l, respectively. Both men received IV ethanol and folic acid for the following 48 hours. The peak methanol concentrations were 230 mg/l and 160 mg/l at approximately 2 hours post exposure. Both patients were discharged well after 48 hours, with no ocular or CNS sequelae (Aufderheide *et al*., 1993).

CLINICAL EFFECTS

Acute exposure

Inhalation

Dizziness, nausea, vomiting and confusion have been reported (Aufderheide *et al.,* 1993). A study of teachers' aides exposed to methanol vapours in the range 365-3,080 ppm found significantly more reports of headaches, blurred vision, dizziness and nausea than in the control group (Frederick *et al.,* 1984). However, owing to its high volatility and rapid evaporation, methanol toxicity following accidental inhalation exposure is rare. Toxicity is usually a result of inhalational abuse of methanol-containing products (Frenia and Schauben, 1993). Under extreme circumstances accidental exposure may result in systemic toxicity (Aufderheide *et al.,* 1993). In these cases there may be systemic effects, see below.

Dermal

Methanol is mildly irritating to the skin. It may cause dryness and erythema with prolonged contact. Although methanol is absorbed dermally, its high volatility and rapid evaporation means that toxicity following accidental dermal exposure is rare. However, systemic effects have occurred following prolonged dermal exposure in an occupational setting (Downie *et al.* 1992) and misuse of methanol as a cooling agent (Kahn and Blum, 1979). For systemic effects, see below.

Eye

Direct eye contact with methanol is not expected to produce serious effects. Application of methanol to rabbit eyes produces only mild, reversible effects. No effects on the optic nerve or retina have been observed following splash exposure (Grant and Schuman, 1993). Systemic ocular effects may occur following ingestion or prolonged, extensive dermal or inhalational exposure, see below.

Ingestion

Gastrointestinal signs include nausea, vomiting and severe epigastric pain (Bennett *et al.,* 1953). Systemic effects are likely from ingestion of methanol, see below.

Systemic effects

After a latent phase of between 6 and 30 hours, the patient may develop dizziness, drowsiness, vomiting, severe abdominal pain and diarrhoea. The extremities may become cold and clammy. In severe cases a marked anion gap acidosis will be present and tachypnoea is common as a result. Coma and convulsions may also occur. The physical signs of methanol poisoning are non-specific and include non-reactive pupils, disorientation, decreased level of consciousness and abdominal tenderness (Bennett *et al,* 1953; Anderson *et al.,* 1989). Headache is a common symptom (Bennett *et al.,* 1953).

Systemic ocular effects following methanol intoxication are a classic sign following methanol exposure (Bennett *et al.,* 1953; Scrimgeour *et al.,* 1980; Frenia and Schauben, 1993; Garner *et al.,* 1995). The presenting complaints are of blurred or 'snowfield' vision, with whiteness and spots or mistiness within the visual field. Funduscopic findings include impaired visual acuity and pupillary response to light, although the pupils may continue to react normally to accommodation. The optic disc may be hyperaemic and the surrounding retina oedematous. In some cases there may be permanent blindness or visual impairment (Bennett *et al.,* 1953; Scrimgeour *et al.,* 1982; Erdener and Ilhan, 1997).

While methanol toxicity is characterised by gastrointestinal, ocular and nervous system symptoms, the effects on the cardiovascular system (CVS) are less well documented. Bennett *et al.* (1953) found that the CVS remained stable even in severely poisoned patients, and of the 323 cases investigated in the outbreak only 7 were tachycardic. However, bradycardia developed terminally in fatal cases.

Heart failure has been reported in one case following acute ingestion of an unknown amount of methanol (formic acid level 1,580 mg/l). The patient presented confused and hyperventilating and was severely acidotic with a pH of 6.77. An ECG revealed tachycardia and right bundle branch block. Cardiomegaly and pulmonary venous congestion and oedema were evident on chest X-ray. The patient was treated with ethanol and haemodialysis and was extubated and awake on day 8, with permanent visual impairment. An ECG and chest X-ray were normal on day 28. The authors felt that the cardiac effects in this patient were not completely attributable to the acidosis (Cavalli *et al*., 1987).

With appropriate treatment, recovery from methanol toxicity is often complete, however, there are reports of neurological sequelae following ingestion of methanol. Visual sequelae include optic disc pallor, retinal oedema and blindness. The development of neurological sequelae in some methanol poisoned patients appears to be associated with a lower presenting pH and higher methanol concentrations (Anderson *et al.,* 1989). Significant damage can occur to white matter and basal ganglia in patients who have ingested methanol (Anderson *et al.,* 1987; Hantson *et al.,* 1997). Changes in CNS white and grey matter may explain most of the various neurological syndromes observed after methanol poisoning. These syndromes include parkinsonism, pseudobulbar palsy, cognitive defects, dementia and frontal release signs (Guggenheim *et al.,* 1971; McLean *et al.,* 1980; Scrimgeour, 1980).

The study by Anderson *et al*. (1989) of 30 patients with methanol poisoning demonstrated that the interval between ingestion and treatment is important. Patients who were treated promptly fared significantly better than those whose treatment was delayed. Fifty percent of their patients had neurological sequelae or died. The mean blood pH was lower and the time to treatment longer in these patients. The blood methanol concentration did not correlate with outcome. Methanol concentrations should not be used as a sole determinant for treatment. Patients with delayed presentation, especially if systemic acidosis has occurred, are at significant risk for the development of long-term sequelae. Jacobsen *et al.* (1982) examined 11 patients and found that symptoms of methanol poisoning correlated with the degree of metabolic acidosis. Early treatment is essential to avoid serious neurological complications.

Pancreatic injury may occur with acute ingestion of methanol. In a series of 22 patients, 11 developed acute pancreatitis (Hantson and Mahieu, 2000). Seven of these patients had a history of chronic ethanol abuse but no previous history of acute or chronic pancreatitis. Pancreatic injury following acute ingestion of methanol may be more common than previously realised, although antidotal treatment with ethanol and prior ethanol abuse may be a contributing factor. In this small study, the occurrence of an acute pancreatic injury was correlated with the magnitude of acidosis, which can be considered as an indicator of severity in methanol poisoning. Of concern is the fact that acute pancreatitis can develop in patients who are not ethanol abusers or before antidotal ethanol administration. This suggests that methanol can have a direct toxic effect on the pancreas. As ethanol treatment may complicate the pancreatic injury, fomepizole may be the preferable antidote (Hantson and Mahieu, 2000).

Chronic exposure

Inhalation

As methanol is eliminated from the body relatively slowly, there is a possibility of cumulative toxicity with repeated exposures. However, there is limited information in the literature on chronic methanol exposure. Workers exposed to an average methanol concentration of 459 ppm complained of eye and nose irritation, headache, forgetfulness at work and increased sensitivity of the skin (Kawai *et al.,* 1991).

Dermal

Repeated skin exposure to methanol may cause contact dermatitis (Bevan, 2001).

Eye

Delayed light reflex was reported in two methanol exposed workers with previously good vision. Another worker from the same group exhibited slight mydriasis (Kawai *et al.,* 1991).

Ingestion

There is no information in the literature on the effects of chronic methanol ingestion.

Carcinogenicity

There are no reports of studies on the carcinogenicity of methanol in humans (IPCS, 1997). There are no studies in the peer-reviewed literature on the potential carcinogenicity of methanol in animals (IPCS, 1997) and it has not been evaluated by the IARC.

Genotoxicity

There is some evidence of chromosome damage in animals (reviewed in IPCS, 1997), but there are no reports of studies on the potential mutagenic effect of methanol in humans (IPCS, 1997).

Reproductive toxicity

There are no reports of studies on the reproductive and developmental effects of methanol in humans (IPCS, 1997).

Burbacher *et al.* (1999) studied the long-term effects of exposure to methanol vapours on the metabolism and reproduction of female adult monkeys (*Macaca fascicularis*) and the developmental effects on their offspring. They found that exposure to methanol vapours (200-1,800 ppm) did not affect the health of the adult monkeys prior to or during pregnancy. There was no effect on the menstrual cycle, conception rate and live birth delivery rate. All methanol exposed animals had a decrease in duration of pregnancy of about 6-8 days. Prenatal exposure to methanol had no effect on infant growth and physical development, however two female offspring, exposed *in utero* to 1,800 ppm methanol, developed a wasting syndrome (growth retardation, malnutrition, and gastroenteritis) at one year of age.

RISK GROUPS

Individuals with folate deficiency may be at greater risk of toxicity from inhalation of low concentrations of methanol compared to the rest of the population. This group includes pregnant women, the elderly, alcoholics, and individuals with poor quality diets (IPCS, 1997).

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Gastric lavage may be considered if ingestion was recent. Activated charcoal is of no benefit. See below for management of systemic effects.

Systemic effects

The electrolytes and blood gases should be monitored and corrected if required. Acidosis should be treated aggressively with bicarbonate; large doses may be required. Blood should be taken for determination of the anion and osmolal gap. As methanol has a latent phase before clinical effects are evident, all patients should be observed for at least 12 hours post exposure. If any clinical effects or biochemical abnormalities are noted, the patient needs to be admitted until asymptomatic.

While waiting for laboratory results, but after taking blood for determination of the methanol/formic acid concentration, anion and osmolal gap, all patients should receive a loading dose of ethanol (McCoy *et al.,* 1979). Fomepizole may be used as an alternative to ethanol therapy (Brent *et al.,* 2001). Folinic acid may be given to aid in the transformation of formic acid. Depending on the results of blood analyses, antidotal therapy may need to be continued. Blood ethanol concentrations of >1,000 mg/l are needed to prevent further formation of the toxic metabolites. The indications for continued antidotal therapy are a methanol concentration >200 mg/l, acidosis, increased osmolal gap (>10 mOsm/kg H_2O) or a formic acid concentration >10 mg/l.

A formic acid concentration of >500 mg/l justifies administration of ethanol and possibly haemodialysis (Mahieu *et al.,* 1989).

Haemodialysis is indicated if the patient has a severe or unresponsive acidosis, ocular signs, or methanol or formic acid concentrations >500 mg/l. Although less effective, peritoneal dialysis has been used and could be considered where haemodialysis facilities are not available. Dialysis should be continued until the methanol concentration is <200 mg/l. During haemodialysis, ethanol treatment should be continued, but as ethanol is also readily dialysed, it will be necessary to increase the dosage by 100 mg/kg/hour, or more, to maintain a blood ethanol concentration of 1,000-1,500 mg/l. It is preferable in this situation to add ethanol to the dialysate to achieve a concentration of 1,000 mg/l (Chow *et al.,* 1997).

Osmolal and anion gap

Blood should be taken to estimate methanol and formic acid concentrations. In many situations an assay for methanol/formic acid (formate) is unavailable routinely. In these cases the calculation of the anion and osmolal gaps can provide an early guide to diagnosis. Formic acid concentrations in blood and urine correlate well with the severity of toxic effects as seen in experimental animals and clinical studies. This is not the case for methanol concentrations (Mahieu *et al.,* 1989). Higher formic acid concentrations and wider anion gaps appear to correlate with the development of sequelae and may be indicative of a poorer prognosis (Barton-Burns *et al*., 1998). It has been suggested that a time interval between ingestion and treatment exceeding 10 hours and a blood formic acid concentration above 500 mg/l are predictive of severe methanol poisoning possibly leading to permanent sequelae (Mahieu *et al.,* 1989).

The anion gap is a measure of organic acids. It is elevated in the presence of organic acids such as formic acid. If the measured osmolality is more than the calculated osmolality by greater than 10 mOsm/kg H_2O, this indicates the presence of an unmeasured substance, which may be methanol (Church and Witting, 1997). Although the serum osmolal gap is useful if elevated, a normal osmolal gap does not rule out toxicity. The osmolal gap may be normal once the methanol has been converted to its metabolites. An elevated osmolal gap may indicate the presence of methanol, and the anion gap may indicate the presence of the metabolite, formic acid.

Antidotes

The main aim of treatment for methanol poisoning is to block the formation of the toxic metabolites. Alcohol dehydrogenase has a higher affinity for ethanol than methanol. Therefore ethanol therapy and haemodialysis,

to enhance the elimination of unmetabolised methanol and formic acid, have long been the standard treatment for methanol toxicity. Recently fomepizole, has been found to be useful as an alternative antidote to ethanol in methanol poisoning (Brent *et al.,* 2001).

Ethanol

The prompt use of ethanol in methanol poisoning is associated with a good outcome. Early and aggressive treatment can completely prevent the toxic effects of methanol (Bergeron *et al.,* 1982). The endpoint for ethanol therapy is controversial but it should be continued until methanol is no longer detectable. Mahieu *et al.* (1989) observed that when ethanol was stopped too soon after methanol concentrations had become undetectable, a rebound of formic acid up to 100 mg/l sometimes followed. In view of the possible ocular risk of local production of formic acid, it is worthwhile maintaining an adequate blood ethanol concentration for at least 48 hours after the disappearance of methanol from the blood. However, in a study of 11 methanol poisoned patients, no rebound effect in whole blood concentrations of methanol were seen after termination of dialysis (Jacobsen *et al.*, 1982).

Fomepizole

Fomepizole (4-methylpyrazole) is an inhibitor of alcohol dehydrogenase that appears to have few of the side effects of ethanol. It is currently only licensed in the UK for the treatment of ethylene glycol poisoning. However, Brent *et al.* (2001) treated 11 methanol poisoned patients with fomepizole. The median duration of therapy was 30 hours (range 0.5-60), and the patients received a median of 4 doses. After the institution of fomepizole therapy, plasma formic acid concentrations fell in all patients, with simultaneous resolution of metabolic acidosis. This also resulted in improvement in mental status and visual symptoms. Methanol elimination in patients who did not receive haemodialysis followed first order kinetics, with a half-life of 54 hours. Adverse events in 6 patients were classified by the treating physicians as possibly related to fomepizole. These were phlebitis, dyspepsia, anxiety, agitation, a local reaction at the site of injection, transient tachycardia, transient rash, and a 'strange' feeling. Two patients died as a result of methanol poisoning, both were comatose and acidotic on admission, and had the highest plasma formic acid concentrations. Fomepizole is a safe and effective antidote for use in the treatment of methanol poisoning (Brent *et al.,* 2001).

Fomepizole may be useful for treatment of the ocular effects of methanol intoxication. Sivilotti *et al.* (1998) report a case of complete visual recovery following treatment with fomepizole.

Folic acid and folinic acid

Administration of folates may be useful in methanol poisoning. They stimulate the folate-mediated oxidation of formic acid to carbon dioxide, thereby decreasing its accumulation (McMartin *et al.,* 1977; Noker *et al.,* 1980). The folates, both when administered before and after methanol, decrease the blood concentrations of formic acid to non toxic concentrations. In most human cases where folates have been administered their effectiveness has been difficult to determine, as ethanol and haemodialysis have also been administered. However studies in monkeys suggest that folates would be useful in humans also (Jacobsen and McMartin, 1997). Pretreatment of monkeys with folic acid for 48 hours, or folinic acid given after methanol administration, decreased formic acid concentrations and reduced the accompanying metabolic acidosis, without affecting the rate of methanol elimination. Folinic acid was still effective in hastening the elimination of formic acid when given 10 hours following methanol administration (Noker *et al.,* 1980).

Thiamine (Vitamin B1)

Thiamine and steroids (prednisone) have been successfully used in the treatment of ocular toxicity following methanol intoxication. As thiamine is used in the treatment of ethanol induced Wernike-Korsakoff syndrome and is effective in the treatment of nutritional ambylopia and infantile necrotising encephalomyopathy, Rotenstreich *et al.* (1997) felt that there was a role for its use in the treatment of methanol induced bilateral

visual loss. The combination of steroids and thiamine proved highly effective in this case, but it is not clear whether using only one drug might have been sufficient. The authors recommend the use of this combination of agents in the treatment of methanol induced ocular toxicity, as the risk of permanent ocular damage is high (Rotenstreich *et al.*, 1997).

Chronic exposure

Occupational exposures to methanol can be quantitatively monitored by urinary formic acid determinations. However, there is great inter-individual variability in formic acid concentrations; 'normal' formic acid values would be considered to be in the range 0-20 mg/l (Baumann and Angerer, 1979). It is important to note that methanol and formic acid are naturally occurring chemicals in animals and plants.

REFERENCES

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Allis JW, Brown BL, Simmons JE, Hatch GE, McDonald A, House DE. 1996 Methanol potentiation of carbon tetrachloride hepatoxicity: the central role of cytochrome P450. *Toxicology* 112:131-140.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6): 272-290.

Anderson TJ, Shuaib A, Becker WJ. 1989 Methanol poisoning: factors associated with neurologic complications. *Can J Neurol Sci* 16:432-435.

Anderson TJ, Shuaib A, Becker WJ. 1987 Neurological sequelae of methanol poisoning. *Can Med Assoc J* 136:1177-1179.

Aufderheide TP, White SM, Brady WJ, Stueven HA. 1993 Inhalational and percutaneous methanol toxicity in two firefighters. *Ann Emerg Med* 22:1916-1918.

Barton-Burns A, Bailie GR, Eisele G, McGoldrick D, Swift T, Rosano TG. 1998 Use of pharmacokinetics to determine the duration of dialysis in management of methanol poisoning. *Am J Emerg Med* 16:538-540.

Baselt RC. 2000 *Disposition of Toxic Drugs and Chemicals in Man,* fifth edition. Chemical Toxicology Institute, Foster City, California.

Baumann K, Angerer J. 1979 Occupational chronic exposure to organic solvents. VI. Formic acid concentration in blood and urine as an indicator of methanol exposure. *Int Arch Occup Environ Health* 42:241-249.

Bennett IL, Cary FH, Mitchell GL, Cooper MN. 1953 Acute methyl alcohol poisoning: A review based on experiences in an outbreak of 323 cases. *Medicine* 32:431-463.

Bergeron R, Cardinal J, Geadah D. 1982 Prevention of methanol toxicity by ethanol therapy [letter]. *N Engl J Med* 304 (24):1528.

Bevan C. 2001 Monohydric alcohols – C_1-C_6. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Brent J, Lucas M, Kulig K, Rumack BH. 1991 Methanol poisoning in a 6-week-old infant. *J Pediatr* 118:644-646.

Brent J, McMartin K, Phillips S, Aaron C, Kulig K. 2001 Fomepizole for the treatment of methanol poisoning. *N Engl J Med* 344:424-429.

Burbacher T, Shen D, Grant K, Sheppard, Damian D, Ellis S, Liberato N. 1999 Reproductive and offspring developmental effects following maternal inhalation exposure to methanol in nonhuman primates [abstract]. *Health Effects Institute Research Report Number 89*.

Cavalli A, Volpi A, Maggioni AP, Tusa M, DePieri G. 1987 Severe reversible cardiac failure associated with methanol intoxication. *Postgrad Med J* 63:867-868.

Chow MT, Di Silvestro VA, Yung CY, Nawab ZM, Leehey DJ, Ing TS. 1997 Treatment of acute methanol intoxication with hemodialysis using an ethanol-enriched, bicarbonate based dialysate. *Am J Kidney Dis* 30:568-570.

Church AS, Witting MD. 1997 Laboratory testing in ethanol, methanol, ethylene glycol and isopropanol toxicities. *J Emerg Med* 15:687-692.

Cornish HH, Adefuin J. 1967 Potentiation of carbon tetrachloride by aliphatic alcohols. *Arch Environ Health* 14:447-449.

Downie A, Khattab, Malik MIA, Samara IN. 1992 A case of percutaneous industrial methanol toxicity. *Occup Med* 42:47-49.

Dutkiewicz B, Kończalik J, Karwacki W. 1980 Skin absorption and per os administration of methanol in men. *Int Arch Occup Environ Health* 47:81-88.

Erdener U, Ilhan B. 1997 Cologne water-induced visual loss. *Ophthal Epidemiol* 4:177-178.

Frederick LJ, Schulte PA, Apol A. 1984 Investigation and control of occupational hazards associated with the use of spirit duplicators. *Am Ind Hyg Assoc J* 45:51-55.

Frenia ML, Schauben JL. 1993 Methanol inhalation toxicity. *Ann Emerg Med* 22:1919-1923.

Garner CD, Lee EW, Terzo TS, Louis-Ferdinand RT. 1995 Role of retinal metabolism in methanol-induced retinal toxicity. *J Toxicol Environ Health* 44:43-56.

Grant WM, Schuman JS. 1993 *Toxicology of the Eye,* fourth edition. Charles C Thomas, Springfield, Illinois.

Guggenheim MA, Couch JR, Weinberg W. 1971 Motor dysfunction as a permanent complication of methanol ingestion. Presentation of case with a beneficial response to levodopa treatment. *Arch Neurol* 24:550-554.

Hantson P, Duprez T, Mahieu P. 1997 Neurotoxicity to the basal ganglia shown by magnetic resonance imaging (MRI) following poisoning by methanol and other substances. *Clin Toxicol* 35:151-161.

Hantson P, Mahieu P. 2000 Pancreatic injury following acute methanol poisoning. *Clin Toxicol* 38:297–303.

Herken W, Rietbrock N. 1968 The influence of blood-pH on ionization, distribution, and toxicity of formic acid. *Naunyn Schmiedebergs Arch Exp Pathol Pharmakol* 260 (2):142-143. Cited in: Jacobsen D, Webb R, Collins TD, McMartin KE. 1988 Methanol and formate kinetics in late diagnosed methanol intoxication. *Med Toxicol* 3:418-423.

IPCS. 1997 *Environmental Health Criteria 196. Methanol.* World Health Organization, International Programme on Chemical Safety, Geneva.

Jacobsen D, Jansen H, Wiik-Larsen E, Bredesen JE, Halvorsen S. 1982 Studies on methanol poisoning. *Acta Med Scand* 212:5-10.

Jacobsen D, McMartin KE. 1997 Antidotes for methanol and ethylene glycol poisoning. *Clin Toxicol* 35:127-143.

Jacobsen D, Webb R, Collins TD, McMartin KE. 1988 Methanol and formate kinetics in late diagnosed methanol intoxication. *Med Toxicol* 3:418-423.

Kahn A, Blum D. 1979. Methyl alcohol poisoning in an 8-month-old boy: An unusual route of intoxication. *J Pediatrics* 94:841-843.

Kawai T, Yasugi T, Mizunuma K, Horiguchi S, Hirase Y, Uchida Y, Ikeda M. 1991 Methanol in urine as a biological indicator of occupational exposure to methanol vapor. *Int Arch Occup Environ Health* 63:311-318.

Liesivuori J, Savolainen H. 1991 Methanol and formic acid toxicity: biochemical mechanisms. *Pharmacol Toxicol* 69:157-163.

Mahieu P, Hassoun A, Lauwerys R. 1989 Predictors of methanol intoxication with unfavourable outcome. *Hum Toxicol* 8:135-137.

Martens J, Westhovens R, Verberckmoes R, Delooz H, Daenens P. 1982 Recovery without sequelae from severe methanol intoxication. *Postgrad Med J* 58:454-456.

McCoy HG, Cipolle RJ, Ehlers SM, Sawchuk RJ, Zaske DE. 1979 Severe methanol poisoning. *Am J Med* 67: 804-807.

McLean DR, Jacobs H, Mielke BW. 1980 Methanol poisoning: a clinical and pathological study. *Ann Neurol* 8:161-167.

McMartin KE, Martin-Amat G, Makar AB, Tephly TR. 1977 Methanol poisoning. V. Role of formate metabolism in monkeys. *J Pharmacol Exp Therap* 201:564-572.

Noker PE, Eells JT, Tephly TR.1980 Methanol toxicity: treatment with folic acid and 5-formyl tetrahydrofolic acid. *Alcohol Clin Exp Res* 4 (4):378-383.

Rotenstreich Y, Assia EI, Kesler A. 1997 Late treatment of methanol blindness. *Br J Ophthalmol* 81:416-417.

Scrimgeour EM, Dethlefs RF, Kevau I. 1982 Delayed recovery of vision after blindness caused by methanol poisoning. *Med J Aust* 2:481-483.

Scrimgeour EM. 1980 Outbreak of methanol and isopropanol poisoning in New Britain, Papua New Guinea. *Med J Aust* 2:36-38.

Šedivec V, Mráz M, Flek J. 1981 Biological monitoring of persons exposed to methanol vapours. *Int Arch Occup Environ Health* 48:257-271.

Sivilotti M, Burns M, McMartin KE, Brent J. 1998 Reversible blindness in methanol poisoning treated with fomepizole [abstract]. *Clin Toxicol* 36:514.

Yant WP, Schrenk HH. 1937 Distribution of methanol in dogs after inhalation and administration by stomach tube and subcutaneously. *J Ind Hyg Toxicol* 19:337-345.

15 Methylene Chloride

Grainne Cullen

SUMMARY

- Methylene chloride is toxic by inhalation and ingestion and may be absorbed after heavy skin contamination
- It is highly volatile and high concentrations may accumulate in unventilated areas
- Methylene chloride is an eye, skin and respiratory tract irritant
- It causes narcosis at high concentrations
- Methylene chloride is partly metabolised to carbon monoxide *in vivo* and elevated carboxyhaemoglobin concentrations may persist for some time after cessation of exposure
- Methylene chloride is possibly carcinogenic to humans
- Methylene chloride is a possible mutagen
- Exposure to high concentrations of methylene chloride has been linked to an increase in spontaneous abortion. However there is insufficient information to establish a causal relationship

DESCRIPTION

Synonyms

Methylene chloride, dichloromethane, DCM, Freon 30, methane dichloride, methylene bichloride, methylenum chloratum.

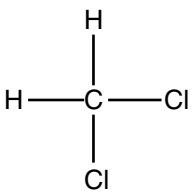
Identification numbers

CAS	75-09-2
UN	1593
RTECS	PA 8050000
EINECS	2008389

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula CH_2Cl_2

molecular formula



molecular mass	84.93
physical form	colourless liquid with a mild, sweet, ether-like odour
relative vapour density (air = 1)	2.93
flash point (°C)	none
boiling point (°C)	40
autoignition temperature (°C)	605
refractive index	1.4237
explosive limits in air (%v/v)	13-22

Odour threshold

250 ppm (Amoore and Hautala 1983); 153 ppm-612 ppm (Ruth, 1986).

OCCUPATIONAL EXPOSURE

Limits in air

TWA (UK): 100 ppm (350 mg/m^3)
TWA (ACGIH): 50 ppm (175 mg/m^3)

Conversion factors

Methylene chloride	**Carbon monoxide**
1 ppm = 3.53 mg/m^3	1 ppm = 1.16 mg/m^3
1 mg/l = 288 ppm	1 mg/l = 860 ppm
1 mg/m^3 = 0.28 ppm	1 mg/m^3 = 0.86 ppm

Biological monitoring

The biological exposure indices (BEI) set by the ACGIH for methylene chloride are a methylene chloride blood concentration of 0.5 mg/l during shift and 0.2 mg/l methylene chloride in end of shift urine (ACGIH, 2000).

Methylene chloride can be detected in exhaled breath for several hours after exposure. The methylene chloride concentration in exhaled air generally reflects the amount inhaled at ambient concentrations of up to 500 ppm. Breathing ambient air concentrations of 200 ppm will result in about 80 ppm in expired air. Methylene chloride can also be measured in blood. Unfortunately, measurement of methylene chloride in expired air or blood is seldom practical in clinical situations and blood concentrations are difficult to interpret. Workers exposed to currently permissible levels usually have blood concentrations of only 1-2 mg/l. Few studies have been published with methylene chloride blood concentrations and these are limited to severe or fatal poisonings (ATSDR, 1993a,b).

Carboxyhaemoglobin can be detected in the blood of non-smokers about 30 minutes after exposure to methylene chloride. An ambient air concentration of 200 ppm methylene chloride corresponds to a carboxyhaemoglobin concentration of 4% to 9%. Exposure to methylene chloride concentrations of 500 ppm for several hours results in a carboxyhaemoglobin concentration as high as 15%. Ratney *et al.* (1974) reported that an 8 hour exposure to 180 ppm methylene chloride would correspond to a carboxyhaemoglobin concentration of 6-12% in non-smokers, and that at a constant exposure to 180 ppm the carboxyhaemoglobin concentration increases at approximately 0.5% per hour. However, other factors may influence the carboxyhaemoglobin concentration, including exercise, smoking and exogenous exposure to carbon monoxide. Therefore, the carboxyhaemoglobin concentration may not correspond directly to inhaled concentrations of methylene chloride.

Urinary concentrations of formic acid (an intermediate product in the metabolism of methylene chloride) have also been used to monitor exposed workers.

It is estimated that an 8 hour exposure to approximately 150 ppm methylene chloride is equivalent to an 8 hour exposure to 35 ppm carbon monoxide in so far as both exposures will result in a carboxyhaemoglobin concentration of approximately 5%. This study was carried out in sedentary volunteers (DiVincenzo and Kaplan, 1981a). Smokers or physically active workers are likely to have higher carboxyhaemoglobin concentrations than sedentary workers exposed to the same ambient concentration of methylene chloride (DiVincenzo and Kaplan, 1981b). Carboxyhaemoglobin concentrations may increase both during and after exposure (Åstrand *et al.,* 1975).

TOXICITY

Methylene chloride is a CNS depressant and profound CNS depression may occur after exposures to high concentrations. Concentrations in excess of 50,000 ppm are thought to be immediately life threatening (Hathaway *et al*., 1996). Signs and symptoms of CNS depression may occur in subjects exposed to vapour concentrations of 1,000 ppm (Stewart *et al*., 1972b).

Methylene chloride is partially metabolised to carbon monoxide. Methylene chloride is lipophilic and concentrations of carbon monoxide are likely to rise after exposure to methylene chloride has ceased, due to the release of methylene chloride from adipose and other tissues and its subsequent metabolism.

Methylene chloride is commonly found in industrial and domestic paint strippers, but exposure may also occur during its production or use as a cleaner, degreaser, pharmaceutical solvent and process solvent (Budavari, 1996). It is also used in the manufacture of photographic film and in urethane foam (Hathaway *et al*., 1996). Some aerosols may also contain methylene chloride and it has been used as an ingredient in personal defence sprays (Dueñas *et al*., 2000).

The main route of exposure is inhalation, but occasionally methylene chloride may be ingested. In industrial situations ingestion may occur as splash contact, or immersion, or heavy contamination. Intentional ingestion of methylene chloride by adults is rare. Accidental ingestion of methylene chloride by children usually involves ingestion of domestic paint strippers although, in rare cases, children may ingest industrial preparations.

Occupational exposure to methylene chloride has resulted in death (Bakinson and Jones, 1985; Manno *et al*., 1989). Deaths have occurred mainly in individuals who have been cleaning with methylene chloride in an enclosed area (Winek *et al*., 1981; Kaufman *et al*., 1989; Leikin *et al*., 1990; Tay *et al*., 1995; Kim *et al*., 1996), emptying tanks of methylene chloride (Goullé *et al.,* 1999), or during disposal of waste methylene chloride in an enclosed space (Manno *et al.,* 1992). Intentional abuse by inhalation of methylene chloride has also been reported (Sturmann *et al*., 1985; Horowitz, 1986).

Absorption

Methylene chloride is most commonly absorbed by inhalation, however it may also be ingested accidentally or deliberately. Dermal absorption is usually low because methylene chloride rapidly evaporates, however in cases of heavy skin contamination (e.g., immersion), or if methylene chloride is trapped against the skin by gloves or clothing, then absorption may be higher and systemic toxicity may occur (ATSDR, 1993a,b). Dermal absorption of methylene chloride has been demonstrated in human volunteer studies (Stewart and Dodd, 1964).

Exposure level and duration, physical activity, smoking and body fat all affect the methylene chloride body burden (Mahmud and Kales, 1999). As much as 70% of the inhaled vapour may be absorbed via the lungs (DiVincenzo and Kaplan, 1981b). Inhalation of methylene chloride appears to result in higher carboxyhaemoglobin concentrations compared to ingestion. For example, a peak carboxyhaemoglobin concentration of 12.1% was recorded in an adult female 26 hours post ingestion of 300 ml of a paint remover containing 81% methylene chloride and 14% methanol (Hughes and Tracey, 1993). This carboxyhaemoglobin concentration is much lower than that of 50% recorded in a 20 year old female after use of a methylene chloride paint remover in a poorly ventilated room (Fagin *et al.,* 1980). A study of human volunteers exposed to 1,000 ppm for 1 to 2 hours showed that carboxyhaemoglobin concentrations may remain elevated for 17 hours (Stewart *et al*., 1972a, b).

Distribution

Following absorption, methylene chloride is distributed to all tissues and principally the liver, brain and subcutaneous adipose tissue. Methylene chloride crosses the placenta and blood brain barrier and is found in breast milk (Schardein, 1993).

Metabolism

In vivo and *in vitro* studies have shown that methylene chloride is metabolised by two different pathways. One is a microsomal oxidation process (involving cytochrome P450) and the other is a glutathione dependent cytosolic pathway. Carbon monoxide is formed by the microsomal oxidation pathway (Gargas *et al.*, 1986).

Methylene chloride is largely metabolised in the liver (a small proportion may undergo transformation in the lungs and kidneys). In the liver, methylene chloride is metabolised by two pathways. The first pathway utilises the mixed function oxidase cytochrome P450 enzymes (including P450 CYP2E1) and converts methylene chloride into carbon monoxide and carbon dioxide. This pathway is the most important in humans and becomes saturated at a few hundred ppm. The second pathway utilises glutathione transferase and results in the formation of carbon dioxide (via formaldehyde and formate). This pathway appears not to be saturable, at least at concentrations up to 10,000 ppm. The metabolic contribution of each pathway appears to vary in humans, particularly with the exposure concentration. These metabolic pathways seem to have a different significance in laboratory animals so that interspecies comparisons are difficult and there may be a possibility of enzyme polymorphism (Their *et al.*, 1991). The metabolic formation of carbon monoxide and its subsequent binding to haemoglobin, producing carboxyhaemoglobin, may continue for several hours after cessation of methylene chloride exposure, as fat and other tissues continue to release accumulations of the lipophilic solvent. This endogenous release of methylene chloride prolongs the duration of cardiovascular stress to about twice that caused by a comparable carboxyhaemoglobin concentration resulting from exposure to carbon monoxide (ATSDR, 1993a,b; IPCS, 1996).

Elimination

The primary route of elimination of methylene chloride is via the lungs. A small amount of unchanged methylene chloride is eliminated in the urine and faeces. At low doses, a large percentage of methylene chloride is metabolised and eliminated as carbon monoxide, whereas at high doses more of the unchanged parent compound is exhaled (ATSDR, 1993a,b). In human volunteer experiments, 25-34% of the methylene chloride absorbed was excreted as carbon monoxide (DiVincenzo and Kaplan, 1981b). Of the methylene chloride absorbed, 25% to 90% is eliminated within 2 hours after exposure, and by 16 hours after exposure none is detected in the blood (ATSDR, 1993a,b). The half-life of excretion of carbon monoxide produced by the metabolism of methylene chloride is approximately 13 hours. This is about 2.5 times the half-life of excretion of inhaled carbon monoxide in a subject breathing air (Baselt, 2000).

Mode of action

Methylene chloride is a CNS depressant and can cause profound CNS depression at high concentrations. The CNS depressant effects are thought to be due to methylene chloride itself rather than an effect of its conversion to carbon monoxide. Fatalities have occurred after methylene chloride inhalation where, although carboxyhaemoglobin concentrations were high, they were not sufficient to cause death. In some of these cases, very high blood concentrations of methylene chloride have been found, suggesting that methylene chloride itself may be responsible for deaths or that high concentrations of toxic metabolites formed from the non-saturable glutathione conjugation pathway are involved. These include formaldehyde and formic acid, which may induce tissue hypoxia and metabolic acidosis (Manno *et al.*, 1992).

It is thought that the neurotoxic effects of methylene chloride depend on a direct, non-specific narcotic action on the CNS as well as an equally non-specific carbon monoxide-induced hypoxic effect (Winneke, 1981). The carbon monoxide produced by the metabolism of methylene chloride binds reversibly to the oxygen carrying sites of the haemoglobin molecule. Carbon monoxide has an affinity for haemoglobin 200 to 300

times greater than oxygen itself, and carboxyhaemoglobin is formed which is then unavailable for oxygen transportation. The metabolic formation of carboxyhaemoglobin after methylene chloride exposure may result in greater cardiovascular stress than that induced by a comparable concentration of carboxyhaemoglobin after exposure to carbon monoxide itself (Stewart and Hake, 1976). This may be particularly problematic for those with pre-existing cardiac disease.

An increased amount of markers of cell damage (protein, hexose, sialic acid, lactate dehydrogenase, acid and alkaline phosphatase) were found in cell-free lavage effluents from lungs of rats exposed to methylene chloride by inhalation, compared to controls (Sahu *et al.*, 1980).

Metabolic interactions

- **Acetone**

  One of the routes of metabolism of methylene chloride is a microsomal oxidation process (involving cytochrome P450). Carbon monoxide is formed by this microsomal oxidation pathway (Gargas *et al.*, 1986) and concurrent exposure to acetone may increase the production of carbon monoxide, by the acetone-induced augmentation of this pathway.

- **Aromatic hydrocarbons**

  Studies in rats have shown that a single oral administration of an aromatic hydrocarbon (benzene, toluene or *m*-xylene) 16-24 hours before the administration of methylene chloride, increases the peak carboxyhaemoglobin concentration. The half-life of methylene chloride in blood was shorter, indicating that the metabolic degradation of methylene chloride is enhanced by the aromatic hydrocarbons. This effect on the peak carboxyhaemoglobin concentration was dependent on the time interval between aromatic hydrocarbon and methylene chloride treatment, since earlier administration of toluene or *m*-xylene decreased the carboxyhaemoglobin elevation. Disulfiram treatment blocked carboxyhaemoglobin elevation completely and corresponding increases in the concentration and half-life of methylene chloride were observed (Kim and Kim, 1996).

- **Ethanol**

  A study in experimental animals found that a one day exposure to 11,000 ppm methylene chloride and 24,000 ppm ethanol produced a decrease in hepatic triglyceride concentrations, histological changes and carboxyhaemoglobin concentrations relative to the effects of methylene chloride exposure alone. Also, exposure to 560-600 ppm methylene chloride and 22,800-23,900 ppm ethanol decreased carboxyhaemoglobin concentrations compared to methylene chloride alone, which suggests an antagonistic effect. However, exposure to 500 ppm methylene chloride and 26,200 ppm ethanol over five days caused an increase in liver damage, suggesting that ethanol may potentiate the effects of methylene chloride (Balmer *et al.*, 1976).

- **Smoking**

  Smoking increases the blood carboxyhaemoglobin concentration, as does exposure to methylene chloride. Smoking, during and after exposure to methylene chloride, produced an additive increase in carboxyhaemoglobin concentrations (DiVincenzo and Kaplan, 1981a).

CASE REPORTS

Occupational exposure and persistent headache

A 26 year old man presented complaining of persistent headaches for one month. He had a history of occasional headaches since adolescence, but, during the past four months, his symptoms had increased in intensity and frequency and were no longer relieved by over-the-counter medication. He had worked as a carpenter in a laminated product manufacturing company for the previous six months, where his duties included working

with lacquer thinner to clean cabinet surfaces and spraying laminating materials over cabinet surfaces. Neither he nor any of the other workers used any type of personal protective equipment. The products he used included a spray contact cement which contained 70% methylene chloride, toluene and methyl ethyl ketone and a lacquer thinner which contained toluene, isopropanol, ethyl acetate, isobutyl alcohol and isobutyl acetate. Physical examination was unremarkable apart from his skin on both hands, which showed marked thickening and was very dry with fissures and cracking. Neurological examination was normal, and laboratory investigations including carboxyhaemoglobin concentration (COHb), were normal. Instructions were given to the patient to have his primary care physician check his COHb concentration after a work shift, particularly when he became symptomatic. The next day, although he was working with the doors of the workroom open, he had a mild headache and his COHb was 6.4%. Four days later he was working with the doors of the workroom closed and he reported that the room was poorly ventilated. He became unwell with nausea and vomiting and left work early. He was reported to have a COHb of 21% approximately 35 minutes after leaving his place of work and subsequently received normobaric oxygen therapy. His workplace was subsequently inspected by officials from the local occupational hygiene division, fire and health departments. The major findings were area samples showing methylene chloride concentrations of 300-500 ppm and a carbon monoxide concentration of 28 ppm. Based on this information the company immediately substituted a water based process for the one previously utilising methylene chloride (Mahmud and Kales, 1999).

Occupational exposure and convulsions

A 53 year old man became unconscious while applying a methylene chloride based paint stripping product. No respirator was worn and the only ventilation was an open window. Two generalised convulsions were noted but no cardiac irregularities were recorded. He developed first and second-degree chemical burns to the areas of his skin that had been in contact with the liquid (about 24% of his body surface area). The highest measured carboxyhaemoglobin concentration was 5.1%. He recovered with supportive care (Hall and Rumack, 1990).

Fatal occupational exposure

Paramedics were called to the scene after building security personnel had pulled two unconscious men from a small washroom, where there was a strong chemical odour and an open container of paint stripper (containing 91.2% methylene chloride and 6% methanol). Both men had been seen well approximately 20-30 minutes prior to their discovery. One was wearing a half mask with organic vapour cartridges. The men were found with intertwined limbs, which suggested that one had been trying to remove the other from the room. Both men were in cardiac arrest and one of the rescuers, who had performed mouth-to-mouth resuscitation on both men, complained of nausea and vomiting. One man was pronounced dead 15 minutes after arrival at hospital when life support measures failed. The second victim was successfully resuscitated to pulse and blood pressure. However, he never regained consciousness or spontaneous respirations and he died on the fourth day in hospital. His carboxyhaemoglobin concentration increased from 2% to 8% over the nine hours following admission despite the administration of oxygen. The cause of death in these patients was not carbon monoxide poisoning secondary to methylene chloride exposure, but solvent induced narcosis due to the methylene chloride itself (Leikin *et al*., 1990).

CLINICAL EFFECTS

Acute exposure

Inhalation

Following acute inhalation exposures to high concentrations of methylene chloride, the major effect is CNS depression. Coma and, occasionally, death, due to respiratory depression have been reported with exposures to concentrations greater than 8,000 ppm. Exposure to lower concentrations (300 to 800 ppm in air) has resulted in impaired sensory and psychomotor functions (ATSDR, 1993a,b). At low concentrations, nausea, dizziness, headache and drowsiness may occur (Bakinson and Jones, 1985). One of the problems associated with exposure to methylene chloride is that intoxication resulting in impaired

sensory and psychomotor functions may result in injury to the user or other people working with the user (Reid, 2001). Studies in volunteers suggest that brief exposures to methylene chloride around the current permissible levels are unlikely to cause any detrimental effect on human psychomotor and cognitive functions (Gamberale *et al.,* 1975). The CNS effects are generally reversible and are thought to be due to methylene chloride alone or a combination of methylene chloride and carbon monoxide, but are not due to carbon monoxide alone.

A study of industrial accidents involving solvents found that, of the methylene chloride cases reported, there was no substantial evidence for hepatorenal or cardiac effects. The principal effects of excessive exposure were headaches, dizziness and nausea. Respiratory effects were not commonly reported (Bakinson and Jones, 1985).

Other effects of acute methylene chloride exposure include irritation to the eyes and upper respiratory tract and cardiac effects (myocardial ischaemia, dysrhythmias) (McGirr *et al*., 1990). Pulmonary oedema is rare following methylene chloride exposure but it has been reported after inhalation of a paint remover (Buie *et al*., 1986). Acute toxic effects may persist for hours after the victim has been removed from the source of exposure because of continued metabolism of methylene chloride. Carboxyhaemoglobin concentrations may continue to rise, peaking 5-6 hours post exposure (ATSDR, 1993a,b) and concentrations of up to 50% have been reported following the use of a methylene chloride paint stripper (Fagin *et al*., 1980). However, cases have occurred where there have been significant CNS effects (coma, convulsions), but without a high carboxyhaemoglobin concentration (Hall and Rumack, 1990).

Neurological effects

Neurological effects may occur from acute methylene chloride exposure. Long-term memory impairment, difficulty with simple intellectual tasks and poor concentration occurred in a 25 year old male accountant who used a methylene chloride paint stripper for 3-4 hours in a confined space. Formal testing showed mental clearing within a few weeks of the exposure, but the patient was unable to resume work for six months (Memon and Davidson, 1981).

Weakness, left sided paraesthesia and flashbacks were reported in a 52 year old woman who had used a methylene chloride based spray paint on the outside of her house four days previously (Nager and O'Connor, 1998). Psychomotor impairment after acute exposure to methylene chloride has been demonstrated in human volunteer studies (Gamberale *et al*., 1975; Winneke, 1982).

Cardiac effects

Sinus bradycardia, right bundle branch block and non-specific ST-T wave changes were reported in a 51 year old patient with a history of ischaemic heart disease who was exposed to a methylene chloride leak at work (Benzon *et al*., 1978). Atrial fibrillation was reported in a 30 year old man who used methylene chloride to remove paint from floor tiles for about 30 minutes. His carboxyhaemoglobin concentration was 11%, which was not thought to be sufficient to account for the arrhythmia. It is more likely that this was caused by sensitisation of the myocardium by methylene chloride. This patient had no risk factors for arrhythmias (McGirr *et al.,* 1990).

Hepatic effects

Hepatic effects from methylene chloride exposure are rare (Bakinson and Jones, 1985; Rioux and Myers, 1988). Hepatotoxicity may result from inhalation of high concentrations of methylene chloride for many hours (Mizutani *et al*., 1988). In one case, serum alanine aminotransferase (ALT) concentrations rose one week after exposure to methylene chloride at work. This patient was accidentally exposed to 10-15 l of methylene chloride at work, when it sprayed onto his face and clothes from a broken tube. He had a shower immediately and the exposure was estimated to be no more than 3-4 minutes duration. Apart from the temporary rise in ALT concentrations, other liver function parameters (serum bilirubin, alkaline phosphatase and aspartate aminotransferase) were all normal (Puurunen and Sotaniemi, 1985).

Renal effects

Renal effects from methylene chloride exposure are rare (Bakinson and Jones, 1985; Rioux and Myers, 1988). Acute tubular necrosis has been reported after a two day exposure to methylene chloride, mineral spirits and methanol, by inhalation at work (Miller *et al*., 1985).

Pulmonary effects

Non-cardiogenic pulmonary oedema has been reported following the use of a methylene chloride paint stripper. However, the exposure in this case is complicated by the fact that the patient used a heat gun after he had applied the paint stripper, which may have caused phosgene to be produced (which can also cause pulmonary oedema) (Snyder *et al*., 1992).

Dermal

Acute exposure to methylene chloride may result in dermatitis, irritation and mild burns. Severe chemical burns may occur from prolonged exposure or immersion (Wells and Waldron, 1984). Dermal absorption of methylene chloride has been demonstrated in humans (Stewart and Dodd, 1964) and skin exposure can contribute to systemic toxicity (Dhillon and Von Burg, 1995). Therefore, particularly in cases involving prolonged or heavy skin contamination, there is a risk of systemic poisoning.

Eye

Most methylene chloride exposures do not result in anything other than an immediate burning sensation to the eye, which should resolve after the eye is thoroughly irrigated. However, there are rare reports of corneal epithelium loss after human exposures and loss of corneal epithelium has been reported from animal experiments (Grant and Schuman, 1993).

Ingestion

Acute ingestion of methylene chloride may result in nausea, vomiting, abdominal pain, sweating, shortness of breath, agitation, confusion, drowsiness progressing rapidly to coma, tachycardia, hypotension and convulsions. Tachypnoea, respiratory depression, pulmonary oedema and cardiac arrhythmias may occur. Metabolic acidosis, haematuria, anuria and renal failure have been described following ingestion of methylene chloride (Chang *et al.,* 1999). Inflammation and burns to the oral mucous membranes and oesophagus may occur and in severe cases there may be a possibility of stricture formation (Roberts and Marshall, 1976). Carboxyhaemoglobin concentrations may be elevated and liver function tests may be abnormal.

Chronic exposure

Inhalation

Intermittent eye, nose and throat irritation, headaches and lethargy were reported in a patient who had repeated exposures to methylene chloride at work over a 2.5 year period. He found that his symptoms improved at weekends and when he was on holiday. Marginally increased liver function test results were also found (Shusterman *et al*., 1990).

There were no differences in symptoms reported in a group of workers who were chronically exposed to a mixture of solvents, including relatively high concentrations of methylene chloride (475 ppm), when compared to a control group. This study found no difference in selected health parameters for cardiac, neurological and hepatic effects (Soden, 1993).

Neurological effects

Dysarthria, unsteady gait and memory loss has been attributed to chronic methylene chloride poisoning (Barrowcliff, 1978). Dementia has been reported following chronic exposure to methylene chloride for three years (Barrowcliff and Knell, 1979). A study of chronic neurological effects of occupational methylene chloride exposure did not find any statistical difference between exposed workers and a control group, although subtle differences in attention and memory were identified (Becker and Lash, 1990).

Confusion, headache, impaired memory, auditory hallucinations and agitation were reported in a 52 year old man, who had a four year history of working as a strip tank operator using a mixture including methylene chloride (as well as formic acid, dodesilbenzene sulphonic acid and a corrosion inhibitor). The patient also reported a 12 month history of blurred vision, shortness of breath and lapses in short-term memory, which occurred at work and were worse at the end of the day (Tariot, 1983).

In a study of retired airline mechanics who had a history of occupational exposure to methylene chloride, there were no statistically significant differences in the results of physiological and psychological tests compared to controls. However, subtle differences in attention and memory were identified. The authors concluded that there was no firm evidence to support the hypothesis of lasting CNS effects in retired mechanics with long-term exposure to methylene chloride (Lash *et al*., 1991).

Cardiac effects

Animal studies suggest that exposure to methylene chloride lowers the myocardial threshold to arrhythmogenic action. However there is no evidence to suggest that this occurs in humans. In one study of 24 healthy workers chronically exposed to methylene chloride at concentrations averaging 60 to 475 ppm, there was no increase in ventricular or supraventricular ectopic activity and no episodic ST-segment depression. There was also no evidence of cardiac susceptibility or ECG abnormalities in several cases of otherwise healthy individuals rendered unconscious by acute exposure to methylene chloride. No studies have addressed the arrhythmogenic effect in individuals with underlying coronary disease (ATSDR, 1993a,b). In an epidemiological study of workers occupationally exposed to methylene chloride (some of them for over 20 years), there was no increase in the incidence of death from ischaemic heart disease (Friedlander *et al*., 1978).

Hepatic effects

Fatty liver has been reported as a feature after chronic inhalation of methylene chloride in laboratory animals (Morris *et al*., 1979). However, liver toxicity has not been reported in epidemiological studies and it is unlikely that serious hepatic effects would occur in exposures within current permissible workplace guidelines. One case of hepatitis and several cases of elevated liver enzymes have been reported (ATSDR, 1993a,b).

After chronic subcutaneous administration of methylene chloride in rats, the degree of liver damage was minimal and the results of most of the histological tests were reported as normal (Loyke, 1973).

Pulmonary effects

Pulmonary oedema and bilateral pleural effusions were reported after stripping furniture for four days using a product made up of methylene chloride, toluol, methanol and acetone (Buie *et al*., 1986).

Immunotoxicity

There are no studies on the immunotoxicity of methylene chloride in humans. Splenic atrophy has been observed in dogs who died after inhaling methylene chloride vapour (1,000 ppm) (MacEwen *et al*., 1972), but effects on the spleen were not consistent.

Dermal

No information available.

Eye

No information available.

Ingestion

No information available.

Carcinogenicity

Methylene chloride has been classified in group 2B as a possible human carcinogen by the IARC (1999). This is based on evidence of carcinogenicity in experimental animal studies. There is insufficient human data to allow a clear interpretation.

Epidemiological studies suggest that there may be long-term health effects from chronic exposure to methylene chloride in the form of pancreatic, hepatic or biliary cancer. Inhalation studies have demonstrated that methylene chloride causes hepatic neoplasms in animals (ATDSR, 1993a,b). Methylene chloride has been reported to cause benign mammary tumors and malignant liver and lung neoplasms in several animal species (ATSDR, 1993a,b; Huff *et al*., 1996).

Cantor *et al*. (1995) used mortality records from a five year period (1984-1989), coded for occupation and industry, and assessed them with regards to workplace exposures and possible breast cancer risk. Suggestive associations for probability and level of exposure were found for several organic solvents including methylene chloride.

A long term epidemiological study of workers chronically exposed to methylene chloride during the manufacture of photographic products, reported no statistically significant excesses in deaths from lung or liver cancer, or from ischaemic heart disease. These investigators did, however, report an increase in deaths from pancreatic cancer. Another study of employees at a fibre production plant reported an excess of deaths from liver and biliary tract cancer among workers exposed to methylene chloride. In both studies, however, the evidence was inconclusive (ATSDR, 1993a,b). In an epidemiological study of workers occupationally exposed to methylene chloride (some of them for over 20 years), there was no increase in the incidence of death from ischaemic heart disease or malignancies, compared with expected deaths in the general population (Friedlander *et al*., 1978).

In a study examining the occupational history of white men who had died of brain cancer an association of astrocytic brain cancer was observed with likely exposure to methylene chloride (Heineman *et al*., 1994).

In a review of the epidemiology literature on the potential cancer risks of methylene chloride, Dell *et al*. (1999) concluded that although the studies cannot rule out the possibility of any cancer risk associated with methylene chloride, there is no substantive cancer risk and that it appears likely that risks associated with methylene chloride exposure are small and limited to rare cancers. The carcinogenicity of methylene chloride is related to the metabolic activation of methylene chloride via the glutathione transferase pathway (Jonsson *et al*., 2001).

Genotoxicity

Methylene chloride is generally regarded as being mutagenic although results of *in vivo* and *in vitro* studies have been conflicting. Methylene chloride has been shown to cause chromosomal aberrations in some *in vitro* studies. There is some evidence that methylene chloride is clastogenic *in vitro* and it is thought to be a weak mutagen in mammalian systems. Both positive and negative results have been reported in *in vivo* studies examining the potential of methylene chloride to induce gene mutation and cause chromosomal aberrations or DNA damage and repair (ATSDR, 1993a,b).

Reproductive toxicity

There is limited information on the reproductive toxicity of methylene chloride in humans. No cases of human malformations have been reported, but high exposure to methylene chloride was associated with the occurrence of spontaneous abortion in a group of women who worked in a pharmaceutical factory (Lindbohm *et al*., 1992). Other studies have not found an increase in spontaneous abortions associated with methylene chloride exposure (Taskinen *et al*., 1994). Methylene chloride crosses the placenta and passes into breast milk (Schardein, 1993).

From studies involving prenatal and postnatal evaluation, methylene chloride caused no gross teratogenic effects in experimental animals (Hardin and Manson, 1980). However, it is thought that there may be slight fetotoxicity and persistent behavioural changes in offspring following premating or gestational exposure to methylene chloride in laboratory animals (Bornschein *et al*., 1980; Barlow and Sullivan, 1982). Schardein (1993) cites studies where methylene chloride was reported to induce post-natal behavioural effects in rats after massive inhalational exposures, but in lower doses it was not teratogenic in rats, mice or rabbits.

Exposure to 1,250 ppm methylene chloride had no effect on the average number of implantation sites per litter, the incidence of fetal resorptions, litter size, fetal sex ratios or fetal body measurements in rats or mice. However, exposure to methylene chloride caused a significant increase in carboxyhaemoglobin concentrations during exposure. Carboxyhaemoglobin concentrations were normal 24 hours after the last exposure to methylene chloride (Schwetz *et al*., 1975).

RISK GROUPS

Some populations may be more susceptible to methylene chloride poisoning. Individuals with a history of cardiovascular disease may be more at risk from cardiac arrhythmias associated with the production of carbon monoxide. Smokers may be at a higher risk of toxicity since they already have elevated carboxyhaemoglobin concentrations (DiVincenzo and Kaplan, 1981a). Obese individuals may also be at a higher risk since methylene chloride is lipophilic, therefore obese subjects will absorb more methylene chloride than lean subjects. Active workers (as opposed to sedentary workers) may also be at a higher risk of methylene chloride poisoning (Åstrand *et al*., 1975).

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The carboxyhaemoglobin concentration should be determined and 100% oxygen given. The ECG, renal function and liver function should be monitored in symptomatic patients. Symptomatic and supportive care. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Methylene chloride is radiopaque (Dally *et al*., 1987) and an X-ray may confirm ingestion. Emesis and gastric lavage are contraindicated due to the corrosive effects of methylene chloride. Nasogastric aspiration up to one hour post-ingestion may be considered if a large volume has been ingested. This is likely to be relevant only in deliberate ingestions. However, aspiration of the stomach contents may prove difficult. An 18 month old boy swallowed an unknown amount of paint stripper (methylene chloride 81%, methanol 14%) and when nasogastric aspiration of the stomach contents was attempted, the tip of the tube dissolved in the paint stripper. Aluminium hydroxide gel was passed down the tube and an hour later when the stomach contents were aspirated, gastric mucosa was found in the aspirate (Bates, 1997).

Oral fluids may be given unless perforation is suspected. In cases of suspected corrosive injury, gastro-oesophagoscopy should be undertaken within 12-24 hours of the event to assess the extent and severity of the injury. Prolonged follow up and treatment including surgical intervention may be required for patients with perforation or stricture. See below for management of systemic effects.

Systemic effects

Carboxyhaemoglobin concentrations should be measured in all cases where systemic effects are present (even in mild cases where headache or nausea are the only symptoms). 100% oxygen should be given. Carboxyhaemoglobin concentrations are thought to increase within two hours of inhalation exposure, but concentrations may continue to rise after exposure to methylene chloride has ceased. The half-life of carboxyhaemoglobin produced by methylene chloride exposure is about 2.5 times longer than after exposure to carbon monoxide, so oxygen therapy is likely to be more prolonged in methylene chloride exposure cases. Oxygen should be administered until the carboxyhaemoglobin is less than 5%. The ECG, arterial blood gases, liver and renal function should be monitored.

Despite the fact that hyperbaric oxygen therapy does not seem to significantly decrease the half-life of carboxyhaemoglobin after methylene chloride exposure, its use has improved the outcome in some cases (Rioux and Myers, 1989). Hyperbaric oxygen therapy may be considered for patients with prolonged CNS effects or persistently elevated concentrations of carboxyhaemoglobin despite normobaric oxygen therapy.

Antidotes

Oxygen

Oxygen is administered following methylene chloride exposure to enhance the dissociation of carboxyhaemoglobin and thereby increase oxygen delivery to tissues. Normobaric oxygen therapy has been shown to decrease the half-life of carboxyhaemoglobin resulting from exposure to methylene chloride, and most cases of methylene chloride poisoning can be managed supportively with 100% oxygen (Tomaszewski and Thom, 1994).

The half-life of carboxyhaemoglobin subsequent to methylene chloride exposure varies as follows:

- 13 hours in a subject breathing normal air (Ratney *et al*., 1974),
- 5.8 hours in a subject breathing 100% oxygen (Rioux and Myers, 1989),
- 4.75-6.8 hours in a subject breathing hyperbaric oxygen (Rioux and Myers, 1989).

Hyperbaric oxygen

Hyperbaric oxygen involves inhalation of oxygen at a pressure greater than 1 atm (usually 2-3 atm). It is commonly used to treat cases of decompression sickness and air embolism, and is also used to treat carbon monoxide poisoning where it has been shown to decrease the half-life of carboxyhaemoglobin (Tomaszewski and Thom, 1994). In contrast, it has not been shown to significantly decrease the half-life of

carboxyhaemoglobin following methylene chloride exposure and did not prevent elevations of carboxyhaemoglobin in two patients (Rioux and Myers, 1989). However, its use has improved clinical outcome in acutely poisoned patients (Rioux and Myers, 1989; Rudge, 1990) and should be considered in patients with prolonged CNS effects or persistently elevated concentrations despite normobaric oxygen therapy.

Chronic exposure

There may be a role for the use of hyperbaric oxygen in the treatment of chronic neurological effects attributed to methylene chloride exposure. However, human case data are lacking.

REFERENCES

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6): 272-290.

Åstrand I, Övrum P, Carlsson A. 1975 Exposure to methylene chloride. I. Its concentration in alveolar air and blood during rest and exercise and its metabolism. *Scan J Work Environ Health* 1:78-94.

ATSDR (Agency for Toxic Substances and Disease Registry). 1993a Methylene chloride toxicity. *Environ Med* 47 (5):1159-1166.

ATSDR. 1993b *Toxicological Profile for Methylene Chloride*. Agency for Toxic Substances and Disease Registry. US Department of Health and Human Services.

Balmer MF, Smith FA, Leach LJ, Yuile CL. 1976 Effects in the liver of methylene chloride inhaled alone and with ethyl alcohol. *Am Ind Hyg J* 37:345-352.

Bakinson MA, Jones RD. 1985 Gassings due to methylene chloride, xylene, toluene and styrene reported to Her Majesty's Factory Inspectorate 1961-1980. *Br J Ind Med* 42:184-190.

Barlow SM, Sullivan FM 1982 *Reproductive Hazards of Industrial Chemicals. An evaluation of animal and human data*. Academic Press, London.

Barrowcliff DF. 1978 Chronic carbon monoxide poisoning caused by methylene chloride paintstripper. *Med Sci Law* 18 (4):238.

Barrowcliff DF, Knell AJ. 1979 Cerebral damage due to endogenous chronic carbon monoxide poisoning caused by exposure to methylene chloride. *J Soc Occup Med* 29:12-14.

Baselt RC. 2000 *Disposition of Toxic Drugs and Chemicals in Man*, fourth edition. Chemical Toxicology Institute, Foster City, California.

Bates N. 1997 Paint Stripper. In: *Paediatric Toxicology. Handbook of Poisoning in Children*. Bates N, Edwards N, Roper J, Volans G (editors). Macmillan Reference Ltd, London.

Becker CE, Lash A. 1990 Study of neurological effects of chronic methylene chloride exposure in airline mechanics. *Vet Hum Toxicol* 32 (4):342.

Benzon HT, Claybon L, Brunner EA. 1978 Elevated carbon monoxide levels from exposure to methylene chloride [letter]. *J Am Med Assoc* 239 (22):2341.

Bornschein RL, Hastings L, Manson JM. 1980 Behavioural toxicity in the offspring of rats following maternal exposure to dichloromethane. *Toxicol Appl Pharmacol* 52:29-37.

Budavari S (editor). 1996 *The Merck Index*, twelfth edition. Merck & Co, Inc, Whitehouse Station, New Jersey.

Buie SE, Pratt DS, May JJ. 1986 Diffuse pulmonary injury following paint remover exposure. *Am J Med* 81:702-704.

Cantor KP, Stewart PA, Brinton LA, Dosemeci M. 1995 Occupational exposures and female breast cancer mortality in the United States. *J Occup Environ Med* 37 (3):336-348.

Chang YL, Yang CC, Deng JF, Ger J, Tsia WJ, Wu ML, Liaw HC, Liaw SJ. 1999 Diverse manifestations of oral methylene chloride poisoning: Report of 6 cases. *Clin Toxicol* 37 (4):497-504.

Dally S, Garnier R, Bismuth C. 1987 Diagnosis of chlorinated hydrocarbon poisoning by x ray examination. *Br J Ind Med* 44:424.

Dell LD, Mundt KA, McDonald M, Tritschler JP 2nd, Mundt DJ. 1999 Critical review of the epidemiology literature on the potential cancer risks of methylene chloride. *Int Arch Occup Environ Health* 72:429-442.

Dhillon S, Von Burg R. 1995 Methylene chloride. *J Appl Toxicol* 15 (4):329-335.

DiVincenzo GD, Kaplan CJ. 1981a Effect of exercise or smoking on the uptake, metabolism and excretion of methylene chloride vapor. *Toxicol Appl Pharmacol* 59:141-148.

DiVincenzo GD, Kaplan CJ. 1981b Uptake, metabolism and elimination of methylene chloride vapor by humans. *Toxicol Appl Pharmacol* 59:130-140.

Dueñas A, Felipe S, Ruiz-Mambrilla M, Martín-Escudero J, García-Calvo C. 2000 CO poisoning caused by inhalation of CH_3Cl (sic) contained in personal defense sprays [letter]. *Am J Emerg Med* 18 (1):120-121.

Fagin J, Bradley J, Williams D. 1980 Carbon monoxide poisoning secondary to inhaling methylene chloride. *Br Med J* 281:1461.

Friedlander BR, Hearne T, Hall S. 1978 Epidemiologic investigation of employees chronically exposed to methylene chloride. Mortality analysis. *J Occup Med* 20 (10):657-666.

Gamberale F, Annwall G, Hultengren M. 1975 Exposure to methylene chloride. II Physiological functions. *Scand J Work Environ Health* 1:95-103.

Gargas ML, Clewell HJ, Andersen ME. 1986 Metabolism of inhaled dihalomethanes in vivo: Differentiation of kinetic constants for two independent pathways. *Toxicol Appl Pharmacol* 82:211-223.

Goullé JP, Lacroix C, Vaz E, Rouvier P, Proust B. 1999 Fatal case of dichloromethane poisoning. *J Anal Toxicol* 23:380-383.

Grant WM, Schuman JS. 1993 *Toxicology of the Eye*, fourth edition. Charles C Thomas, Springfield, Illinois.

Hall AH, Rumack BH. 1990 Methylene chloride exposure in furniture-stripping shops: Ventilation and respirator use practices. *J Occup Med* 32 (1):33-37.

Hardin BD, Manson JM. 1980 Absence of dichloromethane teratogenicity with inhalation exposure in rats. *Toxicol Appl Pharmacol* 52:22-28.

Hathaway GJ, Proctor NH, Hughes JP. 1996 *Proctor & Hughes' Chemical Hazards of the Workplace*, fourth edition. John Wiley & Sons Inc, New York.

Heineman EF, Cocco P, Gomez MR, Dosemeci M, Stewart PA, Hayes RB, Zahm SH, Thomas TL, Blair A. 1994 Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer. *Am J Ind Med* 26:155-169.

Horowitz BZ. 1986 Carboxyhemoglobinemia caused by inhalation of methylene chloride. *Am J Emerg Med* 4 (1):48-51.

Huff J, Bucher J, Barrett JC. 1996 Methylene chloride. *Science* 272 (5265):1083-1084.

Hughes NJ, Tracey JA. 1993 A case of methylene chloride (Nitromors) poisoning, effects on carboxyhaemoglobin levels. *Hum Exp Toxicol* 12:159-160.

IARC (International Agency for Research on Cancer). 1999 *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*. IARC Monograph 71.

IPCS (International Programme on Chemical Safety). 1996 *Environmental Health Criteria 164. Methylene Chloride*. Geneva, World Health Organization.

Jonsson F, Bois F, Johanson G. 2001 Physiologically based pharmacokinetic modelling of inhalation exposure of humans to dichloromethane during moderate to heavy exercise. *Toxicol Sci* 59:209-218.

Kaufman D, Lipscomb JW, Leikin JB, Burda A, Hryhorczuk DO. 1989 Methylene chloride report of 5 exposures and 2 deaths [abstract]. *Vet Hum Toxicol* 31 (4):352.

Kim NY, Park SW, Suh JK. 1996 Two fatal cases of dichloromethane or chloroform poisoning. *J Forensic Sci* 41 (3):527-529.

Kim SK, Kim YC. 1996 Effect of a single administration of benzene, toluene or m-xylene on carboxyhaemoglobin elevation and metabolism in rats. *J Appl Toxicol* 16 (5):437-444.

Lash AA, Becker CE, So Y, Shore M. 1991 Neurotoxic effects of methylene chloride: Are they long lasting effects in humans? *Br J Ind Med* 48:418-426.

Leikin JB, Kaufman D, Lipscomb JW, Burda AM, Hryhorczuk DO. 1990 Methylene chloride: report of five exposures and two deaths. *Am J Emerg Med* 8 (6):534-537.

Lindbohm M-L, Taskinen H, Kyyrönen P, Sallmén M, Anttila A, Hemminki K. 1992 Effects of parental occupational exposure to solvents and lead on spontaneous abortion. *Scand J Work Environ Health* 18 (Suppl 2):37-39.

Loyke HF. 1973 Methylene chloride and chronic renal hypertension. *Arch Pathol* 95:130-131.

MacEwen JD, Vernot EH, Haun CC. 1972 Continuous animal exposure to dichloromethane. Aerospace Medical Research Laboratory. *AMRL-TR-72-28*. Cited in: ATSDR. 1993b *Toxicological Profile for Methylene Chloride*. Agency for Toxic Substances and Disease Registry. US Department of Health and Human Services.

Mahmud M, Kales SN. 1999 Methylene chloride poisoning in a cabinet worker. *Environ Health Perspect* 107 (9):769-772.

Manno M, Chirillo R, Daniotti G, Cocheo V, Albrizio F. 1989 Carboxyhaemoglobin and fatal methylene chloride poisoning [letter]. *Lancet* 2:274.

Manno M, Rugge M, Cocheo V. 1992 Double fatal inhalation of dichloromethane. *Hum Exp Toxicol* 11:540-545.

McGirr J, Burton BT, Kono E. 1990 Atrial fibrillation caused by methylene chloride [abstract]. *Vet Hum Toxicol* 32 (4):342.

Memon NA, Davidson AR. 1981 Multisystem disorder after exposure to paint stripper (Nitromors). *Br Med J* 282:1033-1034.

Miller L, Friederici H. 1985 Acute tubular necrosis after inhalation exposure to methylene chloride. *Arch Intern Med* 145:145-146.

Mitzutani K, Shinomiya K, Shinomiya T. 1988 Hepatotoxicity of dichloromethane. *Forensic Sci Int* 38: 113-128.

Morris JB, Smith FA, Garman RH. 1979 Studies on methylene chloride-induced fatty liver. *Exp Mol Pathol* 30:386-393.

Nager EC, O'Connor RE. 1998 Carbon monoxide poisoning from spray paint inhalation [letter]. *Acad Emerg Med* 5 (1):84-86.

Puurunen J, Sotaniemi E. 1985 Usefulness of follow-up liver function tests after dichloromethane exposure [letter]. *Lancet* 1:822.

Ratney RS, Wegman DH, Elkins HB. 1974 *In vivo* conversion of methylene chloride to carbon monoxide. *Arch Environ Health* 28:223-226.

Reid JB. 2001 Saturated methyl halogenated aliphatic hydrocarbons. In: *Patty's Toxicology*, fifth edition, Volume 5. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Rioux JP, Myers RAM. 1988 Methylene chloride poisoning: A paradigmatic review. *J Emerg Med* 6:227-238.

Rioux JP, Myers RAM. 1989 Hyperbaric oxygen for methylene chloride poisoning: Report on two cases. *Ann Emerg Med* 18:691-695.

Roberts CJC, Marshall FPF. 1976 Recovery after "lethal" quantity of paint remover. *Br Med J* 1:20-21.

Rudge FW 1990 Treatment of methylene chloride induced carbon monoxide poisoning with hyperbaric oxygenation. *Military Med* 155:570-572.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Sahu S, Lowther D, Ulsamer A. 1980 Biochemical studies on pulmonary response to inhalation of methylene chloride. *Toxicol Lett* 7:41-45.

Schardein JL. 1993 *Chemically Induced Birth Defects*, second edition. Marcel Dekker Inc, New York.

Schwetz BA, Leong BKJ, Gehring PJ. 1975 The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform and methylene chloride on embryonal and fetal development in mice and rats. *Toxicol Appl Pharmacol* 32:84-96.

Shusterman D, Quinlan P, Lowengart R, Cone J. 1990 Methylene chloride intoxication in a furniture refinisher. A comparison of exposure estimates utilizing workplace air sampling and blood carboxyhemoglobin measurements. *J Occup Med* 32 (5):451-454.

Snyder RW, Mishel HS, Christensen GC. 1992 Pulmonary toxicity following exposure to methylene chloride and its combustion product, phosgene. *Chest* 101:860-861.

Soden KJ. 1993 An evaluation of chronic methylene chloride exposure. *J Occup Med* 35 (3):282-286.

Stewart RD, Dodd HC. 1964 Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride and 1,1,1-trichloroethane through the human skin. *Ind Hyg J* 25:439-446.

Stewart RD, Fisher TN, Hosko MJ, Peterson JE, Baretta ED, Dodd HC. 1972a Carboxyhemoglobin elevation after exposure to dichloromethane. *Science* 176:295-296.

Stewart RD, Fisher TN, Hosko MJ, Peterson JE, Baretta ED, Dodd HC. 1972b Experimental human exposure to methylene chloride. *Arch Environ Health* 25:342-348.

Stewart RD, Hake CL. 1976 Paint remover hazard. *J Am Med Assoc* 235 (4):398-401.

Sturman K, Mofenson H, Caraccio T. 1985 Methylene chloride inhalation: An unusual form of drug abuse. *Ann Emerg Med* 14:903-905.

Tariot PN. 1983 Delirium resulting from methylene chloride exposure: Case report. *J Clin Psychiatry* 44:340-342.

Taskinen H, Kyrönen P, Hemminki K, Hoikkala M, Lajunen K, Lindbohm ML. 1994 Laboratory work and pregnancy outcome. *J Occup Med* 36 (3):311-319.

Tay P, Tan KT, Sam CT. 1995 Fatal gassing due to methylene chloride – A case report. *Singapore Med J* 36:444-445.

Thier R, Foest U, Deutschmann S, Schroeder KR, Westphal G, Hallier E, Peter H. 1991 Distribution of methylene chloride in human blood. *Arch Toxicol Suppl* 14:254-258.

Tomaszewski CA, Thom SR. 1994 Use of hyperbaric oxygen in toxicology. *Emerg Clin N Am* 12 (2):437-459.

Wells GG, Waldron HA. 1984 Methylene chloride burns. *Br J Ind Med* 41:420.

Winek CL, Collom WD, Esposito F. 1981 Accidental methylene chloride fatality. *Forensic Sci Int* 18:165-168.

Winneke G. 1981 The neurotoxicity of dichloromethane. *Neurobehavioural Toxicol Teratol* 3:391-395.

Winneke G. 1982 Acute behavioural effects of exposure to some organic solvents - psychophysiological aspects. *Acta Neurol Scand* (Suppl 92) 66:117-129.

16 Methyl *n*-Butyl Ketone (MnBK)

Nicola Bates

SUMMARY

- Relatively low acute toxicity; causes mild irritation and CNS depression
- Chronic exposure may result in peripheral polyneuropathy, characteristically distal, symmetrical sensiomotor polyneuropathy
- Neurotoxicity is due to the main metabolite (2,5-hexanedione, a γ-diketone compound) and not methyl *n*-butyl ketone itself
- Insidious onset of clinical effects; there is deterioration after removal from exposure before gradual improvement
- Neurotoxicity usually has a good outcome depending on severity, but recovery may be slow
- Co-exposure to other solvents (e.g., methyl ethyl ketone) potentiates the toxicity of methyl *n*-butyl ketone
- There is limited information on the carcinogenicity, gentoxicity and reproductive toxicity of methyl *n*-butyl ketone

DESCRIPTION

Synonyms

2-hexanone, hexan-2-one, methyl butyl ketone, methyl *n*-butyl ketone, MnBK, MBK, *n*-butyl methyl ketone, propylacetone.

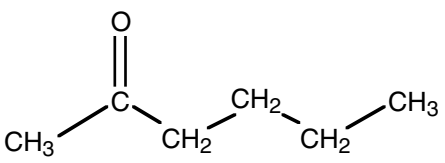
Identification numbers

CAS	591-78-6
UN	none
RTECS	MP 1400000
EINECS	2097311

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula $C_6H_{12}O$

molecular formula



molecular mass	100.16
physical form	clear, colourless liquid
relative vapour density (air=1)	3.5
flash point (°C)	18
boiling point (°C)	127.5
autoignition temperature (°C)	424
refractive index	1.4007
explosive limits in air (%v/v)	1-8

Odour threshold

0.076 ppm (Amoore and Hautala, 1983).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK and ACGIH): 5 ppm (20 mg/m^3)

Conversion factors

1 ppm = 4.10 mg/m^3
1 mg/m^3 = 0.245 ppm
1 mg/l = 245 ppm

Biomonitoring

Urinary concentrations of the metabolite 2,5-hexanedione are used for biological monitoring of *n*-hexane exposure (see Chapter 12), but the ACGIH has not established a biological exposure index for methyl *n*-butyl ketone (ACGIH, 2000). It is not known whether exposure to 1-5 ppm of methyl *n*-butyl ketone in humans will result in a detectable concentration of methyl *n*-butyl ketone or one of its metabolites in blood or urine (Bos *et al.,* 1991). Exposure of human volunteers to methyl *n*-butyl ketone at a level of 100 ppm for 4 hours did not result in detectable concentrations of urinary metabolites, including 2,5-hexanedione (DiVincenzo *et al.,* 1978). Consequently, environmental rather than biological monitoring is used for estimating exposure to methyl *n*-butyl ketone (Bos *et al.,* 1991).

TOXICITY

The first reported cases of neuropathy from methyl *n*-butyl ketone occurred in 1973 in a coated fabrics plant (Mendell *et al*., 1974; Allen *et al*., 1975; Billmaier *et al*., 1975). Much of the data concerning methyl *n*-butyl ketone was published in the 1970s following this incident. Methyl *n*-butyl ketone is a metabolite of *n*-hexane. They also share a neurotoxic metabolite, 2,5-hexanedione and are therefore, similar in their toxicity. However, there is far more information on *n*-hexane (Chapter 12) toxicity compared to methyl *n*-butyl ketone, but much of the data also apply to methyl *n*-butyl ketone.

Polyneuropathy has been reported following methyl *n*-butyl ketone exposure in painters (McDonough, 1974; Mallov, 1976; Saida *et al.,* 1976), a cabinet finisher (Davenport *et al*., 1976), and a print-screen cleaner (Wickersham and Fredericks, 1976). Polyneuropathy has been demonstrated in animals given methyl *n*-butyl ketone (Duckett *et al.,* 1974; McDonough, 1974; Mendell *et al.,* 1974; Spencer *et al*., 1975; Krasavage *et al*., 1979; Katz *et al*., 1980; Abdo *et al*., 1982) and 2,5-hexanedione (Spencer and Schaumburg, 1975). The typical picture of methyl *n*-butyl or *n*-hexane induced polyneuropathy is insidious onset and slow progression (Allen *et al*., 1975; Spencer *et al*., 1980).

Absorption

Methyl *n*-butyl ketone is readily absorbed through the skin, respiratory and gastrointestinal tracts. However, in industrial exposure the major routes of absorption are via inhalation and the skin. In a volunteer study 75-92% of an inhaled dose of methyl *n*-butyl ketone was absorbed after inhalation exposure to 10 or 50 ppm for 7.5 hours and to 100 ppm for four hours (DiVincenzo *et al.,* 1978).

The rate of absorption through the skin in volunteers was found to be 4.2-8.0 μg/min/cm^2 (DiVincenzo *et al.,* 1978). In an average human male (height 175 cm, weight 70 kg, body surface area 1.85 m^2) immersion of both hands (4% of the body surface area, absorption rate 5 μg/min/cm^2) in methyl *n*-butyl ketone for 1 hour could result in absorption of 222 mg. In comparison, inhalation of 25 ppm for one hour (minute volume 20 l/minute and 75% absorption) could result in absorption of 92 mg of methyl *n*-butyl ketone (DiVincenzo *et al*., 1978).

The dermal absorption rate of a mixture of methyl ethyl ketone and methyl *n*-butyl ketone (9:1) was approximately the same as that for methyl *n*-butyl ketone alone (DiVincenzo *et al*., 1978).

Distribution

There is no information on the distribution of methyl *n*-butyl ketone in humans. In rats, tissue distribution was widespread, but the highest concentrations of radioactivity were found in the liver and blood after oral absorption of radiolabelled methyl *n*-butyl ketone (DiVincenzo et al., 1977). Methyl *n*-butyl ketone rapidly crosses the blood-brain barrier in mice (Granvil *et al*., 1994).

Metabolism

There is limited information on methyl *n*-butyl ketone metabolism in humans. Metabolites are believed to be the same as those produced in animals. Methyl *n*-butyl ketone is metabolised by cytochrome P450-dependent monoxygenases and alcohol dehydrogenase in the liver. Metabolites include 2,5-hexanedione, 2-hexanol, 5-hydroxy-2-hexanone, 2,5-dimethylfuran and γ-valerolactone (DiVincenzo et al., 1977). 2,5-Hexanedione (a γ-diketone compound) is believed to be the substance responsible for neurotoxicity.

In the case of *n*-hexane the urinary concentration of 2,5-hexanedione has been shown to correlate with both hexane exposure (Perbellini *et al*., 1981; Iwata *et al*., 1983; Mutti *et al*., 1984; Saito *et al*., 1991; Cardona *et al*., 1993; Periago *et al*., 1993) and the severity of electroneuromyographic changes in exposed workers (Governa *et al*., 1987), and is used as a biological indicator of exposure. There is good correlation between the dose of methyl *n*-butyl ketone and the urinary concentration of 2,5-hexanedione in rats (Pilon *et al*., 1986).

Mode of action

The peripheral rather than the central nervous system is the main target in γ-diketone toxicity. The metabolites of methyl *n*-butyl ketone are more neurotoxic than the parent compound (Krasavage *et al.,* 1980; Abou-Donia *et al*., 1982). In animals, the relative neurotoxicity of compounds in decreasing order of potency were: 2,5-hexanedione, 5-hydroxy-2-hexanone, 2,5-hexanediol, methyl *n*-butyl ketone, 2-hexanol and *n*-hexane (Krasavage *et al.,* 1980; Abou-Donia *et al*., 1982). In terms of neurotoxicity, the potency of 2,5-hexanedione was 3.3 times that of methyl *n*-butyl ketone, and methyl *n*-butyl ketone was 12 times more potent than *n*-hexane (Krasavage *et al.,* 1980). Consequently, methyl *n*-butyl ketone is likely to cause neuropathy sooner and at a lower exposure concentration than *n*-hexane.

2,5-Hexanedione is a γ-diketone compound with a 1,4 spacing of the carbonyl groups. Other γ-diketones (e.g., 2,5-heptanedione, 3,6-octanedione) are also neurotoxic whereas α- and β-diketone compounds (e.g., 2,3-hexanedione and 2,4-hexanedione) are not (Spencer *et al*., 1978; O'Donoghue and Krasavage, 1979; DeCaprio *et al*., 1982). The neurotoxic effect of 2,5-hexanedione is thought to be due to it binding with axonal components (DeCaprio *et al*., 1982). 2,5-Hexanedione has been shown to bind to functional amino (NH_2) groups of axonal proteins forming substituted pyrrole groups (DeCaprio and O'Neill, 1985; Genter *et al*., 1987). Both neurotoxic and non-neurotoxic diketones bind to these amino groups but only the neurotoxic compounds form pyrrole adducts (DeCaprio *et al*., 1982). Rats exposed to 2,5-hexanedione excreted less

pyrroles when given zinc supplementation compared to controls (Mateus *et al.*, 2000). However, this was only a short-term study and the potential protective effect of zinc against 2,5-hexanedione induced neurotoxicity was not investigated.

There are 3 main hypotheses on the causes of the neurofilament accumulation observed in γ-diketone induced neuropathy (DeCaprio and O'Neill, 1985), these are as follows:

- Physicochemical changes triggered by the hydrophobic pyrrole adduct resulting in the disruption of function or transport of neurofilaments (DeCaprio and O'Neill, 1985).
- Auto-oxidation of pyrrole adducts result in crosslinking between the neurofilaments (Graham *et al.*, 1982; Anthony *et al.*, 1983; Graham *et al.*, 1995).
- Disruption of the normal relationships between neurofilaments and cytoskeletal components, particularly microtubules (Griffin *et al.*, 1983).

Whatever the cause of neurofilament accumulation, the ultimate effect of these changes is thought to be physical blockade of the axonal nutrient flow and subsequent nerve degeneration (DeCaprio and O'Neill, 1985).

In animal studies, the number of 'giant' axons was inversely related to the neurotoxic index of the compound and to the length of time required to produce paralysis. This suggests that axonal swelling may not be a pre-requisite for axonal dysfunction and is possibly a secondary phenomenon (Krasavage *et al.*, 1980).

The acute CNS depressant effects of methyl *n*-butyl ketone are thought to be due to the metabolite 2-hexanol, an aliphatic alcohol with general anaesthetic properties (Feldman, 1999). Less marked acute effects are seen with methyl *n*-butyl ketone compared to *n*-hexane, this may be because 2-hexanol is not an obligatory metabolite of methyl *n*-butyl ketone and less is formed (Feldman, 1999).

Elimination

A study following the elimination of radiolabelled methyl *n*-butyl ketone in two volunteers, found that the respiratory excretion of $^{14}CO_2$ peaked four hours after oral dosing (0.1 mg/kg body weight). This then decreased slowly over the following 3 to 5 days. The majority of radioactivity in the urine was excreted within 48 hours and the remainder eliminated within 8 days. The respiratory elimination averaged 39.5% and the urine 26.3% of the dose. The overall recovery of ^{14}C was 65.8% in 8 days. The remainder of the compound was presumed to be involved in further metabolism or stored in fat (DiVincenzo *et al.*, 1978). These figures differ for rats, where 92% of the radioactivity was excreted within six days (DiVincenzo *et al.*, 1977).

The slow elimination of radioactivity after human exposure to radiolabelled methyl *n*-butyl ketone suggests that accumulation of the neurotoxic metabolite in the body may occur, even with low exposure (Topping *et al.*, 1994).

Metabolic interactions

Some substances can potentiate the neurotoxicity of methyl *n*-butyl ketone. Consequently, chronic exposure to methyl *n*-butyl ketone, even at low concentrations, with concurrent exposure to another solvent, may result in neuropathy. Also, because other compounds such as *n*-hexane cause similar toxicity to methyl *n*-butyl ketone, exposure to solvent mixtures containing any neurotoxic hexacarbon should be minimised (Spencer *et al.*, 1980).

- **Acetone**

  The serum and nerve concentration of 2,5-hexanedione was significantly increased in rats treated with 2,5-hexanedione in combination with acetone, compared to 2,5-hexanedione alone. The effect with acetone was weaker than with methyl ethyl ketone, but stronger than with toluene (Zhao *et al.*, 1998).

- **Chloroform**

  MnBK can potentiate the hepato- and nephrotoxicity of chloroform in animals (Hewitt *et al.*, 1980). Similarly, MnBK has been shown to potentiate choleostasis induced by taurolithocholate in rats. Bile flow was unchanged when the animals were exposed to MnBK alone (Plaa and Ayotte, 1985).

- **Enzyme-inducers**

  Animal studies have shown that pretreatment with phenobarbital (phenobarbitone), an enzyme inducing drug, protects against methyl *n*-butyl ketone neurotoxicity (Abdel-Rahman *et al.*, 1976). This results in enhanced metabolism of methyl *n*-butyl ketone by induction of cytochrome P450 enzymes, with increased urinary excretion of metabolites (Feldman, 1999).

- **Ethanol**

  Exposure to ethanol and methyl *n*-butyl ketone has been shown to have an additive acute CNS depressant effect in mice. This is probably due to competition between ethanol and 2-hexanol for alcohol dehydrogenase (Sharkawi *et al.*, 1994).

- ***n*-Hexane**

  Metabolism of both *n*-hexane and methyl *n*-butyl ketone results in production of the same neurotoxic metabolite, 2,5-hexanedione. The toxic effects are therefore additive and workers exposed to both solvents are likely to be at greater risk of neurotoxicity (Feldman, 1999).

- **Methyl ethyl ketone (MEK, 2-butanone)**

  Methyl ethyl ketone is not itself neurotoxic, but animal studies have shown that co-exposure to methyl ethyl ketone increases the neurotoxicity of methyl *n*-butyl ketone (Saida *et al.,* 1976). This is also the case with *n*-hexane. Animal studies have shown that co-exposure to 2,5-hexanedione and methyl ethyl ketone results in more rapid onset of neurotoxicity than administration of 2,5-hexanedione alone (Ralston *et al.*, 1985). The serum and nerve concentration of 2,5-hexanedione was significantly increased in rats treated with 2,5-hexanedione in combination with methyl ethyl ketone compared to 2,5-hexanedione alone. The effect was strongest with methyl ethyl ketone compared to acetone or toluene (Zhao *et al.*, 1998). The mechanism of this phenomenon is unclear (Shibata *et al.*, 1990). It may be due to induction of the hepatic mixed function oxidase system (Topping *et al.,* 2001).

  In animal studies, co-administration of methyl *n*-butyl ketone and methyl ethyl ketone resulted in increased serum concentrations of methyl *n*-butyl ketone (Abdel-Rahman *et al.*, 1976). In rats, inhalation of a methyl *n*-butyl ketone and methyl ethyl ketone mixture caused a significant reduction in the sleep times induced by hexobarbital (hexobarbitone) (Couri *et al.*, 1977; Couri *et al.*, 1978). Methyl *n*-butyl ketone alone did not alter sleep times. Hepatic microsomal enzyme activities were increased in the methyl *n*-butyl ketone/methyl ethyl ketone exposed group (Couri *et al.*, 1977). This suggests that prolonged exposure to methyl ethyl ketone may induce significant changes in the metabolism of several chemicals (Spencer *et al.*, 1980).

- **Toluene**

  The serum and nerve concentration of 2,5-hexanedione was significantly increased in rats treated with 2,5-hexanedione in combination with toluene compared to 2,5-hexanedione alone. The effect with toluene was weaker than that observed with acetone and methyl ethyl ketone (Zhao *et al.*, 1998).

CASE REPORTS

Outbreak of peripheral neuropathy in a coated fabrics plant

The first reported cases of neuropathy from methyl *n*-butyl ketone occurred in 1973 in a US coated fabrics plant (Mendell *et al.*, 1974; Allen *et al.*, 1975; Billmaier *et al.*, 1975). Of 1,157 workers investigated, 28 were

suspected and 68 had definite signs, symptoms and electromyographic findings of peripheral neuropathy. These individuals had worked in the department with the highest frequency of, and most severe cases of, neuropathy for between five weeks and 27 years. The company had started to use methyl *n*-butyl ketone instead of methyl isobutyl ketone in a mixture with methyl ethyl ketone four months before the onset of symptoms of neuropathy. The concentration of methyl *n*-butyl ketone averaged 9.2 ppm in front of the printing machines, and 36 ppm behind (Allen *et al*., 1975). However, it is questionable whether these results actually reflect exposure concentrations (Topping *et al*., 2001). There was extensive skin exposure in these cases. Methyl *n*-butyl ketone was implicated as the causative agent but methyl ethyl ketone may have had a synergistic effect (Allen *et al*., 1975; Mallov, 1976).

A 22 year old male developed peripheral neuropathy following occupational exposure in the coated fabrics plant described above. He was well until February 1973 when he noted intermittent tingling in his arms and legs. He developed weakness of the left leg about three months later. This progressed and by August 1973 he had impairment of grip and foot drop and was hospitalised. He reported having lost 6.7 kg over eight months. He had prominent atrophy and occasional, bilateral fasciculations of the intrinsic muscles of the hands. There was severe weakness of the finger extensors and the dorsal and ventral interossei. There was bilateral foot drop with atrophy of the calves and thighs. Ankle jerks were absent. Nerve conduction velocities were slowed. Electromyography showed evidence of denervation with positive waves, fibrillation and moderate to severe decrease in motor units in distal muscles. He improved slowly and by May 1974 he had improved strength in all weakened muscles. Tendon reflexes were normal and an electromyograph showed marked improvement (Billmaier *et al*., 1974; Allen *et al.*, 1975).

CLINICAL EFFECTS

Acute exposure

Inhalation

There is limited information on acute inhalation exposure to methyl *n*-butyl ketone, but effects of acute exposure are less marked than those seen with *n*-hexane (Feldman, 1999). Methyl *n*-butyl ketone is known to be a respiratory irritant (Topping *et al*., 1994) and would be expected to cause headache, nausea, eye and throat irritation, dizziness and mild CNS depression. Coma may occur after exposure to a high concentration. Polyneuropathy is not expected from an acute exposure to methyl *n*-butyl ketone.

Volunteers exposed to 1,000 ppm of methyl *n*-butyl ketone for several minutes developed moderate eye and nasal irritation (Schrenk *et al.,* 1936). No adverse effects were reported in volunteers inhaling methyl *n*-butyl ketone at 10 or 50 ppm for 7.5 hours or 100 ppm for four hours (DiVincenzo *et al.,* 1978).

Dermal

Methyl *n*-butyl ketone is irritant to the skin (Harbison and Garvey, 1998). Prolonged contact may result in dermatitis because of the defatting action of methyl *n*-butyl ketone (Topping *et al*., 1994).

Eye

Methyl *n*-butyl ketone can cause transient eye irritation (Topping *et al*., 1994). At high concentrations it is a potent lacrimator (Harbison and Garvey, 1998).

Ingestion

There are no cases of ingestion of methyl *n*-butyl ketone. However, ingestion would be expected to cause nausea, vomiting, dizziness, CNS depression with drowsiness and possibly coma. There is a risk of aspiration of methyl *n*-butyl ketone into the lungs, which may cause chemical pneumonitis and pulmonary oedema.

Chronic exposure

Inhalation

Chronic exposure to methyl *n*-butyl ketone may cause peripheral neuropathy with a typical picture of sensory loss followed by motor signs and symptoms. There is usually numbness, which is insidious in onset, typically of hands and feet (a glove and stocking distribution) and rarely beyond the knees or wrists. Weakness is usually present in the legs and then the arms with reduced or absent tendon reflexes. In severe cases there is marked distal atrophy and proximal weakness. Muscle cramping and weight loss commonly occur with γ-diketone induced neuropathy (Allen *et al*., 1975; Smith and Albers, 1997) and there may be general malaise, headache, dizziness and anorexia (Huang *et al*., 1989). Onset of effects often resembles Guillain-Barré syndrome. These neurological changes are also termed 'dying-back' neuropathy or central-peripheral distal axonopathy.

After cessation of exposure the clinical condition may deteriorate further (Allen *et al*., 1975; Davenport *et al.,* 1976; Wicksham and Fredericks, 1976); this is often termed 'coasting'. This phenomenon has also been described with other toxic neuropathies (Huang *et al*., 1989; Smith and Albers, 1997) including *n*-hexane.

Parkinsonism has been reported with occupational exposure to *n*-hexane (Pezzoli *et al*., 1989; Pezzoli *et al*., 1995; Vanacore *et al.,* 2000), but not with methyl *n*-butyl ketone.

Pathologically, γ-diketone induced neuropathy presents as loss of large myelinated fibres with focally enlarged 'giant' axons with massive accumulation of neurofilaments (10 nm) and associated thinning of the overlying myelin (Davenport *et al*., 1976; Saida *et al.,* 1976; Schaumberg and Spencer, 1976). There may also be paranodal myelin retraction and occasional segmental demyelination (Griffin, 1981). These effects have also been observed with other toxic neuropathies. It should be noted that Guillain-Barré syndrome is characterised by myelin pathology whereas γ-diketone-induced neuropathy is characterised by axonal pathology (Spencer *et al*., 1980).

Electroneurophysiological studies reflect the severity of clinical features of neuropathy. There is usually a fall in nerve conduction velocities (NCV), profound amplitude reduction of compound muscle action potentials (CMAP) and sensory nerve action potentials (SNAP) and obvious prolongation of distal latencies (DL). Conduction block has been reported with *n*-hexane (Kuwabara *et al*., 1993). In evoked potential (EP) studies there is usually prolonged conduction time in visual, auditory and somatosensory pathways in the CNS (Chang, 1990). Individuals without signs or symptoms of neuropathy may, however, have evidence of neurological damage (Allen *et al*., 1975).

Standard laboratory investigations (haematological, hepatic, renal) in hexacarbon exposed individuals are usually normal (Spencer *et al*., 1980).

Co-exposure to some other solvents may potentiate the neurotoxic effects of methyl *n*-butyl ketone. In these circumstances exposure to a relatively low concentration of methyl *n*-butyl ketone may cause neuropathy (see Metabolic interactions).

Immunotoxicity

Changes in lymphocyte populations associated with reduced immune function have been demonstrated in floor-laying workers exposed to a number of solvents including methyl *n*-butyl ketone (Denkhaus *et al*., 1986), but functional changes in immunocompetence have not been shown (Topping *et al.,* 2001).

Leucopenia has been demonstrated in animals with clinical signs and pathological changes of methyl *n*-butyl ketone-induced neurotoxicity (Katz *et al.,* 1980).

Dermal

Dermatitis may occur because of the defatting action of methyl *n*-butyl ketone (Topping *et al*., 1994).

Eye

There is only limited information on the long-term effects of methyl *n*-butyl ketone on the eye. In 86 cases of methyl *n*-butyl ketone related peripheral polyneuropathy there was no impairment of the visual fields or loss of visual acuity that could be attributed to abnormality of the optic nerve or retina (Allen *et al.,* 1975).

Blurred vision, constriction of the visual field, optic nerve atrophy and retrobulbar neuritis have been reported in workers exposed to *n*-hexane. However, the ocular effects are usually mild and do not correlate with the severity of neuropathy (IPCS, 1991). Macula changes, particularly macula oedema (Raitta *et al*., 1978) and changes in colour vision (Raitta *et al*., 1978; Chang, 1990) have also been reported in individuals chronically exposed to *n*-hexane.

Studies in rats administered 2,5-hexanedione have shown that 2,5-hexanedione reaches the aqueous humor and retina. This results in damage to the photoreceptor cells of the retina and is more pronounced in the presence of light (Bäckström *et al.,* 1998).

Ingestion

No information available.

Carcinogenicity

There is no information on the potential carcinogenicity of methyl *n*-butyl ketone (Topping *et al*., 2001). It has not been evaluated by the IARC.

Genotoxicity

There is limited information on the genotoxicity of methyl *n*-butyl ketone (Topping *et al*., 2001). Incubation of yeast in methyl *n*-butyl ketone did not induce chromosomal loss except when in the presence of propionitrile. 2,5-Hexanedione was a weak inducer of chromosome loss, but very potent in the presence of propionitrile (Zimmerman *et al*., 1989). However, this test may not be suitable as a predictor of genetic damage because no direct action on genetic material occurs (Topping *et al*., 2001).

Reproductive toxicity

There is no information on the reproductive effects of methyl *n*-butyl ketone in humans. Decreased testes weight (Katz *et al.,* 1980) and atrophy of testicular germinal epithelium has been observed in rats administered methyl *n*-butyl ketone (Krasavage *et al.,* 1980). Testicular atrophy was noted in rats given 2,5-hexanedione in drinking water. These changes were seen before the onset of clinical signs of neuropathy (O'Donoghue *et al*., 1978). Decreased sperm motility has also been described in rats given 2,5-hexanedione, but there were no changes in testicular weight, epididymal weight or sperm count (Horimoto *et al*., 2000).

Pregnant rats exposed to 1,000 or 2,000 ppm of methyl *n*-butyl ketone during 21 days of gestation had reduced weight gain and there was a significant decrease in the number and weight of offspring of the high dose group. Offspring from both groups had behavioural alterations including hyperactivity, which may have resulted in premature ageing in older rats (Peters *et al.,* 1981).

RISK GROUPS

There are no medical conditions that predispose individuals to hexacarbon neuropathy (Spencer *et al*., 1980).

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Methyl *n*-butyl ketone is of low acute toxicity and gastric decontamination is unlikely to be required unless a very large quantity has been ingested. However, because of the risk of aspiration a cuffed endotracheal tube must be used to protect the airway, since methyl *n*-butyl ketone is an aspiration hazard. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive.

Antidote

There is no specific antidote for methyl *n*-butyl ketone.

Chronic exposure

Referral to a neurologist for electroneurophysiological assessment is recommended for any individual with suspected neuropathy. The prognosis of γ-diketone-induced polyneuropathy is usually good (Allen *et al*., 1975; Huang *et al*., 1989; Chang, 1990), although it depends on the severity (Smith and Albers, 1997). Recovery may be slow. In a study of 11 patients with moderate to severe neuropathy due to *n*-hexane, all were able to resume normal daily activities within 1-4 years. The sensory disturbance usually resolves much earlier than motor disturbances (Huang *et al*., 1989; Chang, 1991).

REFERENCES

Abdel-Rahman MS, Hetland LB, Couri D. 1976 Toxicity and metabolism of methyl *n*-butyl ketone. *Am Ind Hyg Assoc J* 37:95-102.

Abdo KM, Graham DG, Timmons PR, Abou-Donia MB. 1982 Neurotoxicity of continuous (90 days) inhalation of technical grade methyl butyl ketone in hens. *J Toxicol Environ Health* 9:199-215.

Abou-Donia MB, Makkawy H-AM, Graham DG. 1982 The relative neurotoxicities of *n*-hexane, methyl *n*-butyl ketone, 2,5-hexanediol and 2,5-hexanedione following oral or intraperitoneal administration in hens. *Toxicol Appl Pharmacol* 62:369-389.

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Allen N, Mendell JR, Billmaier DJ, Fontaine RE, O'Neill J. 1975 Toxic neuropathy due to methyl *n*-butyl ketone. An industrial outbreak. *Arch Neurol* 32:209-218.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Anthony DC, Boekelheide K, Anderson CW, Graham DG. 1983 The effects of 3,4-dimethyl substitution on the neurotoxicity of 2,5-hexanedione. II. Dimethyl substitution accelerates pyrrole formation and protein crosslinking. *Toxicol Appl Pharmacol* 71:372-382.

Bäckström B, Shibata E, Nylén P, Collins PV. 1998 2,5-Hexanedione concentrations and morphological changes within the eye of the albino rat. *Arch Toxicol* 72:597-600.

Billmaier D, Yee HT, Allen N, Craft B, Williams N, Epstein S, Fontaine R. 1974 Peripheral neuropathy in a coated fabrics plant. *Occup Med* 16 (10):665-671.

Bos PMJ, de Mik G, Bragt PC. 1991 Critical review of the toxicity of methyl *n*-butyl ketone: risk from occupational exposure. *Am J Ind Med* 20:175-194.

Cardona A, Marhuenda D, Marti J, Brugnone F, Roel J, Perbellini L. 1993 Biological monitoring of occupational exposure to *n*-hexane by measurement of urinary 2,5-hexanedione. *Int Arch Occup Environ Health* 65:71-74.

Chang YC. 1990 Patients with *n*-hexane induced polyneuropathy: a clinical follow up. *Br J Ind Med* 47:485-489.

Chang YC. 1991 An electrophysical follow up of patients with *n*-hexane polyneuropathy. *Br J Ind Med* 48:12-17.

Couri D, Hetland LB, Abdel-Rahman MS, Weiss H. 1977 The influence of inhaled ketone solvent vapors on hepatic microsomal biotransformation activities. *Toxicol Appl Pharmacol* 41:285-289.

Couri D, Abdel-Rahman MS, Hetland LB. 1978 Biotransformation of *n*-hexane and methyl *n*-butyl ketone in guinea pigs and mice. *Am Ind Hyg Assoc J* 39:295-300.

Davenport JG, Farrell DF, Sumi SM. 1976 "Giant axonal neuropathy" caused by industrial chemicals: neurofilamentous axonal masses in man. *Neurology* 26:919-923.

DeCaprio AP, Olajos EJ, Weber P. 1982 Covalent binding of a neurotoxic *n*-hexane metabolite: conversion of primary amines to substituted pyrrole adducts by 2,5-hexanedione. *Toxicol Appl Pharmacol* 65:440-450.

DeCaprio AP, O'Neill EA. 1985 Alterations in rat axonal cytoskeleton proteins induced by *in vitro* and *in vivo* 2,5-hexanedione exposure. *Toxicol Appl Pharmacol* 78:235-247.

Denkhaus W, Steldern DV, Botzenhardt U, Konietzko H. 1986 Lymphocyte subpopulations in solvent-exposed workers. *Int Arch Occup Med Health* 57:109-115.

DiVincenzo GD, Hamilton ML, Kaplan CJ, Dedinas J. 1977 Metabolic fate and disposition of 14C-labeled methyl *n*-butyl ketone in the rat. *Toxicol Appl Pharmacol* 41:547-560.

DiVincenzo GD, Hamilton ML, Kaplan CJ, Krasavage WJ, O'Donoghue JL. 1978 Studies on the respiratory uptake and excretion and the skin absorption of methyl *n*-butyl ketone in humans and dogs. *Toxicol Appl Pharmacol* 44:593-604.

Duckett S, Williams N, Francis S. 1974 Peripheral neuropathy associated with methyl *n*-butyl ketone. *Experimentia* 30:1283-1284.

Feldman RG. 1999 *Occupational and Environmental Neurotoxicology*. Lippincott-Raven, Philadelphia.

Genter MB, Szakál-Quinn G, Anderson CW, Anthony DC, Graham DG. 1987. Evidence that pyrrole formation is a pathogenic step in γ-diketone neuropathy. *Toxicol Appl Pharmacol* 87:351-362.

Governa M, Calisti R, Coppa G, Tagliavento G, Colombi A, Troni W. 1987 Urinary excretion of 2,5-hexanedione and peripheral polyneuropathies in workers exposed to hexane. *J Toxicol Environ Health* 20:219-228.

Graham DG, Anthony DC, Boekelheide K, Maschmann NA, Richards RG, Wolfram JW, Shaw BR. 1982 Studies of the molecular pathogenesis of hexane neuropathy. II. Evidence that pyrrole derivatization of lysyl residues leads to protein crosslinking. *Toxicol Appl Pharmacol* 64:415-422.

Graham DG, Amarnath V, Valentine WM, Pyle SJ, Anthony DC. 1995 Pathogenetic studies of hexane and carbon disulfide neurotoxicity. *Crit Rev Toxicol* 25 (2):91-112.

Granvil CP, Sharkawi M, Plaa GL. 1994 Metabolic fate of methyl *n*-butyl ketone, methyl ethyl ketone and their metabolites in mice. *Toxicol Lett* 70:263-267.

Griffin JW. 1981 Hexacarbon neurotoxicity. *Neurobehav Toxicol Teratol* 3:437-444.

Griffin JW, Fahnestock KE, Price DL, Cork LC. 1983 Cytoskeleton disorganisation induced by local application of β,β´-iminodipropionitrile and 2,5-hexanedione. *Ann Neurol* 14:55-61.

Harbison RD, Garvey GJ. 1998 Aldehydes and ketones. In: *Hamilton and Hardy's Industrial Toxicology*, fifth edition. Harbison RD (editor). Mosby, St Louis.

Hewitt WR, Miyajima H, Côté MG, Plaa GL. 1980 Acute alternation of chloroform-induced hepato- and nephrotoxicity by *n*-hexane, methyl *n*-butyl ketone, and 2-5-hexanedione. *Toxicol Appl Pharmacol* 53:230-248.

Horimoto M, Isobe Y, Isogai Y, Tachibana M. 2000 Rat epididymal sperm motion changes induced by ethylene glycol monoethyl ether, sulfasalazine and 2,5-hexanedione. *Reprod Toxicol* 14 (1):55-63.

Huang C-C, Chu N-S, Cheng S-Y, Shin T-S. 1989 Biphasic recovery in *n*-hexane polyneuropathy. A clinical and electrophysiological study. *Acta Neurol Scand* 80:610-615.

IPCS. 1991 *Environmental Health Criteria 122. n-Hexane*. World Health Organization, International Programme on Chemical Safety, Geneva.

Iwata M, Takeuchi Y, Hisanaga N, Ono Y. 1983 A study on biological monitoring of *n*-hexane exposure. *Int Arch Occup Environ Health* 51:253-260.

Katz GV, O'Donoghue JL, Divicenzo GD, Terhaar CJ. 1980 Comparative neurotoxicty and metabolism of ethyl *n*-butyl ketone and methyl *n*-butyl ketone in rats. *Toxicol Appl Pharmacol* 52:153-158.

Krasavage WJ, O'Donoghue JL, Terhaar CJ. 1979 Oral chronic toxicity of methyl *n*-propyl ketone, methyl *n*-butyl ketone and hexane in rats [abstract]. *Toxicol Appl Pharmacol* 48 (pt 2):A205.

Krasavage WJ, O'Donoghue JL, DiVincenzo GD, Terhaar CJ. 1980 The relative neurotoxicity of methyl-*n*-butyl ketone, *n*-hexane and their metabolites. *Toxicol Appl Pharmacol* 52:433-441.

Kuwabara S, Nakajima M, Tsuboi Y, Hirayama K. 1993 Multifocal conduction block in *n*-hexane neuropathy. *Muscle Nerve* 16 (2):1416-1417.

Mallov JS. 1976 MBK neuropathy among spray painters. *J Am Med Assoc* 235 (14):1455-1457.

Mateus ML, dos Santos APM, Batoreu MC. 2000 Evidence for zinc protection against 2,5-hexanedione toxicity by co-exposure of rats to zinc chloride. *J Appl Toxicol* 20:211-214.

McDonough JR. 1974 Possible neuropathy from methyl *n*-butyl ketone [letter]. *N Engl J Med* 290 (2):695.

Mendell JR, Saida K, Ganasia MF, Jackson DB, Weiss H, Gardier RW, Chrisman C, Allen N, Couri D, O'Neill B, Marks B, Hetland L. 1974 Toxic polyneuropathy produced by methyl *n*-butyl ketone. *Science* 185:787-789.

Mutti A, Falzoi M, Lucertini S, Arfini G, Zignani M, Lombardi S, Franchini I. 1984 *n*-Hexane metabolism in occupationally exposed workers. *Br J Ind Med* 41:533-538.

O'Donoghue JL, Krasavage WJ, Terhaar CJ. 1978 Toxic effects of 2,5-hexanedione [abstract]. *Toxicol Appl Pharmacol* 45:269.

O'Donoghue JL, Krasavage WJ. 1979 Hexacarbon neuropathy: a γ-diketone neuropathy? *J Neuropathol Exp Neurol* 38:333.

Perbellini L, Brugnone F, Faggionato G. 1981 Urinary excretion of the metabolites of *n*-hexane and its isomers during occupational exposure. *Br J Ind Med* 38:20-26.

Periago JF, Cardona A, Marhuenada D, Roel J, Villanueva M, Marti J, Luna A. 1993 Biological monitoring of occupational exposure to *n*-hexane by exhaled air analysis and urinalysis. *Int Arch Occup Environ Health* 65:275-278.

Peters MA, Hudson PM, Dixon RL. 1981 The effect totigestational exposure to methyl-*n*-butyl ketone has on postnatal development and behavior. *Ecotoxicol Environ Safety* 5:291-306.

Pezzoli G, Barbieri S, Ferrante C, Zecchinelli A, Foa V. 1989 Parkinsonism due to *n*-hexane exposure [letter]. *Lancet* 2:874.

Pezzoli G, Antonini A, Barbieri S, Canesi M, Perbellini L, Zecchinelli A, Mariani CB, Bonetti A, Leenders KL. 1995 *n*-Hexane-induced parkinsonism: pathogenic hypotheses. *Mov Disord* 10 (3):279-282.

Pilon D, Charbonneau M, Brodeur J, Plaa GL. 1986 Metabolites and ketone body production following methyl *n*-butyl ketone exposure as possible indices of MnBK potentiation of carbon tetrachloride hepatotoxicity. *Toxicol Appl Pharmacol* 85:49-59.

Plaa GL, Ayotte P. 1985 Taurolithocholate-induced intrahepatic cholestasis: potentiation by methyl isobutyl ketone and methyl *n*-butyl ketone in rats. *Toxicol Appl Pharmacol* 80:228-234.

Raitta C, Seppäläinen A-M, Huuskonen MS. 1978 *n*-Hexane maculopathy in industrial workers. *Graefes Arch Ophthalmol* 209:99-110.

Ralston WH, Hilderbrand RL, Uddin D, Andersen ME, Gardier RW. 1985 Potentiation of 2,5-hexanedione neurotoxicity by methyl ethyl ketone. *Toxicol Appl Pharmacol* 81:319-729.

Saida K, Mendell JR, Weiss HS. 1976 Peripheral nerve changes induced by methyl *n*-butyl ketone and potentiation by methyl ethyl ketone. *J Neuropathol Exp Neurol* 35 (3):207-225.

Saito I, Shibata E, Huang J, Hisanaga N, Ono Y, Takeuchi Y. 1991 Determination of urinary 2,5-hexanedione concentration by an improved analytical method as an index of exposure to *n*-hexane. *Br J Ind Med* 48:568-574.

Schaumburg H, Spencer PS. 1976 Degeneration in central and peripheral nervous systems produced by pure *n*-hexane: an experimental study. *Brain* 99:183-192.

Schrenk HH, Yant WP, Patty FA. 1936 Hexanone. *US Public Health Report* 51:624. Cited in: Topping DC, Morgott DA, David RM, O'Donoghue JL. 2001 Ketones of six to thirteen carbons. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Sharkawi M, Granvil C, Faci A, Plaa GL. 1994 Pharmacodynamic and metabolic interactions between ethanol and two industrial solvents (methyl *n*-butyl ketone and methyl isobutyl ketone) and the principal metabolite in mice. *Toxicology* 94:187-195.

Shibata E, Huang J, Ono Y, Hisanaga N, Iwata M, Saito I, Takeuchi Y. 1990 Changes in urinary *n*-hexane metabolites by co-exposure to various concentrations of methyl ethyl ketone and fixed *n*-hexane levels. *Arch Toxicol* 64:165-168.

Smith AG, Albers JW. 1997 *n*-Hexane neuropathy due to rubber cement sniffing. *Muscle Nerve* 20:1445-1450.

Spencer PS, Schaumberg HH, 1975 Experimental neuropathy produced by 2,5-hexanedione – a major metabolite of the neurotoxic industrial solvent methyl *n*-butyl ketone. *J Neurol Neurosurg Psychiat* 38:771-775.

Spencer PS, Schaumberg HH, Raleigh RL Terhaar CJ. 1975 Nervous system degeneration produced by the industrial solvent methyl *n*-butyl ketone. *Arch Neurol* 32:219-222.

Spencer PS, Bishoff MC, Schaumburg HH. 1978 On the specific molecular configuration of neurotoxic aliphatic hexacarbon compounds causing central-peripheral distal axonopathy. *Toxicol Appl Pharmacol* 44:17-28.

Spencer PS, Schaumburg HH, Sabri MI, Veronesi B. 1980 The enlarging view of hexacarbon neuropathy. *CRC Crit Rev Toxicol* 7 (4):279-356.

Topping DC, Morgott DA, David RM, O'Donoghue JL. 1994 Ketones. In: *Patty's Industrial Hygiene and Toxicology*, fourth edition, Volume 2, Part C. GD Clayton, FE Clayton (editors). John Wiley and Son, Inc, New York.

Topping DC, Morgott DA, O'Donoghue JL. 2001 Ketones of six to thirteen carbons. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Wickersham CW III, Fredericks EJ. 1976 Toxic polyneuropathy secondary to methyl *n*-butyl ketone. *Conn Med* 40 (5):311-312.

Vanacore N, Gasparini M, Brusa L, Meco G. 2000 A possible association between exposure to *n*-hexane and parkinsonism. *Neurol Sci* 21:49-52.

Zhao W, Misumi J, Yasui T, Aoki K, Kimura T. 1998 Effects of methyl ethyl ketone, acetone, or toluene coadministration on 2,5-hexanedione concentration in the sciatic nerve, serum, and the urine of rats. *Int Arch Occup Environ Health* 71 (4):236-244.

Zimmerman FK, Scheel I, Resnick MA. 1989 Induction of chromosome loss by mixtures of organic solvents including neurotoxins. *Mutat Res* 224:287-303.

17 Methyl Ethyl Ketone (MEK)

Nicola Bates

SUMMARY

- MEK is of low acute toxicity; it is not neurotoxic
- The main hazard of MEK is its ability to potentiate the effects, particularly the neurotoxicity, of other substances
- MEK is not considered to be a reproductive toxin
- MEK is not considered to be genotoxic
- MEK has not been evaluated for carcinogenicity

DESCRIPTION

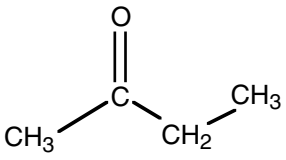
Synonyms

Butanone, 2-butanone, butane-2-one, ethyl methyl ketone, methyl ethyl ketone, MEK, methyl acetone, methylpropanone

Identification numbers

CAS	78-93-3
UN	1193
RTECS	EL 6475000
EINECS	2011590

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	C_4H_8O
molecular formula	
molecular mass	72.10
physical form	clear, colourless volatile liquid with an acetone-like odour
relative vapour density	2.41
flash point (closed cup, °C)	-6
boiling point (°C)	79.6
autoignition temperature (°C)	505

refractive index	1.3788
explosive limits (%v/v)	1.8-12.0

Odour threshold

0.25 ppm (Ruth 1986), 2 ppm (IPCS, 1993), 5.4 ppm (Amoore and Hautala, 1983), 25 ppm (ECETOC, 1983).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK and USA): 200 ppm (600 mg/m^3).

Conversion factors

1 ppm = 2.95 mg/m^3

1 mg/m^3 = 0.34 ppm

1 mg/l = 340 ppm

Biomonitoring

The ACGIH biological exposure index for MEK is an end of shift urinary MEK concentration of 2 mg/l (ACGIH, 2000).

TOXICITY

MEK is of relatively low toxicity (Yang, 1986). There is no record of MEK having caused death or a large scale industrial accident (IPCS, 1993). There is limited information on exposure to MEK alone; most cases involve exposure to mixed solvents. The main hazard of MEK is its ability to potentiate the effects, particularly the neurotoxicity, of other substances (IPCS, 1993). There are many reports in the literature of interactions between MEK and other solvents, including occupational surveys and animal and volunteer studies (reviewed in Noraberg and Arlien-Søborg, 2000).

Absorption

The pulmonary retention of MEK varies between 41-59% (Liira *et al*., 1988a, 1988b; Imbriani *et al*., 1989; Liira *et al*., 1990a). The concentration of MEK in blood correlates with the exposure concentration (Perbellini *et al*., 1984; Brown *et al.,* 1987; Ong *et al.,* 1991).

Dermal absorption of MEK is rapid. In a volunteer study MEK was detected in expired air 15 minutes after 100 ml was applied to normal skin of the forearm. A steady state concentration was achieved within 2-3 hours. The moisture content of the skin determined the rate of absorption. Absorption was slow through dry skin and the plateau did not occur until 4-5 hours after application. With moist skin, absorption was very rapid and MEK was detected in expired air within 30 seconds. The maximum concentration averaged four times the plateau concentration for normal and dry skin. However, absorption subsequently declined as MEK desiccated the skin (Munies and Wurster, 1965).

Ingestion of an unknown quantity of a MEK containing glue resulted in a blood MEK concentration of 950 mg/l (13.2 mmol/l) (Kopelman and Kalfayan, 1983). Following ingestion of approximately 240 ml of an ink cleaning solution thought to contain 47% MEK and 45% methanol the blood concentration of MEK was 1,240 mg/l (17 mmol/l) with 240 mg/l (3.3 mmol/l) 2-butanol (Price *et al*., 1994).

Distribution

MEK is readily soluble in blood and tissues, including fat (Liira *et al.*, 1988a) and solubility is similar in all tissues (Perbellini *et al.*, 1984).

Metabolism

The majority of absorbed MEK is metabolised, but the metabolic pathways have not been fully elucidated. The metabolites of MEK found in experimental animals (DiVincenzo *et al.*, 1976; Dietz and Traiger, 1979) and humans (Perbellini *et al.*, 1984; Kežić and Monster, 1988) are 2-butanol, 3-hydroxy-2-butanone (acetylmethylcarbinol) and 2,3-butanediol.

MEK is reduced to 2-butanol which can be converted back to MEK by alcohol dehydrogenase. MEK is also oxidised by carbon chain ω-1 hydroxylation (probably catalysed by the microsomal monooxygenase system) to 3-hydroxy-2-butanone which is then reduced to produce 2,3-butanediol. In humans less than 5% of the absorbed dose is exhaled as MEK and only about 3% is excreted as 2,3-butanediol. The majority of absorbed MEK is thought to be metabolised to 2,3-butanediol, which then enters the general metabolic pathways and is transformed to simple compounds such as water and carbon dioxide (IPCS, 1993).

Experimental data has shown that at high doses the kinetics of MEK are dose-dependent and saturation kinetics may be reached at 50-100 ppm, depending on the workload (Liira *et al.*, 1990b).

Elimination

Only 2-3% of absorbed MEK is exhaled unchanged (Liira *et al.*, 1988a; 1988b). The concentration of MEK in expired air correlates with the exposure concentration (Tada *et al.*, 1972; Perbellini *et al.*, 1984). In volunteers exposed to MEK, a steady state concentration of MEK in the breath was reached after two hours and was 5-6% of the exposure concentration (Brown *et al.,* 1987; Dick *et al.*, 1988). MEK is rapidly eliminated from the lungs. In a volunteer study more than half the subjects had no detectable MEK in breath samples taken 90 minutes after cessation of exposure (Brown *et al.*, 1987).

In a volunteer study following exposure to 200 ppm MEK for four hours, two elimination phases were identified in blood (Liira *et al.*, 1988a). For the first phase (0-45 minutes after cessation of exposure) the half-life was 30 minutes and for the second (60-320 minutes post-exposure) it was 81 minutes. In another study the half-life of MEK was estimated to be 49 minutes (Dick *et al.*, 1988).

Urinary excretion of MEK and 3-hydroxy-2-butanone only accounts for approximately 0.1% of the absorbed dose (Miyasaka *et al.*, 1982; Perbellini *et al.*, 1984). Only about 3% of MEK is excreted as 2,3-butanediol, however there is wide interindividual variation (Liira *et al.*, 1988a; 1988b).

Using the data of Munies and Wurster (1965), Liira *et al.* (1988a) estimated that following ingestion of 375 mg of MEK in a gelatine capsule about 30% was excreted through the lungs. The half-life of MEK was 10.1 hours in an individual who intentionally ingested a glue containing 28% MEK, 18% acetone and 39% cyclohexanone and 15% polyvinyl chloride and drank ethanol (Sakata *et al.*, 1989).

The urinary concentrations of both MEK (Miyasaka *et al.*, 1982; Perbellini *et al.*, 1984; Imbriani *et al.*, 1989; Ong *et al.,* 1991; Yoshikawa *et al.*, 1995) and 3-hydroxy-2-butanone (Perbellini *et al.*, 1984) are significantly correlated with the exposure concentration of MEK. However, breath concentrations of MEK do not correlate well with the urinary MEK concentration (Ong *et al.,* 1991).

Accumulation of MEK over a working week is not expected because of the short elimination half-life (Liira *et al.*, 1988a). The metabolism of MEK becomes saturated at relatively low concentrations and consequently a larger proportion would be expected to be excreted both through the lungs and the kidney at high exposure concentrations (IPCS, 1993).

Mode of action

There is only very limited information on the mode of action of MEK (IPCS, 1993). In cats and dogs, high concentrations (500-10,000 ppm) caused pulmonary vasoconstriction and hypertension (Zakhari *et al*., 1977). The main hazard of MEK is its ability to potentiate the effects, particularly the neurotoxicity, of other substances (IPCS, 1993).

Metabolic interactions

There are 3 major metabolic interactions of MEK: potentiation of hexacarbon neuropathy and haloalkane toxicity, and inhibition of alcohol metabolism.

Potentiation of hexacarbon neuropathy

It is well recognised that MEK can potentiate the neurotoxicity of some other solvents. Consequently, chronic exposure to such a solvent, even at low concentrations, with concurrent exposure to methyl ethyl ketone may result in neuropathy. MEK is not itself neurotoxic.

- ***n*-Hexane**

  MEK was first suspected of potentiating the neurotoxic effects of *n*-hexane after neuropathy was reported in 18 glue-sniffers following a formulation change. The glue had contained 31% *n*-hexane but neuropathy only developed after the concentration was reduced to 16% and MEK was added to the product. No further cases were reported after the MEK was removed (Altenkirch *et al*., 1978).

  Animal studies have shown that co-exposure to 2,5-hexanedione (the neurotoxic metabolite of *n*-hexane) and methyl ethyl ketone results in more rapid onset of neurotoxicity than administration of 2,5-hexanedione alone (Ralston *et al*., 1985). The serum and nerve concentrations of 2,5-hexanedione were significantly increased in rats treated with 2,5-hexanedione in combination with methyl ethyl ketone compared to 2,5-hexanedione alone. The effect was strongest with methyl ethyl ketone compared with acetone or toluene (Zhao *et al*., 1998).

  The mechanism of this phenomenon is unclear, it is not thought to be due to 2,5-hexanedione alone (Shibata *et al*., 1990). It may be due to induction of the hepatic mixed function oxidase system (Topping *et al.,* 2001). In a toxicokinetic study of human volunteers, co-exposure to MEK had little effect on *n*-hexane toxicokinetics. However, there was a decrease in the rate of formation of 2,5-hexanedione suggesting inhibition of the metabolism of *n*-hexane (van Engelen *et al*., 1997). In contrast, workers exposed simultaneously to MEK and *n*-hexane had increased urinary excretion of 2,5-hexanedione (Cardona *et al*., 1993). In animals the concentration of urinary *n*-hexane metabolites depended on the exposure concentrations of MEK involved. The concentration of the main *n*-hexane metabolites, 2,5-hexanedione and 2-hexanol decreased as the MEK concentration increased (Shibata *et al*., 1990). However, a more recent study demonstrated that although urinary concentrations of 2,5-hexanedione decreased in the short-term with co-exposure to MEK, the concentration of 2,5-hexanedione actually increased with more prolonged exposure (Ichihara *et al*., 1998).

- **Methyl *n*-butyl ketone**

  Methyl *n*-butyl ketone has the same neurotoxic metabolite as *n*-hexane, 2,5-hexanedione. Animal studies have shown that co-exposure to methyl ethyl ketone increases the neurotoxicity of methyl *n*-butyl ketone (Saida *et al.,* 1976). In animal studies, co-administration of methyl *n*-butyl ketone and methyl ethyl ketone resulted in increased serum concentrations of methyl *n*-butyl ketone (Abdel-Rahman *et al*., 1976). In rats, inhalation of a methyl *n*-butyl ketone and methyl ethyl ketone mixture caused a significant reduction in the sleep times induced by hexobarbital (hexobarbitone), an enzyme-inducing drug (Couri *et al*., 1977; Couri *et al*., 1978). Methyl *n*-butyl ketone alone did not alter sleep times. Hepatic microsomal enzyme activities were increased in the methyl *n*-butyl ketone/methyl ethyl ketone exposed group (Couri *et al*., 1977).

Potentiation of haloalkane toxicity

- **Carbon tetrachloride**

  MEK has been shown to potentiate the hepatotoxicity of carbon tetrachloride in rats. This may have been due to the metabolites, 2,3-butanediol and/or 3-hydroxy-2-butanone (Dietz and Traiger, 1979).

- **Chloroform**

  MEK has also been show to potentiate the hepatotoxicity and nephrotoxicity of chloroform in rats. The extent of liver and renal injury was dose related and at the highest dose there was a reduction in the degree of potentiation. The mechanism of potentiation is unknown, but at high doses the ketone may reduce the metabolism of chloroform and so reduce toxicity. Alternatively, high doses of ketones may damage the cells in such a way as to reduce the toxicity of chloroform (Brown and Hewitt, 1984).

Inhibition of alcohol metabolism

- **Ethanol**

  Ethanol appears to inhibit microsomal oxidation of MEK. In a volunteer study, ingestion of ethanol and inhalation of MEK resulted in increased MEK concentrations in the blood, suggesting that ethanol inhibits MEK metabolism. When the ethanol was ingested before the inhalation exposure to MEK, the blood concentration of MEK remained high throughout the exposure. When ethanol was given after cessation of MEK exposure a higher MEK blood concentration was seen in the elimination phase. The concentration of the metabolite 2-butanol was increased almost 10 times in the presence of ethanol. The higher blood concentration of MEK in the presence of ethanol was reflected in increased exhalation and urinary excretion of MEK. The elimination of MEK through the lungs was 8% in the presence of ethanol compared to 3% without ethanol. The elimination of MEK in the urine doubled with co-exposure to ethanol but was still less than 1% of the absorbed dose (Liira *et al.*, 1990a).

  Animal studies have also demonstrated that concomitant MEK exposure slows the metabolism of ethanol (Cunningham *et al.*, 1989) and other studies have shown that MEK increases microsomal activity (Couri *et al.*, 1977) and inhibits alcohol dehydrogenase (Cunningham *et al.*, 1989).

- **Methanol**

  MEK may have inhibited methanol metabolism following ingestion of approximately 240 ml of an ink cleaning solution thought to contain 47% MEK and 45% methanol. There was minimal metabolism of methanol to formate despite a high methanol concentration (2020 mg/l; 63 mmol/l) and the anion gap remained normal. MEK probably acted by inhibiting alcohol dehydrogenase (Price *et al.*, 1994).

Other interactions

- **Acetone**

  In volunteer studies exposure to a mixture of MEK and acetone had no effect on neurobehavioural performance. MEK does not potentiate the effect of acetone and there is no pharmacokinetic interaction between the two ketones (Brown *et al.,* 1987; Dick *et al.*, 1988; Dick *et al.*, 1989).

- **Toluene**

  In a volunteer study investigating solvent exposure and pyschomotor performance, neither MEK or toluene had any effect. In addition, in a mixed exposure neither solvent had any potentiation effects on the other (Dick *et al.*, 1984). Workers exposed simultaneously to methyl ethyl ketone and toluene had reduced urinary excretion of 2,5-hexanedione (Cardona *et al.*, 1993).

- **Xylene**

  MEK appears to inhibit the metabolism of xylene, possibly by interaction with the initial monooxygenase-catalysed step of biotransformation. In volunteers exposed to *m*-xylene and MEK, the blood xylene concentration increased almost two-fold compared to the concentration following exposure to xylene alone. Although the clearance of *m*-xylene and excretion of its metabolite, methyl hippuric acid, were reduced, there appeared to be no effect on the biotransformation of MEK. Exposure to MEK 20 hours before exposure to *m*-xylene did not affect xylene metabolism (Liira *et al*., 1988b).

CASE REPORTS

There are few well-documented cases of occupational exposure to MEK alone.

CLINICAL EFFECTS

Acute exposure

Inhalation

The principal effects of exposure to MEK at doses of up to 200 ppm are limited to sensory and irritant effects (Dick *et al*., 1992). Volunteers exposed for 3-5 minutes to MEK at 200 ppm complained of mild nose, throat and eye irritation (Nelson *et al*., 1943). Acute inhalation may also cause nausea, headache and confusion. Exposure to a high concentration may cause CNS depression and possibly convulsions (ECETOC, 1983).

MEK exposure had no effects on neurobehavioural (Dick *et al*., 1989; Dick *et al*., 1992) or pyschomotor performance (Dick *et al*., 1984) in volunteer studies. Exposure to MEK did not affect the accuracy of performance of a match-to-sample task in baboons, but it did cause a delay in response time (Geller *et al*., 1978; Geller *et al*., 1979).

Dermal

MEK dries out and defats skin, although there may be no signs of irritation or inflammation (Munies and Wurster, 1965). Contact with 1.5 ml of analytical grade MEK, confined to a 2 cm circle for 5 minutes on the forearm, produced a temporary whitening of the skin but no erythema or signs of irritation (Wahlberg, 1984b). In rabbits, 0.5 ml of MEK produced mild to moderate skin irritation in some cases (Weil and Scala, 1971).

Eye

MEK is irritant to eyes and causes moderate reversible injury (Grant and Schuman, 1993). A dose of 0.1 ml (80 mg) of MEK produced minimal to moderate irritation in rabbit eyes (Weil and Scala, 1971).

A case of severe anterior uveitis has been reported which developed a few days after a splash of methyl ethyl ketone into the eye. However, this may have been due to a tendency to uveitis following mild trauma (Grant and Schuman, 1993).

Headache, dizziness and a decrease in vision was reported after using a paint remover containing MEK. Eye examination was normal except for decreased visual acuity and transient superior arcuate scotomas (blind or dark spots in the visual field). The diagnosis was retrobulbar neuritis and vision returned to normal in 36 hours. However, both methanol and formaldehyde were found in the patient's blood at unspecified concentrations (Berg, 1971). There was no measurement or comment on the presence of either of these compounds in the paint remover.

Ingestion

Coma, hyperventilation, tachycardia, hypotension and marked anion gap metabolic acidosis with a high lactate concentration occurred following ingestion of a glue containing methyl ethyl ketone (Kopelman and Kalfayan, 1983). The acidosis may have been due to hypoxia rather than a direct effect of MEK.

There is a risk of aspiration of MEK into the lungs (Panson and Winek, 1980), which may result in chemical pneumonitis and pulmonary oedema.

Chronic exposure

Inhalation

Headache, inappetance, weight loss, gastrointestinal upset, dizziness and muscular hypertrophy were reported in 51 Italian workers exposed to MEK. There was slight, but not significantly, reduced nerve conduction velocities, but there were no clinically recognisable cases of neuropathy (Freddi *et al*., 1982). Numbness of fingers and arms has also been reported in workers exposed to 300-600 ppm (Smith and Mayers, 1944).

Myoclonus, tremor, ataxia and ocular flutter have been reported in a worker following 2 years of exposure to MEK. The effects resolved within 1 month of cessation of exposure. However, despite numerous blood tests and investigations which were negative, there was no measurement of MEK in blood or urine, and no measurement of the concentration of MEK or any other solvent in the workplace. He was apparently the only worker affected (Ortí-Pareja *et al.,* 1996).

Neurotoxicity has been reported in a group of workers exposed to MEK (Mitran *et al*., 1997; Mitran, 2000), but this study and its findings have been strongly criticised (Graham, 2000). MEK has been implicated in other cases of neuropathy (e.g., Viader *et al*., 1975; Oh and Kim, 1976; Dyro, 1978; Callender, 1995), but the evidence from studies in animals shows that exposure to MEK alone does not cause neurological damage (Saida *et al*., 1976; Spencer and Schaumberg, 1976; Altenkirch *et al.,* 1978; 1979; Spencer *et al.,* 1980; Cavender *et al*., 1983). A transient decrease in nerve conduction velocity was reported in rats after 4 weeks exposure to 200 ppm (590 mg/m^3) for 12 hours a day for 24 weeks, but no changes in nerve conduction velocity was found at a later stage of the study (Takeuchi *et al*., 1983).

Abuse of MEK has also been reported. Effects usually start within a few minutes and last 15-30 minutes unless the solvent is repeatedly inhaled. Effects reported included dizziness, excitement, hallucinations and 'pins and needles' (Glatt, 1977).

Immunotoxicity

There is limited information on the immunotoxicity of MEK. Workers exposed to *n*-hexane (mean breathing air zone concentration 58 ppm; range 4.3-300 ppm), toluene (mean 27 ppm; range 5.37-115.2 ppm) and MEK (mean 11 ppm; range 2.43-47 ppm) had no impairment of natural killer cell activity or changes in interleukin-2 or gamma interferon concentrations (Yücesoy *et al*., 1999).

Dermal

MEK (0.1 ml) rubbed into the forearm daily for 18 days did not produce any persistent erthyema or swelling (Wahlberg, 1984a).

Dermatoses (Smith and Mayers, 1944) including contact dermatitis (Varigos and Nurse, 1986) have been reported. In a painter who developed contact dermatitis after 18 months exposure to a spray paint, a patch test of MEK caused the skin to became bright red and itchy within 10 minutes. The reaction was at its maximum after 15 minutes and then gradually faded. A similar test in volunteers produced no response (Varigos and Nurse, 1986).

Eye

No information available.

Ingestion

No information available.

Carcinogenicity

There is no information on the carcinogenicity of MEK (IPCS, 1993), but it is not thought to be carcinogenic (Strickland, 1993).

In a historical prospective mortality study of 446 male workers in two MEK dewaxing plants with an average follow up of 13.9 years, the observed number of deaths (46) was less than the expected number (55.51). The number of deaths from neoplasms was less than expected, but there was a slight increase in deaths from cancer of the buccal cavity and pharynx (2 observed; 0.13 expected). There were fewer deaths from lung cancer than expected (1 observed: 6.02 expected). It was concluded that there was no clear evidence of a cancer hazard in these workers (Alderson and Rattan, 1980).

In a retrospective American study of 1,008 lubricating-dewaxing workers, with 43 years of follow up, there were no deaths from cancers of the buccal cavity or pharynx. Mortality from diseases of the circulatory system, cerebrovascular disease, diseases of the digestive system and accidents were lower than expected. These workers were exposed to MEK and to a lesser extent to toluene. Other solvents (benzene, *n*-hexane, xylene and methyl isobutyl ketone) were present in very low concentrations, generally less than 0.1 ppm. There was an increase in the incidence of prostate cancer but this appeared to be associated with the lubricating process, where MEK exposure was very low, rather than the dewaxing process where MEK exposure was higher. In addition, all cases of prostate cancer occurred in non-white workers and in the USA this is one of the most common cancers in non-white males (Wen *et al*., 1985).

Genotoxicity

Most studies of MEK have found little or no evidence for mutagenicity or genotoxicity (ECETOC, 1983; Yang, 1986; IPCS, 1993).

Reproductive toxicity

There is no information on the reproductive toxicity of MEK in humans. There are several studies in animals (Schwetz *et al*., 1974; Deacon *et al*., 1981) which suggest that MEK may be a low grade teratogen in animals (Barlow and Sullivan, 1982 and IPCS, 1993).

MEK crosses the placenta and is present in cord blood in concentrations similar to that of maternal blood (Dowty *et al*., 1976).

RISK GROUPS

Exposure to methyl ethyl ketone can potentiate the neurotoxicity of some other solvents, e.g., *n*-hexane and methyl *n*-butyl ketone. Consequently, chronic exposure to such a solvent, even at low concentrations, with concurrent exposure to methyl ethyl ketone may result in neuropathy (see Metabolic interactions).

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

MEK is of low acute toxicity and gastric decontamination is unlikely to be required unless a very large quantity has been ingested. However, because of the risk of aspiration a cuffed endotracheal tube must be used to protect the airway, since MEK is an aspiration hazard. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive.

Antidotes

There is no specific antidote for methyl ethyl ketone.

Chronic exposure

In most cases of chronic poisoning clinical effects resolve gradually once exposure has ceased. Symptomatic and supportive care.

REFERENCES

Abdel-Rahman MS, Hetland LB, Couri D. 1976 Toxicity and metabolism of methyl *n*-butyl ketone. *Am Ind Hyg Assoc J* 37:95-102.

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Alderson MR, Rattan NS. 1980 Mortality of workers on an isopropyl alcohol plant and two MEK dewaxing plants. *Br J Ind Med* 37:85-89.

Altenkirch H, Stoltenberg G, Wagner HM. 1978 Experimental studies on hydrocarbon neuropathies induced by methyl-ethyl-ketone (MEK). *J Neurol* 219:159-170.

Altenkirch H, Stoltenburg-Didinger G, Wagner HM. 1979 Experimental data on the neurotoxicity of methyl-ethyl-ketone (MEK). *Experimentia* 35 (4):503-504.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Barlow SM, Sullivan FM. 1982 *Reproductive Hazards of Industrial Chemicals. An evaluation of animal and human data*. Academic Press, London.

Berg EF. 1971 Retrobulbar neuritis. *Ann Ophthalmol* 3:1351-1353.

Brown EM, Hewitt WR. 1984 Dose-response relationships in ketone-induced potentiation of chloroform hepato- and nephrotoxicity. *Toxicol Appl Pharmacol* 76:437-453.

Brown WD, Setzer JV, Dick RB, Phipps FC, Lowry LK. 1987 Body burden profiles of single and mixed solvent exposures. *J Occup Med* 29 (11):877-883.

Callender TJ. 1995 Neurotoxic impairment in a case of methylethyl-ketone exposure. *Arch Environ Health* 50 (5):392.

Cavender FL, Casey HW, Salem H, Swenberg JA, Gralla EJ. 1983 A 90-day vapor inhalation toxicity study of methyl ethyl ketone. *Fundam Appl Toxicol* 3:264-270.

Cardona A, Marhuenda D, Marti J, Brugnone F, Roel J, Perbellini L. 1993 Biological monitoring of occupational exposure to *n*-hexane by measurement of urinary 2,5-hexanedione. *Int Arch Occup Environ Health* 65:71-74.

Couri D, Hetland LB, Abdel-Rahman MS, Weiss H. 1977 The influence of inhaled ketone solvent vapors on hepatic microsomal biotransformation activities. *Toxicol Appl Pharmacol* 41:285-289.

Couri D, Abdel-Rahman MS, Hetland LB. 1978 Biotransformation of *n*-hexane and methyl *n*-butyl ketone in guinea pigs and mice. *Am Ind Hyg Assoc J* 39:295-300.

Cunningham J, Sharkawi M, Plaa GL. 1989 Pharmacological and metabolic interactions between ethanol and methyl *n*-butyl ketone, methyl isobutyl ketone, methyl ethyl ketone, or acetone in mice. *Fundam Appl Toxicol* 13:102-109.

Deacon MM, Pilny MD, John JA, Schwetz BA, Murray FJ, Yakel HO, Kuna RA. 1981 Embryo- and fetotoxicity of inhaled methyl ethyl ketone in rats. *Toxicol Appl Pharmacol* 59:620-622.

Dick RB, Setzer JV, Wait R, Hayden MB, Taylor BJ, Tolos B, Putz-Anderson V. 1984 Effects of acute exposure of toluene and methyl ethyl ketone on pyschomotor performance. *Int Arch Occup Environ Health* 54 (2):91-109.

Dick RB, Brown WD, Setzer JV, Taylor BJ, Shukla R. 1988 Effects of short duration exposures to acetone and methyl ethyl ketone. *Toxicol Lett* 43 (1-3):31-49.

Dick RB, Setzer JV, Taylor BJ, Shukla R. 1989 Neurobehavioural effects of short duration exposure to acetone and methyl ethyl ketone. *Br J Ind Med* 46:111-121.

Dick RB, Krieg EF Jr, Setzer J, Taylor B. 1992 Neurobehavioral effects from acute exposures to methyl isobutyl ketone and methyl ethyl ketone. *Fundam Appl Toxicol* 19 (3):453-473.

Dietz FK, Traiger GJ. 1979 Potentiation of CCl_4 heptatotoxicity in rats by a metabolite of 2-butanone: 2,3-butanediol. *Toxicology* 14:209-215.

DiVincenzo GD, Kaplan CJ, Dedinas J. 1976 Characterization of the metabolites of methyl *n*-butyl ketone, methyl iso-butyl ketone, and methyl ethyl ketone in guinea pig serum and their clearance. *Toxicol Appl Pharmacol* 36:511-522.

Dowty BJ, Laseter JL, Storer J. 1976 The transplacental migration and accumulation in blood of volatile organic constituents. *Pediatr Res* 10:696-701.

Dyro FM. 1978 Methyl ethyl ketone polyneuropathy in shoe factory workers. *Clin Toxicol* 13 (3):371-376.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 1983 Methyl ethyl ketone. *Joint Assessment of Commodity Chemicals No. 3*.

Freddi A, Paci A, Vittori O, De Ciantis R, Ottaviano PF. 1982 Indagine clinico - elettromiografica su soggetti esposti a vapori di metil-etil-chetone [Clinical and electromyographic study of workers exposed to methyl ethyl ketone vapour]. *Ann Med Perugia* 73:111-136.

Geller I, Martinez RL, Hartmann RJ, Kaplan HL. 1978 Effects of ketones on a match to sample task in the baboon. *Proc West Pharmacol Soc* 21:439-442.

Geller I, Gause E, Kaplan H, Hartmann RJ. 1979 Effects of acetone, methyl ethyl ketone and methyl isobutyl ketone on a match-to-sample task in the baboon. *Pharmacol Biochem Behav* 11:401-406.

Glatt MM. 1977 Abuse of solvents "for kicks" [letter]. *Lancet* 1:485.

Graham DG. 2000 Critical analysis of Mitran *et al*. 1997. Neurotoxicity associated with occupational exposure to acetone, methyl ethyl ketone and cyclohexanone [letter]. *Environ Res* 73:181-188.

Grant WM, Schuman, JH. 1993 *Toxicology of the Eye,* fourth edition. Charles C Thomas, Springfield.

Ichihara G, Saito I, Kamijima M, Yu X, Shibata E, Toida M, Takeuchi V. 1998 Urinary 2,5-hexanedione increases with potentiation of neurotoxicity in chronic coexposure to *n*-hexane and methyl ethyl ketone. *Int Arch Occup Environ Health* 71:100-104.

Imbriani M, Ghittori S, Pezzagno G, Capodaglio E. 1989 Methyl ethyl ketone (MEK) in urine as biological index of exposure. *G Ital Med Lav* 11 (6):255-261.

IPCS (International Programme on Chemical Safety). 1993 *Environmental Health Criteria 143. Methyl Ethyl Ketone*. World Health Organization, Geneva.

Kežić S, Monster AC. 1988 Determination of methyl ethyl ketone and its metabolites in urine using capillary gas chromatography. *J Chromatog* 428:275-280.

Kopelman PG, Kalfayan PY. 1983 Severe metabolic acidosis after ingestion of butanone. *Br Med J* 286:21-22.

Liira J, Riihimäki V, Pfäffli P. 1988a Kinetics of methyl ethyl ketone in man: absorption, distribution and elimination in inhalation exposure. *Int Arch Occup Environ Health* 60:195-200.

Liira J, Riihimäki V, Engström K, Pfäffli P. 1988b Coexposure of man to *m*-xylene and methyl ethyl ketone. Kinetics and metabolism. *Scand J Work Environ Health* 14 (5):322-327.

Liira J, Riihimäki V, Engström K. 1990a Effects of ethanol on the kinetics of methyl ethyl ketone in man. *Br J Ind Med* 47:325-330.

Liira J, Johansson G, Riihimäki V. 1990b Dose-dependent kinetics of inhaled methylethylketone in man. *Toxicol Lett* 50:195-201.

Mitran E, Callender T, Orha B, Dragnea P, Botezatu G. 1997 Neurotoxicity associated with occupational exposure to acetone, methyl ethyl ketone and cyclohexanone. *Environ Res* 73 (1-2):181-188.

Mitran E. 2000 Neurotoxicity associated with occupational exposure to acetone, methyl ethyl ketone and cyclohexanone [author's reply]. *Environ Res* 82:184-185.

Miyasaka M, Kumai M, Koizumi A, Watanabe T, Kurasako K, Sato K, Ikeda M. 1982 Biological monitoring of occupational exposure to methyl ethyl ketone by means of urinalysis for methyl ethyl ketone itself. *Int Arch Occup Environ Health* 50 (2):131-137.

Munies R, Wurster DE. 1965 Investigation of some factors influencing percutaneous absorption. III. Absorption of methyl ethyl ketone. *J Pharm Sci* 54 (9):1281-1284.

Nelson KW, Ege JF Jr, Ross M, Woodman LE, Silverman L. 1943 Sensory response to certain industrial vapors. *J Ind Hyg Toxicol* 25:282-285.

Noraberg J, Arlien-Søborg P. 2000 Neurotoxic interactions of industrially used ketones. *Neurotoxicology* 21(3):409-418.

Oh SJ, Kim JM. 1976 Giant axonal swelling in "huffer's" neuropathy. *Arch Neurol* 33:583-586.

Ong CN, Sia GL, Ong HY, Phoon WH, Tan KT. 1991 Biological monitoring of occupational exposure to methyl ethyl ketone. *Int Arch Occup Environ Health* 63 (5):319-324.

Ortí-Pareja M, Jiménez-Jiménez FJ, Miquel J, Montero E, Cabrera-Valdiva F, Benito A, García-Albea E. 1996 Reversible mcyolonus, tremor, and ataxia in a patient exposed to methyl ethyl ketone. *Neurology* 46 (1):272.

Panson RD, Winek CL. 1980 Aspiration toxicity of ketones. *Clin Toxicol* 17 (2):271-317.

Perbellini L, Brugnone F, Mozzo P, Cocheo V, Caretta D. 1984 Methyl ethyl ketone exposure in industrial workers. Uptake and kinetics. *Int Arch Occup Environ Health* 54 (1):73-81.

Price EA, D'Alessandro A, Kearney T, Olson KR, Blane PD. 1994 Osmolar gap with minimal acidosis in combined methanol and methyl ethyl ketone ingestion. *Clin Toxicol* 32 (10):79-84.

Ralston WH, Hilderbrand RL, Uddin DE, Andersen ME, Gardier RW. 1985 Potentiation of 2,5-hexanedione neurotoxicity by methyl ethyl ketone. *Toxicol Appl Pharmacol* 81:319-327.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Saida K, Mendell JR, Weiss HS. 1976 Peripheral nerve changes induced by methyl *n*-butyl ketone and potentiation by methyl ethyl ketone. *J Neuropath Exp Neurol* 35 (3):207-225.

Sakata M, Kikuchi J, Haga M, Ishiyama N, Maeda T, Ise T, Hikita N. 1989 Disposition of acetone, methyl ethyl ketone and cyclohexanone in acute poisoning. *Clin Toxicol* 27 (1&2):67-77.

Schwetz BA, Leong BKJ, Gehring PJ. 1974 Embryo- and fetotoxity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. *Toxicol Appl Pharmacol* 28:452-464.

Shibata E, Huang J, Ono Y, Hisanaga N, Iwata M, Saito I, Takeuchi Y. 1990 Changes in urinary *n*-hexane metabolites by co-exposure to various concentrations of methyl ethyl ketone and fixed *n*-hexane levels. *Arch Toxicol* 64:165-168.

Smith AR, Mayers MR. 1944 Study of poisoning and fire hazards of butanone and acetone. *NY State Labor Ind Bull* 23:174-176.

Spencer PS, Schaumberg HH. 1976 Feline nervous system response to chronic intoxication with commercial grades of methyl *n*-butyl ketone, methyl isobutyl ketone, and methyl ethyl ketone. *Toxicol Appl Pharmacol* 37:301-311.

Spencer PS, Schaumburg HH, Sabri MI, Veronesi B. 1980 The enlarging view of hexacarbon neuropathy. *CRC Crit Rev Toxicol* 7 (4):279-356.

Strickland GD. 1993 Methyl ethyl ketone and methyl isobutyl ketone not carcinogenic [letter]. *Environ Health Perspect* 101:566.

Tada O, Nakaaki N, Fukabori S. 1972 An experimental study on acetone and methyl ethyl ketone concentrations in urine and expired air after exposure to those vapours. *J Sci Lab* 48 (6):305-336.

Takeuchi Y, Ono Y, Hisanaga N, Iwata M, Aoyama M, Kitoh J, Sugiura Y. 1983 An experimental study of the combined effects of *n*-hexane and methyl ethyl ketone. *Br J Ind Med* 40:199-203.

Topping DC, Morgott DA, O'Donoghue JL. 2001 Ketones of six to thirteen carbons. In: *Patty's Toxicology,* fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Viader F, Lechevalier B, Morin P. 1975 Polynévrite toxique chez un travailleur du plastique. Rôle possible du méthyl-éthyl-cétone. [Toxic polyneuritis in a plastic worker. The possible role of methyl ethyl ketone]. *La Nouvelle Presse Med* 4 (24):1813-1814.

van Engelen JGM, Rebel-el Haan W, Opdam JG, Mulder GJ. 1997 Effect of coexposure to methyl ethyl ketone (MEK) on *n*-hexane toxicokinetics in human volunteers. *Toxicol Appl Pharmacol* 144:385-395.

Varigos GA, Nurse DS. 1986 Contact urticaria from methyl ethyl ketone. *Contact Dermatitis* 15 (4):259-260.

Wahlberg JE. 1984a Edema-inducing effects of solvents following topical administration. *Dermatosen* 3:91-94.

Wahlberg JE. 1984b Erythema-inducing effects of solvents following epicutaneous administration to man - studied by laser Doppler flowmetry. *Scand J Work Environ Health* 10:159-162.

Weil CS, Scala RA. 1971 Study of intra- and interlaboratory variability in the results of rabbit eye and skin irritation tests. *Toxicol Appl Pharmacol* 19:276-360.

Wen CP, Tsai SP, Weiss NS, Gibson RL, Wong O, McClellan WA. 1985 Long-term mortality study of oil refinery workers. IV. Exposure to the lubricating-dewaxing process. *J Natl Cancer Inst* 74 (1):11-18.

Yang RSH. 1986 The toxicology of methyl ethyl ketone *Residue Rev* 97:121-143.

Yoshikawa M, Kawamoto T, Murata K, Arashidani K, Katoh T, Kodama Y. 1995 Biological monitoring of occupational exposure to methyl ethyl ketone in Japanese workers. *Arch Environ Contam Toxicol* 29 (1):135-139.

Yücesoy B, Yücel A, Erdem O, Bergaz S, Imir T, Karakaya AE, Karakaya A. 1999 Effects of occupational chronic co-exposure to *n*-hexane, toluene, and methyl ethyl ketone on NK cell activity and some immunoregulatory cytokine levels in shoe workers. *Hum Exp Toxicol* 18:541-546.

Zakhari S, Leibowitz M, Levy P, Aviado DM. 1977 *Isopropanol and Ketones in the Environment*. CRC Press, Cleveland, Ohio. Cited in: IPCS (International Programme on Chemical Safety). 1993 *Environmental Health Criteria 143. Methyl Ethyl Ketone*. World Health Organization, Geneva.

Zhao W, Misumi J, Yasui T, Aoki K, Kimura T. 1998 Effects of methyl ethyl ketone, acetone, or toluene coadministration on 2,5-hexanedione concentration in the sciatic nerve, serum, and the urine of rats. *Int Arch Occup Environ Health* 71 (4):236-244.

18 Methyl Isobutyl Ketone (MIBK)

Nicola Bates

SUMMARY

- MIBK is of low acute toxicity
- It is not thought to be neurotoxic
- MIBK is not considered to be a reproductive toxin
- MIBK is not considered to be genotoxic
- MIBK has not been evaluated for carcinogenicity

DESCRIPTION

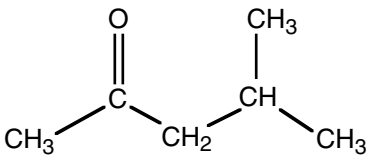
Synonyms

Methyl isobutyl ketone, MIBK, 4-methyl-2-pentanone, hexanone, hexone, isopropyl acetone, 4-methyl pentan-2-one, 4-methyl-2-oxopentane, 2-methyl propyl methyl ketone, isobutyl methyl ketone

Identification numbers

CAS	108-10-1
UN	1245
RTECS	SA9275000
EINECS	2035051

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	$C_6H_{12}O$
molecular formula	
molecular mass	100.2
physical form	colourless liquid with a sweet, sharp odour
relative vapour density	3.45
flash point (°C)	18
boiling point (°C)	79.6
autoignition temperature (°C)	460
refractive index	1.3959
explosive limits (%v/v)	1.4-7.6

Odour threshold

0.1 ppm (Ruth, 1986); 0.68 ppm (Amoore and Hautala, 1983); 10 ppm (Dalton *et al*., 2000).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK & USA): 50 ppm (208 mg/m^3)

Conversion factors

1 ppm = 4.1 mg/m^3

1 mg/m^3 = 0.244 ppm

1 mg/l = 244 ppm

Biomonitoring

The ACGIH biological exposure index for MIBK is an end of shift urinary MIBK concentration of 2 mg/l (ACGIH, 2000).

TOXICITY

MIBK is of low toxicity (Topping *et al*., 1994). There are several reports in the literature of interactions between MIBK and other solvents, including occupational surveys and animal and volunteer studies (reviewed in Noraberg and Arlien-Søborg, 2000).

Absorption

There is limited information on the absorption of MIBK in humans. In a volunteer study the pulmonary retention of MIBK was 60% (Hjelm *et al.,* 1990).

Distribution

The concentration in blood correlates with the exposure concentration (Hjelm *et al.,* 1990). In two individuals who died after exposure to a mixture of solvents including MIBK, the range of MIBK in tissues and body fluids was 1.4-2.5 and 0.2-0.8 mg/kg, respectively. The former worker had died after a fall into the water storage tank that was being spray painted, the concentration was highest in the vitreous humour, liver and lung tissue. The other was removed from the exposure but died nine hours later, the highest concentration was in the liver. Thus, the distribution of MIBK was different in the two workers (Bellanca *et al*., 1982).

Metabolism

There is limited information on the metabolism of MIBK. In mice and guinea pigs, the MIBK metabolites are 4-hydroxy-4-methyl-2-pentanone (4-hydroxymethyl isobutyl ketone) and 4-methyl-2-pentanol (DiVincenzo *et al*., 1976; Granvil *et al*., 1994). 4-Hydroxy-4-methyl-2-pentanone is formed by the oxidation of MIBK, whereas the minor metabolite 4-methyl-2-pentanol is formed by reduction (IPCS, 1990). The majority of absorbed MIBK probably enters the general metabolism and is transformed to simple compounds such as water and carbon dioxide (Hjelm *et al.,* 1990).

Table 18.1 Elimination phases of MIBK (Hjelm *et al.*, 1990)		
Half-life (mins)	**Time Post Exposure (mins)**	**Exposure**
11 59	0-30 60-180	100 mg/m^3 (24 ppm) MIBK
13 74	0-30 60-180	200 mg/m^3 (49 ppm) MIBK
12 81	0-30 60-180	200 mg/m^3 (24 ppm) MIBK and 150 mg/m^3 (40 ppm) toluene

Elimination

In a volunteer study of exposure to MIBK two elimination phases were observed (**Table 18.1**) (Hjelm *et al.*, 1990). Only 0.04% of the absorbed dose of MIBK was excreted unchanged in the urine up to three hours post exposure. The urinary concentration of 4-hydroxy-4-methyl-2-pentanone and 4-methyl-2-pentanol was below the detection limit of 5 nmol/l (Hjelm *et al.*, 1990).

Mode of action

There is no information on the mode of action of MIBK.

Metabolic interaction

- **Chloroform**

  MIBK and its metabolites, 4-hydroxy-4-methyl-2-pentanone and 4-methyl-2-pentanol, can potentiate the hepatotoxicity of chloroform in animals. None of the three compounds had any hepatotoxic effects when given alone (Vézina *et al.*, 1990). Similarly MIBK has been shown to potentiate choleostasis induced by taurolithocholate in rats. Bile flow was unchanged when the animals were exposed to MIBK alone (Plaa and Ayotte, 1985). This potentiation of hepatotoxicity is probably due to the induction of cytochrome P450 enzymes (Vézina *et al.*, 1990).

- **Ethanol**

  Animal studies have shown that MIBK can increase the CNS depressant effects of ethanol. However, this is probably due to the depressant effects of MIBK and its metabolites rather than through changes in ethanol metabolism (Sharkawi *et al.*, 1994).

CASE REPORTS

Chronic occupational exposure and memory impairment

A 44 year old man had worked from 1966 to 1982 as a chemical operator. He wore gloves and coveralls and was intermittently exposed to acetone 1,000 ppm, *n*-butyl acetone 100 ppm, isopropyl ether 500 ppm, isopropanol 400 ppm and MIBK 100 ppm. He had remained well during this period. From 1982 until 1987 he worked as a supervisor in a poorly ventilated area of a solvent extraction facility. He was exposed daily to concentrations of MIBK in excess of 100 ppm for 8 hours daily. Several times a day he also became soaked in the solvent when he climbed into a large chamber. He had daily headaches which cleared during the weekend. Following each period in the chamber he also experienced sedation and syncope. He also worked regular double shifts in 1985 and 1986.

In early 1986 he experienced increasing anxiety, irritability, poor concentration, forgetfulness and severe olfactory impairment. He lost his job because of poor performance. On evaluation 18 months later he reported moderate improvement in cognitive ability, but still had memory and concentration difficulties. Olfaction had improved and he experienced increased sensitivity to some chemical odours. This eventually resolved. During the following 10 year period he had neuropsychological testing six times. He performed poorly in tests involving strategic self-guided retrieval (e.g., verbal fluency, free recall), but was better with tasks that provided direct retrieval cues (e.g., picture naming, vocabulary). He performed poorly on tasks that depended on temporary storage and rapid information processing. Initial neuroimaging showed only slight cerebral atrophy, which was still present on the final evaluation. After 11 years his cognitive deficits still affected his daily life and he occasionally displayed impulsive behaviour and disinhibition. The neurological effects in this case were thought to be due to MIBK. Another worker who worked as a supervisor also experienced cognitive dysfunction with slowed information processing and impaired attention. Other workers who wore protective breathing apparatus were unaffected. No other causes for his memory impairment were found (Grober and Schaumburg, 2000).

CLINICAL EFFECTS

Acute exposure

Inhalation

The principal effects of exposure to MIBK at doses of up to 100 ppm are limited to sensory and irritant effects (Dick *et al*., 1992). Most subjects exposed to concentrations above 100 ppm developed eye irritation, with nose and throat irritation at concentrations above 200 ppm (Silverman *et al*., 1946). Nausea, headache and dizziness may occur from acute exposure (Hjelm *et al*., 1990; Dick *et al*., 1992; Gagnon *et al*., 1994). A high concentration may cause CNS depression and coma.

There were no significant effects on performance in tests of reaction time or simple arithmetic in volunteers exposed to MIBK at 100 mg/m^3 (24 ppm) or 200 mg/m^3 (50 ppm) (Hjelm *et al*., 1990; Dick *et al*., 1992; Iregren *et al*., 1993; Gagnon *et al*., 1994). There was no effect on heart rate at exposures of up to 50 ppm (Iregren *et al*., 1993). Exposure to MIBK did not affect the accuracy of performance of a match-to-sample task in baboons, but it did cause in a delay in response time (Geller *et al*., 1978; Geller *et al*., 1979).

Dermal

In a collaborative study involving 23 laboratories, 0.5 ml of MIBK on rabbit skin was found to be relatively non-irritating (Weil and Scala, 1971).

Eye

In a collaborative study involving 23 laboratories, a dose of 0.1 ml of MIBK produced minimal irritation in rabbit eyes (Weil and Scala, 1971).

Ingestion

There is no information on ingestion of MIBK. The main is hazard is likely to be the risk of aspiration of MIBK into the lungs (Panson and Winek, 1980), which may cause chemical pneumonitis and pulmonary oedema.

Chronic exposure

Inhalation

Symptoms reported in 19 workers exposed to MIBK (80-500 ppm) for 20-30 minutes daily (and to 80 ppm for the rest of the day), for six months to one year, included anorexia, eye and throat irritation, nausea and

vomiting. CNS effects included headache, drowsiness, sleep disturbances and weakness, which lasted weeks after cessation of exposure. Four workers had slightly enlarged liver and six had complaints indicative of non-specific colitis. Clinical biochemistry tests were normal (Linari *et al*., 1964). Five years later, following improvement in work practices (50 ppm MIBK with peaks of 105 ppm), only a few workers complained of gastrointestinal and CNS effects. Slight liver enlargement had persisted in two workers, but the other effects had resolved (Armeli *et al.,* 1968).

Cognitive impairment with slowed information processing and impaired attention was reported in a worker exposed to high concentrations of MIBK over a 6 year period. He also had temporary severe olfactory impairment (Grober and Schaumburg, 2000).

In a study of volunteers exposed to 20 ppm and 40 ppm, the perceived odour intensity was high at the start of the exposure but stabilised after about two hours. This suggests that olfactory adaptation may occur and this will hinder odour detection of MIBK (Gagnon *et al*., 1994).

MIBK has been implicated in cases of neuropathy (e.g., Oh and Kim, 1976; AuBuchon *et al*., 1979) but this has been questioned (Tyrer, 1979). The evidence from studies in animals demonstrates that exposure to MIBK alone does not cause neurological damage (Spencer *et al.,* 1980; ECETOC, 1987).

Dermal

Chronic exposure to MIBK on the skin may cause drying and cracking (Hathaway *et al*., 1996). Dermatitis may occur due to its defatting action (Topping *et al.,* 1994).

Eye

No information available.

Ingestion

No information available.

Carcinogenicity

There is no information on the carcinogenicity of MIBK (IPCS, 1990), but it is not thought to be carcinogenic (Strickland, 1993).

Genotoxicity

Mutagenicity tests (reviewed in ECETOC, 1987 and IPCS, 1990; Topping *et al*., 2001) suggest that MIBK is not genotoxic.

Reproductive toxicity

There is no information on the reproductive toxicity of MIBK in humans, but it is not considered to pose a reproductive risk (ECETOC, 1987). A study in rats and mice found no evidence of embryo or fetal toxicity at concentrations of 300 or 1,000 ppm. Maternal and fetotoxicity was seen in both species at 3,000 ppm (Tyl *et al*., 1987). This suggests that MIBK is unlikely to cause teratogenicity or embryotoxicity in animals at exposure levels which are not maternally toxic (ECETOC, 1987).

MIBK crosses the placenta and is present in cord blood in concentrations similar to that of maternal blood (Dowty *et al*., 1976).

RISK GROUPS

None identified.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

MIBK is of low acute toxicity and gastric decontamination is unlikely to be required unless a very large quantity has been ingested. However, because of the risk of aspiration a cuffed endotracheal tube must be used to protect the airway, since MIBK is an aspiration hazard. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive.

Antidote

There is no specific antidote for methyl *n*-butyl ketone.

Chronic exposure

Treatment is symptomatic and supportive. There is only one well documented case of chronic MIBK exposure. There was still cognitive impairment 11 years after cessation of exposure (Grober and Schaumburg, 2000).

REFERENCES

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Armeli G, Linari F, Mastorano G. 1968 Rilievi clinici ed ematochimici in operai esposti all'azione di un chetone superiore (MIBK) ripetuti a distanza di 5 anni [Clinical and haematological examinations in workers exposed to the action of a complex ketone (MIBK) repeated after 5 years]. *Lavoro Umano* 20:418-424.

AuBuchon J, Robins HI, Viseskul C. 1979 Peripheral neuropathy after exposure to methyl-isobutyl ketone in spray paint [letter]. *Lancet* 2:363-364.

Bellanca JA, Davis PL, Donnelly B, Dal Cortivo LA, Weinberg SB. 1982 Detection and quantitation of multiple volatile compounds in tissues by GC and GC/MS. *J Anal Toxicol* 6:238-240.

Dalton PH, Dilks DD, Banton MI. 2000 Evaluation of odor and sensory irritation thresholds for methyl isobutyl ketone in humans. *AIHAJ* 61 (3):340-350.

Dick RB, Krieg EF Jr, Setzer J, Taylor B. 1992 Neurobehavioral effects from acute exposures to methyl isobutyl ketone and methyl ethyl ketone. *Fundam Appl Toxicol* 19 (3):453-473.

DiVincenzo GD, Kaplan CJ, Dedinas J. 1976 Characterization of the metabolites of methyl n-butyl ketone, methyl iso-butyl ketone, and methyl ethyl ketone in guinea pig serum and their clearance. *Toxicol Appl Pharmacol* 36:511-522.

Dowty BJ, Laseter JL, Storer J. 1976 The transplacental migration and accumulation in blood of volatile organic constituents. *Pediatr Res* 10:696-701.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 1987 Methyl isobutyl ketone. *Joint Assessment of Commodity Chemicals* No. 8.

Gagnon P, Mergler D, Lapare S. 1994 Olfactory adaptation, threshold shift and recovery at low levels of exposure to methyl isobutyl ketone (MIBK). *Neurotoxicology* 15 (3):637-642.

Geller I, Martinez RL, Hartmann RJ, Kaplan HL. 1978 Effects of ketones on a match to sample task in the baboon. *Proc West Pharmacol Soc* 21:439-442.

Geller I, Gause E, Kaplan H, Hartmann RJ. 1979 Effects of acetone, methyl ethyl ketone and methyl isobutyl ketone on a match-to-sample task in the baboon. *Pharmacol Biochem Behav* 11:401-406.

Granvil CP, Sharkawi M, Plaa GL. 1994 Metabolic fate of methyl n-butyl ketone, methyl isobutyl ketone and their metabolites in mice. *Toxicol Lett* 70:263-267.

Grober E, Schaumburg HH. 2000 Occupational exposure to methyl isobutyl ketone causes lasting impairment in working memory. *Neurology* 54 (9):1853-1855.

Hathaway GJ, Proctor NH, Hughes JP. 1996 *Proctor and Hughes' Chemical Hazards of the Workplace*, fourth edition. John Wiley & Sons Inc, New York, p.431-2.

Hjelm EW, Hagberg M, Iregren A, Löf A. 1990 Exposure to methyl isobutyl ketone: toxicokinetics and occurrence of irritative and CNS symptoms in man. *Int Arch Occup Environ Health* 62 (1):19-26.

IPCS (International Programme on Chemical Safety). 1990 *Environmental Health Criteria 117. Methyl Isobutyl Ketone*. World Health Organization, Geneva.

Iregren A, Tesarz M, Wigaeus-Hjelm E. 1993 Human experimental MIBK exposure: effects on heart rate, performance, and symptoms. *Environ Res* 63 (1):101-108.

Linari F, Perrelli G, Vance D. 1964 Riliveri clinici ed ematochimici in operai eposti all'azione di un chetone superiore: metil-isobutil-chetone [Clinical observations and blood biochemistry findings in workers exposed to a complex ketone: methyl isobutyl ketone]. *Arch Sci Med* 117:226-237.

Noraberg J, Arlien-Søborg P. 2000 Neurotoxic interactions of industrially used ketones. *Neurotoxicology* 21 (3):409-418.

Oh SJ, Kim JM. 1976 Giant axonal swelling in "huffer's" neuropathy. *Arch Neurol* 33:583-586.

Panson RD, Winek CL. 1980 Aspiration toxicity of ketones. *Clin Toxicol* 17 (2):271-317.

Plaa GL, Ayotte P. 1985 Taurolithocholate-induced intrahepatic cholestasis: potentiation by methyl isobutyl ketone and methyl n-butyl ketone in rats. *Toxicol Appl Pharmacol* 80:228-234.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Sharkawi M, Granvil C, Faci A, Plaa GL. 1994 Pharmacodynamic and metabolic interactions between ethanol and two industrial solvents (methyl *n*-butyl ketone and methyl isobutyl ketone) and their principal metabolites in mice. *Toxicology* 94:187-195.

Silverman L, Schulte HF, First MW. 1946 Further studies on sensory response to certain industrial solvent vapors. *Ind Hyg Toxicol* 28:262-266.

Spencer PS, Schaumburg HH, Sabri MI, Veronesi B. 1980 The enlarging view of hexacarbon neuropathy. *CRC Crit Rev Toxicol* 7 (4):279-356.

Strickland GD. 1993 Methyl ethyl ketone and methyl isobutyl ketone not carcinogenic [letter]. *Environ Health Perspect* 101:566.

Topping DC, Morgott DA, David RM, O'Donoghue JL. 1994 Ketones. In: *Patty's Industrial Hygiene and Toxicology*, fourth edition, Volume 2, Part C. GD Clayton, FE Clayton (editors). John Wiley & Sons Inc, New York.

Topping DC, Morgott DA, O'Donoghue JL. 2001 Ketones of six to thirteen carbons. In: *Patty's Toxicology*, fifth edition, Volume 6. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Tyl RW, France KA, Fisher LC, Pritts IM, Tyler TR, Phillips RD, Moran EJ. 1987 Developmental toxicity evaluation of inhaled methyl isobutyl ketone in Fischer 344 rats and CD-1 mice. *Fundam Appl Toxicol* 8 (3):310-327.

Tyrer FH. 1979 Peripheral neuropathy after exposure to methyl-isobutyl ketone in spray paint [letter]. *Lancet* 2:424.

Vézina M, Kobusch AB, du Souich P, Greselin E, Plaa GL. 1990 Potentiation of chloroform-induced hepatotoxicity by methyl isobutyl ketone and two metabolites. *Can J Physiol Pharmacol* 68 (8):1055-1061.

Weil CS, Scala RA. 1971 Study of intra- and interlaboratory variability in the results of rabbit eye and skin irritation tests. *Toxicol Appl Pharmacol* 19:276-360.

19 *N*-Methyl-2-Pyrrolidone (NMP)

Catherine Farrow

SUMMARY

- NMP is of low acute toxicity
- NMP is not neurotoxic
- It is a skin irritant
- NMP may affect fetal growth and subsequent development following maternal dermal exposure
- It is not considered to be teratogenic or a reproductive toxin
- NMP is potentially genotoxic, but is not considered to be mutagenic
- NMP has not been evaluated for carcinogenicity in humans and there is no evidence for carcinogenicity in animals

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DESCRIPTION

Synonyms

NMP, *n*-methyl-2-pyrrolidone, *n*-methyl-γ-butyrolactone, 1-methylazacyclopentan-2-one, 1-methylpyrrolidinone, 1-methyl-2-pyrrolidinone, 1-methylpyrrolidone, *n*-methylpyrrolidinone, 1-methyl-2-pyrrolidone, *n*-methylpyrrolidone, *n*-methyl-α-pyrrolidinone, methylpyrrolidone, MP, M-pyrol™, M-pyrrole.

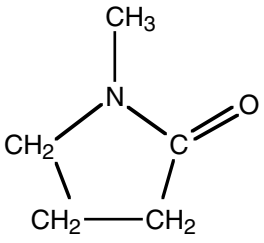
Identification numbers

CAS	872-50-4
UN	no data available
RTECS	UY 5790000
EINECS	212-828-1

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula C_5H_9NO

molecular formula



molecular mass	99.13
physical form	clear, colourless liquid
relative vapour density (air=1)	1.027
flash point (closed cup, °C)	93
boiling point (°C)	202
autoignition temperature (°C)	346
refractive index	1.4690
explosive limits (%v/v)	1-10

Odour threshold

No information available.

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK): 25 ppm (103 mg/m^3)
TWA (ACGIH): not recorded

Conversion factors

1 ppm = 4.1 mg/m^3
1 mg/m^3 = 0.2 ppm

Biomonitoring

No biological exposure index (BEI) has been established for NMP by ACGIH. The three metabolites 5-HNMP, MSI and 2-HMSI have been investigated as possible biomarkers for exposure to NMP (see metabolism) (Åkesson and Jönsson, 1997). Methods are available for their determination in urine and plasma (Jönsson and Åkesson, 1997a and b; Åkesson and Jönsson, 2000). Plasma 5-HNMP is considered the best of these biomarkers (Åkesson and Jönsson, 2000).

TOXICITY

NMP is a cyclic amide and an aprotic, dipolar solvent (Solomon *et al.*, 1996). Its strong and selective solvent capacity led to its introduction as a substitute for more inherently toxic solvents, e.g., dichloromethane, trichloroethane, trichloroethylene and glycol ethers.

NMP is readily absorbed via all routes. Most exposures are occupational, and inhalation and dermal routes are of most significance. There are few data regarding the toxic effects of NMP in humans; however, these along with animal studies suggest that this solvent is of low toxicity.

Absorption

NMP is freely soluble in both polar and non-polar solvents. It can cross biological membranes readily and is efficiently absorbed by skin, respiratory tract and gastrointestinal tract (Wells and Digenis, 1988; Midgely *et al.*, 1992; Åkesson and Jönsson, 1997). The transcutaneous permeability rate of NMP was measured as 171 g/m^2/h (157 cm^3/m^2/h) using living human skin (Ursin *et al.*, 1995). After an 8 hour inhalation exposure to NMP the peak 5-HNMP concentrations occurred at 1 hour in plasma and zero to two hours in urine (Åkesson and Jönsson, 2000).

Distribution

Limited data suggest NMP has a large volume of distribution. It was rapidly and widely distributed in rats after intravenous administration of double-labelled NMP. The liver, small and large intestines, testes, stomach and kidneys were reported to contain the greatest amounts of radioactivity six hours post injection. Only the liver and intestines still contained considerable amounts of radioactivity at 24 hours (Wells and Digenis, 1988).

Metabolism

NMP is readily converted to three polar metabolites, 5-hydroxy-*N*-methylpyrrolidone (5-HNMP), *N*-methyl succinimide (MSI) and 2-hydroxy-*N*-methylsuccinimide (2-HMSI). These compounds are not detected in unexposed subjects (Åkesson and Jönsson, 1997).

In rats, the liver is thought to be the main site of NMP metabolism. Minor routes of metabolism with differing rates are thought to account for the remainder. Three metabolites were detected (Wells and Digenis, 1988), and one was identified as 5-HNMP (Wells *et al.*, 1992).

In humans, 5-HNMP is the major metabolite identified (Åkesson and Jönsson, 1997). A close correlation was observed between plasma and urine 5-HNMP concentrations and air NMP concentrations (Åkesson and Jönsson, 2000). It is postulated that NMP is primarily hydroxylated to 5-HNMP, which is then oxidised to MSI, and this in turn is further hydroxylated to 2-HMSI. However, another as yet unidentified metabolite was eluted before 5-HNMP (Åkesson and Jönsson, 1997).

Neither 5-HNMP nor 2-HMSI undergo conjugation with glucuronic acid or sulphate (Åkesson and Jönsson, 1997). Conjugates of the major metabolite resulting after acid hydrolysis (not identified but proposed to be 4-(methylamino)butanoic acid) were not detected in rat urine after a single intravenous injection of double-labelled NMP (Wells and Digenis, 1988). One glucuronide was detected in the urine of a one day old neonate following chronic exposure to ethosuximide, a succinimide thought to undergo metabolism similar to NMP (Horning *et al.*, 1973; Åkesson and Jönsson, 1997).

Elimination

The small fraction of unchanged NMP remaining is excreted renally. The metabolites 5-HNMP, MSI and 2-HMSI are readily eliminated via the kidneys (Åkesson and Jönsson, 1997; Åkesson and Paulsson, 1997).

Unchanged NMP was detected in urine only on day 1 following oral administration of 100 mg NMP (Åkesson and Jönsson, 1997). Following inhalation exposure, the mean elimination half-life of NMP in plasma was calculated as 4 hours (range 2.9-5.8 hours) and in urine, 4.5 hours (range 3.5-6.6 hours) (Åkesson and Paulsson, 1997). The mean fraction of the orally administered dose of NMP excreted in urine was 0.8% (Åkesson and Jönsson, 1997). The 2% fraction of NMP excreted renally following inhalation was possibly overestimated due to concommitant dermal exposure (Åkesson and Paulsson, 1997; Åkesson and Jönsson, 2000). One third of the ingested NMP was not excreted in the urine and incomplete absorption by the gastrointestinal tract or other, unidentified metabolites may account for the balance (Åkesson and Jönsson, 1997).

Following oral administration of 100 mg NMP, 5-HNMP was detected in urine on days 1 and 2 post-exposure. The urinary elimination half-life of 5-HNMP was estimated at 4 hours (Åkesson and Jönsson, 1997). The calculated mean 5-HNMP plasma and urine half-lives of 6.3 and 7.3 hours respectively, following inhalation of NMP, may have been influenced by additional NMP absorption across the skin (Åkesson and Jönsson, 2000). The mean fraction of the orally administered dose of NMP excreted as 5-HNMP in urine was 44% (Åkesson and Jönsson, 1997).

MSI was detected during the first three days post ingestion, with an estimated half-life of eight hours. 2-HMSI was excreted on the first 6 days, with an estimated half-life of 17 hours. Concentrations of NMP and these metabolites were below detection limits on day seven. The mean fractions of the orally administered dose of NMP excreted as MSI and 2-HMSI were 0.4% and 20% respectively (Åkesson and Jönsson, 1997).

In rats, the elimination profile from plasma following a single intravenous injection of double-labelled NMP was slow, suggesting slow release into plasma from a deep compartment or storage depot, e.g., fat. There was limited excretion in bile indicating that no enterohepatic circulation occurred. Excretion of radioactivity in urine was found to be the major route of elimination; faeces and carbon dioxide in exhaled air were found to be minor routes of elimination (Wells and Digenis, 1988).

Mode of action

The mechanism of NMP toxicity is not known. Both the parent compound and its metabolites may be responsible for the putative effects reported. Other succinimides, which undergo similar hydroxylation as the conversion of MSI to 2-HMSI, are known to have physiological activity and may be teratogenic (Horning *et al.*, 1973; Mallow *et al.*, 1980; Kuhnz *et al.,* 1984; Åkesson and Jönsson, 1997). However, NMP was reported to induce chromosome loss in *Saccharomyces cerevisiae* under specific conditions, whereas succinimide, a compound structurally similar to MSI, does not (Mayer *et al.*, 1988; Zimmermann *et al.*, 1989).

Metabolic interactions

NMP has been shown to enhance transcutaneous penetration of both polar and non-polar substances. In *in vivo* mimic studies NMP significantly increased the rate and quantity permeating human skin of acetone-deposited ibuprofen, flurbiprofen and mannitol films. Following a single application of NMP the accelerant effect was transient and shown to be reversible; the drugs redeposited on the skin as the NMP was absorbed and its content in the membrane depleted (Akhter and Barry, 1985; Barry and Bennett, 1987). NMP enhanced penetration, as evidenced by increased rate of permeation, was also shown for hydrocortisone and progesterone (Barry and Bennett, 1987). In the occupational setting NMP may enhance the penetration of other dermally absorbed substances.

CASE REPORTS

A 23 year old female laboratory technician was employed as an atomic spectrophotometer operator. She was normally fit and well, did not smoke, drink alcohol or use caffeine, although she was taking prenatal vitamins daily including 4000 IU of vitamin A (UK adult recommended daily amount 2500 IU). Working without personal protective equipment, she was exposed daily to NMP and small quantities of methanol and/or acetone. Ultrasound examination revealed a healthy fetus at 14 weeks gestation. After raising concerns with an occupational medicine consultant about an NMP material safety data sheet listing reports of fetotoxicity and teratogenicity in rats, she was given a respirator and protective clothing including latex gloves, a lab coat and goggles. The latex gloves dissolved and extensive dermal exposure to the hands occurred at 16 weeks gestation, when she cleaned up a spillage of NMP. Over the following four days she experienced malaise, headache, nausea and vomiting. Staining of the hands was still apparent two weeks later. After a week of sick leave, she returned to work and daily exposures to NMP continued for 42 hours per week until week 20 of gestation. No measurement of air NMP concentrations was made during the period of her exposure. A follow up ultrasound at 25 weeks of gestation revealed intrauterine growth retardation as evidenced by humerus and femur lengths and abdominal circumference corresponding to 21 weeks gestation. This was confirmed by a further ultrasound scan at week 28 and fetal demise occurred at week 31 of gestation (Solomon *et al.*, 1996). Although vitamin A, to which the patient was also exposed daily, is a known teratogen, it affects fetal development as opposed to survival or growth (Briggs *et al.*, 1994).

CLINICAL EFFECTS

Acute exposure

Inhalation

No discomfort to the upper airways, changes in nasal volume or spirometric data were reported in male adults exposed to up to 50 mg/m^3 (12.3 ppm) for eight hours (Åkesson and Paulsson, 1997). No respiratory effects were described by employees exposed to concentrations of up to 83 ppm (336.6 mg/m^3) in a study of industrial hygiene at two microelectronics manufacturers (Beaulieu and Schmerber, 1991).

Dermal

Ten of twelve workers in an electrotechnical company developed acute irritant contact dermatitis of the hands within three days of using NMP; latex gloves were used only intermittently. Varying degrees of itching, redness, swelling, and small vesicle formation on the volar aspect of the fingers were reported. The severity of the reaction appeared to relate to the degree and duration of exposure, and the effects were reversible on cessation of exposure. One worker developed skin peeling after a week and cutaneous effects resolved within three weeks after cessation of exposure. Skin thickening and brownish discoloration were reported in the worst case. Systemic effects were not reported (Leira *et al.*, 1992).

Solomon *et al.* (1996) reported staining of the hands, which was still apparent two weeks after cleaning up a spillage of NMP. In this case, however, malaise, headache, nausea and vomiting were reported for four days after exposure.

No dermal effects were reported in a study of industrial hygiene at two microelectronic semiconductor manufacturer facilities. Areas with and without NMP distillation were studied and neoprene gloves were used as standard (Beaulieu and Schmerber, 1991).

Natural rubber gloves are specially designed and packaged to minimise particulate generation. These gloves were demonstrated to provide protection from NMP at room temperature only. Permeation of NMP through natural rubber gloves has been shown to increase with increasing temperatures, however, the integrity of these gloves is not affected by prolonged contact with NMP (Zellers and Sulewski, 1993). Polyvinyl chloride (PVC), latex, neoprene and nitrile gloves are permeable to NMP (Leira *et al.*, 1992; Zellers and Sulewski, 1993). While natural rubber gloves are commonly used in microelectronics industry clean rooms, often where NMP is used at high temperatures, there are relatively few reports of dermal effects in the literature. Butyl rubber gloves are treated with talc as an adhesion inhibitor during packaging and are not used in clean rooms. However, they were shown to provide complete protection from NMP under all test conditions (Zellers and Sulewski, 1993).

Eye

There is little information on the ocular effects of NMP. Ocular effects have been reported after occupational exposure to NMP vapour (Beaulieu and Schmerber, 1991), however, these findings have not been reproduced in experimental settings.

Unbearable eye irritation was described after brief exposures to concentrations of 49 to 83 ppm (198 to 336.5 mg/m^3) NMP vapour in a study of industrial hygiene at two microelectronics manufacturers. In the same study, immediate discomfort and minor eye irritation were described at 15 to 17 ppm (61 to 69 mg/m^3), and 0.72 to 1.50 ppm (3 to 6 mg/m^3) was perceived as uncomfortable after about 30 minutes (Beaulieu and Schmerber, 1991). It is unclear, however, how these concentrations were derived from the data presented.

In contrast, no discomfort to the eyes was reported in male adults exposed to up to 50 mg/m^3 (12.3 ppm) for 8 hours (Åkesson and Paulsson, 1997).

Ingestion

Only one study could be found in the literature involving ingestion of NMP. While no effects were documented in three healthy males administered 100 mg NMP orally, the main objective of this study was not to report clinical effects but to determine the major metabolic pathway of NMP in humans (Åkesson and Jönsson, 1997).

Chronic exposure

Inhalation

There is no information on the effects of chronic inhalation of NMP in humans. Rats exposed to 0.1, 0.5 or 1.0 mg/l (25, 123 or 247 ppm) aerosol-vapour mixture of NMP for six hours per day, for five days per week for four

weeks, developed lethargy and respiratory effects. Effects developed three to four hours after onset of exposure, continued throughout exposure and into the recovery period. The severity of clinical effects was dose related, with excessive mortality at the highest concentration. Only a few rats at the highest dosage had recovered by 18 hours post exposure. No effects were reported in the control group. Marked pulmonary oedema and congestion were found at postmortem examination in animals that died. Those killed *in extremis* were found to have focal interstitial pneumonitis, increased neutrophils in alveolar capillaries and bone marrow haemorrhage. Rats surviving 1.0 mg/l and those killed *in extremis* had bone marrow hypoplasia, haematopoietic cell necrosis and atrophy of lymphoid tissue in thymus, spleen and lymph nodes. Increases in relative and absolute numbers of neutrophils and decreased relative numbers of lymphocytes in rats surviving 1.0 mg/l, returned to normal values following 2 weeks of recovery. These abnormalities were not found in rats exposed to 0.1 or 0.5 mg/l (Lee *et al.*, 1987).

Exposure of rats to NMP vapour for six hours per day, five days per week for two years, at concentrations of 0.04 or 0.4 mg/l (10 or 100 ppm) resulted in no life threatening toxic effects. Dose related darker yellow urine was reported. In the absence of a similar increase in renal lesions, this change was considered to be of no biological significance. Males in the highest treatment group had a slightly reduced mean bodyweight (6% less than controls) (Lee *et al.*, 1987).

There were no effects on food consumption or bodyweight gain of rats exposed to 165 ppm for 6 hours each day on days 4 to 20 of gestation (Hass *et al.*, 1995).

Dermal

No information available.

Eye

Eye irritation described as uncomfortable after half an hour, was reported by some employees after occupational exposure to as little as 0.72 ppm NMP vapour (8 hour TWA) for full shifts (Beaulieu and Schmerber, 1991). However, it is not clear how this concentration was derived from the data reported.

Ingestion

No information available.

Carcinogenicity

The carcinogenicity of NMP has not been evaluated by the IARC. Chronic long term exposure (six hours per day, five days per week for two years) to concentrations of 0.04 or 0.4 mg/l (10 or 100 ppm) NMP vapour resulted in no carcinogenic effects in rats (Lee *et al.*, 1987).

Genotoxicity

NMP was reported to induce chromosome loss in *Saccharomyces cerevisiae* (Mayer *et al.*, 1988; Zimmermann *et al.*, 1989) at concentrations between 150 and 230 mM. The cellular target for inducing aneuploidy has not been identified. There was no increase in the induction of other nuclear genetic effects (Mayer *et al.*, 1988). NMP was not mutagenic in the mouse lymphoma L5178Y cell line, *Salmonella typhimurium* (Lee *et al.*, 1987), or in the Ames *Salmonella typhimurium*/microsome assay, in either the presence or absence of metabolic activation (Wells *et al.*, 1988).

Reproductive toxicity

Only one report of the reproductive effects of NMP in humans could be found in the literature. Intrauterine growth retardation and subsequent fetal demise at week 31 of gestation was attributed to dermal exposure to NMP at week 16 of gestation (Solomon *et al.*, 1996). Animal data, although lacking and inconsistent in

dosing regimes and routes of exposure, suggests that maternal exposure to NMP during organogenesis may affect fetal survival and growth, and cause subsequent delays in development. Fetal effects of NMP may be secondary to maternal toxicity (Becci *et al.*, 1982), however, similar effects have been described in the absence of effects on exposed dams (Hass *et al.*, 1994; 1995).

An increase in skeletal abnormalities was attributed to dermal administration of 750 mg/kg/day of NMP to pregnant rats on days 6 to 15 of gestation, inclusive (Becci *et al.*, 1982). In other rat studies, inhalation of up to 165 ppm for 6 hours each day, for treatment periods throughout gestation, did not result in a similar increase in malformations (Lee *et al.*, 1987; Hass *et al.*, 1994; 1995).

The reproductive performance of rats exposed to 116 ppm (6 hours/day 7 days/week until end of mating in males or weaning in females) was not affected. Their offspring also had normal reproductive performance when mated with unexposed adults (Solomon *et al.*, 1995). However, the incidence and numbers of pre-implantation losses in rats increased after inhalation of NMP on days 4-20 post mating (Hass *et al.*, 1995).

In a study of the effects on rats exposed dermally, throughout organogenesis, to 75, 237 and 750 mg/kg/day NMP, fewer live fetuses, increased percentage of resorptions and skeletal abnormalities, and decreased fetal birth weights were reported at the highest dosage. Skeletal abnormalities were attributed to the teratogenicity of NMP. Other effects were indicative of delayed fetal development and considered likely to be secondary to the maternal toxicity observed at 750 mg/kg (evidenced by reduced body weight). Dose dependent brightly coloured urine and dry skin were also observed. No fetal or maternal toxicity was reported at 75 or 237 mg/kg (Becci *et al.*, 1982).

Sporadic lethargy and irregular respiration on the first three days were the only effects observed in rats exposed to 0.1-0.36 mg/l (25-89 ppm) for 6 hours each day from days 6-15 of gestation. There was no effect on fetal survival, growth or development (Lee *et al.*, 1987).

Brightly coloured urine, but no maternal toxicity was exhibited in female rats exposed to 150 ppm NMP for 6 hours daily from day 7 until day 20 of gestation. While significantly reduced bodyweights at birth and pre-weaning were observed in their offspring compared with controls, there was no decrease in viability. The weight reduction was recovered by five weeks *post partum*. Delays in achieving behavioural development milestones were attributed generally to delayed physical development (Hass *et al.*, 1994).

Delayed fetal skeletal ossification and a significantly lower mean fetal body weight (4-5% less than controls) after adjustment for litter size were reported in rats exposed to 165 ppm, for 6 hours daily, on days 4 to 20 of gestation, when compared with controls. A significant increase in the incidence of pre-implantation loss (20 dams compared with 11 in controls) and an increase in pre-implantation losses were also observed in treated dams (20.5% compared with 13.4% in controls). These effects occurred in the absence of maternal toxicity (Hass *et al.*, 1995).

In a two generation reproductive and developmental inhalation study, the reproductive performance of exposed rats did not differ significantly from controls. Slight decreases in fetal weights were recorded when both parental rats were exposed to 116 ppm NMP. This reduction in body weight was reflected at birth in offspring (particularly in females), and it persisted until 21 days *post partum* when maternal exposure ceased and the pups were weaned. Thereafter the body weights were comparable to controls. The reproductive performance of the offspring was not affected (Solomon *et al.*, 1995).

RISK GROUPS

None identified.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Symptomatic and supportive care.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Symptomatic and supportive care.

Antidotes

There is no specific antidote for NMP.

Chronic exposure

Symptomatic and supportive care.

REFERENCES

Åkesson B, Jönsson BAG. 1997 Major metabolic pathway for *N*-methyl-2-pyrrolidone in humans. *Drug Metab Dispos* 25 (2):267-269.

Åkesson B, Jönsson BAG. 2000 Biological monitoring of *N*-methyl-2-pyrrolidone using 5-hydroxy-*N*-methyl-2-pyrrolidone in plasma and urine as the biomarker. *Scand J Work Environ Health* 26 (3):213-218.

Åkesson B, Paulsson K. 1997 Experimental exposure of male volunteers to *N*-methyl-2-pyrrolidone (NMP): acute effects and pharmacokinetics of NMP in plasma and urine. *Occup Environ Med* 54:236-240.

Akhter SA, Barry BW. 1985 Absorption through human skin of ibuprofen and flurbiprofen; effect of dose variation, deposited drug films, occlusion and the penetration enhancer *N*-methyl-2-pyrrolidone. *J Pharm Pharmacol* 37:27-37.

Barry BW, Bennett SL. 1987 Effects of penetration enhancers on the permeation of mannitol, hydrocortisone and progesterone through human skin. *J Pharm Pharmacol* 39:535-546.

Beaulieu HJ, Schmerber KR. 1991 M-Pyrol™ (NMP) use in the microelectronics industry. *Appl Occup Environ Hyg* 6 (10):874-880.

Becci PJ, Knickerbocker MJ, Reagan EL, Parent RA, Burnette LW. 1982 Teratogenicity study of *N*-methylpyrrolidone after dermal application to Sprague-Dawley rats. *Fundam Appl Toxicol* 2:73-76.

Briggs GG, Freeman RK, Yaffe SJ. 1994 *A Reference Guide To Fetal And Neonatal Risk. Drugs In Pregnancy And Lactation,* fourth edition. Williams and Wilkins, Baltimore, Maryland.

Hass U, Jakobsen BM, Lund SP. 1995 Developmental toxicity of inhaled *N*-methylpyrrolidone in the rat. *Pharmacol Toxicol* 76:406-409.

Hass U, Lund SP, Elsner J. 1994 Effects of prenatal exposure to *N*-methylpyrrolidone on postnatal development and behaviour in rats. *Neurotoxicol Teratol* 16 (3):241-249.

Horning MG, Stratton C, Nowlin J, Harvey DJ, Hill RM. 1973 Metabolism of 2-ethyl-2-methylsuccinimide (ethosuximide) in the rat and human. *Drug Metab Dispos* 1 (3):569-576.

Jönsson BAG, Åkesson B. 1997a Determination of 5-hydroxy-*N*-methylpyrrolidone and 2-hydroxy-*N*-methylsuccinimide in human urine. *J Chromatogr B* 694:351-357.

Jönsson BAG, Åkesson B. 1997b Determination of *N*-methylsuccinimide and 2-hydroxy-*N*-methylsuccinimide in human urine and plasma. *J Chromatogr B* 704:151-158.

Kuhnz W, Koch S, Jakob S, Hartmann A, Helge H, Nau H. 1984 Ethosuximide in epileptic women during pregnancy and lactation period. Placental transfer, serum concentrations in nursed infants and clinical status. *Br J Clin Pharmacol* 18:671-677.

Lee KP, Chromey NC, Culik R, Barnes JR, Schneider PW. 1987 Toxicity of *N*-methyl-2-pyrrolidone (NMP): Teratogenic, subchronic, and two-year inhalation studies. *Fundam Appl Toxicol* 9:222-235.

Leira HL, Tiltnes A, Svendsen K, Vetlesen L. 1992 Irritant cutaneous reactions to *N*-methyl-2-pyrrolidone (NMP). *Contact Dermatitis* 27:148-150.

Mallow DW, Herrick MK, Gathman G. 1980 Fetal exposure to anticonvulsant drugs. *Arch Pathol Lab Med* 104:215-218.

Mayer VW, Goin CJ, Taylor-Mayer RE. 1988 Aneuploidy induction in *Saccharomyces cerevisiae* by two solvent compounds, 1-methyl-2-pyrrolidinone and 2-pyrrolidinone. *Environ Mol Mutagen* 11 (1):31-40.

Midgely I, Hood AJ, Chasseaud LF, Brindley CJ, Baugham S, Allan G. 1992 Percutaneous absorption of co-administered *N*-methyl-2-[^{14}C]pyrrolidinone and 2-[^{14}C]pyrrolidinone in the rat. *Fd Chem Toxicol* 30 (1):57-64.

Solomon GM, Morse EP, Garbo MJ, Milton DK. 1996 Stillbirth after occupational exposure to *N*-methyl-2-pyrrolidone. *J Occup Environ Med* 38 (7):705-713.

Solomon HM, Burgess BA, Kennedy GL Jr, Staples RE. 1995 1-Methyl-2-pyrrolidone (NMP): reproductive and developmental toxicity study by inhalation in the rat. *Drug Chem Toxicol* 18 (4):271-293.

Ursin C, Hansen CM, Van Dyk JW, Jensen PO, Christensen IJ, Ebbehoej J. 1995 Permeability of commercial solvents through living human skin. *Am Ind Hyg Assoc J* 56:651-660.

Wells DA, Digenis GA. 1988 Disposition and metabolism of double-labeled [^{3}H and ^{14}C] *N*-methyl-2-pyrrolidinone in the rat. *Drug Metab Dispos* 16 (2):243-249.

Wells DA, Hawi AA, Digenis GA. 1992 Isolation and identification of the major urinary metabolite of *N*-methylpyrrolidinone in the rat. *Drug Metab Dispos* 20 (1):124-126

Wells DA, Thomas HF, Digenis GA. 1988 Mutagenicity and cytotoxicity of *N*-methyl-2-pyrrolidinone and 4-(methylamino)butanoic acid in the Salmonella/microsome assay. *J Appl Toxicol* 8 (2):135-139.

Zellers ET, Sulewski R. 1993 Modeling the temperature dependence of *N*-methylpyrrolidone permeation through butyl- and natural-rubber gloves. *Am Ind Hyg Assoc J* 54 (9):465-479.

Zimmermann FK, Scheel I, Resnick MA. 1989 Induction of chromosome loss by mixtures of organic solvents including neurotoxins. *Mutat Res* 224:287-303.

20 Tetrachloroethylene

Nicola Bates

SUMMARY

- Tetrachloroethylene is irritant and causes CNS depression
- Renal and hepatic toxicity may occur but are relatively rare and usually only result from exposure to high concentrations
- The metabolism of tetrachloroethylene is minimal and it is slowly excreted
- The metabolites are probably responsible for the toxic effects
- Tetrachloroethylene is denser than air and dangerous concentrations may occur in confined spaces
- Tetrachloroethylene is probably carcinogenic in humans
- The mechanisms of carcinogenicity in experimental animals are probably not relevant to humans
- Tetrachloroethylene is not mutagenic
- Tetrachloroethylene may be a reproductive hazard but human data are lacking

DESCRIPTION

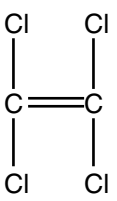
Synonyms

Carbon bichloride, carbon dichloride, ethylene tetrachloride, perchloroethylene, PCE, perc, tetrachloride ethylene, 1,1,2,2- tetrachloroethylene, tetrachloroethene

Identification numbers

CAS	127-18-4
UN	1897
RTECS	KX3850000
EINECS	2048259

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	C_2Cl_4
molecular formula	

molecular mass	165.82
physical form	colourless liquid with an ethereal odour
relative vapour density (air=1)	5.8
flash point (closed cup °C)	none
boiling point (°C)	121
autoignition temperature (°C)	No data available
refractive index	1.5055
explosive limits	none

Odour threshold

27 ppm (Amoore and Hautala, 1983); 50 ppm (Gold, 1969); 4.6-69 ppm (Ruth, 1986).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK): 50 ppm (345 mg/m^3)
TWA (ACGIH): 25 ppm (170 mg/m^3)

Conversion factors

1 ppm = 6.78 mg/m^3
1 mg/m^3 = 0.147 ppm
1 mg/l = 147 ppm

Biomonitoring

The ACGIH recommends several biological exposure indices to monitor exposure to tetrachloroethylene (see **Table 20.1**). The majority of absorbed tetrachloroethylene is excreted unchanged through the lungs and only a small percentage is metabolised.

Table 20.1 Biological exposure indices for tetrachloroethylene (ACGIH, 2000)

Determinant	Sampling time	BEI
tetrachloroethylene in end-exhaled air	prior to last shift of work week	5 ppm
tetrachloroethylene in blood	prior to last shift of work week	0.5 mg/l
trichloroacetic acid in urine	end of shift at end of work week	3.5 mg/l

TOXICITY

Tetrachloroethylene is a chlorinated aliphatic hydrocarbon. It is a synthetic chemical with no natural sources, but because of its widespread use as a degreaser and dry cleaning chemical it is ubiquitous in air and water (Anon, 1988). The main effect of tetrachloroethylene is CNS depression and, once a victim is unconscious and lying on the floor, they continue to inhale high concentrations of this solvent because it is 5.8 times heavier than air.

Much of the information on occupational exposure to tetrachloroethylene relates to exposure in the dry cleaning industry. There are numerous studies on the effects of chronic exposure in dry cleaners and cases of chronic (Gold, 1969; Bennett, 1984) and acute exposure (Meckler and Phelps, 1966; Patel *et al*., 1973; 1977) including fatalities (Lukaszewki, 1979; Levine *et al.,* 1981; Dehon *et al*., 2000). There are also cases of poisoning following the use of tetrachloroethylene as an industrial degreaser (Stewart, 1969; Chmielewski *et al*., 1976), and in the chemical industry (McMullen, 1976; Nakatsuka *et al.,* 1992). In 44 cases of tetrachloroethylene poisoning reported to a Factory Inspectorate in the UK between 1961 and 1980, 3 were fatal. Of the total cases, 26 involved the use of tetrachloroethylene in dry cleaning and all occurred in association with either faulty equipment or during maintenance work (McCarthy and Jones, 1983).

A fatal case of tetrachloroethylene abuse has been reported (Isenschmid *et al*., 1998). Death occurred in a two year old child exposed to tetrachloroethylene. He was found dead 90 minutes after having been put to bed for an afternoon sleep in a room in which improperly dried curtains had been hung after dry cleaning (Gaillard *et al*., 1995; Garnier *et al*., 1996). Other, milder, cases of poisoning have been reported from exposure to tetrachloroethylene in dry cleaned material including clothes, sleeping bags, carpets, soft toys and pillows. In most cases the incident involved overloading of dry cleaning machines, with subsequent retention of high concentrations of tetrachloroethylene in the material (Garnier *et al*., 1995). Acute ingestion may cause poisoning (Köppel *et al*., 1985). Accidental poisoning has also been described in a patient requiring ventilation, where the compressed air lines in the hospital system were contaminated with tetrachloroethylene (Lackore and Perkins, 1970).

Absorption

Tetrachloroethylene can be absorbed through the lungs and gastrointestinal tract, and to a lesser extent through the skin. Inhalation is the main route of exposure in the occupational setting. The pulmonary uptake of tetrachloroethylene is approximately 60% (Monster *et al*., 1979; Imbriani *et al*., 1988). The initial uptake of tetrachloroethylene is rapid but then declines as blood and body tissues become saturated (Fernandez *et al*., 1976; Monster *et al.,* 1979). The concentration of tetrachloroethylene in alveolar air samples correlates with the exposure concentration (Lauwerys *et al*., 1983; Aggazzotti *et al*., 1994; Altmann *et al*., 1995). Exercise increases the uptake of tetrachloroethylene (Monster, 1979; Monster *et al.,* 1979; Hake and Stewart, 1977; Stewart *et al*., 1977; Imbriani e*t al*., 1988). A period of 30 minutes of moderate exercise during exposure to 100 ppm increased the blood concentration approximately four-fold over the expected concentration (Hake and Stewart, 1977).

Dermal absorption of tetrachloroethylene is less than that of other chlorinated aliphatic hydrocarbons and is unlikely to be a hazard under normal working conditions (Stewart and Dodd, 1964). The mean peak breath concentration of tetrachloroethylene after immersion of a subject's thumb in tetrachloroethylene for 40 minutes was 0.31 ppm, and 0.23 ppm 2 hours later (Stewart and Dodd, 1964).

The blood concentration of tetrachloroethylene approximately one hour after ingestion of 545-727 mg/kg (total 8-10 ml) in a 6 year old child was 22 mg/l (Köppel *et al.,* 1985).

Distribution

Tetrachloroethylene is highly lipophilic, and tissues with a high lipid content act as reservoirs; therefore the higher the lipid content the more tetrachloroethylene the tissue will retain. Using a mathematical model of a simulated eight hour exposure test, it was calculated that at the end of exposure half the tetrachloroethylene taken up is distributed to the tissues (Guberan and Fernandez, 1974). Individuals with a higher percentage of body fat can usually carry a higher body burden before clinical features of toxicity manifest (Feldman, 1999). The fat to blood ratio for tetrachloroethylene is 90:1 (Monster, 1979).

Tissue concentrations of tetrachloroethylene reported in fatal cases are given in **Table 20.2.** Tetrachloroethylene concentrations are usually highest in the brain and liver.

Table 20.2 Tetrachloroethylene tissue concentrations in fatal cases of poisoning

Circumstance	Blood (mg/l)	Brain (mg/kg)	Kidney (mg/kg)	Liver (mg/kg)	Lung (mg/kg)	Urine (mg/kg)	Reference
Occupational accident	44	360	na	na	3	negative	Lukaszewski, 1979
Occupational accident	4.5	69	71	240	30	na	Levine *et al.*, 1981
2 year-old child sleeping in a room with improperly dried curtains after cleaning	66	79	na	na	46	0.3 1.7 TCE 0.9 TCA	Gaillard *et al.*, 1995; Garnier *et al.*, 1996
Intentional abuse	62	na	na	341	47	na	Isenschmid *et al.*, 1998

na = not analysed, TCE = trichloroethanol, TCA trichloroacetic acid

Metabolism

In humans less than 3% of absorbed tetrachloroethylene is metabolised (Ogata et al., 1971; Fernandez *et al.,* 1976; Monster, 1979; Monster *et al.*, 1979). Tetrachloroethylene undergoes mainly oxidative metabolism, but when this becomes saturated, reductive metabolism occurs. Saturation of tetrachloroethylene metabolism has been demonstrated in experimental animals (Ikeda *et al.*, 1972; Pegg *et al.*, 1979; Schumann *et al.*, 1980; Buben and O'Flaherty, 1985) and humans (Fernandez *et al.*, 1976; Monster *et al.,* 1979).

Tetrachloroethylene is oxidised by cytochrome P450 enzymes to the epoxide (tetrachlorooxiram), which spontaneously rearranges to trichloroacetyl chloride (Bonse et al., 1975; Pegg *et al.*, 1979). This is then hydrolysed to trichloroacetic acid which is excreted in the urine (Yllner, 1961; Daniel, 1963). This can be detected days after exposure (Daniel, 1963; Ikeda, 1977; Monster *et al.*, 1979).

In experimental animals, dichloroacetic acid (Yllner, 1961; Dekant *et al.,* 1986), oxalic acid (Yllner, 1961; Daniel, 1963; Pegg *et al.*, 1979; Dekant *et al.,* 1986), oxalylaminoethanol (Dekant *et al.,* 1986) and tetrachloroacetylaminoethanol (Dekant *et al.,* 1986) have also been detected in urine. The latter is formed from trichloroacetyl chloride and its reaction with phosphatidylaminoethanol, whereas oxalylaminoethanol derives from the intermediate dichlorooxalic acid (BUA, 1996). Animals treated with radiolabelled tetrachloroethylene have been found to excrete a small quantity of radioactivity in the faeces (Yllner, 1961; Schumann *et al.*, 1980).

Information on the presence of the metabolite 2,2,2-trichloroethanol is conflicting. It has been detected in humans (Ikeda *et al.*, 1972; Ikeda, 1977; Monster *et al.,* 1983; Gaillard *et al.*, 1995; Birner *et al.,* 1996; Garnier *et al.*, 1996) exposed to tetrachloroethylene but may be due to contamination with trichloroethylene (Skender *et al.*, 1991).

Once the oxidative cytochrome P450 metabolic pathway is saturated, tetrachloroethylene is metabolised via reductive pathways resulting in 1,2,2-trichlorovinylcysteine and 1,2,2-trichlorovinyl-*N*-acetylcysteine. The former is formed by binding of tetrachloroethylene to glutathione which is transformed through *N*-acetylation to 1,2,2-trichlorovinyl-*N*-acetylcysteine. Since this is the stable metabolite, it is excreted in the urine (BUA, 1996) and has been detected in animals (Dekant *et al.,* 1986) and humans (Birner *et al.,* 1996) exposed to tetrachloroethylene. This pathway of glutathione conjugation is less efficient in humans compared to rodents (Birner *et al.,* 1996).

Elimination

Approximately 80-100% of absorbed tetrachloroethylene is excreted unchanged by the lungs (Monster *et al.,* 1979). Elimination is slow. In a volunteer study more than two weeks was required to eliminate tetrachloroethylene after 8 hours of exposure to 100 ppm (Fernandez *et al.,* 1976). The respiratory and urinary half-lives of tetrachloroethylene are 65 hours and 144 hours, respectively (Ikeda, 1977). The urinary concentration of tetrachloroethylene correlates with the exposure concentration (Imbriani e*t al*., 1988). Tetrachloroethylene can be detected in breath days after cessation of exposure (Stewart *et al.,* 1961a; 1961b; Stewart *et al.,* 1970).

Elimination of tetrachloroethylene from the blood after ingestion of 545-727 mg/kg (total 8-10 ml) in a 6 year old child was biphasic, with half-lives of 30 minutes and 36 hours during hyperventilation therapy. This treatment reduced the rapid elimination phase from 160 to 30 minutes but the slow phase was unchanged (Köppel *et al.,* 1985).

Only about 1% of absorbed tetrachloroethylene is excreted as trichloroacetic acid in the urine. The half-life of this metabolite in urine and blood is 65-90 hours (Monster *et al*., 1979; Monster *et al.,* 1983). In the work by Ikeda (1977) the half-life of the total trichloro compound metabolites was 123 hours in six male (30-100 ppm, 8 hours/day, 5 days/week) and 190 hours in six female workers (10-20 ppm, 8 hours/day, 5 days/week). Although this extreme difference was questioned, it probably reflects the larger proportion of body fat in females. The urinary concentration of total trichloro compounds does not reflect the exposure concentration (Ikeda *et al*., 1972). A plateaux metabolite concentration is reached at tetrachloroethylene concentrations well below 100 ppm (Ikeda *et al.,* 1972; Ikeda, 1977).

Tetrachloroethylene is excreted in breast milk. A mother who was exposed to tetrachloroethylene during lunchtime visits to her husband at work, had a blood tetrachloroethylene concentration of 3 mg/l about 2 hours later. The concentration of tetrachloroethylene in breast milk about 1 hour after a visit was 10 mg/l; 24 hours later it was 3 mg/l. No metabolites were detected in the mother's urine (Bagnell and Ellenberger, 1977). Preferential uptake of lipophilic compounds such as tetrachloroethylene into breast milk occurs because it is high in fat.

There is accumulation of tetrachloroethylene in fatty tissues with prolonged exposure because of slow elimination. In subjects exposed to 100 ppm for 7 hours on 5 consecutive days, those with a greater body mass had higher alveolar concentrations of tetrachloroethylene in the post exposure period. The difference was more pronounced at 300 hours than 100 hours after exposure (Stewart *et al.,* 1970). In a study of workers exposed to tetrachloroethylene the decrease in blood and breath concentrations over a weekend of non-exposure was more pronounced in slim subjects than in those who were obese (Monster *et al.,* 1983). The cumulative behaviour of tetrachloroethylene has been confirmed with mathematical modelling (Guberan and Fernandez, 1974).

In experimental animals, elimination of tetrachloroethylene is primarily thorough the lungs (Daniel, 1963). In some cases a greater proportion of absorbed tetrachloroethylene is metabolised compared to humans (Yllner, 1961; Pegg *et al*., 1979; Schumann *et al*., 1980). This is probably a dose dependent effect.

Mode of action

The toxicity of tetrachloroethylene is due to biologically active metabolites rather than the parent compound itself. Covalent binding to hepatic macromolecules by reactive metabolites has been demonstrated *in vivo* (Pegg *et al*., 1979; Schumann *et al*., 1980) and *in vitro* (Bonse *et al*., 1975). However, binding to hepatic DNA has not been observed (Schumann *et al*., 1980).

Liver carcinogenicity observed in B6C3F1 mice may be due to repeated cytotoxicity and exacerbation of the high incidence of liver tumours in this strain (Schumann *et al*., 1980), or due to trichloroacetic acid-induced hepatic peroxisome proliferation (Odum *et al*., 1988). Both of these hypotheses involve a non-genotoxic mechanism for carcinogenicity. Trichloroacetic acid has been shown to cause hepatocellular carcinoma in male B6C3F1 mice when administered in their drinking water (Herren-Freund *et al*., 1987). Trichloroacetic acid does not induce peroxisome proliferation in human hepatocytes (Elcombe, 1985) and primates do not

respond to peroxisome proliferation to the same extent as rodents (Cohen and Grasso, 1981). As the metabolites are the cause of the toxic effects of tetrachloroethylene, the greater the metabolism the greater the risk of toxicity. This was demonstrated in a study comparing B6C3F1 mice and Sprague-Dawley rats. The mice metabolised more tetrachloroethylene and produced a greater quantity of active metabolites. This resulted in a greater degree of liver damage when compared to the rats (Schumann *et al.*, 1980).

The mechanism by which tetrachloroethylene induces renal injury is unknown. The metabolite 1,2,2,-trichlorovinylcysteine can be cleaved by renal β-lyase and the products, pyruvate and ammonia, indicate that trichlorovinylthiol is produced as a third cleavage product. This compound is unstable and can react (through hydrogen chloride elimination) to form dichlorothioketene or (through molecular rearrangement) dichloroethylthionyl chloride. Both these compounds are reactive species which can cause DNA damage and renal toxicity (BUA, 1996). This pathway of glutathione conjugation is less efficient in humans compared to rodents and this would suggest that humans are at less risk of renal toxicity (Birner *et al.,* 1996). However, low concentrations of 1,2,2-trichlorovinyl-*N*-acetylcysteine could indicate more efficient metabolism through the β-lyase pathway, which would mean that humans were at greater risk of renal toxicity. However, the activity of this enzyme in humans is much less than that in rats (Green *et al.*, 1990) and this would not support the latter hypothesis (Birner *et al.,* 1996). Renal toxicity of tetrachloroethylene may involve the formation of free radicals (Salahudeen, 1998). Depletion of glutathione (a free radical scavenger) may make cells more susceptible to free radical damage. Also, the pathway for the epoxide metabolite may involve nucleophilic attack, and reactive oxygen metabolites may also result from peroxidase proliferation.

Renal toxicity may be rare in humans because the metabolism of tetrachloroethylene may become saturated (Ikeda *et al.*, 1972; Ikeda, 1977). As a result the kidney concentration of reactive metabolites may remain low (Solet and Robins, 1991).

The metabolites of tetrachloroethylene, like other chlorinated hydrocarbons, may interact with the tubero-infundibular dopaminergic system forming tetrahydroisoquinolones resulting in dopamine depletion (Mutti and Franchini, 1987). This may manifest as changes in neuroendocrine function and be the cause of the behavioural changes (Mutti and Franchini, 1987) and reproductive effects reported with tetrachloroethylene (Ferroni *et al.*, 1992). 2,2,2-Trichloroethanol, a possible metabolite of tetrachloroethylene, has been shown to potentiate the GABA-activated current in CNS neurones *in vitro* and this may contribute to the depressant effect of this solvent (Peoples and Weight, 1994).

Metabolic interactions

- **Chlorinated aliphatic hydrocarbons**

  In vivo and *in vitro* studies demonstrated that combinations of tetrachloroethylene with trichloroethylene or 1,1,1-trichloroethane or both, were more toxic than the individual chemicals alone. Measures of effects were parameters of cell integrity (leak of potassium, lactate dehydrogenase and alanine aminotransferase in hepatocytes) for the *in vitro* tests and measures of hepatic and renal function (liver weight, alanine aminotransferase, sorbital dehydrogenase and urea) in rats. The effect of the three solvents together was greater than mixtures of two. This study did not investigate the mechanism of interaction (Stacey, 1989).

- **Diazepam**

  In a volunteer study, diazepam blood concentrations of 70-300 μg/l had no effect on tetrachloroethylene blood or breath concentrations during exposure to 100 ppm. There were no interactive effects of diazepam and tetrachloroethylene on neurobehavioural or neurophysiological tests (Hake and Stewart, 1977). In another study, exposure to tetrachloroethylene (25 ppm or 100 ppm) and diazepam 6 mg/day or 10 mg/day did not affect the tetrachloroethylene blood concentration. Performance in behavioural tests was unaffected by simultaneous exposure and it was concluded that low doses of diazepam in tetrachloroethylene-exposed workers did not pose a hazard (Stewart *et al.,* 1977).

- **Enzyme inducers**

  Enzyme induction increases tetrachloroethylene metabolism. Pretreatment with pentobarbital or Aroclor 1254, both inducers of the hepatic mixed function oxidase system, resulted in a five- and seven-fold increase in tetrachloroethylene metabolism, respectively. Hepatic injury also occurred in the Aroclor 1254-treated animals, probably due to tetrachloroethylene metabolites (Moslen *et al*., 1977).

- **Ethanol**

  In a volunteer study, ethanol blood concentrations of 0.3-1 g/l had no effect on tetrachloroethylene blood or breath concentrations during exposure to 100 ppm. There were no interactive effects of ethanol and tetrachloroethylene on neurobehavioural or neurophysiological tests (Hake and Stewart, 1977). However, in another study, co-exposure to tetrachloroethylene (25 ppm) and ethanol doses of 0.75 and 1.5 ml of 100°-proof vodka/kg body weight (to achieve blood concentrations of 400 and 800 mg/l) significantly increased blood tetrachloroethylene concentrations. In contrast, blood tetrachloroethylene levels were not increased at 100 ppm as there was already saturation of tetrachloroethylene metabolism at this dose. Performance in behavioural tests was unaffected by simultaneous exposure and it was concluded that low doses of ethanol in tetrachloroethylene exposed workers did not pose a hazard (Stewart *et al.,* 1977). Animal studies have shown that ethanol does not potentiate the liver toxicity of tetrachloroethylene (Cornish and Adefuin, 1966; Klassen *et al*., 1966).

CASE REPORTS

Chronic inhalation with acute over-exposure

A 47 year old woman was admitted to hospital with a history of heavy exposure to tetrachloroethylene two weeks previously, when the equipment at the dry cleaning establishment where she had worked for 2.5 months was cleaned. No measurement of air concentrations of tetrachloroethylene was available. She worked for 10 hours that day in the room where the solvent was being used and complained of dizziness, headache and malaise. These had resolved and she complained of only mild weakness and inappetance. Two days prior to admission she had acholic stools, scleral icterus, nausea, vomiting and generalised pruritus. On examination, vital signs and ECG were normal and there was diffuse icteric discoloration of the skin with a palpable liver. There was also a large mass in the right upper quadrant, thought to be an enlarged gall bladder. Liver function tests were markedly elevated. The mass in the right upper quadrant decreased over the next week and the liver enzymes returned to normal over the following two months. A liver biopsy two weeks after admission showed degeneration of parenchymal cells in the central part of lobules, with exaggeration of the sinusoids and focal infiltration of mononuclear cells. Six months later the liver was still enlarged but there was no evidence of jaundice (Meckler and Phelps, 1966).

Accidental acute inhalation

A 25 year old male was overcome by tetrachloroethylene fumes while using it to clean a tank. He wore a general purpose chemical mask and scrubbed the walls with tetrachloroethylene from an open five-gallon bucket. After five minutes the odour became so strong that he left the tank. He removed the mask suspecting it was faulty. He then re-entered the tank but quickly left and put the mask back on to resume work. He was found approximately 10 minutes later unconscious inside the tank. About 30 minutes after he had been removed he was drowsy but well orientated. Vital signs were normal. Neurological examination was also normal except for the Romberg test (swaying of the body when the feet are placed together and the eyes closed). The breath concentration of tetrachloroethylene 90 minutes after cessation of exposure was 105 ppm. This had fallen to less than 5 ppm by 48 hours. LFTs, urinalysis, haematology and a chest X-ray were all normal. He remained drowsy for the rest of the day with fatigue for the next 4 days. There was a mild, transient increase in AST on the 3rd and 4th day and elevation of the urinary urobilinogen on the 9th day (Stewart, 1969).

CLINICAL EFFECTS

Acute exposure

Inhalation

Acute exposure to tetrachloroethylene may cause nausea, vomiting, drowsiness, dizziness, headache, tinnitus and coma (McCarthy and Jones, 1983; Garnier *et al.*, 1996). Respiratory effects (cough, breathlessness and chest tightness) may occur and cyanosis, dyspnoea and pulmonary oedema have been reported (Patel *et al.*, 1973; Patel *et al.*, 1977). Convulsions have been reported occasionally (Hake and Stewart, 1977; Algren and Rogers, 1992). There are a number of volunteer studies on the acute effects of exposure to tetrachloroethylene. The results are listed in **Table 20.3**. Exposure to 50 ppm caused no adverse effects although the odour of tetrachloroethylene was detectable (Carpenter, 1937).

Table 20.3 Dose-response effects of acute exposure to tetrachloroethylene

Concentration (ppm)	Duration	Clinical effects	Reference
75-80	after 1-4 minutes	mild irritation of eyes with burning	Stewart *et al.*, 1961b
100	7 hours	headache, mucosal irritation, nausea, drowsiness, gastro-intestinal complaints, dizziness, abnormal Romberg test	Stewart *et al.,* 1970
100-120	after 4-6 minutes	oral mucosal irritation and dryness	Stewart *et al.*, 1961b
106	1 hour	eye irritation	Rowe *et al.*, 1952
210	after 30 minutes	lightheadedness and CNS depression	Stewart *et al.*, 1961b
280	45-120 minutes	eye irritation, dizziness, tiredness	Rowe *et al.*, 1952
280	2 hours	burning of eyes, lacrimation, nausea, CNS depression	Rowe *et al.*, 1952
500	130 minutes	salivation, nausea, increased perspiration of the hands and mild irritation of eyes and nose	Carpenter, 1937
600	10 minutes	dizziness, irritation of eyes and nasal mucosa	Rowe *et al.*, 1952
1,000	95 minutes	lassitude, mental fogginess, stinging eyes, nasal irritation, increased perspiration of the hands and exhilaration	Carpenter, 1937
1,000	1-2 minutes	irritation of eyes and respiratory tract, dizziness	Rowe *et al.*, 1952
1,500	not specified	mild inebriation followed by dizziness, faintness, mental sluggishness and dyspnoea on exertion	Carpenter, 1937
2,000	7.5 minutes	intolerable; nausea, weakness and dizziness followed by nausea, tinnitus and dizziness; dyspnoea on exertion	Carpenter, 1937
5,000	6 minutes	intolerable; nausea, dizziness, salivation, eye irritation, mental sluggishness	Carpenter, 1937

Volunteers exposed to tetrachloroethylene (50 ppm for 4 hours on 4 consecutive days) had significant performance deficits for vigilance and eye-hand co-ordination compared to controls (10 ppm for same time period). There was also an increase in latencies of visual evoked potentials (Altmann *et al*., 1992).

Liver toxicity following acute exposure to tetrachloroethylene is rare and is usually minimal and transient (Stewart *et al.,* 1961a; Saland, 1967; Stewart, 1969; Hake and Stewart, 1977; McCarthy and Jones, 1983). Renal toxicity may occur from acute exposure, particularly with high doses. Mild haematuria and albuminuria have been reported following a brief inhalation exposure to tetrachloroethylene (Saland, 1967). In another case a patient had proteinuria for 20 days and haematuria for eight days after lying unconscious in a pool of tetrachloroethylene for approximately 12 hours (Hake and Stewart, 1977).

Cardiotoxicity is a potential risk following acute exposure, because tetrachloroethylene may sensitise the heart to endogenous catecholamines. Cardiotoxicity (unspecified) was observed in dogs given epinephrine to sensitise the heart while inhaling tetrachloroethylene (Johnson and Shanor, 1968).

Dermal

A burning sensation may occur following direct skin contact for 5-10 minutes (Stewart and Dodd, 1964). Marked erythema occurred after experimental immersion of a thumb for 40 minutes; it resolved over 1-2 hours (Stewart and Dodd, 1964). Blisters and burns may occur from prolonged contact with the liquid, for example when lying unconscious in a pool of tetrachloroethylene or in soaked clothing (Morgan, 1969; Ling and Lindsay, 1971; Hake and Stewart, 1977).

Eye

Vapour concentrations of 500-600 ppm are irritating to eyes; at 1,000 ppm the vapour is painful. Serious injury from exposure to tetrachloroethylene vapour was not reported in these volunteer studies (Carpenter, 1937; Rowe *et al*., 1952).

Ingestion

Tetrachloroethylene was used, particularly in the 1920s and 1930s as an anthelmintic for animals and humans. It was used for the treatment of hookworms (*Ancylostoma* and *Necator*) and given as a liquid or in capsules. The usual dose was 1-5 ml (1.6-8 g) as a single dose, repeated after a few days if necessary. Side effects reported from this use included nausea, vomiting, abdominal cramps, diarrhoea, headache and dizziness (Berberian, 1966; Blacow and Wade, 1972). Tetrachloroethylene is no longer used for this purpose and has been replaced by less toxic substances.

Ingestion of 8-10 ml (12-16 g) of tetrachloroethylene caused coma within an hour in a 6 year old (22 kg) child. There was no evidence of hepatic or renal toxicity (Köppel *et al.,* 1985). Aspiration following ingestion of a tetrachloroethylene dry cleaning product has been reported (Algren and Rogers, 1992).

Haemolysis occurred in a 13 month old child after ingestion of an unknown quantity of a dry cleaning product containing tetrachloroethylene. However, this child had sickle cell trait (Algren and Rogers, 1992).

Chronic exposure

Inhalation

Neurological effects

Common neurological effects reported with chronic exposure to tetrachloroethylene are dizziness, drowsiness, headache and fatigue. Other effects include ataxia, confusion, disorientation, irritability, difficulty with concentration and memory, agitation, restlessness and a feeling of intoxication (Coler and Rossmiller, 1953; Gold, 1969; Chmielewski *et al.,* 1976; Cai *et al*., 1991). Tolerance to the subjective effects (e.g., mucous

membrane irritation, headache, odour) of tetrachloroethylene has been demonstrated in chronically exposed individuals (Stewart *et al*., 1970).

Chronic tetrachloroethylene exposure affects neurobehavioural performance. A survey of 101 exposed workers found significant differences in neurobehavioural testing compared to controls. There was no difference between workers exposed to high (average 54 ppm) and low (average 12 ppm) concentrations (Seeber, 1989). Another study of exposed workers found prolonged reactions times in all tests compared to controls. Performance did not correlate with air (median 15 ppm, range 1-67 ppm) or blood (median 145 mg/l, range 12-864 mg/l) tetrachloroethylene concentrations or duration of exposure (Ferroni *et al*., 1992).

In a behavioural assessment of four individuals exposed chronically to tetrachloroethylene they consistently complained of fatigue and confusion. They had cognitive deficits on tasks assessing memory, motor, visuospatial and executive function with milder attention deficit. In general, verbal and formal language functions were intact supporting the hypothesis that solvents affect the cerebral frontal lobes (involved in complex organisation, behaviour, attention, executive function and reasoning) and the limbic system (mediating mood and memory). There were no exposure measurements in these subjects. This study also examined 65 tetrachloroethylene-exposed dry cleaning workers who were divided into three exposure groups of 11.2, 23.2 and 40.8 ppm. In these workers there was subclinical impairment of visually-mediated functions including memory (Echeverria *et al*., 1995).

Altmann *et al.* (1995) examined individuals living near dry cleaning establishments with a mean residential time of 10.6 years. The mean blood tetrachloroethylene concentration was 0.018 ± 0.047 mg/l and the median air concentration was 0.2 ppm. The performance of subjects exposed to tetrachloroethylene differed significantly in neurobehavioural tests for vigilance, simple reaction time and visual memory, compared to controls. There were also differences in visual evoked potential latencies, but this was not statistically significant. Although this study is limited by the small number of subjects (only 14) it does suggest that low level tetrachloroethylene exposure may affect CNS function.

Two cases of neuritis have been reported in workers exposed to tetrachloroethylene. One case involved a 48 year old female who worked in a dry cleaners. Her clinical features included nausea, cyanosis, coughing and tremor. A diagnosis of peripheral neuritis was made but no further details were given. In the second case, a man was diagnosed with toxic neuritis of the right facial nerve after experiencing numbness and an inability to close the right eyelid after splashing tetrachloroethylene on the right side of his face, the previous day (NIOSH, 1976). Feldman (1999) also reported several cases of peripheral neuropathy in tetrachloroethylene exposed workers. Some of these individuals also had residual neurological impairment including memory and cognitive deficits.

Hepatic effects

Liver toxicity has been demonstrated in experimental animals treated with tetrachloroethylene (Klassen *et al*., 1966; Klassen *et al*., 1967; Schumann *et al*., 1980; Buben and O'Flaherty, 1985; Odum *et al*., 1988). Several studies have found no evidence of hepatic toxicity in tetrachloroethylene exposed workers (Lauwerys *et al*., 1983; Cai *et al*., 1991; Gennari *et al.,* 1992). However, mild to moderate hepatic parenchymal changes were detected by ultrasonography in tetrachloroethylene exposed dry cleaners (mean time-weighted average of 16 ppm). The incidence was nearly 2-fold higher than in controls, and the changes were underestimated by measured serum hepatic transaminase activity. Although the specific hepatic changes could not be identified in this study, they were suggestive of steatosis (Brodkin *et al*., 1995). In a survey of nine workers exposed to concentrations of 232-385 ppm, three had evidence of hepatic damage and one of these had cirrhosis of the liver (Coler and Rossmiller, 1953)

Renal effects

Evidence for tetrachloroethylene induced renal toxicity in chronically exposed workers is contradictory. Although renal toxicity has been demonstrated in experimental animals exposed to high tetrachloroethylene concentrations (Carpenter, 1937; Klassen *et al*., 1966; Klassen *et al*., 1967; Goldsworthy *et al*., 1988; Green *et al*., 1990), several studies have failed to find evidence of renal damage in tetrachloroethylene exposed

workers (Lauwerys *et al*., 1983; Cai *et al*., 1991; Solet and Robins, 1991). In contrast, Franchini *et al.* (1983) found significantly increased urinary concentrations of lysozyme and urinary β-glucuronidase in tetrachloroethylene exposed workers. The latter may represent a faster cellular turnover in tubular epithelium, whereas high urinary lysozyme concentrations and proteinuria may be markers of more definite lesions in the renal tubules (Franchini *et al.* 1983). Another study also found increased urinary concentrations of lysozyme in tetrachloroethylene exposed workers. However, there were no differences in other markers of renal function (albumin, β2-microglobulin, lactic dehydrogenase, total proteins and glucose) compared to controls (Vyskočil *et al*., 1990). A study of 50 dry cleaners exposed to low concentrations of tetrachloroethylene (median 15 ppm) did find evidence of subclinical renal disturbances compared to controls. There was increased release of laminin fragments, fibronectin and glycosaminoglycans; also increased shedding of epithelial membrane components from tubular cells and high molecular weight proteinuria. These abnormalities suggest diffuse structural and functional changes in the kidney, which may be due to generalised membrane disturbances from the action of the solvent itself or reactive metabolites (Mutti *et al*., 1992).

Haematological effects

Haematotoxicity is not a typical feature of tetrachloroethylene toxicity. A study of 56 dry cleaning workers exposed to an average concentration of 20 ppm tetrachloroethylene (range 3.8-94.4 ppm) found no evidence of haematotoxicity (Cai *et al*., 1991).

A father and son developed polycythaemia after intermittent exposure to a number of solvents including tetrachloroethylene. However, the role of tetrachloroethylene in the aetiology of this condition in these two individuals is unclear (Ratnoff and Gress, 1980).

Cardiac effects

Cardiac effects following tetrachloroethylene exposure are uncommon. The ECG was normal in two groups of workers (9 and 16 individuals, respectively) exposed to 30 ppm of tetrachloroethylene or concentrations 2-15 fold higher (Chmielewski *et al.,* 1976).

Headache, dizziness and ventricular premature beats were reported in a dry cleaning worker exposed to tetrachloroethylene. These effects resolved when in hospital but returned when he went back to work and he had to change his employment (Abedin *et al*., 1980).

Immunotoxicity

In one case, severe acrocyanosis (blue or pale extremities), mild hepatitis and polymyopathy with muscle weakness, wasting and tenderness have been reported after chronic occupational exposure to tetrachloroethylene. There was also oedema and thickening of the skin on the hands with multiple nail haemorrhages. This patient had a history of alopecia areata and vitiligo, and a borderline high immunoglobulin G (IgG), absent IgA and normal IgM. These clinical effects may have been due to an idiosyncratic reaction or an immune-mediated response (Sparrow, 1977).

Other effects

Gastrointestinal effects reported from chronic tetrachloroethylene exposure include vomiting, abdominal pain, diarrhoea and inappetance. There may also be nasal irritation, breathlessness and cough (Chmielewski *et al.,* 1976; Cai *et al*., 1991).

Dermal

Tetrachloroethylene defats skin and repeated dermal exposure may result in rough (Cai *et al*., 1991), cracked (Hake and Stewart, 1977), dry, scaly skin (Gold, 1969). Contact dermatitis has been reported (Redmond and Schappert, 1987).

Eye

Chronic exposure to tetrachloroethylene can cause colour vision loss (dyschromatopsia), although the mechanism is unclear (Cavalleri *et al.,* 1994). In a study of 35 dry cleaners there was a higher proportion of individuals with subclinical visual loss (mainly in the blue-yellow range) compared to controls. The mean tetrachloroethylene concentration was 6.23 ppm (range 0.38-31.19 ppm). When comparing workers involved in dry cleaning with those ironing the clothing it was found that the dry cleaners had significantly higher test scores (high colour confusion) compared to controls. There was no difference in the test scores of those involved in ironing compared to controls. The dry cleaners may be exposed to high peak concentrations during the course of their work and this may not be reflected in the measured air concentrations (Cavalleri *et al.,* 1994). In a follow up study of 33 of these workers 2 years later, the colour vision had deteriorated in 19 workers with increased tetrachloroethylene exposure. There was no apparent change in 14 workers with reduced exposure. It is not clear whether the lack of improvement in this latter group was due to continued exposure or irreversible tetrachloroethylene induced vision loss (Gobba *et al.*, 1998).

In contrast, no cases of blue-yellow colour loss were found in 64 dry cleaner workers exposed to 13 ppm of tetrachloroethylene (Nakatsuka *et al.,* 1992). However, the tests used may not have been as sensitive and there was no mention of the exclusion criteria used in this study (Cavalleri *et al.,* 1994).

Optic atrophy has been attributed to tetrachloroethylene in one case, but no details were given (NIOSH, 1976). Acute, severe, bilateral optic neuritis was reported in a dry cleaner exposed to tetrachloroethylene. She was blind in the left eye for 9 days and 11 days in the right eye. There was also pain on eye movement. Electroretinograms and visual evoked potential measurements were abnormal. The blood tetrachloroethylene concentration 48 hours after onset was 1.08 mg/l. Three weeks after onset she could only see the central 2-3° radius of the visual fields. This was unchanged one year later. Other causes of optic neuritis (e.g., vascular, genetic and retinopathy) were eliminated and it is likely that tetrachloroethylene was the cause. Experimental replication of her work found that the concentration of tetrachloroethylene near a basket of freshly dried clothes was 64 ppm, and 252 ppm in the stream rising from the clothing during ironing (Onofrj *et al.,* 1998).

Ingestion

No information available.

Carcinogenicity

There is limited evidence in humans of tetrachloroethylene carcinogenicity and sufficient evidence in experimental animals. Consequently, tetrachloroethylene is assigned to Group 2A; it is probably carcinogenic in humans (IARC, 1995).

There are many studies on the risk of cancer from tetrachloroethylene exposure. They have shown a possible association of tetrachloroethylene with cancer of the larynx (Vaughan *et al*., 1994), tongue (Vaughan *et al*., 1994; Ruder *et al*., 2001), lung (Blair *et al.,* 1979; Duh and Asal, 1984; Ruder *et al*., 2001), liver (Blair *et al.,* 1979; Lynge and Thygesen, 1990), kidney (Katz and Jowett, 1981; Duh and Asal, 1984; reviewed in McLaughlin and Blot, 1997), urinary tract (Katz and Jowett, 1981; Brown and Kaplan, 1987; Ashengrau *et al*., 1994; Ruder *et al*., 2001), oesophagus (Vaughan *et al*., 1994; Weiss, 1995; Ruder *et al*., 2001), intestine (Ruder *et al*., 2001), lymphatic and haematopoeitic system (Blair *et al*., 1990), including leukaemia (Blair *et al.,* 1979; Ashengrau *et al*., 1994), breast (Ashengrau *et al*., 1998) and cervix (Blair *et al.,* 1979; Ruder *et al*., 2001). Some of these findings (e.g., excess cancers of the lung, larynx, oesophagus and cervix) may be due to confounding factors and represent tobacco and alcohol use and socioeconomic status.

These studies are very variable. Many involved dry cleaners (e.g., Blair *et al.,* 1979; Katz and Jowett, 1981; Duh and Asal, 1984; Brown and Kaplan, 1987; Blair *et al*., 1990; Vaughan *et al*., 1994; Weiss, 1995; Ruder *et al*., 2001), who may be exposed to several solvents but primarily tetrachloroethylene. There are also studies involving tetrachloroethylene exposure though contaminated drinking water (Ashengrau *et al*., 1994), where tetrachloroethylene leached into water from the lining of water pipes. Other studies have looked at aircraft manufacturing workers who are exposed to a number of solvents, (Boice *et al*., 1999) and workers

exposed to chlorinated aliphatic hydrocarbons (Heinemann *et al.*, 1994). In all of these studies individual solvent exposure could not be assessed.

Several studies, mainly by the National Toxicology Program (NTP) and National Cancer Institute (NCI), have demonstrated that tetrachloroethylene is carcinogenic in experimental animals (reviewed in ECETOC, 1990; BUA, 1996). Increased rates of hepatocellular carcinoma have been demonstrated in male and female B6C3F1 mice. Male and female F344 rats had an increased incidence of mononuclear cell leukaemia when treated with tetrachloroethylene, but this strain is known to have a high and variable incidence of this condition and it was probably a strain specific effect. There was no increased incidence of mononuclear cell leukaemia in Osborne-Mendel or Sprague-Dawley rats. Male F344 rats (more than females) have also been shown to develop renal damage when treated with tetrachloroethylene. This damage could represent a preliminary stage of tumourigenesis. All these findings are apparently the result of species-specific effects and are probably not applicable to humans (ECETOC, 1990; BUA, 1996). This is true for both liver (Schumann *et al.*, 1980; Odum *et al.*, 1988) and renal (Green *et al.,* 1990) carcinogenicity.

Genotoxicity

Most mutagenicity tests on tetrachloroethylene have been negative (reviewed in ECETOC, 1990; BUA, 1996; ATSDR, 1997). However, tests have shown that tetrachloroethylene and trichlorovinylglutathione (the gluthathione conjugate of tetrachloroethylene) are mutagenic under conditions of reductive metabolism and only in the presence of a metabolic activating system from the rat kidney including glutathione, glutathione-s-transferase, γ-glutamyl-transpeptidase and β-lyase (Vamvakas *et al.*, 1989). The latter two enzymes occur particularly in the kidney and so tetrachloroethylene may have a mutagenic effect in that organ (BUA, 1996).

A study of dry cleaners exposed to tetrachloroethylene (geometric mean 10 ppm) and chemical workers exposed to tetrachloroethylene (17 ppm) and trichloroethylene (8 ppm), found no increase in the rates of sister chromatid exchanges (SCEs) when comparing exposed smokers with control smokers and exposed non-smokers with control non-smokers. However, in males, comparison of smokers exposed to either tetrachloroethylene or tetrachloroethylene and trichloroethylene with exposed non-smokers did show a significant increase in SCEs. This was postulated to be due to a synergistic effect between smoking and solvent exposure (Seiji *et al.*, 1990).

Reproductive toxicity

Exposure to tetrachloroethylene may pose a reproductive hazard. However, due to study design or the small number of cases, the relationship of impaired fertility or adverse reproductive outcome to tetrachloroethylene exposure cannot be adequately evaluated (van der Gulden and Zielhuis, 1989; BUA, 1996; ATSDR, 1997).

Fertility

Exposure to tetrachloroethylene may have subtle effects on sperm quality but it is not known whether the effects are associated with changes in fertility. In the study by Eskenazi *et al.* (1991a) the average sperm concentration was the same in dry cleaners and controls. The proportion of abnormal forms was also similar, but sperm of dry cleaners were significantly more likely to be round and less likely to be narrow. These effects were related to dose and expired air tetrachloroethylene concentrations. Average sperm motility was similar in both groups, but the sperm of dry cleaners tended to swim with greater amplitude of head displacement. In multiple regression analysis the expired air concentration was a significant predictor of this effect. The sperm linearity swim path was decreased in dry cleaners and this was significantly negatively correlated with exposure concentration (Eskenazi *et al.*, 1991a). Rachootin and Olsen (1983) reported a slightly higher but non-significant risk of abnormal sperm in men exposed to dry cleaning chemicals, compared to infertile men with conditions unlikely to be caused by their occupation.

In a study using various animal species there were slight degenerative changes in the germinal epithelium in the testes of guinea pigs exposed to 1,600 ppm tetrachloroethylene on eight occasions. Testicular changes in the other species were not reported (Rowe *et al.,* 1952).

In a study of female workers exposed to tetrachloroethylene, there was an increased risk of almost all menstrual disorders, but particularly premenstrual syndrome and menorrhagia, compared to controls. However, the study was limited by small size and absence of exposure measurements (Zielhaus *et al.,* 1989). A study of female workers found that during the proliferative phase of the menstrual cycle tetrachloroethylene exposed workers had increased serum prolactin concentrations compared to controls. However, in both groups the values were within the normal range. Increased prolactin levels did not correlate with air (median 15 ppm, ranges 1-67 ppm) or blood (median 145 mg/l, range 12-864 mg/l) tetrachloroethylene concentrations or duration of exposure (Ferroni *et al*., 1992). A Danish investigation of infertile couples and their occupations found an association of increased risk of hormonal disturbances and delayed conception in women working in dry cleaning establishments (Rachootin and Olsen, 1983).

Pregnancy

A number of studies have shown that exposure to tetrachloroethylene is associated with an increase in spontaneous abortions (Hemminki *et al*., 1980; Kyyrönen *et al*., 1989; Olson *et al*., 1990; Windham *et al*., 1991; Lindbohm *et al.,* 1992; Doyle *et al.,* 1997). Other studies have found no association between tetrachloroethylene exposure and increased risk of spontaneous abortion (Bosco *et al.,* 1987; McDonald *et al.,* 1987; Taskinen *et al.,* 1989; Ahlborg, 1990; Eskenazi *et al*., 1991b). However, some of these studies were not specifically designed to measure the association of spontaneous abortion to solvent exposure and the numbers in the other studies were small. The risk of spontaneous abortion may depend on the exposure concentration. Doyle *et al*. (1997) postulate that the results of these studies of tetrachloroethylene exposed workers suggest that exposure to high concentrations may increase the risk of spontaneous abortion, but that there is no risk in workers with lower levels of exposure.

A study in rats exposed to 300 ppm tetrachloroethylene found no evidence of embryotoxicity, fetotoxicity or teratogenicity. In mice there was delayed ossification of skull bones and split sternebrae (Schwetz *et al.,* 1975), which could be interpreted as teratogenic effects. However, evaluation of these findings is difficult because the number of animals used was too small and no indication is given of the number of fetuses affected within each litter (NIOSH, 1976; Barlow and Sullivan, 1982).

Lactation

Using a physiologically based pharmacokinetic (PBPK) model, Fisher *et al*. (1997) determined that when a lactating woman is exposed to the theshold limit value, the concentration of tetrachloroethylene in breast milk will exceed the Environmental Protection Agency (EPA) non-cancer drinking water ingestion rates for children, and may therefore pose a hazard to nursing infants. Tetrachloroethylene excreted in breast milk caused obstructive jaundice and hepatomegaly in a 6 week old infant (Bagnell and Ellenberger, 1977).

RISK GROUPS

Individuals may differ in the metabolism of chemicals depending on their ethnic group owing, for example, to physiological differences in renal function, body size and composition, and genetic differences. However, this is a comparatively new area of research and the significance of these differences, particularly in terms of biological monitoring, has not been fully elucidated.

Jang *et al*. (1997) compared the differences in pharmacokinetics and urinary metabolite concentrations of several solvents in a small group of Caucasian and Oriental volunteers. In the case of tetrachloroethylene exposure (50 ppm for 6 hours) the Caucasian group had a higher (about 15%) average concentration of tetrachloroethylene in exhaled air after cessation of exposure than the Oriental group. There was no difference in the breath concentration during exposure. The Caucasian group also had higher (about 25%) average urinary concentrations of trichloroacetic acid. The average peak concentration was significantly higher in the Caucasians. Blood concentrations of tetrachloroethylene were similar in both groups.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Tetrachloroethylene is radiopaque (Dally *et al*., 1987) and an X-ray may confirm ingestion. Gastric lavage may be considered if ingestion was recent, however, because of the risk of aspiration due to CNS depression, a cuffed endotracheal tube must be used to protect the airway. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive. See below for management of systemic effects.

Systemic effects

The ECG, renal and liver functions should be monitored. Oxygen may be given if required.

Antidotes

There is no specific antidote for tetrachloroethylene.

Chronic exposure

Symptomatic and supportive care. The neurological effects of tetrachloroethylene may persist for several years (Gold, 1969; Echeverria *et al*., 1995) and there may be residual impairment (Echeverria *et al*., 1995; Feldman, 1999).

REFERENCES

Abedin Z, Cook RC, Milberg RM. 1980 Cardiac toxicity of perchloroethylene (a dry cleaning agent). *South Med J* 73 (8):1081-1083.

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Aggazzotti G, Fantuzzi G, Righi E, Predieri G, Gobba FM, Paltrinieri M, Cavalleri A. 1994 Occupational and environmental exposure to perchloroethylene (PCE) in dry cleaners and their family members. *Arch Environ Health* 49 (6):487-493.

Ahlborg G Jr. 1990 Pregnancy outcome among women working in laundries and dry-cleaning shops using tetrachloroethylene. *Am J Ind Med* 17:567-575.

Algren JT, Rodgers GC. 1992 Intravascular hemolysis associated with hydrocarbon poisoning. *Pediatr Emerg Care* 8 (1):34-35.

Altmann L, Wiegand H, Böttger A, Elstermeier F, Winneke G. 1992 Neurobehavioural and neurophysiological outcomes of acute repeated perchloroethylene exposure. *Appl Psychol* 41 (3):260-279.

Altmann L, Neuhann H-F, Krämer U, Witten J, Jermann E. 1995 Neurobehavioral and neurophysiological outcome of chronic low-level tetrachloroethylene exposure measured in neighborhoods of dry cleaning shops. *Environ Res* 69:83-89.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Anon. 1988 Tetrachloroethylene. *Rev Environ Contam Toxicol* 106:175-188.

Aschengrau A, Ozonoff D, Coogan P, Vezina R, Heeeren T, Zhang Y. 1993 Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts. *Arch Environ Health* 48 (5):284-292.

Ashengrau A, Paulu C, Ozonoff D. 1998 Tetrachloroethylene-contaminated drinking water and the risk of breast cancer. *Environ Health Perspect* 106:947-953.

ATSDR. 1997 *Toxicological Profile for Tetrachloroethylene*. Agency for Toxic Substances and Disease Registry. US Department of Health and Human Services.

Bagnell PC, Ellenberger HA. 1977 Obstructive jaundice due to a chlorinated hydrocarbon in breast milk. *Can Med J* 117:1047-1048.

Barlow SM, Sullivan FM. 1982 *Reproductive Hazards of Industrial Chemicals. An evaluation of animal and human data*. Academic Press, London.

Bennett JR. 1984 The dangers of dry cleaning [letter]. *Br Med J* 289:255.

Berberian DA. 1966 Hookworm infections. *J Am Med Assoc* 196 (10):233.

Birner G, Rutkowska A, Dekant W. 1996 *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-*L*-cysteine and 2,2,2,-trichloroethanol. Two novel metabolites of tetrachloroethene in humans after occupational exposure. *Drug Metabol Dispost* 24 (1):41-48.

Blacow NW, Wade A. 1972 *Martindale. The Extra Pharmacopoeia*, 26th edition. The Pharmaceutical Press, London.

Blair A, Decoufle P, Grauman D. 1979 Causes of death among laundry and dry cleaning workers. *Am J Public Health* 69 (5):508-511.

Blair A, Stewart PA, Tolbert PE, Grauman D, Moran FX, Vaught J, Rayner J. 1990 Cancer and other causes of death among a cohort of dry cleaners. *Br J Ind Med* 47:162-168.

Boice JD Jr, Marano DE, Fryzek JP, Sadler CJ, McLaughlin JK. 1999 Mortality among aircraft manufacturing workers. *Occup Environ Med* 56:581-597.

Bonse G, Urban T, Reichert D, Henschler D. 1975 Chemical reactivity, metabolic oxirane formation and biological reactivity of chlorinated ethylenes in the isolated perfused rat liver preparation. *Biochem Pharmacol* 24:1829-1834.

Bosco MG, Figà-Talamanca I, Salerno S. 1987 Health and reproductive status of female workers in dry cleaning shops. *Int Arch Occup Environ Health* 59:295-301.

Brodkin CA, Daniell W, Checkoway H, Echeverria D, Johnson J, Wang K, Sohaey S, Green D, Redlich C, Gretch D, Rosenstock L. 1995 Hepatic ultrasonic changes in workers exposed to perchloroethylene. *Occup Environ Med* 52:679-685.

Brown DP, Kaplan SD. 1987 Retrospective cohort mortality study of dry cleaner workers using perchloroethylene. *J Occup Med* 29 (6):535-541.

BUA (Beratergremium für Umweltrelevante Altstoffe). 1996 *Tetrachloroethylene*. BUA Report 139 (August 1993). S Hirzel, Stuttgart.

Buben JA, O'Flaherty EJ. 1985 Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: a dose-effects study. *Toxicol Appl Pharmacol* 78:105-122.

Cai S-X, Huang M-Y, Chen Z, Liu Y-T, Jin C, Watanabe T, Nakatsuka H, Seiji K, Inonue O, Ikeda M. 1991 Subjective symptom increase among dry-cleaning workers exposed to tetrachloroethylene vapor. *Ind Health* 29:111-121.

Carpenter CP. 1937 The chronic toxicity of tetrachloroethylene. *J Ind Hyg Toxicol* 19:323-336.

Cavalleri A, Gobba F, Paltrinieri M, Fantuzzi G, Righi E, Aggazzotti G. 1994 Perchloroethylene exposure can induce colour vision loss. *Neurosci Lett* 179:162-166.

Chmielewski J, Tomaszewski R, Glombiowksi P, Kowalewsi W, Kwiatkowski SR, Szczekocki W, Winnicka A. 1976 Clinical observations of the occupational exposure to tetrachloroethylene. *Bull Inst Marit Trop Med Gdynia* 27 (2):197-205.

Cohen AJ, Grasso P. 1981 Review of the hepatic response to hypolipidaemic drugs in rodents and assessment of its toxicological significance to man. *Fd Chem Toxicol* 19:585-605.

Coler HR, Rossmiller HR. 1953 Tetrachloroethylene exposure in small industry. *Arch Ind Hyg* 8:227-233.

Cornish HH, Adefuin J. 1966 Ethanol potentiation of halogenated aliphatic solvent toxicity. *An Ind Hyg Assoc J* 27 (1):57-61.

Dally S, Garnier R, Bismuth C. 1987 Diagnosis of chlorinated hydrocarbon poisoning by x ray examination. *Br J Ind Med* 44:424-425.

Daniel JW. 1963 The metabolism of ^{36}Cl-labelled trichloroethylene and tetrachloroethylene in the rat. *Biochem Pharmacol* 12:795-802.

Dehon B, Humbert L, Devisme L, Stievenart M, Mathieu D, Houdret N, Lhermitte M. 2000 Tetrachloroethylene and trichloroethylene fatality: case report and simple headspace SPME-capillary gas chromatographic determination in tissues. *J Anal Toxicol* 24:22-26.

Dekant W, Metzler M, Henschler D. 1986 Identification of *S*-1,2,2-trichlorovinyl-*n*-acetylcysteine as a urinary metabolite of tetrachloroethylene: bioactivation through glutathione conjugation as a possible explanation of its nephrocarcinogenicity. *J Biochem Toxicol* 1:57-72.

Doyle P, Roman E, Beral V, Brookes M. 1997 Spontaneous abortion in dry cleaning workers potentially exposed to perchloroethylene. *Occup Environ Med* 54:848-853.

Duh R, Asal NR. 1984 Mortality among laundry and dry cleaning workers in Oklahoma. *Am J Public Health* 74:1278-1280.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 1990 Tetrachloroethylene: Assessment of human carcinogenic hazard. *Technical Report No. 37*.

Echeverria D, White RF, Sampaio C. 1996 A behavioral evaluation of PCE exposure in patients and dry cleaners: a possible relationship between clinical and preclinical effects. *J Occup Environ Med* 37 (6):667-680.

Elcombe CR. 1985 Species differences in carcinogenicity and peroxisome proliferation due to trichloroethylene: a biochemical human hazard assessment. *Arch Toxicol* (Suppl 8):6-17.

Eskenazi B, Wyrobek AJ, Fenster L, Katz DF, Sadler M, Lee J, Hudes M, Rempel DM. 1991a A study of the effect of perchloroethylene on semen quality in dry cleaning workers. *Am J Ind Med* 20:575-591.

Eskenazi B, Fenster L, Hudes M, Wyrobek AJ, Katz DF, Gerson J, Rempel DM. 1991b A study of the effect of perchloroethylene exposure on the reproductive outcomes of wives of dry-cleaning workers. *Am J Ind Med* 20:593-600.

Feldman RG. 1999 *Occupational and Environmental Neurotoxicology*. Lippincott-Raven, Philadelphia.

Fernandez J, Guberan E, Caperos J. 1976 Experimental human exposures to tetrachloroethylene vapor and elimination in breath after inhalation. *Am Ind Hyg Assoc J* 37:143-150.

Ferroni C, Seilis L, Mutti A, Folli D, Bergamaschi E, Franchini I. 1992 Neurobehavioral and neuroendocrine effects of occupational exposure to perchloroethylene. *Neurotoxicology* 13:243-248.

Fisher J, Mahle D, Bankston L, Greene R, Gearhart J. 1997 Lactational transfer of volatile chemicals in breast milk. *Am Ind Hyg Assoc J* 58:425-431.

Franchini I, Cavatorta A, Falzoi M, Lucertini S, Mutti A. 1983 Early indicators of renal damage in workers exposed to organic solvents. *Int Arch Occup Environ Health* 52:1-9.

Gaillard Y, Billault F, Pépin G. 1995 Tetrachloroethylene fatality: case report and simple gas chromatographic determination in blood and tissues. *Forensic Sci Int* 76:161-168.

Garnier R, Bédouin J, Pépin G, Gaillard Y. 1996 Coin-operated dry cleaning machines may be responsible for acute tetrachloroethylene poisoning: report of 26 cases including one death. *Clin Toxicol* 34 (2):191-197.

Gennari P, Naldi M, Motta R, Nucci MC, Giacomini C, Violante FS, Raffi GB. 1992 Gamma glutamyl-transferase isoenzyme pattern in workers exposed to tetrachloroethylene. *Am J Ind Med* 21:661-671.

Gobba F, Righi E, Fantuzzi G, Predieri G, Cavazzuti L, Aggazzotti G. 1998 Two-year evolution of perchloroethylene-induced color-vision loss. *Arch Environ Health* 53 (3):196-198.

Gold JH. 1969 Chronic perchloroethylene poisoning. *Can Psychiatr Assoc J* 14:627-630.

Goldsworthy TL, Lyght O, Burnett VL, Popp JA. 1988 Potential role of α-2μ-globulin, protein droplet accumulation, and cell replication in the renal carcinogenicity of rats exposed to trichloroethylene, perchloroethylene, and pentachloroethane. *Toxicol Appl Pharmacol* 96:367-379.

Green T, Odum J, Nash JA, Foster R. 1990 Perchloroethylene-induced rat kidney tumours: an investigation of the mechanisms involved and their relevance to humans. *Toxicol Appl Pharmacol* 103:77-89.

Guberan E, Fernandez J. 1974 Control of industrial exposure to tetrachloroethylene by measuring alveolar concentrations: theoretical approach using a mathematical model. *Br J Ind Med* 31:159-167.

Hake CL, Stewart RD. 1977 Human exposure to tetrachloroethylene: inhalation and skin contact. *Environ Health Perspect* 21:231-238.

Heinemann EF, Cocco P, Gómez MR, Dosemeci M, Stewart PA, Hayes RB, Zahm SH, Thomas TL, Blair A. 1994 Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer. *Am J Ind Med* 26:155-169.

Hemminki K, Franssila E, Vainio H. 1980 Spontaneous abortion among female chemical workers in Finland. *Int Arch Occup Environ Health* 45:123-126.

Herren-Freund SL, Pereira MA, Khoury MD, Olson G. 1987 The carcinogenicity of trichloroethylene and its metabolites, trichloroacetic acid and dichloroacetic acid, in mouse liver. *Toxicol Appl Pharmacol* 90:183-189.

IARC. 1995 Dry cleaning, some chlorinated solvents and other industrial chemicals. *IARC Monograph 63*.

Ikeda M, Ohtsuji H, Imamura T, Komoike Y. 1972 Urinary excretion of total trichlorocompounds, trichloroethanol, and trichloroacetic acid as a measure of exposure to trichloroethylene and tetrachloroethylene. *Br J Ind Med* 29:328-333.

Ikeda M. 1977 Metabolism of trichloroethylene and tetrachloroethylene in human subjects. *Environ Health Perspect* 21:219-245.

Imbriani M, Ghittori S, Pezzagno G, Capodaglio E. 1988 Urinary excretion of tetrachloroethylene (perchloroethylene) in experimental and occupational exposure. *Arch Environ Health* 43 (4):292-293.

Isenschmid DS, Cassin BJ, Hepler BR, Kanluen S. 1998 Tetrachloroethylene intoxication in an autoerotic fatality. *J Forensic Sci* 43 (1):231-234.

Jang J-Y, Droz PO, Berode M. 1997 Ethnic differences in biological monitoring of several organic solvents I. Human exposure experiment. *Int Arch Occup Environ Health* 70:4343-349.

Johnson HE, Shanor SP. 1968 Electrocardiographic findings in dogs inhaling the vapors of diverse chlorinated hydrocarbons [abstract]. *Toxicol Appl Pharmacol* 12:297.

Katz RM, Jowett D. 1981 Female laundry and dry cleaning workers in Wisconsin: a mortality analysis. *Am J Public Health* 71 (3):305-307.

Klassen CD, Plaa GL. 1966 Relative effects of various chlorinated hydrocarbons on liver and kidney function in mice. *Toxicol Appl Pharmacol* 9:139-151.

Klassen CD, Plaa GL. 1967 Relative effects of various chlorinated hydrocarbons on liver and kidney function in dogs. *Toxicol Appl Pharmacol* 10:119-131.

Köppel C, Arendt U, Koeppe P. 1985 Acute tetrachloroethylene poisoning - blood elimination kinetics during hyperventilation therapy. *Clin Toxicol* 23 (2-3):103-115.

Kyyrönen P, Taskinen H, Lindbohm M-L, Hemminki K, Heinonen OP. 1989 Spontaneous abortions and congenital malformation among women exposed to tetrachloroethylene in dry cleaning. *J Epidemiol Comm Health* 43:346-351.

Lackore LK, Perkins HM. 1970 Accidental narcosis. Contamination of compressed air system. *J Am Med Assoc* 21 (11):1846.

Lauwerys R, Herbrand J, Buchet JP, Bernard A, Gaussin J. 1983 Health surveillance of workers exposed to tetrachloroethylene in dry-cleaning shops. *Int Arch Occup Environ Health* 52:69-77.

Levine B, Fierro MF, Goz SW, Valentour JC. 1981 A tetrachloroethylene fatality. *J Forensic Sci* 26 (1):206-209.

Lindbohm M-L, Taskinen H, Kyyrönen P, Sallmén M, Anttila A, Hemminki K. 1992 Effects of parental occupational exposure to solvents and lead on spontaneous abortion. *Scand J Work Environ Health* 18 (Suppl 2):37-39.

Ling S, Lindsay WA. 1971 Perchloroethylene burns [letter]. *Br Med J* 3:115.

Lukaszewski T. 1979 Acute tetrachloroethylene fatality. *Clin Toxicol* 15 (4):411-415.

Lynge E, Thygesen L. 1990 Primary liver cancer among women in laundry and dry-cleaning work in Denmark. *Scand J Work Environ Health* 16:108-112.

McCarthy TB, Jones RD. 1983 Industrial gassing poisonings due to trichloroethylene, perchloroethylene, and 1,1,1, trichloroethane, 1961-80. *Br J Ind Med* 40:450-455.

McDonald AD, McDonald JC, Armstrong B, Cherry N, Delorme C, D-Nolan A, Robert D. 1987 Occupation and pregnancy outcome. *Br J Ind Med* 44:521-526.

McLaughlin JK, Blot WM. 1997 A critical review of epidemiology studies of trichloroethylene and perchloroethylene and risk of renal-cell cancer. *Int Arch Occup Environ Health* 70:222-231.

McMullen JK. 1976 Perchloroethylene intoxication [letter]. *Br Med J* 2:1563-1564.

Meckler LC, Phelps DK. 1966 Liver disease secondary to tetrachloroethylene exposure. A case report. *J Am Med Assoc* 197 (8):144-145.

Monster AC. 1979 Difference in uptake, elimination, and metabolism in exposure to trichloroethylene, 1,1,1-trichloroethane and tetrachloroethylene. *Int Arch Occup Environ Health* 42:311-317.

Monster AC, Boersma G, Steenweg H. 1979 Kinetics of tetrachloroethylene in volunteers: influence of exposure concentration and work load. *Int Arch Occup Environ Health* 42:303-309.

Monster A, Regouin-Peeters W, Van Schijndel A, van der Tuin J. 1983 Biological monitoring of occupational exposure to tetrachloroethylene. *Scand J Work Environ Health* 9:273-281.

Morgan B. 1969 Dangers of perchloroethylene [letter]. *Br Med J* 2:513.

Moslen MT, Reynolds ES, Szabo S. 1977 Enhancement of the metabolism and hepatotoxicity of trichloroethylene and perchloroethylene. *Biochem Pharmacol* 26:369-375.

Mutti A, Franchini I. 1987 Toxicity of metabolites to dopaminergic systems and the behavioural effects of organic solvents. *Br J Ind Med* 44:721-723.

Mutti A, Alinovi R, Bergamaschi E, Biagini C, Cavazzini S, Franchini I, Lauwerys RR, Bernard AM, Roels H, Gelpi E, Rosello J, Ramis I, Price RG, Taylor SA, De Broe M, Nuyts GD, Stolte H, Fels LM, Herbort C. 1992 Nephropathies and exposure to perchloroethylene in dry-cleaners. *Lancet* 340:189-93.

Nakatsuka H, Watanabe T, Takeuchi Y, Hisanaga N, Shibata E, Suzuki H, Huang M-Y, Chen Z, Qu Q-S, Ikeda M. 1992 Absence of blue-yellow colour vision loss among workers exposed to toluene or tetrachloroethylene mostly at levels below occupational exposure limits. *Int Arch Occup Environ Health* 64:113-117.

NIOSH (National Institute for Occupational Safety and Health). 1976 Criteria for a recommended standard occupational exposure to tetrachloroethylene (perchloroethylene). *DHEW Publication 76-185*.

Odum J, Green T, Foster JR, Hext PM. 1988 The role of trichloroacetic acid and peroxisome proliferation in the differences in carcinogenicity of perchloroethylene in the mouse and rat. *Toxicol Appl Pharmacol* 92:103-112.

Ogata M, Takatsuka Y, Tomokuni K, Muroi K. 1971 Excretion of organic chlorine compounds in the urine of persons exposed to vapours of trichloroethylene and tetrachloroethylene. *Br J Ind Med* 28:386-391.

Olsen J, Hemminki K, Ahlborg G, Bjerkedal T, Kyyrönen P, Taskinen H, Lindbohm M-L, Heinonen OP, Brandt L, Kolstad H, Halvorsen BA, Egenaes J. 1990 Low birthweight, congenital malformations, and spontaneous abortions among dry-cleaning workers in Scandinavia. *Scand J Work Environ Health* 16:163-168.

Onofrj M, Thomas A, Paci C, Rotilio D. 1998 Optic neuritis with residual tunnel vision in perchloroethylene toxicity. *Clin Toxicol* 36 (6):603-607.

Patel R, Janakiraman N, Johnson R, Elman JB. 1973 Pulmonary edema and coma from perchloroethylene [letter]. *J Am Med Assoc* 223 (13):1510.

Patel R, Janakiraman N, Towne WD. 1977 Pulmonary edema due to tetrachloroethylene. *Environ Health Perspect* 21:247-249.

Pegg DG, Zemple JA, Braun WH, Watanabe PG. 1979 Disposition of tetrachloro(^{14}C)ethylene following oral and inhalation exposure in rats. *Toxicol Appl Pharmacol* 51:465-474.

Peoples RW, Weight FF. 1994 Trichloroethanol potentiation of γ-aminobutyric acid-activated chloride current in mouse hippocampal neurones. *Br J Pharmacol* 13:555-563.

Rachootin P, Olsen J. 1983 The risk of infertility and delayed conception associated with exposures in the Danish workplace. *J Occup Med* 25 (5):394-402.

Ratnoff WD, Gress RE. 1980 The familial occurrence of polycythemia vera: report of a father and son, with consideration of the possible etiologic role of exposure to organic solvents, including tetrachloroethylene. *Blood* 56 (2):233-236.

Redmond SF, Schappert KR. 1987 Occupational dermatitis associated with garments. *J Occup Med* 29 (3):243-244.

Rowe VK, McCollister DD, Spencer HC, Adams EM, Irish DD. 1952. Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects. *AMA Arch Ind Hyg Occup Med* 5:566-579.

Ruder AM, Ward EM, Brown DP. 2001 Mortality in dry-cleaning workers: an update. *Am J Ind Med* 39:121-132.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Salahudeen AK. 1988 Perchloroethylene-induced nephrotoxicity in dry cleaning workers: is there a role for free radicals? *Nephrol Dial Transplant* 13:1122-1124.

Saland G. 1967 Accidental exposure to perchloroethylene. *NY State J Med* 67:2359-2361.

Schumann AM, Quast JF, Watanabe PG. 1980 The pharmacokinetics and macromolecular interactions of perchloroethylene in mice and rats as related to oncogenicity. *Toxicol Appl Pharmacol* 55:207-219.

Schwetz BA, Leong BKJ, Gehring PJ. 1975 The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform, and methylene chloride on embryonal and fetal development in mice and rats. *Toxicol Appl Pharmacol* 32:84-96.

Seeber A. 1989 Neurobehavioral toxicity of long-term exposure to tetrachloroethylene. *Neurotoxicol Teratol* 11:579-583.

Seiji K, Jin C, Watanabe T, Nakasuka H, Ikdea M. 1990 Sister chromatid exchanges in peripheral lymphocytes of workers exposed to benzene, trichloroethylene or tetrachloroethylene, with reference to smoking habits. *Int Arch Occup Environ Health* 62:171-176.

Skender L, Karačić V, Prpić-Majić D. 1991 A comparative study of human levels of trichloroethylene and tetrachloroethylene after occupational exposure. *Arch Environ Health* 46 (3):174-178.

Solet D, Robins TG. 1991 Renal function in dry cleaning workers exposed to perchloroethylene. *Am J Ind Med* 20:601-614.

Sparrow GP. 1977 A connective tissue disorder similar to vinyl chloride disease in a patient exposed to perchloroethylene. *Clin Exp Dermatot* 2:17-22.

Stacey NH. 1989 Toxicity of mixtures of trichloroethylene, tetrachloroethylene and 1,1,1-trichloroethane: similarity of *in vitro* and *in vivo* responses. *Toxicol Ind Health* 5 (3):441-449.

Stewart RD. 1969 Acute tetrachloroethylene intoxication. *J Am Med Assoc* 208 (8):1490-1492.

Stewart RD, Erley DS, Schaffer AW, Gay HH. 1961a Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene. *Ind Med Surg* 30:327-330.

Stewart RD, Gay HH, Erley DS, Hake CL, Schaffer AW. 1961b Human exposure to tetrachloroethylene vapor. Relationship of exposure air and blood concentrations to exposure and toxicity. *Arch Environ Health* 2:40-46.

Stewart RD, Dodd HC. 1964 Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through human skin. *Am Ind Hyg Assoc J* 25:439-466.

Stewart RD, Dodd HC, Torkelson TR. 1970 Experimental human exposure to tetrachloroethylene. *Arch Environ Health* 20:224-229.

Stewart RD, Hake CL, Wu A, Kalbfleisch J, Newton PE, Marlow SK, Vucicevic-Salama M. 1977 Effects of perchloroethylene/drug interaction on behavior and neurological function. Final report. National Institute for Occupational Safety and Health. *NIOSH PB83-17460*.

Taskinen H, Anttila A, Lindbohm M-L, Sallmén M, Hemminki K. 1989 Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand J Work Environ Health* 15:345-352.

Vamvakas S, Herkenhoff M, Dekant W, Henschler D. 1989 Mutagenicity of tetrachloroethene in the Ames test-metabolic activation by conjugation with glutathione. *J Biochem Toxicol* 4 (1):21-27.

van der Gulden JWJ, Zielhuis GA. 1989 Reproductive hazards related to perchloroethylene. A review. *Int Arch Occup Environ Health* 61:235-242.

Vaughan TL, Stewart PA, Davis S, Thomas DB. 1997 Work in dry cleaning and the incidence of cancer of the oral cavity, larynx, and oesophagus. *Occup Environ Med* 54:692-695.

Vyskočil A, Emminger S, Tejral J, Fiala Z, Ettlerova E, Cermanová A. 1990 Study on kidney function in female workers exposed to perchloroethylene. *Hum Exp Toxicol* 9:337-380.

Weiss NS. 1995 Cancer in relation to occupational exposure to perchloroethylene. *Cancer Causes and Control* 6 (5):257-266.

Windham GC, Shusterman D, Swan SH, Fenster L, Eskenazi B. 1991 Exposure to organic solvents and adverse pregnancy outcome. *Am J Ind Med* 20:241-259.

Yllner S. 1961 Urinary metabolites of ^{14}C-tetrachloroethylene in mice. *Nature* 191:820.

Zielhuis GA, Gijsen R, van der Gulden JWJ. 1989 Menstrual disorders among dry-cleaning workers. *Scand J Work Environ Health* 15:238.

21 Toluene

Nicola Bates

SUMMARY

- Toluene is well absorbed by inhalation and ingestion, but less so dermally
- The target organ of toxicity is the CNS
- The mechanism of toxicity is unknown
- Acute exposure results in respiratory irritation and CNS depression
- Death may occur due to hypoxia or cardiac arrhythmia
- Chronic abuse of toluene causes slowly progressive multifocal CNS dysfunction
- Renal tubular acidosis and severe electrolyte imbalance have been reported from chronic abuse
- Urinary concentrations of hippuric acid may be used for biomonitoring
- Toluene is not classifiable as to its carcinogenicity in humans
- It is not mutagenic or genotoxic
- Fetal abnormalities have been reported with toluene abuse during pregnancy

DESCRIPTION

Synonyms

Methacide, methylbenzene, methylbenzol, phenylmethane, toluol. Commercial toluene is of high purity, however in the past it was contaminated with considerable quantities of benzene and xylenes (Low *et al*., 1988). The possible presence of contaminants must be borne in mind when reviewing toxicological reports.

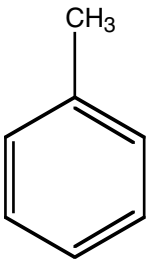
Identification numbers

CAS	108-88-3
UN	1294
RTECS	XS 5250000
EINECS	2036259

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula C_7H_8

molecular formula



molecular mass	92.13
physical form	clear, colourless liquid
relative vapour density (air=1)	0.866
flash point (°C closed cup)	4.4
boiling point (°C)	110.6
autoignition temperature (°C)	480
refractive index	1.4969
explosive limits in air (%v/v)	1.1-7.1

Odour threshold

0.39 ppm (Gusev, 1965); 2.9 ppm (Amoore and Hautala, 1983); 2-40 ppm (Ruth, 1986).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK and ACGIH): 50 ppm (191 mg/m^3)

Conversion factors

1 ppm = 3.75 mg/m^3
1 mg/m^3 = 0.266 ppm
1 mg/l = 266 ppm

Biomonitoring

There are five methods to monitor exposure to toluene (Angerer and Krämer, 1997). These are measurement of:

- Toluene in expired air (Nomiyama and Nomiyama, 1974; Brugnone *et al*., 1976; Övrum *et al*., 1978; Apostoli *et al*., 1982; Monster *et al*., 1993)
- Toluene in blood (Brugnone *et al*., 1976; Brugnone *et al*., 1986; Campbell *et al*., 1987; Gill *et al*., 1988; Pekari *et al*., 1989; Kawai *et al*., 1994)
- Toluene in urine (Ghittori *et al*., 1987; Monster *et al*., 1993)
- Hippuric acid in urine (Caperos and Fernàndez, 1977; Kira, 1977; Apostoli *et al*., 1982; De Rosa *et al*., 1987)
- *Ortho*-cresol (but not *para*- or *meta*-cresol) in urine (Truchon *et al*., 1996; Angerer and Krämer, 1997).

The current ACGIH recommendations for biological exposure indices are listed in **Table 21.1**.

Table 21.1 Biological exposure indices for toluene (ACGIH, 2000)

Determinant	Sampling time	Biological exposure index (BEI)
o-cresol in urine	end of shift	0.5 mg/l
hippuric acid in urine	end of shift	1.6 g/g creatinine
toluene in blood	prior to last shift of workweek	0.05 g/l

Diet can affect the urinary concentration of hippuric acid. Benzoic acid and benzoic acid precursors (which are metabolised to hippuric acid) are present in food and drink (e.g., fish and egg products and soft drinks), particularly as preservatives. Benzoic acid is also formed from the amino acid phenylalanine. In the case of occupational exposure it may be impossible to eliminate the effect of diet when estimating the individual uptake of toluene using the urinary hippuric acid concentration (Campbell *et al.*, 1987; Löf, *et al.,* 1993; Angerer and Krämer, 1997). This is particularly a problem at low exposure concentrations (Campbell *et al.*, 1987). In addition, the concentration of hippuric acid in the urine may be increased in individuals taking drugs which induce liver enzymes (e.g., phenobarbital) (Cohr and Stokholm, 1979).

Ortho-cresol is not a normal constituent of urine and normal concentrations are less than 0.9 µmol/l (Truchon *et al.*, 1996). However, the concentration can vary and smokers have a 3-4-fold increase of *ortho*-cresol in urine (Nise, 1992).

Para-cresol is a normal constituent of urine, probably due to metabolism of the amino acid tyrosine (Angerer and Krämer, 1997). In 85 volunteers the urinary *p*-cresol concentration varied from 3.3-63 mg/g creatinine (Meulenbelt *et al.*, 1990). Another study found that non-exposed individuals excreted up to 29 mg/l of *p*-cresol in urine (Woiwode *et al.,* 1979). Consequently, *p*-cresol is not a suitable index of toluene exposure (Meulenbelt *et al.*, 1990).

Although *m*-cresol is not a normal constituent of urine, it is usually only found following exposure to a high concentration of toluene (Meulenbelt *et al.*, 1990). The concentration of *m*-cresol is usually much less than that of *o*- or *p*-cresol and it cannot be used as a biological indicator of low-level exposure. However, it was detected in 10 workers exposed to an average concentration of 280 ppm (range 100-600 ppm) of toluene, but did not correlate with toluene exposure (Woiwode *et al.*, 1979).

There was also no correlation between air concentrations of toluene and o- or *p*-cresol in the urine (Woiwode *et al.*, 1979). Urinary concentrations of hippuric acid and *o*-cresol have been correlated to air concentrations of toluene, but the correlation was weaker for *o*-cresol (De Rosa *et al.,* 1987). Another study in volunteers exposed to a range of toluene concentrations found that urinary *o*-cresol concentrations were highly correlated with toluene exposure (Truchon *et al.*, 1996).

Differences in methods of extraction and analysis (Angerer and Krämer, 1997) and co-exposure to other solvents may be a factor in the variation in results reported in different studies.

TOXICITY

Most cases of toluene poisoning are due to intentional abuse. However, acute poisoning from spillages at work (Reisin *et al.*, 1975) and from the use of toluene containing products in poorly ventilated areas, has been reported (Brugnone *et al.,* 1983; Meulenbelt *et al.*, 1990; Knight *et al.,* 1991; Shibata *et al.*, 1994; Carder and Fuerst, 1997; Tan and Seow, 1997; Hobara *et al.*, 2000). Deaths at work due to falls and drowning while under the influence of toluene have also occurred (Takeichi *et al.*, 1986). Occasionally toluene abuse may occur following occupational exposure (Tarsh, 1979).

Much of the information concerning the toxicity of toluene derives from studies on individuals who have chronically abused this solvent. These individuals are exposed to very high concentrations but the dose is difficult, if not impossible, to determine. Workers are usually exposed to much lower concentrations of toluene and extrapolation of the clinical effects of toluene exposure between these two groups may not be appropriate (Harbison, 1998). Consequently, where it has been possible, a distinction has been made in this review between effects reported from occupational exposure and those reported with abuse of toluene.

At low concentrations or in a short exposure toluene is excitatory, whereas at higher concentrations or longer duration the effects are depressant (Benignus, 1981b). Toluene induced effects are reversible except for effects on the nervous system (Benignus, 1981b). Death from acute toluene poisoning is believed to be due to hypoxia during CNS depression or cardiac arrhythmia (Bakinson and Jones, 1985; Ikeda *et al.,* 1990).

Absorption

The mean uptake of toluene is initially 75-80% (Åstrand *et al.*, 1972) and then falls to 40-60% of the quantity inhaled (Övrum *et al.,* 1978; Veulemans and Masschelein, 1978a; Carlsson, 1982; IPCS, 1985; Löf *et al.*, 1993; Morata *et al.,* 1995). Absorption is rapid; toluene can be detected in arterial blood after 10 seconds of inhalation exposure (Åstrand *et al.*, 1972). After the first 10-15 minutes the concentration of toluene increases more slowly and reaches a plateau concentration after about 25 minutes (Åstrand *et al.*, 1972).

There is a correlation between the toluene blood concentration and the alveolar air concentration (Åstrand *et al.*, 1972; Brugnone *et al.*, 1976; Övrum *et al.,* 1978). Uptake of toluene appears to be independent of the amount of body fat (Veulemans and Masschelein, 1978a). However, some workers have found uptake to be influenced by body fat percentage (Carlsson, 1982). These differences may be due to other physiological differences between lean and obese individuals, e.g., respiration rate. Exercise increases the total uptake of toluene (Åstrand *et al.*, 1972; Åstrand, 1975; Veulemans and Masschelein, 1978a,b; Carlsson, 1982) due to increased respiration and heart rate.

Dermal absorption of toluene is less than that of some other hydrocarbon solvents. After immersion of one hand in toluene for one minute, hardly any toluene was detected in the blood. After a 30 minute immersion the maximum blood concentration did not exceed a quarter of the concentration reached in a two hour inhalation exposure at 100 ppm (Sato and Nakajima, 1978). Washing of hands in toluene for five minutes did not contribute significantly to the total toluene exposure (Monster *et al.*, 1993). Dermal absorption of toluene vapour is less than that for liquid toluene. The risk of systemic toxicity from dermal exposure is low, because any toluene absorbed through the skin rapidly diffuses out again after cessation of exposure (Cohr and Stokholm, 1979).

Toluene is absorbed from the gastrointestinal tract but more slowly than by inhalation (Pyykkö *et al.,* 1977).

Distribution

Toluene is distributed widely throughout the body but it is highly lipophilic and tissues with a high lipid content act as reservoirs; therefore the higher the lipid content the more toluene the tissue will retain (Benignus, 1981a). The half-life of toluene in lipid-rich tissue is long at almost 80 hours (Cohr and Stokholm, 1979; Nise *et al.,* 1989). The rate of rise in the tissue toluene concentration is proportional to the vascularisation and diffusion of toluene into tissue (Åstrand, 1975). A study of exposed workers found a correlation between the air concentration of toluene and the concentration in the subcutaneous adipose tissue (Nise *et al.*, 1989).

Death occurred 30 minutes after ingestion of 60 ml of toluene in a 51 year old male. Tissue distributions were highest in the stomach contents followed by the liver, pancreas, brain, heart, blood, fat and cerebrospinal fluid (Ameno *et al.*, 1989).

Metabolism

The main mechanism of toluene metabolism is oxidation of the aliphatic chain. The product is benzoic acid. This is produced by oxidation of the methyl group of toluene via benzyl alcohol and benzaldehyde, involving alcohol dehydrogenase. Benzaldehyde is metabolised to benzoic acid via aldehyde dehydrogenase. Benzoic acid is further conjugated with glycine to form hippuric acid or with glucuronic acid to produce benzoyl glucuronic acid. The minor route of oxidation involves the aromatic ring with the formation of *ortho*-, *meta*- and *para*-cresol. Less than 1% of the absorbed toluene is metabolised by this route (De Rosa *et al.*, 1987). The cresols are excreted in urine as glucuronide and sulphate conjugates.

Elimination

About 5-20% of absorbed toluene is excreted by the lungs unchanged (Cohr and Stokholm, 1979; Carlsson, 1982; IPCS, 1985). The concentration of toluene in expired alveolar air correlates with the concentration in inspired air (Cohr and Stokholm, 1979; Apostoli *et al.*, 1982) and blood (Brugnone *et al.*, 1976; Carlsson,

1982; Brugnone *et al*., 1986). After cessation of exposure, the toluene concentration in expired air decreases rapidly and is highly correlated with blood concentrations (Veulemans and Masschelein, 1978a,b). Elimination of toluene from blood is rapid (Veulemans and Masschelein, 1978b; Carlsson, 1982; Nise *et al*., 1989; Löf *et al*., 1993) and is influenced by the respiratory and heart rates.

The breath of volunteers exposed to 75 and 150 ppm of toluene contained on average 7.65 ppm and 16.06 ppm of toluene respectively. The concentrations had dropped to 2.2 ppm and 4.05 ppm 20 minutes after exposure ceased. The expired air concentrations were 10.5% of the exposure dose at 75 ppm and 11.2% at 150 ppm, measured using a mixed air, not an alveolar air, sample (Echeverria *et al.,* 1989).

Studies in workers have shown that the rate of elimination of toluene from blood is complex with at least three exponential components. The first two had median estimated half-lives of nine minutes and two hours. The third component had a median half-life of 90 hours. This reflected the decline of toluene in adipose tissue, where it had a median half-life of 79 hours (Nise *et al.,* 1989). In another study of exposed workers the mean elimination half-life of toluene in alveolar air was 3.8 hours and in blood 4.5 hours (Brugnone *et al*., 1986). In chronic abusers the blood elimination half-life for toluene was 35-54 minutes in the first hour after cessation of exposure and 79-111 minutes in the second hour (Garriott *et al*., 1981). Elimination studies in two men found unconscious after acute exposure, found toluene in the blood and alveolar air 5 days later. This was due to the slow release of toluene from fat tissue. The elimination half-life from alveolar air and blood was 18.7 and 21.2 hours respectively (Brugnone *et al*., 1983).

About 80% of benzoic acid is excreted as hippuric acid and about 20% as benzoyl glucuronic acid (Cohr and Stokholm, 1979). In a volunteer study, 65% of the total toluene absorbed by inhalation was excreted as hippuric acid 4 hours after cessation of exposure; this rose to 78% by 20 hours post exposure (Löf *et al*., 1993).

Mode of action

The brain is the main target organ in toluene toxicity (Benignus, 1981b), but the mechanism of action is not known. Toluene has high lipid solubility and distributes in brain lipids. The toluene concentration in fatty tissue may be 80 times that in blood, however, accumulation in fatty tissue is slow due to poor blood supply. Nervous tissue is well supplied with blood and as a result toluene may accumulate and the concentration may be relatively high causing neurological effects (Cohr and Stokholm, 1979).

It has been suggested that the neurological changes seen on MRI scans of chronic toluene abusers (loss of grey and white matter differentiation, increased periventricular white matter signal intensity, diffuse cerebellar, cerebral and brainstem atrophy) may be due to increased water content of white matter or toluene induced metabolic changes in myelin (Rosenberg *et al*., 1988).

Electrolyte imbalance (usually associated with renal tubular acidosis) may cause ECG changes. Tachyarrhythmias are believed to be due to sensitisation of the myocardium to the potential arrhythmogenic effects of endogenous catecholamines.

The mechanism of toluene induced renal tubular acidosis seen with chronic toluene abuse has not been fully elucidated. The impaired ability to sustain a steep pH gradient in the collecting tubule, with normal or enhanced kidney bicarbonate reabsorption capacity, is evidence of distal renal tubular acidosis. There is also impairment of proximal nephron transport giving rise to aminoaciduria, hypophosphataemia, hyponatraemia, hypokalaemia and hypocalcaemia. The metabolite hippuric acid plays an important role in metabolic acidosis (Carlisle *et al*., 1991). The loss of sodium ions leads to extracellular fluid volume contraction and a decrease in the glomerular filtration rate. This may result in a high anion gap due to accumulation of hippuric acid and other anions (Carlisle *et al*., 1991). Distal renal tubular dysfunction may be due to decreased conductance of hydrogen ions through the active transport pathway resulting in distal acidification (Batlle *et al*., 1988).

Metabolic interactions

Benzene, styrene, xylene and toluene are metabolised by the same enzyme systems and may competitively inhibit the metabolism of each other (Cohr and Stokholm, 1979; Tardif *et al.,* 1991). Consequently, there may be an increased concentration of unchanged solvent in the blood and decreased or delayed urinary

excretion of metabolites (Tardif *et al.,* 1991; Tardif *et al.,* 1992). This may result in overestimation of the toxic risk where blood concentrations are used for monitoring or underestimation where the urinary metabolites are used (Tardif *et al.,* 1992).

- **Benzene**

  Metabolism of benzene to phenolic compounds and toluene to hippuric acid and *ortho*-cresol has been shown to be suppressed in workers exposed to a mixture of toluene and benzene (Inoue *et al.*, 1988). In the case of benzene and toluene this is unlikely to be a problem if exposure is minimised, e.g., if concentrations remain below the threshold limit values (Sato and Nakajima, 1979).

- **Ethanol**

  Ethanol also affects toluene metabolism and the specific effect depends on whether ethanol ingestion is acute or chronic. Even a low blood ethanol concentration can decrease toluene metabolism (Baelum *et al.*, 1993). Inhalation of toluene (80 ppm for 4 hours) and acute ingestion of ethanol (1.5 ml/kg of vodka after 3 hours of toluene exposure) resulted in a 42.5% increase in the blood toluene concentration. However, in this study workers who drank ethanol regularly had lower blood toluene concentrations than those who seldom drank, probably due to induction of liver enzymes by ethanol (Waldron *et al.*, 1983). In another survey, workers with the highest exposure to toluene and ethanol had lower liver enzyme concentrations compared to controls with high ethanol but low toluene exposure (Boewer *et al.,* 1988). The reason for this is unclear.

  Experimental studies in volunteers have shown that ingestion of ethanol during inhalation exposure to toluene decreases the total uptake and the relative uptake (the fraction absorbed per breath). Ethanol also inhibits the distribution and/or elimination of toluene from the blood (Wallèn *et al.*, 1984).

- **Methylene chloride**

  Studies in rats have shown that a single oral administration of an aromatic hydrocarbon (benzene, toluene or *m*-xylene) 16-24 hours before the administration of methylene chloride increases the peak concentration of carboxyhaemoglobin (carbon monoxide is a metabolite of methylene chloride). The half-life of methylene chloride in blood is shorter, indicating that the metabolic degradation of methylene chloride is enhanced by the aromatic hydrocarbons. This effect on the peak carboxyhaemoglobin concentration was dependent on the time interval between aromatic hydrocarbon and methylene chloride treatment, since earlier administration of toluene or *m*-xylene decreased the carboxyhaemoglobin elevation. Disulfiram treatment blocked the carboxyhaemoglobin elevation completely and corresponding increases in the concentration and half-life of methylene chloride were observed (Kim and Kim, 1996).

- **Xylene**

  In a volunteer study co-exposure to xylene (40 ppm) and toluene (50 ppm) did not affect the concentration of solvent in blood or inhaled air; the urinary excretion of metabolites was unchanged. However, exposure to higher concentration (80 ppm and 95 ppm respectively) resulted in an increase in the blood and end-exhaled air concentration of these solvents. Excretion of the toluene metabolite (hippuric acid) was affected but excretion of methylhippuric acid was unchanged (Tardif *et al.*, 1991). Animal studies suggest that metabolic interaction of xylene and toluene is only likely to occur when the concentration of both solvents exceeds 50 ppm (Tardif *et al.*, 1993).

CASE REPORTS

Acute dermal and inhalational exposure

A 49 year old male arrived in hospital after being found unconscious at work about 18 hours after a hose containing toluene had ruptured. He had superficial burns over the shoulder and arm (about 10% of the body surface area) and was thought to have aspirated toluene. He had dyspnoea and was dehydrated with

mild hypothermia. Black urine was noted on catheterisation. A chest X-ray showed a shadow on the lower left side. Laboratory analyses revealed acidosis, raised creatinine and hyperkalaemia; the urine was positive for myoglobin and he was oliguric. Toluene was present in blood and urine. He was rehydrated with sodium bicarbonate and intravenous fluids which reduced the hyperkalaemia within 12 hours. Administration of mannitol increased the urine output but by the next day furosemide (frusemide) was required. However, the urea continued to rise and he was haemodialysed. The burns were treated supportively. Liver function tests were elevated on day five. By 10 days after admission the lung shadow had resolved and he had moderate polyuria. He recovered completely (Reisin *et al.*, 1975).

Fatal acute dermal and inhalational exposure

A 22 year old male arrived in hospital unconscious in impending cardiac arrest. There was a glue-like odour on his breath and his clothes were damp. He was resuscitated and ventilated. Blood gas analysis revealed acidosis. He had erythema of the face, trunk, arms and thighs. He had been painting a bathroom using a primer containing toluene 65%, acetone 20% and acrylic resin 12%. About an hour after starting he had been found unconscious in the bath with an empty can of primer beside him. It was thought that he had been overcome by the fumes, collapsed and spilt the primer over himself. The depth and extent of skin injury progressed with blistering resembling second degree burns over the neck and chest, approximately five hours after exposure the skin was irrigated. The burns covered more than 70% of the total body surface area and by the second day had worsened with extensive necrosis and massive fluid loss. The urine was dark brown, acidic (pH 5) and contained high concentrations of myoglobin. He was not oliguric but creatinine clearance was decreased. Serum creatine phosphokinase values rose from 1,170 IU/l on admission to 30,110 IU/l at 42 hours. Non-organic renal failure caused by rhabdomyolysis was diagnosed. He was started on diuresis and alkalinisation of the urine and creatinine clearance increased. Urinary concentrations of hippuric acid were 1.9, 0.5 and 0.3 g/l on the second, third and fourth days. He developed disseminated intravascular coagulation (DIC) and a prolonged prothrombin time. He suffered a cardiac arrest with subsequent brain damage and died from uncal herniation on the sixth hospital day (Shibata *et al.*, 1994).

Acute ingestion

A 46 year old male presented to hospital 30 minutes after ingestion of about 1 quart (940 ml) of a toluene containing paint thinner. He complained of abdominal pain and developed vomiting and diarrhoea. On examination he was alert but mildly ataxic and became disorientated. He had a non-anionic gap metabolic acidosis. Toxicological analysis of serum was positive for benzodiazepines, opioids and tetrahydrocannabinnol (cannabis). His CNS depression worsened and he was electively intubated to protect the airway during gastric lavage. Gastric contents were bloody. He recovered within 36 hours with supportive treatment (Caravati and Bjerk, 1997).

CLINICAL EFFECTS

Acute exposure

Inhalation

Respiratory irritation (Baelum *et al.*, 1990) with cough and tight chest has been reported with acute toluene exposure (Bakinson and Jones, 1985). Systemic effects may also occur, see below. For the dose-response effects of acute exposure to toluene see **Table 21.2**.

Myocardial infarction (Carder and Fuerst, 1997) and acute myocarditis (Knight *et al.,* 1991) have been reported after acute heavy exposure to toluene. Chemical pneumonitis, acidosis, hyperkalaemia, myoglobinuria and renal failure occurred in a worker found unconscious 18 hours after a hose containing toluene ruptured (Reisin *et al.*, 1975).

Volunteers exposed to toluene (3.25 mmol/m^3, 80 ppm), *p*-xylene (2.84 mmol/m^3, 70 ppm) or a mixture (2.20 mmol/m^3 toluene, 54 ppm; 0.94 mmol/m^3 xylene, 23 ppm) performed tests of reaction time and

Table 21.2 Dose-response effects of acute exposure to toluene (IPCS, 1985; Echeverria et al., 1989)

Concentration		Effects
ppm	mg/m^3	
2.5	9.4	odour threshold
37	138.8	probably perceptible to most individuals
50-100	188-375	subjective complaints (fatigue, drowsiness, mild headache) but probably no effect on reaction time or co-ordination
100	375	slight impairment in vigilance, manual dexterity and perhaps visual memory
200	750	mild throat and eye irritation, prolonged eye-to-hand reaction time, some impairment of cognitive function, mild headache, dizziness, sensation of intoxication, after effects of fatigue, general confusion, moderate insomnia
300	1,125	signs of inco-ordination during exposure of up to 8 hours
400	1,500	irritation of eyes and throat, skin paraesthesia, confusion and gross signs of inco-ordination expected during exposure for up to 8 hours
500-600	1,875-2,250	nausea, anorexia, staggering gait, transient memory loss, significant reduction in reaction time
800	3,000	nausea (after 3 hours), confusion, lack of self-control, fatigue, insomnia
1,500	5,625	extreme weakness, inco-ordination, unlikely to be lethal for exposure up to 8 hours
4,000	15,000	rapid impairment of reaction time, inco-ordination, exposure for 1 hour or more may result in severe CNS depression and possibly death
10,000-30,000	37,500-112,500	CNS depression within a few minutes, may be fatal

short-term memory. The tests were performed immediately after exposure started and then repeated at 2 and 4 hours. They also performed the tests in control conditions without solvent exposure. Their performance was unaffected by the solvent exposure (Anshelm Olson *et al.*, 1985). Acute inhalation of 200 ppm toluene in volunteers caused a decrease in pulse rate and systolic blood pressure but the change was only significant for the pulse rate. Reaction time was also prolonged (Ogata *et al.*, 1970).

Electroneurophysiological tests on 6 subjects 15 days after an accidental acute exposure to toluene showed abnormal EEG (asymmetry, slow activity) and vestibular findings. Similar EEG changes were found 6 months later, but the vestibular changes were much improved (Biscaldi *et al.,* 1981).

Subtle changes were found in a volunteer study on the acute neurobehavioural effects of toluene at 75 and 150 ppm. There was also an increased incidence of sleep during the afternoon: 7%, 14% and 22% at 0, 75 ppm and 150 ppm toluene, respectively (Echeverria *et al.,* 1989). In an experimental study of constant exposure to 100 ppm toluene or variable exposure with peaks of 300 ppm every 30 minutes for a 7 hour period with three 15 minute exercise periods, individuals showed little or no effect on vigilance, psychomotor or visual tests. However, there was a significant increase in complaints of poor air quality, altered temperature and noise perception, feelings of intoxication and irritation of the nose and lower airways (Baelum *et al.*, 1990).

Dermal

Irritation and burns may occur. In an experimental study immersion of a hand in toluene for 30 minutes caused a mild burning sensation and erythema (Sato and Nakajima, 1978). Contact with 1.5 ml of analytical grade toluene confined to a 2 cm circle for 5 minutes on the forearm produced transient erythema (Wahlberg, 1984).

Extensive skin burns have been reported in a fatal case of toluene poisoning. The victim was thought to have been overcome by fumes, collapsed and spilt a toluene containing primer over himself (see case report; Shibata *et al*., 1994). Although dermal absorption may have contributed to total toluene uptake it is likely that inhalation was the main route of absorption in this case.

Eye

Toluene is a slight eye irritant (Wolf *et al*., 1956). Splashes of toluene in the eye may cause immediate pain with irritation and blepharospasm. Hyperaemia and corneal epithelial oedema may occur. However, effects are usually mild with full recovery (Cohr and Stokholm, 1979; Grant and Schuman, 1993). Colour vision does not appear to be affected in acute toluene exposure (Muttray *et al*., 1999).

Ingestion

Abdominal pain, vomiting, diarrhoea and haemorrhagic gastritis may occur (Caravati and Bjerk, 1997). There is a risk of aspiration of toluene into the lungs, which may cause chemical pneumonitis and pulmonary oedema (Gerade, 1960). Systemic effects may occur, see below.

Systemic effects

Acute exposure to toluene may cause nausea, vomiting, dizziness, euphoria, headache, tinnitus, behavioural inhibition and CNS depression with confusion, slurred speech, drowsiness, incoordination, a feeling of inebriation (Bakinson and Jones, 1985; Ukai *et al*., 1993), coma, hypotension, hypothermia and respiratory depression. Amnesia and paresis have also been reported (Meulenbelt *et al*., 1990). Recovery from the acute neurological effects of toluene is usually rapid (Meulenbelt *et al*., 1990; Tan and Seow, 1997). Laboratory analysis may reveal metabolic acidosis, hypokalaemia, hypocalcaemia and raised creatinine phosphokinase. The anion gap may be raised. Acute complications include hypoxia, rhabdomyolysis, DIC and renal failure.

ECG changes include inverted T wave, AV block, prolonged PR interval and ST segment depression (Einav *et al*., 1997). Tachyarrhythmias are typical but bradyarrhythmias have been reported (Zee-Cheng *et al*., 1985; Einav *et al*., 1997).

Chronic exposure

Inhalation

Neurological effects

- Occupational exposure

  Schizophreniform psychosis has been reported following occupational exposure to toluene (Goldbloom and Chouinard, 1985) and intentional inhalation of toluene at work (Tarsh, 1979).

  Neurobehavioural tests for manual dexterity, visual scanning and verbal memory were statistically different in toluene exposed workers (88 ppm, range 49-130 ppm) compared to controls (13 ppm). The exposed workers had no clinical signs or symptoms of toxicity (Foo *et al*., 1990). A psychiatric study of workers exposed to toluene (50-80 ppm) found a significantly greater prevalence of mild chronic encephalopathy and organic affective syndrome compared to controls (Larsen and Leira, 1988). In another study there was no significant difference in neurophysical measures, motor conduction velocity, sensory conduction,

amplitude and distal latency in ulnar and median nerves in toluene exposed workers compared to controls (Cherry *et al*., 1985).

Toluene exposure is known to result in auditory and vestibular function alterations with hearing loss, motor inco-ordination and cerebellar dysfunction; in experimental animals there is strong evidence of toluene ototoxicity (Morata *et al*., 1995).

- Abuse of toluene

Blurred vision, nystagmus, tremor, anorexia, weight loss, inappropriate speech and behaviour, hallucinations, sensory function impairment including anosmia (loss of sense of smell) and hearing loss, memory loss, convulsions and cerebellar ataxia have been reported from toluene abuse (Streicher *et al*., 1981; Lazar *et al*., 1983; Hormes *et al*., 1986; Maas *et al*., 1991). Nausea, vomiting and haematemesis may also occur (Streicher *et al*., 1981).

Pancerebellar dysfunction, pyramidal tract abnormality, personality changes, emotional instability, paranoid psychosis (Byrne and Zibin, 1991), cognitive impairment and dementia (Hormes *et al*., 1986), central pontine myelinolysis (Hong *et al*., 1996) and Bell's palsy (Aleguas *et al*., 1991) have been reported from toluene abuse.

Hypothalamic syndrome with diabetes insipidus, adipsia, hypoprolactinaemia and poikilothermia with central sleep apnoea has been reported following use of a toluene-containing glue in a poorly ventilated over a period of 2 years (Teelucksingh *et al*., 1991).

EEG changes include slow wave abnormality (Lewis *et al*., 1981). Brain imaging of patients with chronic toluene abuse has shown diffuse atrophy including cerebral hemispheres, brain stem and cerebellum (Lewis *et al*., 1981; Hormes *et al*., 1986; Maas *et al*., 1991), cerebral perfusion impairment (Ryu *et al*., 1998), diffuse cortical atrophy (Hormes *et al*., 1986) and poor differentiation of grey and white matter (Rosenberg *et al*., 1988). Persistent neurological abnormality may occur in spite of some spontaneous recovery (Hormes *et al.,* 1986).

Severe muscle weakness with paralysis (Taher *et al*., 1974; Bennett and Forman, 1980; Kroeger *et al*., 1980; Streicher *et al*., 1981) due to marked hypokalaemia and hypophosphataemia (Streicher *et al*., 1981) has been reported. This clinical picture may be mistaken for Guillain-Barré syndrome (Streicher *et al*., 1981).

Renal, electrolyte and hepatic effects

Although there are isolated cases of hepatorenal failure following abuse of toluene (O'Brien *et al.,* 1971; Taverner *et al*., 1988) and accidental over-exposure at work (Knight *et al.,* 1991), chronic exposure to toluene in the work environment is generally not associated with severe renal or hepatic effects (Low *et al*., 1988; Ukai *et al*., 1993). However, chronic abuse of toluene can cause renal toxicity.

- Occupational exposure

A study of 452 exposed workers found no significant differences in hepatic and renal function tests compared to controls (Ukai *et al*., 1993). A study of 181 male workers in a rotogravure printing plant found that 54 had evidence of liver damage (elevated AST, ALT, GGT or hepatomegaly). However, liver damage was related to alcohol use and obesity in most cases. The workers with the greatest exposure to toluene had lower liver enzyme concentrations than the controls.

In a survey of 289 workers exposed primarily to toluene, 8 were found to have consistently abnormal liver enzyme values (i.e., on 3 or more occasions). All had mild elevations of ALT and AST (less than 2-3 times normal) with a marked increase in the ratio of ALT/AST (this is opposite to that observed in individuals with alcoholic liver disease). Liver biopsy showed mild, pericentral fatty changes. Other causes of these liver changes (obesity, diabetes and alcoholism) were excluded. The toluene concentration was less than 200 ppm and the duration of exposure varied from 2-8 hours a day. Exposure to other solvents was minimal but included ethanol, methanol, trichloroethylene and diethyl ether. No measurements of solvent concentrations were made (Guzelian *et al*., 1988).

Workers exposed to toluene (<100 ppm) had a significantly higher and increased prevalence of elevated retinol-binding protein in the urine. The concentration was found to correlate with *o*-cresol, but not with hippuric acid. No difference in the urinary albumin was found compared to the controls. Increased urinary concentrations of retinol-binding protein suggests impaired proximal tubular function (Ng *et al.*, 1990).

- Abuse of toluene

  Jaundice and raised bilirubin and liver enzymes (O'Brien *et al.*, 1971; Taverner *et al.*, 1988) and heptaomegaly (Taverner *et al.*, 1988) have been reported from toluene abuse.

  Elevated creatine phosphokinase concentrations and rhabdomyolysis (due to marked hypokalaemia and hypophosphataemia), haematuria, pyuria, albuminuria (Streicher *et al.*, 1981), myoglobinuria, glucosuria (Kamijima *et al.*, 1994), aminoaciduria (Moss *et al.*, 1980; Batlle *et al.*, 1988), oliguric renal failure (Gupta *et al.*, 1991) and anuria (O'Brien *et al.*, 1971) have been reported. Ammonia excretion may be high but this is probably due to chronic potassium depletion (Batlle *et al.*, 1988).

  There are many cases of renal tubular acidosis reported from toluene abuse (Taher *et al.*, 1974; Bennett and Forman, 1980; Kroeger *et al.*, 1980; Kirk *et al.*, 1984; Weinstein *et al.*, 1985; Patel and Benjamin, 1986; Lavoie *et al.,* 1987; Batlle *et al.*, 1988; Goodwin, 1988; Kamijima *et al.*, 1994; Carlisle *et al.*, 1991; Hong *et al.*, 1996; Gerkin and LoVecchio, 1998; Kamijo *et al.*, 1998). Distal renal tubular acidosis is more common, but proximal renal tubular acidosis and Fanconi's syndrome (Moss *et al.*, 1980) have been reported. There is usually hypokalaemia with hyperchloraemic acidosis (Taher *et al.,* 1974) and respiratory compensation (Streicher *et al.*, 1981). The anion gap is usually normal but may be elevated in patients with advanced renal failure (Hong *et al.*, 1996). Hypomagnesaemia may produce severe hypocalcaemia secondary to parathyroid hormone suppression (Wilkins-Haug and Gabow, 1991). Rhabdomyolysis induced renal failure has also been reported (Kao *et al.*, 2000).

  Fatal bilateral adrenal haemorrhage (Kamijo *et al.*, 1998) and nephrolithiasis (Kroeger *et al.*, 1980; Lazar *et al.*, 1983; Weinstein *et al.*, 1985) have been reported from chronic toluene abuse.

Haematological effects

Haematological effects are not a common feature of toluene toxicity. Haematological effects reported in the older literature may have been due to the presence of benzene, which was a common contaminant of toluene before the 1950s (Hayden *et al.*, 1977; Cohr and Stokholm, 1979; King, 1982).

A study of 452 toluene exposed workers found no significant differences in haematological parameters compared to controls (Ukai *et al.*, 1993). Mild anaemia, moderate thrombocytopenia and leucopenia were reported in 7 of 24 workers exposed to toluene for 3-15 years (mean 9.75 years) (Forni *et al.,* 1971).

Anaemia with low haemoglobin and haematocrit, anisocytosis and poikilocytosis on blood smear was reported in a worker exposed to toluene for 40 years. Biopsy confirmed myelofibrosis and osteosclerosis, megakaryocytic hyperplasia and decreased erthyroid and myeloid elements. No benzene was found in the solvent used (Bosch *et al.,* 1988).

Immunotoxicity

A study of 35 painters exposed to benzene, toluene and xylene found that they had significantly lower immunoglobulin A (IgA) and IgG concentrations, but increased IgM. This was thought to be due to a suppressive action of benzene on immunoglobulin producing cells, resulting in inhibition of DNA synthesis (Lange *et al.,* 1973). Serum complement concentrations were decreased in 62 of 79 workers exposed to benzene, toluene and xylene for 0.25 to 18 years (Smolik *et al.*, 1973).

Workers exposed to *n*-hexane (mean breathing air zone concentration 58 ppm; range 4.3-300 ppm), toluene (mean 27 ppm; range 5.37-115.2 ppm) and methyl ethyl ketone (mean 11 ppm; range 2.43-47 ppm) had no impairment of natural killer cell activity or changes in interleukin-2 or gamma-interferon concentrations (Yücesoy *et al.*, 1999).

Other effects

ECG changes including multifocal premature ventricular contractions and supraventricular tachycardia have been reported in toluene abusers (Streicher *et al*., 1981). These changes are probably due to electrolyte imbalance, particularly hypokalaemia and hypomagnesaemia. Myocardial infarction (Cunningham *et al*., 1987), including recurrent non-Q-wave myocardial infarction (Hussain *et al*., 1996), has been reported after chronic abuse of toluene.

Myelofibrosis and focal segmental glomerulosclerosis have been reported in a worker exposed to toluene for 40 years (Bosch *et al.,* 1988). Transient hypothyroidism has been reported from toluene abuse (Hong *et al*., 1996).

Behavioural studies in animals exposed to toluene have shown hyperactivity, ataxia, addiction, insomnia and memory disturbance (Saito and Wada, 1993).

Dermal

Contact dermatitis may occur following chronic dermal exposure to toluene (Gerarde, 1960; Low *et al*., 1988). Repeated application of toluene to rabbit skin caused erythema, oedema, exfoliation, blistering and slight necrosis (Wolf *et al*., 1956).

Eye

Chronic exposure to toluene can cause neuro-ophthalmological changes and affect colour vision.

- Occupational exposure

  Workers exposed long-term to low concentrations of toluene (as confirmed by measurement of hippuric acid and *ortho*-cresol in the urine) had changes in evoked visual potentials compared to controls (Vrca *et al*., 1995). Another survey found abnormal visual evoked potentials in 24% of exposed workers. The visual evoked potential measurements were repeated two years later in 78% of the group and no significant differences were found. Exposure was confirmed by urine hippuric acid and blood toluene measurements (Urban and Lukas, 1990). Such results are interpreted as a subclinical sign of dysfunction of the CNS.

  Erythopsia (red vision) has occasionally been reported following occupational exposure and abuse of toluene (Grant and Schuman, 1993). Loss of colour vision has been reported with some organic solvents including toluene (Muttray *et al*., 1999), however some studies have demonstrated no colour vision loss with toluene exposure (Nakatsuka *et al*., 1992).

- Abuse of toluene

  Neuro-ophthalmological changes have been reported after chronic abuse of toluene. These include pendular nystagmus, ocular flutter, opsoclonus, oscillopsia, ocular dysmetria and bilateral internuclear ophthalmoplegia (Lazar *et al*., 1983; Hormes *et al*., 1986; Maas *et al*., 1991; Hunnewell and Miller, 1998) and optic neuropathy (Keane, 1978).

Ingestion

No information available.

Carcinogenicity

There is inadequate evidence in humans for the carcinogenicity of toluene and evidence suggesting lack of carcinogenicity in animals. Consequently, toluene has been placed in Group 3 by IARC and is not classifiable as to its carcinogenicity in humans (IARC, 1999).

In a study of 1,020 printers exposed to toluene for at least 3 months there was no increase in mortality. There was no increase in non-malignant diseases of the lungs, nervous system or gastrointestinal or urinary tract. There was no excess of tumours. Only cancers of the respiratory tract were significantly increased, but the significance of this was lost when only those exposed for more than 5 years and a latency of 10 years were included (Svensson *et al*., 1990). A large study of toluene exposed rotogravure workers (6,830 individuals) found an increased, but not significant, elevation of mortality from lung cancer, and an elevated mortality from cancer of the bone and connective tissue; these were both highly significant (Wiebelt and Becker, 1999).

Genotoxicity

Data on chromosome damage in peripheral lymphocytes in toluene exposed workers are conflicting, with small numbers studied and insufficient information on exposure to other chromosome damaging chemicals (particularly benzene). Consequently, unequivocal evaluation of the genotoxic potential of toluene cannot be made (IPCS, 1985; Von Burg, 1993). Studies on the mutagenicity and genotoxicity of toluene in experimental animals and cell culture have usually been negative (Dean, 1985; IPCS, 1985; McGregor, 1994).

A study of the peripheral lymphocytes of workers exposed to toluene for 3-15 years (mean 9.75 years) found that the incidence of aberrations was slightly higher than in the controls but the difference was not statistically significant (Forni *et al.,* 1971). A study of 32 rotogravure workers (average concentration of toluene 7-112 ppm, the level of benzene contamination in the toluene was benzene <0.05%) found no significant increase in the number of sister chromatid exchanges (SCEs) or chromosome aberrations compared to controls (Mäki-Paakkanen *et al*., 1980). A study of 17 workers (employed 0.8-44 years, average 22.8 years) exposed to several solvents but particularly toluene (1-1257 mg/m^3; 0.27-334 ppm) and xylene (14-6,074 mg/m^3, 3.2-1397 ppm) found no differences in SCEs or chromosome aberrations compared to controls (Haglund *et al*., 1980).

Shoe workers exposed to a mixture of organic solvents, including toluene, showed no induction of DNA damage as measured by the alkaline single-cell gel electrophoresis (or Comet) assay. Toluene exposure correlated with the urinary hippuric acid concentration (Pitarque *et al*., 1999).

An experimental study of exposure to toluene, xylene or a mixture of the two (toluene 50 ppm, xylene 40 ppm for 7 hours a day for 3 consecutive days on 3 occasions, 2 weeks apart) in 5 individuals, found no significant effect on SCEs, cell cycle delay or cell mortality. Also, exposure of human lymphocytes *in vitro* to toluene (0-2.5 mM), xylene (0-2 mM) or their mixture had no observable effect at low concentrations, with only increased cell mortality occurring at higher concentrations (Richer *et al*., 1993).

Another study of 20 rotogravure workers exposed to toluene (200-300 ppm for >16 years, the level of benzene contamination in the toluene was benzene <0.3%) found a significantly higher incidence of structural chromosome changes (chromatid breaks, exchanges and gaps) and SCEs (Bauchinger *et al*., 1982). A study of lymphocytes from 14 workers exposed to toluene (possibly containing a low concentration of benzene) showed an excess of chromosome aberrations compared to controls. In most cases exposure was sufficient to cause headache, fatigue, and sometimes nausea, vertigo and a feeling of inebriation (Funes-Cravioto *et al*., 1977).

In vitro studies on human lymphocytes exposed to various toluene concentrations found no increase in SCEs or the number of chromosome aberrations. However, at the higher concentrations there was significant cell growth inhibition (Gerner-Smidt and Friedrich, 1978).

DNA damage has been observed with minor metabolites of toluene in an *in vitro* study (Murata *et al.,* 1999). The compounds studied were methylhydroquinone and methylbenzoquinone (derivatives of hydroquinone and 1,4-benzoquinone which are also metabolites of benzene, a known human carcinogen). Hydroxylation of cresol produces methylhydroquinone, which undergoes spontaneous oxidation to produce methylbenzoquinone.

Reproductive toxicity

There is some evidence to suggest that toluene exposure may have adverse effects on reproductive parameters. However, the data are conflicting and no definite conclusion can be reached.

Fertility

Male workers exposed to toluene have lower luteinising hormone (LH), follicle stimulating hormone (FSH) and testosterone levels (Svensson *et al*., 1992a,b). This may be due to toluene induced suppression of LH and FSH secretion by the pituitary and/or suppression of hypothalamic gonadotrophic releasing hormone (GnRH). This is supported by the findings in animals and a human postmortem, that toluene preferentially distributes to the brainstem, including the hypothalamus (Ameno *et al*., 1992). An experimental study in men and women found no changes in LH or FSH secretion after a 3 hour exposure to toluene (Luderer *et al*., 1999). A study of toluene exposed workers found that low level exposure was associated with reduced fertility in women but not in men (Plenge-Bönig and Karmaus, 1999).

Testicular atrophy with evidence of impaired or suppressed spermatogenesis was noted at postmortem examination of a 28 year old male who was found dead after toluene abuse (Suzuki *et al*., 1983).

Some studies suggest that women exposed to toluene have a higher incidence of menstrual disorders (reviewed in Barlow and Sullivan, 1982). However, these data are difficult to evaluate; there may have been other factors affecting gynaecological function and the workers were exposed to a mixture of solvents. A more recent study did not demonstrate a higher incidence of menstrual disorders in workers exposed to toluene (Ng *et al.,* 1992a).

Pregnancy

Extrapolation from animal data, suggests that well controlled occupational exposure to toluene does not pose a significant risk to the fetus (Wilkins-Haug, 1997). Teratogenicity can occur, however, following exposure through intentional abuse (Toutman and Lippmann, 1979; Streicher *et al*., 1981; Hersh *et al.,* 1985; Goodwin, 1988; Wilkins-Haug and Gabow, 1991; Arnold *et al*., 1994; Pearson *et al*., 1994; Wilkins-Haug, 1997) and chronic or excessive industrial accidents (Wilkins-Haug, 1997). The teratogenic effects of toluene *in utero* may be influenced by co-exposure to other substances, particularly ethanol, and intermittent toluene induced metabolic acidosis which may cause fetal hypoxia (Wilkins-Haug, 1997).

In a study of laboratory workers exposed to various chemicals, exposure to toluene was associated with an increased risk of spontaneous abortion (Taskinen *et al*., 1994). Similarly, there were higher rates of spontaneous abortion in workers exposed to high concentrations of toluene (mean 88 ppm, range 50-150 ppm; 12.4 per 100 pregnancies) compared to controls. There were two groups of controls, workers exposed to little or no toluene (0.25 ppm; 2.9 per 100 pregnancies) and women from a community antenatal and postnatal clinic (4.5 per 100 pregnancies). Among the exposed workers there were also differences in the rate of spontaneous abortion before (2.9 per 100 pregnancies) and after employment (12.6 per 100 pregnancies) in the factory (Ng *et al*., 1992b).

A study of men exposed to a mixture of solvents found that spontaneous abortion in their partners was significantly associated with paternal exposure to organic solvents in general, high/frequent exposure to toluene and miscellaneous organic solvents (Taskinen *et al*., 1989).

Abuse of toluene during pregnancy has caused fetal abnormalities (Streicher *et al*., 1981) which resemble those seen with fetal alcohol syndrome (Toutman and Lippmann, 1979; Wilkins-Haug and Gabow, 1991; Pearson *et al*., 1994). These include microcephaly, narrow bi-frontal diameter, short palpebral fissures, deep set eyes, flat mid-face, flat nasal bridge and small nose (Wilkins-Haug, 1997). Digital hypoplasia and minor urinary tract abnormalities have also been reported (Hersh *et al.,* 1985; Goodwin, 1988; Pearson *et al*., 1994). There is also a risk of interuterine growth retardation and developmental and neurological effects including language impairment, developmental delays, hyperactivity and cerebellar dysfunction (Streicher *et al*., 1981; Hersh *et al.,* 1985; Goodwin, 1988; Wilkins-Haug and Gabow, 1991; Arnold *et al*., 1994; Pearson *et al*., 1994; Wilkins-Haug, 1997). A study of 18 children born to mothers who abused toluene during pregnancy found that 83% had craniofacial features similar to those seen with fetal alcohol syndrome; in addition 89% of these children had other minor anomalies. Other findings were: 39% of children were born prematurely, 9% died during the perinatal period, 54% were small for their gestational age, 52% had continued postnatal growth deficiency, 33% had prenatal microcephaly, 67% had postnatal microcephaly and 80% had developmental delay (Pearson *et al*., 1994).

Hyperchloraemic acidosis was reported in 2 neonates born to mothers who presented with renal tubular acidosis after chronic toluene abuse (Goodwin, 1988). The hyperchloraemic acidosis resolved in the newborns within 72 hours. The urinary hippurate concentration was not elevated in these babies but toluene was found in the serum (1.2 mg/l) of one child. Hypocalcaemia has also been reported in neonates born to mothers admitted to hospital with toluene abuse (Wilkins-Haug and Gabow, 1991).

Toluene has also been implicated in cases of congenital abnormalities where the mother was occupationally exposed to organic solvent mixtures during pregnancy (Holmberg, 1979; McDonald *et al.,* 1987). In a study of occupational chemical exposure in 301 women, there was an excess of congenital defects in those exposed to aromatic hydrocarbons compared to controls. Of this group most of the cases involved toluene, and the defects were predominantly renal or gastrointestinal (McDonald *et al*., 1987).

In animal studies toluene does not appear to be teratogenic but it is fetotoxic (Barlow and Sullivan, 1982; IPCS, 1985). However, this may be because the concentrations used may not reflect those which cause abnormalities in children borne to mothers who abuse toluene. A study in pregnant mice using high intermittent exposure, to mimic exposure in toluene abusers, found behavioural and neurological effects consistent with those findings in children born to mothers abusing toluene during pregnancy. These effects occurred in the absence of obvious maternal or fetal toxicity (Jones and Balster, 1997).

RISK GROUPS

The enzyme aldehyde dehydrogenase (ALDH) is involved in the metabolism of toluene; it converts benzaldehye to benzoic acid. Genetic polymorphisms may result in deficiency of this enzyme in some populations (e.g., Japanese and Native Americans). Complete deficiency of this enzyme, which is also involved in ethanol metabolism, results in intolerance to alcohol. A study in Japanese workers demonstrated lower urinary hippuric acid concentrations in individuals homozygous for the inactive form of ALDH, reflecting lower rates of toluene metabolism. As a consequence, these individuals would be expected to have higher benzaldehyde concentrations (Kawamoto *et al*., 1994).

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Gastric lavage may be considered if ingestion was recent, however, because of the risk of aspiration a cuffed endotracheal tube must be used to protect the airway. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive. See below for management of systemic effects.

Systemic effects

It is essential to check electrolytes, blood gases, renal and hepatic function, urinalysis and creatine phosphokinase (CPK) particularly in patients with generalised weakness. Monitor ECG in symptomatic patients.

Renal tubular acidosis is treated conventionally with correction of hypokalaemia then acidosis. It is essential to correct the hypokalaemia before giving sodium bicarbonate as bicarbonate worsens hypokalaemia and hypocalcaemia. This can result in arrhythmias and rhabdomyolysis. No attempt should be made to correct acidosis until the potassium concentration is above 3 mmol/l (Kroeger *et al*., 1980). Potassium chloride should not be used since patients usually have hyperchloraemic acidosis. Regular monitoring of electrolytes, blood gases and ECG is essential. Hypocalcaemia (resulting in tetany) may occur during fluid and electrolyte repletion and should be managed with calcium supplementation if necessary.

Antidotes

There is no specific antidote for toluene.

Chronic exposure

In most cases of chronic poisoning clinical effects resolve gradually once exposure has ceased. There is no withdrawal syndrome (Hormes *et al*., 1986). A chronic toluene abuser with progressive cerebellar dysfunction and visual deterioration (reduced acuity and defective colour vision) did not improve with 5 months of abstinence, but showed dramatic improvement after amantadine administration for 3 months. When amantadine was stopped his condition deteriorated. After two years of therapy he showed great improvement and had only mild dysarthria, visual acuity (6/12) and mildly impaired colour vision (Deleu and Hanssens, 2000).

REFERENCES

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Aleguas A, Linakis JG, Lewander WJ. 1991 Bell's palsy associated with toluene exposure. *Vet Hum Toxicol* 33 (4):372.

Ameno K, Fuke C, Ameno S, Kiriu T, Sogo K, Ijiri I. 1989 A fatal case of oral ingestion of toluene. *Forensic Sci Int* 41:255-260.

Ameno K, Kiriu T, Fuke C, Ameno S, Shinohara T, Ijiri I. 1992 Regional brain distribution of toluene in rats and in a human autopsy. *Arch Toxicol* 66:153-156.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Angerer J, Krämer A. 1997 Occupational chronic exposure to organic solvents. XVI. Ambient and biological monitoring of workers exposed to toluene. *Int Arch Occup Environ Health* 69:91-96.

Anshelm Olson B, Gamberale F, Iregren A. 1985 Co-exposure to toluene and *p*-xylene in man: central nervous functions. *Br J Ind Med* 42:117-122.

Apostoli P, Brugnone F, Perbellini L, Cocheo V, Bellomo ML, Silvestri R. 1982 Biomonitoring of occupational toluene exposure. *Int Arch Occup Environ Health* 50:153-168.

Arnold G, Kirby RS, Langendoerfer S, Wilkins-Haug L. 1994 Toluene embryopathy: clinical delineation and development follow-up. *Pediatrics* 93 (2):216-220.

Åstrand I, Ehrner-Samuel H, Kilbom Å, Övrum P. 1972 Toluene exposure I: Concentration in alveolar air and blood at rest and during exercise. *Work Environ Health* 9:119-130.

Åstrand I. 1975 Uptake of solvents in the blood and tissues of man. *Scand J Work Environ Health* 1:199-218.

Baelum J, Lundqvist GR, Mølhave L, Andersen NT. 1990 Human response to varying concentrations of toluene. *Int Arch Occup Environ Health* 62:65-71.

Baelum J, Mølhave L, Hansen ST, Døssing M. 1993 Hepatic metabolism of toluene after gastrointestinal uptake in humans. *Scand J Work Environ Health* 19:55-62.

Bakinson MA, Jones RD. 1985 Gassings due to methylene chloride, xylene, toluene, and styrene reported to Her Majesty's Factory Inspectorate 1961-80. *Br J Ind Med* 42:184-190.

Barlow SM, Sullivan FM. 1982 *Reproductive Hazards of Industrial Chemicals. An evaluation of animal and human data*. Academic Press, London.

Batlle DC, Sabatini S, Kurtzman NA. 1988 On the mechanism of toluene-induced renal tubular acidosis. *Nephron* 49:210-218.

Bauchinger M, Schmid E, Dresp J, Kolin-Gerresheim J, Hauf R, Suhr E. 1982 Chromosome changes in lymphocytes after occupational exposure to toluene. *Mutat Res* 102:439-445.

Benignus VA. 1981a Health effects of toluene: a review. *Neurotoxicology* 2:567-588.

Benignus VA. 1981b Neurobehavioral effects of toluene: a review. *Neurobehav Toxicol Teratol* 3:407-415.

Bennett RH, Forman HR. 1980 Hypokalaemic periodic paralysis in chronic toluene exposure. *Arch Neurol* 37:673.

Biscaldi GP, Mingardi M, Pollini G, Moglia A, Bossi MC. 1981 Acute toluene poisoning. Electroneurophysiological and vestibular investigations. *Toxicol Eur Res* 3 (6):271-273.

Boewer C, Enderlain G, Wollgast U, Mawka S, Palowski H, Bliber R. 1988 Epidemiological study on the hepatotoxicity of occupational toluene exposure. *Int Arch Occup Environ Health* 60:181-186.

Bosch X, Campistol JM, Montoliu J, Revert L. 1988 Myelofibrosis and focal segmental glomerulosclerosis associated with toluene poisoning. *Hum Toxicol* 7:357-361.

Brugnone F, Perbellini L, Grigolini L, Cazzadori A, Gaffuri E. 1976 Alveolar air and blood toluene concentration in rotogravure workers. *Int Arch Occup Environ Health* 38:45-54.

Brugnone F, Perbellini L, Apostoli P, Locatelli M, Mariotto P. 1983 Decline of blood and alveolar toluene concentration following two accidental human poisonings. *Int Arch Occup Environ Health* 53:157-165.

Brugnone F, de Rosa E, Perbellini L, Bartolucci GB. 1986 Toluene concentration in the blood and alveolar air of workers during the workshift and the morning after. *Br J Ind Med* 43:56-61.

Byrne A, Zibin T. 1991 Toluene-related psychosis. *Br J Psychiatry* 158:578.

Campbell L, Marsh DM, Wilson HK. 1987 Towards a biological monitoring strategy for toluene. *Ann Occup Hyg* 31 (2):121-133.

Caperos JR, Fernàndez JG. 1977 Simultaneous determination of toluene and xylene metabolites in urine by gas chromatography. *Br J Ind Med* 34:229-233.

Carder JR, Fuerst RS. 1997 Myocardial infarction after toluene inhalation. *Pediatr Emerg Care* 13 (2):117-119.

Caravati EM, Bjerk PJ. 1997 Acute toluene ingestion toxicity [letter]. *Ann Emerg Med* 30 (6):838-839.

Carlisle EJF, Donnelly SM, Vasuvattakul S, Kamel KS, Tobe S, Halperin ML. 1991 Glue-sniffing and distal renal tubular acidosis: sticking to the facts. *J Am Soc Nephrol* 1 (8):1019-1027.

Carlsson A. 1982 Exposure to toluene. Uptake, distribution and elimination in man. *Scand J Work Environ Health* 8:43-55.

Cherry N, Hutchins H, Pace T, Waldron HA. 1985 Neurobehavioural effects of repeated occupational exposure to toluene and paint solvents. *Br J Ind Med* 42:291-300.

Cohr K-H, Stokholm J. 1979 Toluene. A toxicologic review. *Scan J Work Environ Health* 5 (2):71-90.

Cunningham SR, Dalzell GWN, McGirr P, Khan MM. 1987 Myocardial infarction and primary ventricular fibrillation after glue sniffing. *Br Med J* 294:739.

Dean BJ. 1985 Recent findings on the genetic toxicology of benzene, toluene and xylene. *Mutat Res* 154:153-181.

Deleu D, Hanssens Y. 2000 Cerebellar dysfunction in chronic toluene abuse: beneficial response to amantadine hydrochloride. *Clin Toxicol* 38 (1):37-41.

De Rosa E, Bartolucci GB, Sigon M, Callegaro R, Perbellini L, Brugnone F. 1987 Hippuric acid and *ortho*-cresol as biological indicators of occupational exposure to toluene. *Am J Ind Med* 11:529-537.

Echverria D, Fine L, Langolf G, Schork A, Sampaio C. 1989 Acute behavioural effects of toluene. *Br J Ind Med* 46:483-495.

Einav S, Amitai Y, Reichman J, Geber D. 1997 Bradycardia in toluene poisoning. *Clin Toxicol* 35 (3):295-298.

Foo SC, Jeyaratnam J, Koh D. 1990 Chronic neurobehavioural effects of toluene. *Br J Ind Med* 47:480-484.

Forni A, Pacifico E, Limonta A. 1971 Chromosome studies in workers exposed to benzene or toluene or both. *Arch Environ Health* 22:373-378.

Funes-Cravioto F, Zapata-Gayon C, Kolmodin-Hedman B, Lambert B, Lindsten J, Norberg E, Nordenskjöld M, Olin R, Swensson Å. 1977 Chromosome aberrations and sister chromatid exchange in workers in chemical laboratories and a rotoprinting factory and in children of women laboratory workers. *Lancet* 2:322-325.

Garriott JC, Foerster E, de la Garza F, Mendiola I, Curoe J. 1981 Measurement of toluene in blood and breath in cases of solvent abuse. *Clin Toxicol* 18 (4):471-479.

Gerarde HW. 1960 *Toxicology and Biochemistry of Aromatic Hydrocarbons*. Elsevier, Amsterdam.

Gerkin RD, LoVecchio F. 1998 Rapid reversal of life-threatening toluene-induced hypokalaemia with hemodialysis. *J Emerg Med* 16 (5):723-725.

Gerner-Schmit P, Friedrich U. 1978 The mutagenic effects of benzene, toluene and xylene studied by the SCE technique. *Mutat Res* 58:313-316.

Ghittori S, Imbriani M, Pezzagno G, Capodaglio E. 1987 The urinary concentration of solvents as a biological indicator of exposure: proposal for the biological equivalent exposure limit for nine solvents. *Am Ind Hyg Assoc* 48:786-790.

Gill R, Hatchett SE, Osselton ND, Wilson HK, Ramsey JD. 1988 Sample handling and storage for the quantitative analysis of volatile compounds in blood: the determination of toluene by headspace gas chromatography. *J Anal Toxicol* 12:141-146.

Goldbloom D, Chouinard G. 1985 Schizophreniform psychosis associated with chronic industrial toluene exposure: case report. *J Clin Psychiatry* 46:350-351.

Goodwin TM. 1988 Toluene abuse and renal tubular acidosis in pregnancy. *Obstet Gynecol* 71 (5):715-718.

Grant WM, Schuman, JH. 1993 *Toxicology of the Eye,* fourth edition. Charles C Thomas, Springfield, Illinois.

Gupta RK, van der Meulen J, Johny KV. 1991 Oliguric acute renal failure due to glue-sniffing. *Scand J Urol* 25:247-250.

Gusev IS. 1965. Reflective effects of microconcentrations of benzene, toluene and xylene and their comparative assessment. *Hyg Sanit* 30:331-336.

Guzelian P, Mills S, Fallon HJ. 1988 Liver structure and function in print workers exposed to toluene. *J Occup Med* 30 (10):791-796.

Haglund U, Lundberg I, Zech L. 1980 Chromosome aberrations and sister chromatid exchanges in Swedish paint industry workers. *Scand J Work Environ Health* 6:291-298.

Harbison RD. 1998 Aromatic hydrocarbons. in *Hamilton and Hardy's Industrial Toxicology*, fifth edition. Harbison RD (editor). Mosby, St Louis.

Hayden JW, Peterson RG, Bruckner JV. 1977 Toxicology of toluene (methylbenzene): review of current literature. *Clin Toxicol* 11 (*5*):549-559.

Hersh JH, Podruch PE, Rogers G, Weisskopf B. 1985 Toluene embryopathy. *J Pediatr* 106 (6):922-927.

Hobara T, Okuda M, Gotoh M, Oki K, Segawa H, Kunitsugu I. 2000 Estimation of lethal toluene concentration from the accidental death of painting workers. *Ind Health* 38:228-231.

Holmberg PC. 1979 Central-nervous-system defects in children born to mothers exposed to organic solvents during pregnancy. *Lancet* 2:177-179.

Hong J-J, Lin J-L, Wu M-S, Huang C-C, Verberckmoes R. 1996 A chronic glue sniffer with hyperchloremia, metabolic acidosis, rhabdomyolysis, irreversible quadriplegia, central pontine myelinolysis, and hypothyroidism. *Nephrol Dial Tranplant* 11:1848-1849.

Hormes JT, Filley CM, Rosenberg NL. 1986 Neurological sequelae of chronic solvent abuse. *Neurology* 36:698-702.

Hunnewell J, Miller NR. 1998 Bilateral internuclear ophthalmoplegia related to chronic toluene abuse. *J Neuro-Ophthalmol* 18 (4):277-280.

Hussain TF, Heidenreich PA, Benowitz N. 1996 Recurrent non-Q-wave myocardial infarction associated with toluene abuse. *Am Heart J* 131 (3):65-616.

IARC (International Agency for Research on Cancer). 1999 *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*. IARC Monograph 71.

Ikeda N, Takahashi H, Umetsu K, Suzuki T. 1990 The course of respiration and circulation in 'toluene-sniffing'. *Forensic Sci Int* 44:151-158.

Inoue O, Seiji K, Watanabe T, Kasahara M, Nakatsuka H, Yin S, Li G, Cai S, Jin C, Ikeda M. 1988 Mutual metabolic suppression between benzene and toluene in man. *Int Arch Occup Environ Health* 60:15-20.

IPCS. 1985 *Environmental Health Criteria 52: Toluene*. World Health Organization, International Programme on Chemical Safety, Geneva.

Jones HE, Balster RL. 1997 Neurobehavioral consequences of intermittent prenatal exposure to high concentrations of toluene. *Neurotoxicol Teratol* 19 (4):305-313.

Kamijima M, Nakazawa Y, Yamakawa M, Shibata E, Hisanaga E, Ono Y, Toida M, Takeuchi Y. 1994 Metabolic acidosis and renal tubular injury due to pure toluene inhalation. *Arch Environ Health* 49 (5):410- 413.

Kamijo Y, Soma K, Hasegawa I, Ohwada T. 1998 Fatal bilateral adrenal hemorrhage following acute toluene poisoning: a case report. *Clin Toxicol* 36 (4):365-368.

Kao K-C, Tsai Y-H, Lin M-C, Huang C-C, Tsao C-Y, Chen Y-C. 2000 Hypokalemic muscular paralysis causing acute renal failure due to rhabdomyolysis with renal tubular acidosis in a chronic glue sniffer. *Clin Toxicol* 38 (67):679-681.

Kawai T, Mizunuma K, Yasugi T, Horiguchi S, Ikeda M. 1994 Toluene in blood as a marker of choice for low-level exposure to toluene. *Int Arch Occup Environ Health* 66:309-313.

Kawamoto TK, Matsuno Y, Kodama Y, Murata K, Matsuda S. 1994 ALDH2 polymorphism and biological monitoring of toluene. *Arch Environ Health* 49 (5):332-336.

Keane JR. 1978 Toluene optic neuropathy. *Ann Neurol* 4 (4):390.

King MD. 1982 Neurological sequelae of toluene abuse. *Hum Toxicol* 1:281-287.

Kira S. 1977 Measurement by gas chromatography of urinary hippuric acid and methylhippuric acid as indices of toluene and xylene exposure. *Br J Ind Med* 34:305-309.

Kirk LM, Anderson RJ, Martin K. 1984 Sudden death from toluene abuse. *Ann Emerg Med* 13:68-69.

Kim SK, Kim YC. 1996 Effect of a single administration of benzene, toluene or *m*-xylene on carboxyhaemoglobin elevation and metabolism in rats. *J Appl Toxicol* 16(5):437-444.

Knight AT, Pawsey CGK, Aroney RS, Lawrence JR, Jones DB, Newland RC. 1991 Upholsters' glue associated with myocarditis, hepatitis, acute renal failure and lymphoma. *Med J Aust* 154 940:360-362.

Kroeger RM, Moore RJ, Lehman TH, Giesy JG, Skeeters CE. 1980 Recurrent urinary calculi associated with toluene sniffing. *J Urol* 123:89-91.

Lange A, Smolik R, Zatoński W, Szymańska J. 1973 Serum immunoglobulin levels in workers exposed to benzene, toluene and xylene. *Int Arch Arbeitsmed* 31:37-44.

Larsen F, Leira HL. 1988 Organic brain syndrome and long-term exposure to toluene: a clinical psychiatric study of vocationally active printing workers. *J Occup Med* 30 (11):875-878.

Lavoie FW, Dolan MC, Danzi DF, Barber RL. 1987 Recurrent resuscitation and 'no code' orders in a 27 year old spray paint abuser. *Ann Emerg Med* 16:1266-1273.

Lazar RB, Ho SU, Melen O, Daghestani AN. 1983 Multifocal central nervous system damage caused by toluene abuse. *Neurology* 33:1337-1340.

Lewis JD, Moritz D, Mellis LP. 1981 Long-term toluene abuse. *Am J Psychiatry* 138 (3):368-370.

Löf A, Wigaeus Hjelm E, Collmsjö A, Lundmark B-O, Norström Å, Sato A. 1993 Toxicokinetics of toluene and urinary excretion of hippuric acid after human exposure to $^{2}H_{8}$-toluene. *Br J Ind Med* 50:55-59.

Low LK, Meeks JR, Mackerer CR. 1988 Health effects of the alkylbenzenes. I. Toluene. *Toxicol Ind Health* 4 (1):49-75.

Luderer U, Morgan MS, Brodkin CA, Kalman DA, Faustman EA. 1999 Reproductive endocrine effects of acute exposure to toluene in men and women. *Occup Environ Med* 56:657-666.

Maas EF, Ashe J, Spiegel P, Zee DS, Leigh RJ. 1991 Acquired pendular nystagmus in toluene addiction. *Neurology* 41:282-285.

Mäki-Paakkanen J, Husgafvel-Pursiainen K, Kalliomäki P-L, Tuominen J, Sorsa M. 1980 Toluene-exposed workers and chromosome aberrations. *J Toxicol Environ Health* 6:775-781.

McDonald JC, Lavoie J, Côté R, McDonald AD. 1987 Chemical exposures at work in early pregnancy and congenital defect: a case-referent study. *Br J Ind Med* 44:527-533.

McGregor D. 1994 The genetic toxicology of toluene. *Mutat Res* 317:213-228.

Meulenbelt J, de Groot G, Savelkoul TJF. 1990 Two cases of acute toluene intoxication. *Br J Ind Med* 47:417-420.

Monster AC, Kezic S, van de Gevel I, de Wolff FA. 1993 Evaluation of biological monitoring parameters for occupational exposure to toluene. *Int Arch Occup Environ Health* 65:S159-S162.

Morata TC, Nylén P, Johnson A-C, Dunn DE. 1995 Auditory and vestibular functions after single or combined exposure to toluene: a review. *Arch Toxicol* 69:431-443.

Moss AH, Gabow PA, Kaehny WD, Goodman SI, Haut LL, Haussler MR. 1980 Fanconi's syndrome and distal renal tubular acidosis after glue sniffing. *Ann Intern Med* 92:69-70.

Murata M, Tsujikawa M, Kawanishi S. 1999 Oxidative DNA damage by minor metabolites of toluene may lead to carcinogenesis and reproductive dysfunction. *Biochem Biophys Res Comm* 261:478-483.

Muttray A, Wolters V, Jung D, Konietzko J. 1999 Effects of high doses of toluene on color vision. *Neurotoxicol Teratol* 21 (1):41-45.

Nakatsuka H, Watanabe T, Takeuchi Y, Hisanaga N, Shibata E, Suzuki H, Huang M-Y, Chen Z, Qu Q-S, Ikeda M. 1992 Absence of blue-yellow colour vision loss among workers exposed to toluene or tetrachloroethylene mostly at levels below occupational exposure limits. *Int Arch Occup Environ Health* 64:113-117.

Ng TP, Ong SG, Lam WK, Jones MG, Cheung CK, Ong CN. 1990 Urinary levels of proteins and metabolites in workers exposed to toluene. *Int Arch Occup Environ Health* 62:43-46.

Ng TP, Foo SC, Yoong T. 1992a Menstrual function in workers exposed to toluene. *Br J Ind Med* 49:799-803.

Ng TP, Foo SC, Yoong T. 1992b Risk of spontaneous abortion in workers exposed to toluene. *Br J Ind Med* 49:804-808.

Nise G, Attewell R, Skerfving S, Ørbæk P. 1989 Elimination of toluene from venous blood and adipose tissue after occupational exposure. *Br J Ind Med* 46:407-411.

Nise G. 1992 Urinary excretion of *o*-cresol and hippuric acid after toluene exposure in rotogravure printing. *Int Arch Occup Environ Health* 63:377-381.

Nomiyama K, Nomiyama H. 1974 Respiratory elimination of organic solvents in man. *Int Arch Arbeitsmed* 32:85-91.

O'Brien ET, Yeoman WB, Hobby JAE. 1971 Hepatorenal damage from toluene in a 'glue sniffer'. *Br Med J* 2:29-30.

Ogata M, Tomokuni K, Takatsuka Y. 1970 Urinary excretion of hippuric acid and *m*- or *p*-methylhippuric acid in the urine of persons exposed to vapours of toluene and *m*- or *p*-xylene as a test of exposure. *Br J Ind Med* 27:43-50.

Övrum P, Hultengren M, Lindqvist T. 1978 Exposure to toluene in a photogravure printing plant. Concentration in ambient air and uptake in the body. *Scand J Work Environ Health* 4:237-245.

Patel R, Benjamin J. 1986 Renal disease associated with toluene inhalation. *Clin Toxicol* 24 (3):213-223.

Pearson MA, Hoyme HE, Seaver LH, Rimsza ME. 1994 Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome. *Pediatrics* 93 (2):211-215.

Pekari K, Riekkola M-L, Aitio A. 1989 Simultaneous determination of benzene and toluene in the blood using headspace gas chromatography. *J Chromatog* 491:309-320.

Pitarque M, Vaglenov A, Nosko M, Hirvonen A, Norppa H, Creus A, Marcos R. 1999 Evaluation of DNA damage by the Comet assay in shoe workers exposed to toluene and other organic solvents. *Mutat Res* 441:115-127.

Plenge-Bönig A, Karmaus W. 1999 Exposure to toluene in the printing industry is associated with subfecundity in women but not in men. *Occup Environ Med* 56:445-448.

Pyykkö K, Tähti H, Vapaatalo H. 1977 Toluene concentrations in various tissues of rats after inhalation and oral administration. *Arch Toxicol* 38:169-176.

Reisin E, Teicher A, Jaffe R, Eliahou HE. 1975 Myoglobinuria and renal failure in toluene poisoning. *Br J Ind Med* 32:163-168.

Richer C-L, Chakrabarti S, Senécal-Quevillon M, Duhr MA, Zhang XX, Tardif R. 1993 Cytogenetic effects of low-level exposure to toluene, xylene and their mixture on human blood lymphocytes. *Int Arch Occup Environ Health* 64:581-585.

Rosenberg NL, Kleinschmidt-DeMasters BK, Davis KA, Dreisbach JN, Hormes JT, Filley CM. 1988 Toluene abuse causes diffuse central nervous system white matter changes. *Ann Neurol* 23:611-614.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Ryu YH, Lee JD, Yoon PH, Jeon P, Kim DI, Shin DW. 1998 Cerebral perfusion impairment in a patient with toluene abuse. *J Nucl Med* 39 (4):632-633.

Saito K, Wada H. 1993 Behavioral approaches to toluene intoxication. *Environ Res* 62:53-62.

Sato A, Nakajima T. 1978 Differences following skin or inhalation exposure in the absorption and excretion kinetics of trichloroethylene and toluene. *Br J Ind Med* 35:43-49.

Sato A, Nakajima T. 1979 Dose-dependent metabolic interaction between benzene and toluene *in vivo* and *in vitro*. *Toxicol Appl Pharmacol* 48:249-256.

Shibata K, Yoshita Y, Matsumoto H. 1994 Extensive chemical burns from toluene. *Am J Emerg Med* 12:353-355.

Smolik R, Grzybek-Hryncewicz K, Lange A, Zatoński W. 1973 Serum complement level in workers exposed to benzene, toluene and xylene. *Int Arch Arbeitsmed* 31:243-247.

Streicher HZ, Gabow PA, Moss AH, Kono D, Kaehny WD. 1981 Syndromes of toluene sniffing in adults. *Ann Intern Med* 94:758-762.

Svensson BG, Nise G, Englander V, Attewell R, Skerfving S, Möller T. 1990 Deaths and tumours among rotogravure printers exposed to toluene. *Br J Ind Med* 47:372-379.

Svensson BG, Nise G, Erfurth EM, Olsson H. 1992a Neuroendocrine effects in printing workers exposed to toluene. *Br J Ind Med* 49:402-408.

Svensson BG, Nise G, Erfurth E-M, Nilsson A, Skerfving S. 1992b Hormone status in occupational toluene exposure. *Am J Ind* 22:99-107.

Suzuki T, Kasmiura S, Umetsu K. 1983 Thinner abuse and aspermia. *Med Sci Law* 23 (3):199-202.

Taher SM, Anderson RJ, McCartney R, Popovtzer MM, Schrier RW. 1974 Renal tubular acidosis associated with toluene 'sniffing'. *N Engl J Med* 290 (14):765-768.

Takeichi S, Yamada T, Shikata I. 1986 Acute toluene poisoning during painting. *Forensic Sci Int* 32:109-115.

Tan WP, Seow E. 1997 Case reports on acute toluene poisoning during parquet flooring. *Ann Acad Med Singapore* 26:138-140.

Tardif R, Laparé S, Plaa GL, Brodeur J. 1991 Effects of simultaneous exposure to toluene and xylene on their respective biological exposure indices in humans. *Int Arch Occup Environ Health* 63:279-284.

Tardif R, Goyal R, Brodeur J. 1992 Assessment of occupational health risk from multiple exposure: review of industrial solvent interaction and implication for biological monitoring of exposure. *Toxicol Ind Health* 8 (1/2):37-52.

Tardif R, Laparé S, Krishnan K, Brodeur J. 1993 A descriptive and mechanistic study of the interaction between toluene and xylene in humans. *Int Arch Occup Environ Health* 65:S135-S137.

Tarsh MJ. 1979 Schizophreniform psychosis caused by sniffing toluene. *J Soc Occup Med* 29:131-133.

Taskinen H, Anttila A, Lindbohm M-L, Sallmén M, Hemminki K. 1989 Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand J Work Environ Health* 15:345-352.

Taskinen H, Kyyrönen P, Hemminki K, Hoikkala M, Lajunen K, Lindbohm M-L. 1994 Laboratory work and pregnancy outcome. *J Occup Med* 36 (3):311-319.

Taverner D, Harrison DJ, Bell GM. 1988 Acute renal failure due to interstitial nephritis induced by 'glue-sniffing' with subsequent recovery. *Scot Med J* 33:246-247.

Teelucksingh S, Steer CR, Thompson CJ, Seckl JR, Douglas NJ, Edwards CRW. 1991 Hypothalamic syndrome and central sleep apnoea associated with toluene exposure. *Q J Med* 78 (286):185-190.

Toutman C, Lippmann S. 1979 Fetal solvents syndrome. *Lancet* 1:1356.

Truchon G, Tardif R, Brodeur J. 1996 Gas chromatograph determination of urinary *o*-cresol for the monitoring of toluene exposure. *J Anal Toxicol* 20:309-312.

Ukai H, Watanabe T, Nakatsuka H, Satoh T, Liu SJ, Qiao X, Yin H, Jin C, Li G-L, Ikeda M. 1993 Dose-dependent increase in subjective symptoms among toluene-exposed workers. *Environ Res* 60:274-289.

Urban P, Lukas E. 1990 Visual evoked potentials in rotogravure printers exposed to toluene. *Br J Ind Med* 47:819-823.

Veulemans H, Masschelein R. 1978a Experimental human exposure to toluene. I. Factors influencing the individual respiratory uptake and elimination. *Int Arch Occup Environ Health* 42:91-103.

Veulemans H, Masschelein R. 1978b Experimental human exposure to toluene. II. Toluene in venous blood during and after exposure. *Int Arch Occup Environ Health* 42:105-117.

Von Burg R. 1993 Toluene. *J Appl Toxicol* 13 (6):441-446.

Vrca A, Božičevic D, Karačić V, Fuchs R, Prpić-Majić D, Malinar M. 1995 Visual evoked potentials in individuals exposed to long-term low concentrations of toluene. *Arch Toxicol* 69:337-340.

Wahlberg JE. 1984 Erythema-inducing effects of solvents following epicutaneous administration to man - studied by laser Doppler flowmetry. *Scand J Work Environ Health* 10:159-162.

Waldron HA, Cherry N, Johnston JD. 1983 The effects of ethanol on blood toluene concentrations. *Int Arch Occup Environ Health* 51:365-369.

Wallèn M, Näslund PH, Byfält Nordqvist M. 1984 The effects of ethanol on the kinetics of toluene in man. *Toxicol Appl Pharmacol* 76:414-419.

Weinstein S, Scottolini AG, Bhagvan NV. 1985 Low neutrophil alkaline phosphatase in renal tubular acidosis with hypophosphatemia after toluene sniffing. *Clin Chem* 31 (2):330-331.

Wiebelt H, Becker N. 1999 Mortality in a cohort of toluene exposed employees (rotogravure printing plant workers). *J Occup Environ Med* 41 (12):1134-1139.

Wilkins-Haug L, Gabow PA. 1991 Toluene abuse during pregnancy: obstetric complications and perinatal outcomes. *Obstet Gynecol* 77 (4):504-509.

Wilkins-Haug L. 1997 Teratogen update: toluene. *Teratology* 55:145-151.

Woiwode W, Wodarz R, Drysch K, Weichardt H. 1979 Metabolism of toluene in man: gas-chromatograph determination of o-, *m*- and *p*-cresol in urine. *Arch Toxicol* 43:93-98.

Wolf MA, Rowe VK, McCollister DD, Hollingsworth RL, Oyen F. 1956 Toxicological studies of certain alkylated benzenes and benzene. *Arch Ind Health* 14:387-398.

Yücesoy B, Yücel A, Erdem O, Bergaz S, Imir T, Karakaya AE, Karakaya A. 1999 Effects of occupational chronic co-exposure to n-hexane, toluene, and methyl ethyl ketone on NK cell activity and some immunoregulatory cytokine levels in shoe workers. *Hum Exp Toxicol* 18:541-546.

Zee-Cheng C-S, Mueller CE, Gibbs HR. 1985 Toluene sniffing and severe sinus bradycardia [letter]. *Ann Intern Med* 103 (3):482.

22 1,1,1-Trichloroethane (1,1,1-TCE)

Maeve McParland

SUMMARY

- 1,1,1-TCE is one of the least toxic of the chlorinated hydrocarbon solvents
- The risk of acute or chronic toxicity is low except at very high concentrations
- The main route of exposure is via inhalation but exposure from dermal contact and ingestion may also occur
- It is a CNS and respiratory depressant, as well as a skin and mucous membrane irritant
- It can cause sensitisation of the myocardium to catecholamines, hence at high concentrations sudden death can occur from cardiac arrest
- The main circumstances of poisoning are accidental occupational exposure and solvent abuse
- 1,1,1-TCE vapour is denser than air and dangerous concentrations may occur in confined spaces, e.g., "empty" storage tanks. This has been the circumstance of several fatal occupational exposures
- 1,1,1-TCE is not classifiable as to its carcinogenicity in humans

DESCRIPTION

1,1,1-TCE is a synthetic chemical and has no natural sources, however it is a common environmental contaminant. It was first prepared in 1840 by the action of chlorine on 1,1,1-dichloroethane, and first produced commercially in 1946. It is now produced commercially by chlorination of ethane, or hydrochlorination of 1,1-dichloroethylene or, more commonly, via hydrochlorination of vinyl chloride (Durrans, 1971; IARC, 1979).

1,1,1-TCE is used industrially and domestically as a degreaser, dry cleaning agent, and solvent in paints, glues and aerosol products. A common source is correction fluid and correction fluid thinners, in commercial products such as Tipp-ex®. It is an important chemical intermediate, and is used as an additive to raise the flash point of many flammable chemicals. 1,1,1-TCE has rapid anaesthetic action and was used for this purpose medically but was abandoned with the advent of safer agents.

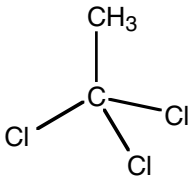
Synonyms

1,1,1-TCE, methyl chloroform, alpha-trichloroethane, methyl trichloromethane, chlorothene, trichloromethylmethane

Identification numbers

CAS	71-55-6
UN	831
RTECS	KJ 2975000
EINECS	2007563

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula	$C_2H_3Cl_3$
Molecular formula	
Molecular mass	133.41
Physical form	colourless non-viscous liquid
Relative vapour density (air=1)	4.6
Flash point	none
Boiling point (°C)	74.1
Auto ignition temperature (°C)	537
Refractive index (at 20 °C)	1.43838
Explosive limits in air (% v/v)	8.0-10.5

Odour threshold

The odour may be noticeable at 100 ppm, which is well below the concentration necessary to cause physiological response. The odour at 1,000 ppm, however, is not unpleasant enough to discourage exposure (Reid, 2001). Ruth *et al.* (1986) recorded the odour threshold as 100-703 ppm.

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK): 200 ppm (1,080 mg/m^3)
TWA (ACGIH): 350 ppm (1,890 mg/m^3)

Conversion factors

1 ppm = 5.40 mg/m^3
1 mg/m^3 = 0.185 ppm
1 mg/l = 185 ppm

Biomonitoring

The ACGIH (2000) recommends several biological exposure indices to monitor exposure to 1,1,1-TCE (see **Table 22.1**).

Table 22.1 Biological exposure indices for 1,1,1-trichloroethane (ACGIH, 2000)		
Determinant	**Sampling time**	**BEI**
1,1,1-TCE in end-exhaled air	Prior to last shift of work week	40 ppm
Trichloroethanol in urine	End of work week	30 mg/l
Trichloroacetic acid in urine	End of shift at end of work week	10 mg/l
Trichloroethanol in blood	End of shift at end of work week	1 mg/l

TOXICITY

1,1,1-TCE sensitises the heart to catecholamines, is a CNS and respiratory system depressant, and a skin and mucous membrane irritant. 1,1,1-TCE is less toxic than other chlorinated hydrocarbons, which may be explained in part by its lesser degree of metabolism, since the majority of an inhaled dose is excreted unchanged via the lungs. It is weakly anaesthetic when compared to other chlorinated hydrocarbons (Kelafant *et al.,* 1994).

Most cases of poisoning with 1,1,1-TCE result from accidental exposure or intentional abuse, commonly referred to as volatile solvent abuse (VSA). Accidents involving the accumulation of high concentrations are rare; the highest risk group are intentional abusers. A review of industrial accidents reported to the Factory Inspectorate in the UK during the period 1961-1980 revealed 52 incidents due to 1,1,1-TCE (McCarthy and Jones, 1983).

Absorption

1,1,1-TCE is rapidly absorbed through the lungs and gastrointestinal tract. Absorption through skin also occurs (Stewart and Dodd, 1964), but is of minor significance compared to uptake via inhalation. 1,1,1-TCE has a relatively low blood/air partition coefficient, therefore steady state tissue concentrations are attained slowly and the vapour is eliminated relatively rapidly in expired air after exposure.

Studies with human volunteers (males), exposed by inhalation to 1,1,1-TCE at concentrations from around 35 ppm to 350 ppm for 6 hours, demonstrated that about 25-40% of the 1,1,1-TCE inhaled was absorbed by the lungs. The amount varied depending on the 1,1,1-TCE concentrations in the inhaled air, duration of exposure, body weight and amount of adipose tissue, blood circulation and other factors (Åstrand *et al.,* 1973: Monster *et al.,* 1979; Nolan *et al.,* 1984). Uptake from inhalation increases with physical activity.

Distribution

1,1,1-TCE has a high lipid/blood partition coefficient and is therefore expected to distribute widely into body tissues, particularly into those with high lipid content such as the brain and adipose tissue. It passes readily through the human blood-brain barrier and is also believed to cross the placental barrier to the fetus. In one postmortem examination following an acute lethal exposure (from VSA), 1,1,1-TCE was detected in the blood, brain and liver (D'Costa and Gunasekera, 1990).

Metabolism

1,1,1-TCE is mainly (90%) excreted unchanged through the lungs (Nolan *et al.,* 1984). Small amounts of 1,1,1-TCE are slowly metabolised by oxidation to trichloroethanol, which is conjugated with glucuronic acid before excretion in the urine. This accounts for only about 2% of an absorbed dose. Trichloroethanol is further oxidised to form trichloroacetic acid and this is also found in the urine to the extent of about 1.5% of a dose (Monster *et al.,* 1979). Simultaneous exposure to other solvents tends to increase the retention and decrease the metabolism of 1,1,1-TCE (Savolainen *et al.,* 1981).

Elimination

Regardless of the route of absorption, exhalation via the lungs is the main excretory route for 1,1,1-TCE. Studies with human volunteers show that over 90% of the absorbed 1,1,1-TCE is excreted unchanged in expired air. Initial excretion is fairly rapid with 70% reduction of the concentration in expired air within two hours (Monster *et al.,* 1977), but this is followed by slower elimination, with small amounts being detected in the breath for up to several days post-exposure. Only minor quantities (5-6%) of the absorbed solvent are excreted in the urine (as trichloroethanol glucuronide and trichloroacetic acid) (Monster *et al.,* 1979). Less than 1% of an absorbed dose remained in the body after nine days (Nolan *et al.,* 1984). Between 60% to 80% of an absorbed dose is exhaled within one week, however traces may found in the post exposure expired breath for as long as one month (Baselt, 2000).

At, or below, the TLV of 350 ppm, elimination (in expired air) was reported to be tri-exponential with an initial phase of 44 minutes, intermediate phase 5-7 hours and terminal phase 53 hours. The half-lives of the metabolites in urine were 13 hours for 2,2,2-trichloroethanol, and 51 hours for trichloroacetic acid. Urinary excretion of the two metabolites is very variable and provides only a rough estimate of exposure (Nolan *et al.,* 1984).

Mode of action

1,1,1-TCE sensitises the heart to catecholamines (e.g., epinephrine), is a central nervous system and respiratory system depressant, and a skin and mucous membrane irritant.

Acute intoxication with 1,1,1-TCE causes initial excitement and euphoria followed by depression of the central nervous system with dizziness, drowsiness, ataxia and headache, progressing to coma and death from respiratory depression in severe cases. Death also occurs from ventricular arrhythmias as at high concentrations the solvent sensitises the myocardium to epinephrine (adrenaline) and other catecholamines. Vasospasm or myocardial sensitisation to endogenous catecholamines caused by trichloroethane toxicity may precipitate arrhythmias or ischaemia secondary to increased oxygen demand (Bailey *et al.,* 1997).

The vapour and liquid are irritating to the skin and mucous membranes. Nausea, vomiting and diarrhoea have all been reported following ingestion.

Metabolic interactions

Simultaneous exposure to other solvents tends to increase the retention and decrease the metabolism of 1,1,1-TCE (Savolainen *et al.,* 1981); hence occupational exposure to mixed solvents may put workers at greater risk of 1,1,1-TCE toxicity.

- **Aliphatic organochlorines**

  Thiele *et al.* (1982) suggested that pre-exposure to other chlorinated hydrocarbons might increase the potential for hepatic damage from 1,1,1-TCE. They report a case of hepatic cirrhosis after several years of heavy exposure to trichloroethylene, followed by three months of work that involved using an aerosolised degreaser containing 1,1,1-TCE. They suggest that an individual suffering hepatic injury from a chlorinated hydrocarbon may be at risk of further progression of the disease upon subsequent exposure to even a relatively non-toxic member of this family of organic solvents (in this case 1,1,1-TCE).

  In vivo and *in vitro* studies demonstrated that combinations of trichloroethylene with tetrachloroethylene or 1,1,1-trichloroethane or both, were more toxic than the individual chemicals alone. Measures of effects were parameters of cell integrity (leak of potassium, lactate dehydrogenase and alanine aminotransferase in hepatocytes) for the *in vitro* tests and measures of hepatic and renal function (liver weight, alanine aminotransferase, sorbital dehydrogenase and urea) in rats. The effect of the three solvents together was greater than mixtures of two. This study did not investigate the mechanism of interaction (Stacey, 1989).

- **Halothane anaesthesia**

  McLeod *et al*. (1987) postulate that an interaction occurs between exposure to 1,1,1-TCE and subsequent administration of halothane for anaesthesia. An adolescent boy who intentionally sniffed 1,1,1-TCE presented with multiple ventricular arrhythmias during tonsillectomy, and follow-up showed mild chronic left ventricular impairment. In a second case, a 54-year old man with repeated industrial exposure to 1,1,1-TCE, received halothane anaesthesia and deteriorated from mild stable cardiac failure to end stage cardiac failure.

- **Surface active agents**

  Woo *et al*. (1983) reported a case of hypoxaemia and chest pain following inhalation of a 1,1,1-TCE aerosol product. The solvent was combined with a surface active agent in the product. The combined formulation increased the water solubility of 1,1,1-TCE and enhanced deposition in the upper airway thus causing considerable respiratory distress. The authors concluded that the symptoms could not be attributed to the propellant, surface active agent or 1,1,1-TCE alone.

CASE REPORTS

Death on industrial premises attributed to 1,1,1-trichloroethane

A 20 year old apprentice electrician was found dead on the floor of a fume filled room, where he had earlier been using 1,1,1-TCE from an open bowl, as a degreasing solvent. The exact circumstances of the solvent's use leading to the incident are not known, although an upright, half-full can of solvent was on the workbench and there was evidence of some spillage on the floor. The man had been seen two hours previously by a colleague and had appeared well. At postmortem examination, the deceased had blistering and second degree burns on his face and neck, the skin changes being in line with the folds of his clothing, and consistent with prolonged contact of the solvent with the body. There was oedema and congestion of the brain and lungs, and small serous effusions in both pleural cavities. The stomach showed mucosal congestion and a few scattered petechial haemorrhages. The blood concentration of 1,1,1-TCE was 4.2 mg/100 ml, the brain concentration was 123 mg/100 g, and it was detected in the liver. At inquest it was concluded that death resulted from suppression of the respiratory centre secondary to severe central nervous system depression (Jones and Winter, 1983).

Fatal poisoning by 1,1,1-trichloroethane after prolonged survival

An 18 year old male was found with his head submerged in a bath of 1,1,1-TCE. He had respiratory and cardiac arrest with fixed, dilated pupils. Artificial respiration and cardiac massage were initiated about 15 minutes after his discovery and he was intubated and ventilated. Spontaneous respiration was resumed but he did not regain consciousness. Cerebral atrophy was evident on a CT scan carried out two months after the accident, and the protective eye reflex was absent on both sides suggesting a lesion of the occipital cortex, while the pupils remained dilated and inactive to light. There was restlessness and jerking of the limbs and trunk, and fixed flexion of all four limbs developed. There were recurrent urinary infections and the patient died 39 months after the accident. At postmortem examination the brain showed symmetrical infarction of the lenticular nuclei and of the occipital cortex, these changes possibly being the cause of the neurological manifestations during life. It was noted that the pattern of cerebral hypoxia was similar, although not identical to that found in carbon monoxide poisoning and suggested it may be specific for 1,1,1-TCE poisoning (Gresham and Treip, 1983).

Peripheral sensory neuropathy associated with 1,1,1-trichloroethane

A 44 year old woman previously in good health, developed perioral tingling and a burning sensation on her tongue, accompanied by discomfort in her hands and feet. The oral and hand symptoms disappeared quickly after removal from work, but she was left with sensations of burning and cramping in her feet, which made it difficult to walk or stand for prolonged periods of time. She had no history of diabetes mellitus or excessive alcohol ingestion or any other conditions associated with peripheral neuropathy.

Approximately 18 months prior to the development of her symptoms, she had begun work as a hydraulic pump dismantler and parts cleaner. She estimated that approximately half of her daily work activities involved contact with a degreasing solvent (1,1,1-TCE with 1-5% dimethylene ether), with the exposure occurring by both inhalation and skin contact. Although she wore protective gloves she said that they often leaked, as did her respirator. There was no other exposure at work to agents known to cause peripheral neuropathy, and no history of prior occupational exposure to such agents.

On examination she had diminished vibration sense in the big toes bilaterally, as well as absent position sense. Tendon reflexes were normal, and there was no muscle atrophy or demonstrable muscle weakness. Clinical examination did not indicate any evidence of hepatic, cardiac, or CNS abnormalities. The evoked potential studies were normal, and the initial neurophysiological studies indicated a normal electromyogram. The initial sensory nerve conduction tests indicated reduced amplitudes of sural sensory responses bilaterally and normal nerve conduction velocities and sensory latencies consistent with a toxic axonopathy. Within 2 months after removal from work, she began to notice improvement in lower limb symptoms of paraesthesia and cramping, and six months after removal her symptoms had resolved almost entirely. Her physical examination at the time was normal except for a very slight reduction of vibration sensation in the big toes bilaterally. Repeat nerve conduction studies seven months after removal from exposure demonstrated improved sural sensory amplitudes and no other changes, compared with the initial studies. On the basis of her nerve conduction studies and the previous reports of peripheral neuropathy following 1,1,1-TCE exposure in degreasing operators, the peripheral neuropathy claim was accepted as being work-related by the workers' compensation board in her province (House *et al.,* 1994).

CLINICAL EFFECTS

Acute exposure

Inhalation

1,1,1-TCE vapours are irritating to the eyes and mucous membranes causing coughing and chest tightness as the concentration increases (IPCS, 1992). It has a depressant action on the CNS and is narcotic at high concentrations.

With intentional abuse an initial excitatory phase occurs which may be followed by depression and a hangover effect (similar although less severe than that caused by alcohol) (Watson, 1982). This initial euphoria may progress to confusion, disorientation, dizziness, headache, incoordination, drowsiness, hallucinations and aggressive behaviour, while continued exposure may cause coma, convulsions, respiratory depression, cardiovascular collapse and death (Stewart, 1971). Vomiting can occur with the risk of aspiration of stomach contents (Hall and Hine, 1966). Recovery from 1,1,1-TCE induced narcosis is usually complete with no serious sequelae (Torkelson *et al.,* 1958; McCarthy and Jones, 1983).

Sensitisation of the myocardium to epinephrine (adrenaline) and other catecholamines may occur, causing potentially fatal arrhythmias (Hall and Hine, 1966; Bass, 1970; Stewart, 1971; Reinhardt *et al.* 1973; Travers, 1974).

1,1,1-TCE causes minimal hepatic dysfunction, except in high concentrations, and animal livers are relatively resistant to all except lethal levels of 1,1,1-TCE (Stewart, 1971). There is only one report of liver damage following acute occupational exposure to 1,1,1-TCE, and this may well have been an individual hypersensitivity reaction. Halevy *et al.* (1980) report a case in which acute occupational over-exposure to 1,1,1-TCE fumes resulted in very mild transient neurological symptoms immediately after exposure, with the development of short-term liver and renal damage two days later. At follow-up one year later the patient had no evidence of disturbed liver or kidney function. In considering other features of the patient's illness (urticarial rash, positive migration inhibition factor against 1,1,1-TCE, eosinophilic infiltration found in the liver tissue) the authors conclude that their patient may have had individual hypersensitivity to 1,1,1-TCE.

Dermal

Like many solvents 1,1,1-TCE will defat the skin. Absorption through the skin can occur but it is not a significant route of exposure. Despite its widespread use, only a few cases of skin irritancy have been reported. In a volunteer study, immersion of a hand in liquid 1,1,1-TCE for 30 minutes resulted in mild erythema, which persisted for one hour (Stewart and Dodd, 1964). Blistering and second degree chemical burns were evident at postmortem examination on a man overcome by 1,1,1-TCE fumes while using the solvent at work as a degreaser. The victim had appeared well two hours previous but was found dead on the floor, beside a spillage of the solvent (Jones and Winter, 1983).

Eye

Only superficial and transient eye irritation occurs following 1,1,1-TCE contact with the eye. 1,1,1-TCE tested by drop application to rabbit eyes caused slight conjunctival irritation and no corneal damage (Grant and Schuman, 1993).

Ingestion

Ingestion of 1,1,1-TCE causes irritation to the gastrointestinal tract with subsequent nausea, vomiting, abdominal pain and diarrhoea. Symptoms have been noted within 30 minutes of ingestion (Gerace, 1981). It is well absorbed by ingestion (Gerace, 1981) and causes CNS depression with dizziness, drowsiness, headache and ataxia, progressing to coma and death from respiratory depression in severe cases (Stewart, 1966). Convulsions may occur. The irritant effect of 1,1,1-TCE on the gastrointestinal tract with concurrent decrease in conscious level presents the risk of aspiration.

Sensitisation of the myocardium to epinephrine and other catecholamines may occur causing potentially fatal arrhythmias (Bass, 1970; Hall and Hine, 1966; Reinhardt *et al*. 1973; Stewart 1971; Travers, 1974).

In a report of accidental ingestion of 1 oz (approximately 28 ml) of 1,1,1-TCE, severe gastrointestinal irritation developed shortly after ingestion requiring hospital admission, where a gastric lavage was performed. No CNS disturbance or neurological abnormalities were observed on examination four hours post exposure (Stewart and Andrews, 1966).

Dickerson and Biesemer (1982) from studies in rats, concluded that 1,1,1-TCE was capable of lung injury and posed an aspiration risk from aspiration of the volatile hydrocarbon itself. Hall and Hine (1966) reported postmortem pulmonary findings consistent with aspiration of the liquid.

Chronic exposure

Inhalation

A Japanese study on women chronically exposed to concentrations of up to 350 ppm (the established TLV) found no evidence of any disturbances in the central or peripheral nervous system (Fielder *et al.,* 1984).

Kelafant *et al.* (1994) studied 28 workers with long-term repetitive high exposures to 1,1,1-TCE (exposure levels were not known but thought to be very high as environmental controls were poor and subjects frequently complained of mild neurological symptoms while working). The workers were evaluated for complaints of short-term memory loss, moodiness, disequilibrium, irritability and decreased ability to concentrate. As a group they had significant deficits on neuropsychological testing, and platform posturography demonstrated deficits in vestibular, somatosensory and ocular components of balance. They concluded that the encephalopathic picture in these subjects is similar to that reported with other solvents. Peripheral neuropathy has been reported from chronic exposure to 1,1,1-TCE (Liss 1988; House *et al.,* 1994).

Wright and Strobl (1984) report a case of occupational exposure to high concentrations of 1,1,1-TCE resulting in persistent ventricular dysrythmias for more than two weeks after cessation of exposure. A 14 year old boy with a history of irregularly abusing 1,1,1-TCE over the period of a few months, collapsed and died suddenly.

Postmortem findings revealed myocardial degeneration changes including interfibrillary oedema, and swollen and ruptured myofibrils (Banathy and Chan, 1983).

Hepatotoxicity is not a feature of 1,1,1-TCE toxicity (Marjot and McLeod, 1989).

Immunotoxicity

Flindt-Hansen and Isager (1987) report two cases of scleroderma with positive anti-nuclear antibodies (ANAs) after chronic occupational exposure to both 1,1,1-TCE and trichloroethylene, however, definite causal relationships have not been established. Eosinophilic pneumonia has been reported in a 15 year old male following intentional inhalational abuse of a product containing 1,1,1-TCE (Kelly and Ruffing, 1993).

Dermal

Prolonged or repeated skin contact with 1,1,1-TCE may lead to dermatitis, due to its defatting action. Despite its widespread use only a few cases of skin irritancy have been reported. Skin vesication and erythema may occur with prolonged contact (Jones and Winter, 1983). Repeated topical application of 1,1,1-TCE to abraded and non-abraded rabbit skin for up to 90 days, resulted in slight reversible irritation (Torkelson *et al.,* 1958). Allergic contact dermatitis presenting as severe eczema has been reported following exposure to 1,1,1-TCE (Ingber, 1991).

Eye

Repeated daily application of about 50 µl of 1,1,1-TCE to eyes of rabbits (five days a week for two weeks) led to the development of a mild inflammatory reaction. This resolved within 48 hours of the last application (Fielder *et al.,* 1984).

Ingestion

There is no information on chronic ingestion of 1,1,1-TCE in humans.

Carcinogenicity

The IARC has concluded that there is inadequate evidence for the carcinogenicity of 1,1,1-TCE either in humans or in experimental animals (IARC, 1999). 1,1,1-TCE is therefore classed in IARC Group 3 and is not classifiable as to its carcinogenicity in humans.

The results from a cohort study of workers exposed to 1,1,1-TCE in Finland indicated an increased risk for central nervous system cancer (not specified) and multiple myeloma. These findings were not confirmed by two case control studies carried out in the United States and Canada, however an increased risk for cancer of the lung and kidney was shown in the Canadian study (IARC, 1999).

In a carcinogenicity study, rats and mice were orally administered 1,1,1-TCE in two different dose levels, five days a week for 78 weeks. Both male and female test animals exhibited early mortality compared with untreated controls, and a variety of neoplasms were found in both treated animals and controls. Although rats of both sexes demonstrated a positive dose-related trend, no relationship was established between the dosage group and the species, sex, type of neoplasm or sites of occurrence (National Cancer Institute, 1977).

Genotoxicity

Sixteen halogenated aliphatic hydrocarbons were assayed for genotoxicity using the Ara mutagenicity assay with *Salmonella typhimurium* (Roldan-Arjona *et al.,* 1991). The authors concluded that 1,1,1-TCE was non-mutagenic after being assayed both in the presence and absence of metabolic activation with a rat liver microsomal fraction (S9).

In their review of the toxicity of 1,1,1-TCE, Fielder *et al.* (1984) conclude that although extensively investigated, there is no evidence from the available data to indicate that the compound is mutagenic. However, they highlight the fact that studies have mainly been on bacterial systems, and that data for mammalian cells is limited, with no published data on point mutations in mammalian cells. Hence, although claiming there is no evidence for mutagenicity of 1,1,1-TCE, they expressed the reservation that when the limitations of the data are considered, no definite conclusions may be drawn.

Reproductive toxicity

No structural damage has been reported in reproductive toxicity studies of 1,1,1-TCE in rats and mice, but delayed development, particularly of neurological attributes, has been reported in one study with mice (IARC, 1999).

RISK GROUPS

Simultaneous exposure to other solvents tends to increase the retention and decrease the metabolism of 1,1,1-TCE (Savolainen *et al.,* 1981); so occupational exposure to mixed solvents may put workers at greater risk of 1,1,1-TCE toxicity.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The patient should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

1,1,1-TCE is radiopaque (Dally *et al.*, 1987) and an X-ray may confirm ingestion. Gastric lavage may be considered if ingestion was recent, however, because of the risk of aspiration a cuffed endotracheal tube must be used to protect the airway. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing, or wheezing then the patient will need to be assessed to see if aspiration has occurred. Treatment is supportive. See below for management of systemic effects.

Systemic effects

Treatment is primarily symptomatic, with support of the cardiovascular and respiratory systems. Use of epinephrine (adrenaline) or related sympathomimetic stimulants is contraindicated due to the risk of inducing ventricular fibrillation.

The level of consciousness, ECG and respiratory rate function should all be monitored, along with liver and kidney function in severe cases. A chest X-ray is indicated in patients with respiratory symptoms and in cases of suspected aspiration.

The efficacy of enhanced elimination techniques (e.g., haemodialysis, haemoperfusion, etc.) has not been established, but on theoretical grounds they are unlikely to be effective.

Antidotes

There is no specific antidote for 1,1,1-TCE.

Chronic exposure

In most cases of chronic poisoning clinical effects resolve gradually once exposure has ceased. Symptomatic and supportive care.

REFERENCES

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Åstrand I, Kilbom A, Wahlberg I, Övrum P. 1973 Methyl chloroform exposure. I. Concentrations in alveolar air and blood at rest and during exercise. *Scand J Work Environ Health* 100:69-81.

Bailey B, Lai C, McGuigan MA. 1997 Two cases of chlorinated hydrocarbon-associated myocardial ischaemia. *Vet Hum Toxicol* 39 (5):298-301.

Banathy LJ, Chan LTF 1983 Fatality caused by inhalation of "liquid paper" correction fluid. *Med J Aust* 2:606.

Baselt RC. 2000 *Disposition of Toxic Drugs and Chemicals in Man*, fifth edition. Chemical Toxicology Institute, Foster City, California.

Bass M. 1970 Sudden sniffing death. *J Am Med Assoc* 212:2075-2079.

Dally S, Garnier R, Bismuth C. 1987 Diagnosis of chlorinated hydrocarbon poisoning by X-ray examination. *Br J Ind Med* 44:424-425.

Dickerson CL, Biesemeier JA. 1982 Aspiration of methyl chloroform. *Vet Hum Toxicol* 24 (3):167-168.

Durrans TH. 1971 *Solvents*, eighth revised edition, Chapman and Hall Ltd., London.

D'Costa DF, Gunaskera NPR. 1990 Fatal cerebral oedema following trichloroethane abuse. *J R Soc Med* 83:533-534.

Fielder FJ, Williams SD, Sorrie GS, Bishop CM, Chandra FA, Gompertz D, Lucas EG, Van Den Heuvel MJ, Mackay CJ. 1984 1,1,1-Trichloroethane. Health and Safety Executive, *Toxicity Review* 9.

Flindt-Hansen H, Isager H. 1987 Scleroderma after occupational exposure to trichloroethylene and trichloroethane. *Acta Derm Venereol* 67 (3): 263-264.

Gerace RV. 1981 Near fatal intoxication by 1,1,1-trichloroethane. *Ann Emerg Med* 10 (10):533-534.

Grant WM, Schuman JS. 1993 *Toxicology of the Eye*, fourth edition. Charles C Thomas, Springfield, Illinois.

Gresham GA, Treip CS. 1983 Fatal poisoning by 1,1,1-trichloroethane after prolonged survival. *Forensic Sci Int* 23:249-253.

Halevy J, Pitlick S, Rosenfeld J. 1980 1,1,1-trichloroethane intoxication: A case report with transient liver and renal damage. Review of the literature. *Clin Toxicol* 16 (4):467-472.

Hall FB, Hine CH. 1966 Trichloroethane intoxication: A report of two cases. *J Forensic Sci* 11:404-413.

House RA, Liss GM, Wills MC. 1994 Peripheral sensory neuropathy associated with 1,1,1-trichloroethane. *Arch Environ Health* 49:196-199.

IARC (International Agency for Research on Cancer). 1979 *Some Halogenated Hydrocarbons*. IARC Monograph 20.

IARC (International Agency for Research on Cancer). 1999 *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*. IARC Monograph 71.

IPCS. 1992 *Environmental Health Criteria 136. 1,1,1- Trichloroethane*. World Health Organization, International Programme on Chemical Safety, Geneva.

Ingber A. 1991 Occupational allergic contact dermatitis from methyl chloroform (1,1,1-trichloroethane). *Contact Dermatitis* 25:193.

Jones RD, Winter DP. 1983 Two case reports of death on industrial premises attributed to 1,1,1-trichloroethane. *Arch Environ Health* 38:59-61.

Kelafant GA, Berg RA, Schleenbaker R. 1994 Toxic encephalopathy due to 1,1,1-trichloroethane exposure. *Am J Ind Med* 25:439-446.

Kelly KJ, Ruffing R. 1993 Acute eosinophilic pneumonia following intentional inhalation of Scotchguard. *Ann Allergy* 71 (4):338-339.

Liss GM. 1988 Peripheral neuropathy in two workers exposed to 1,1,1-trichloroethane [letter]. *J Am Med Assoc* 260:2217.

Marjot R, McLeod AA. 1989 Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 8:301-306.

McCarthy TB, Jones RD. 1983 Industrial gassing poisonings due to trichloroethylene, perchloroethylene, and 1,1,1-trichloroethane 1961-1980. *Br J Ind Med* 400:450-455.

McLeod AA, Marjot R, Monaghan MJ, Hugh-Jones P, Jackson G. 1987 Chronic cardiac toxicity after inhalation of 1,1,1-trichloroethane. *Br Med J* 294:727-729.

Monster AC, Boersma G, Steenweg H. 1979 Kinetics of 1,1,1-trichloroethane in volunteers: influence of exposure concentration and workload. *Int Arch Occup Environ Health* 42:293-301.

National Cancer Institute. 1977 Bioassay of 1,1,1-trichloroethane for possible carcinogenicity. *Technical Report Series No. 3* US Department of Health, Education and Welfare. Publication Number: National Institute of Health (NIH) 77803.

Nolan RJ, Freshour NL, Rich DL, McCarty DL, Saunders JH. 1984 Kinetics and metabolism of inhaled methyl chloroform (1,1,1-trichloroethane) in male volunteers. *Fundam Appl Toxicol* 4:654-662.

Reid JB. 2001 Saturated halogenated aliphatic hydrocarbons two to four carbons. In: *Patty's Toxicology*, fifth edition, Volume 5. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Reinhardt RA, Mullen LS, Maxfield ME. 1973 Epinephrine-induced cardiac arrhythmia potential of some common industrial solvents. *J Occup Med* 15:953-955.

Roldan-Arjona T, Garcia-Pedrajas MD, Luque-Romero FL, Hera C, Pueyo C. 1991 An association between mutagenicity of the Ara test of Salmonella typhimurium and carcinogenicity in rodents for 16 halogenated aliphatic hydrocarbons. *Mutagenesis* 6 (3): 199-205.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Savolainen K, Riihimäki V, Laine A, Kekoni J. 1981 Short-term exposure of human subjects to m-xylene and 1,1,1-trichloroethane. *Int Arch Occup Environ Health* 49:89-98.

Stacey NH. 1989 Toxicity of mixtures of trichloroethylene, tetrachloroethylene and 1,1,1-trichloroethane: similarity of in vitro to in vivo responses. *Toxicol Ind Health* 5(3):441-450.

Stewart RD. 1971 Trichloroethane intoxication: diagnosis and treatment. *J Am Med Assoc* 215:1789-1792.

Stewart RD, Andrews JT. 1966 Acute intoxication with methyl chloroform. *J Am Med Assoc* 195 (11):904-906.

Stewart RD, Dodd HC. 1964 Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride and 1,1,1-trichloroethane through the human skin. *Am Ind Hyg Assoc J* 25:439-446.

Thiele DL, Eigenbrodt EH, Ware AJ. 1982 Cirrhosis after repeated trichloroethylene and 1,1,1-trichloroethane exposure. *Gastroenterology* 83:926-929.

Torkelson TR, Oyen F, McCollister DD, Rowe VK. 1958 Toxicity of 1,1,1-trichloroethane as determined on laboratory animals and human subjects. *Am Ind Hyg Assoc J* 19:353-362.

Travers H. 1974 Death from 1,1,1-trichloroethane abuse: case report. *Milt Med* 139:889-890.

Watson JM. 1982 Solvent abuse: prevention and clinical diagnosis. *Hum Toxicol* 1:249-256.

Wright MF, Strobl DJ. 1984 1,1,1-Trichloroethane cardiac toxicity: report of a case. *J Am Osteopath Assoc* 84 (3):285-288.

Woo OF, Healey KM, Sheppard D, Tong TD. 1983. Chest pain and hypoxemia from inhalation of a trichloroethane aerosol product. *J Toxicol Clin Toxicol* 20 (4):331-341.

23 Trichloroethylene

Grainne Cullen

SUMMARY

- Trichloroethylene is a CNS depressant and causes narcosis at high concentrations
- It is irritant to the eyes and skin and burns may occur after prolonged exposure
- Trichloroethylene may cause acute hepatic dysfunction, but this is only likely at concentrations sufficient to produce significant CNS depression
- Hepatic and renal dysfunction has been reported after occupational use
- Ventricular fibrillation may occur due to sensitisation of the myocardium to catecholamines
- Trichloroethylene is probably carcinogenic in humans
- There is insufficient information on the genotoxicity of trichloroethylene
- Trichloroethylene is not teratogenic

DESCRIPTION

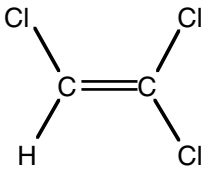
Synonyms

Acetylene trichloride, ethylene trichloride, trichloroethylene, TCE, TRI, trichloroethene.

Identification numbers

CAS	79-01-6
UN	1710
RTECS	KX4550000
EINECS	2011674

PHYSICAL AND CHEMICAL PROPERTIES

chemical formula	C_2HCl_3
molecular formula	
molecular mass	131.40
physical form	volatile, clear colourless liquid

relative vapour density (air =1)	4.53
flash point	None under normal working conditions
boiling point (°C)	86.7
autoignition temperature (°C)	410
refractive index	1.4782
explosive limits in air (%v/v)	8.0-10.5

Odour threshold

28 ppm (Amoore and Hautala, 1983); 0.2 ppm-396 ppm (Ruth, 1986).

OCCUPATIONAL EXPOSURE

Exposure Limits

TWA (UK): 100 ppm (550 mg/m^3)
TWA (ACGIH): 50 ppm (275 mg/m^3)

Conversion factors

1 ppm = 5.46 mg/m^3
1 mg/l = 183 ppm
1 mg/m^3 = 0.183 ppm

Biomonitoring

The ACGIH biological exposure indices for trichloroethylene are given in **Table 23.1**. In some cases the determinant is labelled as semi-quantitative and is an indicator of exposure to the chemical, but the quantitative interpretation of the measurement is ambiguous. These determinants should be used as a screening test if a quantitative test is not practical, or as a confirmatory test if the quantitative test is not specific and the origin of the determinant is in question (ACGIH, 2000).

Table 23.1 Trichloroethylene biomonitoring (ACGIH, 2000)

Determinant	Sampling Time	Biological Exposure Index	Notation
Trichloroacetic acid in urine	end of work week	100 mg/g creatinine	The determinant is nonspecific since it is also observed after exposure to other chemicals
Trichloroacetic acid and trichloroethanol in urine	end of shift at end of work week	300 mg/g creatinine	
Free trichloroethanol in blood	end of shift at end of work week	4 mg/l	
Trichloroethylene in blood			semi-quantitative
Trichloroethylene in end-exhaled air			semi-quantitative

The most representative sample of trichloroethylene exposure is the urine sample taken the morning after exposure. The excretion of trichloroacetic acid does not directly correlate with the degree of exposure to trichloroethylene, but it can be used for the qualitative evaluation of the previous days' exposure (Droz and Fernández, 1978). The best method for determining individual uptake of trichloroethylene is the measurement of blood concentrations of trichloroethylene itself. Using simultaneously measured concentrations in expired air or urine does not improve the estimate (Monster and Houtkooper, 1979).

TOXICITY

Trichloroethylene was first described in 1864 and has been used as an anaesthetic and analgesic. It is widely used as a solvent and thinner, refrigerant, heat exchange fluid, dry cleaning agent and degreaser (Maull *et al*., 1997). Occupational exposures may involve exposure to both vapour and liquid. The highest levels of occupational exposure occur in metal cleaning processes (IPCS, 1985).

Trichloroethylene is a CNS depressant and can cause narcosis at high concentrations. Deaths have occurred after exposure to concentrations greater than 15,000 ppm (Lemen, 2001). Trichloroethylene can sensitise the heart to catecholamines and cardiac arrest has been reported in industrial accidents (Annau, 1981) and from intentional inhalation of trichloroethylene (Thomas and Baud, 1987; Wodka and Jeong, 1989). The main route of exposure is inhalation but occasionally trichloroethylene may be ingested. In industrial situations ingestion may occur as splash contact or as part of immersion or heavy contamination. Intentional ingestion of trichloroethylene by adults and accidental ingestion by children is rare.

A study of deaths from trichloroethylene exposure in the USA between 1975-1992 found that eight deaths were attributable to trichloroethylene. All the deaths occurred in young men who usually worked in confined spaces without adequate ventilation. The study also revealed an absence of engineering controls, proper work practices and appropriate personal protective equipment in these cases (Ford *et al*., 1995).

Organic halocarbons including trichloroethylene are some of the most frequent drinking water contaminants (Condie, 1985) and trichloroethylene and trichloroacetic acid have been measured in blood and urine of people with no history of solvent exposure (Skender and Karačić, 1996).

Absorption

In mammals, trichloroethylene absorption may occur after inhalation, ingestion or skin exposure. Intraperitoneal uptake has been reported in experimental animals (IPCS, 1985).

In a study of five male volunteers inhaling trichloroethylene at a concentration of 70 ppm for 4 hours on 5 consecutive days, the uptake of trichloroethylene was calculated as 6.6 ± 0.4 mg/kg lean body mass in 4 hours. The trichloroethylene concentration in blood and exhaled air 18 hours after the fifth exposure, was twice as high as the concentration 18 hours after the first exposure (Monster *et al*., 1979). The relatively high and almost constant absorption per minute of trichloroethylene is explained by the relatively high partition coefficient between blood and air (Monster, 1979).

Trichloroethylene is readily absorbed across the skin but, in industrial situations, skin exposure is likely to be limited by the irritant nature of trichloroethylene on the skin (Sato and Nakajima, 1978).

Distribution

Trichloroethylene has a high volume of distribution (10 l/kg). It is cleared slowly from the blood with a half-life of about 20 hours. Following acute ingestion trichloroethylene reaches its highest concentration in adipose tissue and accumulates for about 6 hours post ingestion. The trichloroethylene concentration in blood and other tissues (particularly nervous tissue) depends on slow elimination from adipose tissue. Adipose tissue has concentrations of trichloroethylene 100 times higher than in blood.

The solubility coefficient of trichloroethylene vapour for fat is much higher than for other tissues. In experimental animals, the tissue/blood partition coefficient was about 70 for fat and 1-3 for most other

tissues. This high solubility of trichloroethylene in fat compared with blood was confirmed with fat and blood from humans (Sato *et al.*, 1977).

The concentration of trichloroethylene in nervous tissue is around twice that of blood but 50 times lower than that in adipose tissue, indicating that the solvent does not accumulate in nervous tissue. However, the high blood flow to the CNS increases the concentration of trichloroethylene in nervous tissue, but also means that trichloroethylene is cleared from the CNS once absorption ceases. Adipose tissue slowly releases solvent to the blood where the concentration decreases with a half-life similar to that of adipose tissue.

Trichloroethylene blood concentrations greater than 1,500 µg/l are associated with deep coma (Perbellini *et al.*, 1991).

Metabolism

Trichloroethylene undergoes extensive first pass metabolism after oral administration (Köppel *et al.*, 1988). It is principally metabolised in the liver (a small amount may be metabolised in other tissues) by two competing pathways – oxidation by cytochrome P450 and conjugation with glutathione.

Chloral hydrate is produced as an intermediary metabolite and the major urinary metabolites are trichloroacetic acid and trichloroethanol (which appears largely as a glucuronide conjugate urochloralic acid) (Baselt, 2000). Glutathione conjugation of trichloroethylene also leads to the formation of *N*-acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine and *N*-acetyl-*S*-(2,2-dichlorovinyl)-L-cysteine which can be detected in urine. Other urinary metabolites include chloroacetic acid and dichloroacetic acid (Brüning *et al.*, 1998).

Elimination

Only a relatively small amount of trichloroethylene is excreted unchanged by the lungs after exposure because of the relatively high partition coefficient between blood and air and rapid metabolism (Monster, 1979). Most trichloroethylene is metabolised in the liver. Only about one third of the absorbed trichloroethylene is excreted in urine during the work period (Ikeda *et al.*, 1972).

In a study of 5 male volunteers inhaling trichloroethylene at a concentration of 70 ppm for 4 hours on 5 consecutive days, trichloroethanol in blood and urine increased during the exposure days. The total recovery of the amount of absorbed trichloroethylene was 78%. Of this, 11% was excreted as unchanged trichloroethylene by the lungs, 43% as trichloroethanol in urine and 24% as trichloroacetic acid in urine. The quantity of trichloroethanol and trichloroacetic acid excreted in urine were related to body mass (Monster *et al.*, 1979). The blood half-life of trichloroethylene has been calculated as 21.7 hours (Kostrzewski *et al.*, 1993). The mean urinary biological half-life is estimated to be 41 hours, but may be as long as 73 hours in some cases (Ikeda, 1977).

In a human volunteer study of skin exposure and trichloroethylene absorption, trichloroethylene concentrations in alveolar air samples decayed rapidly once exposure ceased (Stewart and Dodd 1964). This study also concluded that trichloroethylene is not likely to be absorbed in sufficient quantities to cause systemic toxicity when contact is limited to the skin of the hands and forearms.

Mode of action

Trichloroethylene is a CNS depressant and most deaths from acute trichloroethylene exposure are due to anaesthesia (Lemen, 2001). Toxic metabolites of trichloroethylene may affect dopaminergic transmission in the brain resulting in CNS dysfunction (Mutti and Franchini, 1987).

Trichloroethylene, like other halogenated hydrocarbons, is thought to sensitise the myocardium to catecholamines, thus causing cardiac arrhythmias (Brüning *et al.,* 1998). This action has been demonstrated in experimental animals where trichloroethylene was shown to be cardiotoxic following sensitisation of the heart with epinephrine (adrenaline) (Johnson and Shanor 1968). It is likely that sensitisation of the heart is due to the action of trichloroethylene itself, since compounds which block the metabolism of trichloroethylene increase the sensitisation of the heart (Lemen, 2001).

Glutathione conjugation of trichloroethylene by glutathione-S-transferases results in the formation of *S*-(dichlorovinyl)glutathione (DCVG). This is cleaved by the enzymes of the mercapturic acid pathway to form *S*-(-1,2-dichlorovinyl)-L-cysteine (DCVC). DCVC is a substrate for renal cysteine conjugate β-lyases leading to the formation of chlorothioketene. The formation of *S*-conjugates of trichloroethylene and the action of β-lyases may be responsible for the nephrotoxic effects of trichloroethylene (Brüning *et al*., 1998) and have been linked with the development of renal cell cancer (Henschler *et al*., 1995).

Metabolic interactions

- **Acetone**

  Trichloroethylene is metabolised principally in the liver by two pathways, one of which is by oxidation via cytochrome P450. Induction of this isoenzyme system by acetone may increase the metabolism of trichloroethylene to toxic metabolites.

- **Aliphatic organochlorines**

  In vivo and *in vitro* studies demonstrated that combinations of trichloroethylene with tetrachloroethylene or 1,1,1-trichloroethane or both, were more toxic than the individual chemicals alone. Measures of effects were parameters of cell integrity (leak of potassium, lactate dehydrogenase and alanine aminotransferase in hepatocytes) for the *in vitro* tests and measures of hepatic and renal function (liver weight, alanine aminotransferase, sorbital dehydrogenase and urea) in rats. The effect of the three solvents together was greater than mixtures of two. This study did not investigate the mechanism of interaction (Stacey, 1989).

- **Carbon tetrachloride**

  Carbon tetrachloride induced hepatotoxicity in rats is enhanced by the simultaneous administration of trichloroethylene and this response is potentiated by pre-treatment with acetone (Charbonneau *et al*., 1988). This may be relevant for individuals who work with a mixture of solvents.

- **Cimetidine**

  Cimetidine (which inhibits the hepatic microoxygenase system) decreased the *in vivo* metabolism of trichloroethylene in experimental animals (Landriault *et al.,* 1989).

- **Ethanol**

  Alcohol dehydrogenase is thought to be one of the main enzymes involved in the metabolism of trichloroethylene. Concurrent exposure to ethanol appears to greatly alter the metabolism of trichloroethylene, increasing the concentration of trichloroethylene and its metabolites. There may also be an increase in ethanol and acetaldehyde concentrations (Hills and Venable, 1982; Köppel *et al.,* 1988).

  In one study, volunteers inhaled 50 ppm trichloroethylene for 6 hours per day for 5 days. Simultaneous ethanol ingestion (blood ethanol level 600 mg/l) inhibited the metabolism of trichloroethylene to trichloroethanol and trichloroacetic acid by approximately 40%. During this time, the blood trichloroethylene concentration increased by 2.5-fold and that in the expired air rose by 4-fold, as compared to trichloroethylene inhalation without concomitant ethanol ingestion. The alcohol intolerance noted after exposure to trichloroethylene is due to the accumulation of trichloroethylene in the CNS resulting from the inhibition of the oxidation of trichloroethylene (Müller *et al*., 1975).

  Ingestion of ethanol before or during work (but not after work), produced increases in the blood trichloroethylene concentration and decreases in the urinary excretion rates of trichloroethylene metabolites. This effect lasted until the next day. These effects were smaller with increased exposure concentrations of trichloroethylene. Induction of trichloroethylene metabolism by consumption of ethanol the evening before work caused small changes in trichloroethylene metabolism at 50 ppm, but greater changes at 500 ppm (Sato *et al*., 1991).

Ethanol may also enhance the hepatotoxic effects of trichloroethylene. Studies in rats found that ethanol potentiated trichloroethylene hepatotoxicity at trichloroethylene concentrations as low as 500 ppm (Nakajima *et al.,* 1988). In another animal study, rats receiving ethanol prior to trichloroethylene exposure had AST concentrations approximately 75% higher than trichloroethylene exposed animals without ethanol pre-treatment (Cornish and Adefuin, 1966).

One effect of the combination of ethanol and trichloroethylene has been termed 'degreasers flush'. Workers exposed to 200 ppm of trichloroethylene daily for three weeks reported extreme dermal flushing and red blotches on the face, neck and shoulders after consumption of as little as one-half pint of beer (Stewart *et al.,* 1974).

CASE REPORTS

Burns and elevated liver enzymes after accidental exposure

A 44 year old man sustained 25% total body surface burns (second degree partial thickness) to the legs, buttocks, back and patches of the chest and upper extremities following exposure to trichloroethylene fumes. Exposure had occurred as he was retrieving metal parts from a container of trichloroethylene. One of his colleagues, who was with him, died during the accident. The patient was treated with decontamination, fluid resuscitation and dressings. He was also electively ventilated. There were no signs of cardiotoxicity. His liver enzymes (transaminases and alkaline phosphatase) were raised and bilirubin was normal. The burns healed and his liver enzyme values returned to normal within 6 weeks (Balakrishnan *et al*., 1993).

Acute renal failure due to occupational exposure

A 34 year old man working in a factory manufacturing computer ribbons was exposed to trichloroethylene for 8 hours while cleaning the ink off old ribbons for subsequent reuse. He wore gloves but no mask and used 7.5 l of trichloroethylene (99.5% pure). He began to feel unwell the next day with drowsiness and a distaste for alcohol and cigarettes. He became short tempered and began vomiting after meals. Swelling of the feet and face began one week after exposure with bilateral loin tenderness, frequency of micturition and dysuria. He attended hospital 3 weeks after exposure. On examination he was hypertensive, with bilateral renal angle and suprapubic tenderness. Pronounced pedal oedema was also present. Chest X-ray revealed small bilateral pleural effusions but the lung fields were clear. His ECG was normal. The diagnosis was acute interstitial nephritis. He made a slow recovery and eight months later his renal function was normal (David *et al*., 1989).

Pulmonary oedema after acute poisoning

A 58 year old man accidentally fell, face first, into a reservoir of trichloroethylene at work. He was rescued by a work colleague and it was estimated that he had been in the reservoir for about 3-5 minutes. On admission to hospital he had 30% burns mainly to his face, buttocks and back. He was deeply comatose and tachycardic. His pharynx and larynx were found to be markedly oedematous. Chest X-ray showed evidence of diffuse chemical pneumonitis. Liver enzymes were slightly elevated but renal function was normal. A gastric lavage was performed and respiratory depression necessitated mechanical ventilation. His level of consciousness gradually recovered and he was successfully extubated on day 24. There was no evidence of pneumonitis on chest X-ray on day 25 and the patient was eventually discharged in good health on day 44 (Yoshida *et al*., 1996).

CLINICAL EFFECTS

Acute exposure

Inhalation

Dose dependent CNS depression may occur, ranging from decreased psychomotor function and confusion to respiratory failure, coma and death at high concentrations. Deaths have occurred after exposure to concentrations greater than 15,000 ppm trichloroethylene (Lemen, 2001).

In 288 cases of occupational exposure to trichloroethylene reported to a factory inspectorate, 125 individuals became unconscious, 128 other victims had CNS signs and symptoms, 76 had nausea and/or vomiting and 55 had respiratory symptoms including cough and breathlessness (McCarthy and Jones, 1983).

Neurological effects

Bilateral trigeminal neuropathy has been reported after accidental exposure to a spill of trichloroethylene at work (Noseworthy and Rice, 1988).

Renal effects

Acute renal failure has been reported after exposure to trichloroethylene in the workplace. This was thought to be due to acute allergic interstitial nephritis with secondary tubular necrosis and tubular obstruction from intraluminal casts. The patient in this case did not present to hospital until 3 weeks after the exposure (David *et al*., 1989).

Cardiac effects

Trichloroethylene causes sensitisation of the myocardium to catecholamines. Ventricular fibrillation, ventricular bigeminy, ventricular premature beats and cardiac arrest have been reported following deliberate inhalation of trichloroethylene (Thomas *et al*., 1987; Wodka and Jeong, 1989) and cardiac arrest has been reported in fatal cases of trichloroethylene poisoning (Dehon *et al*., 2000). Sudden death has been reported in adolescents who deliberately inhaled typewriter correction fluid containing trichloroethylene and 1,1,1-trichloroethane (King *et al*., 1985).

In one volunteer study, a significant decrease in diastolic blood pressure was noted after 3 hours of exposure to 170 ppm trichloroethylene (Ogata *et al*., 1971).

Dermal

Skin irritation and burns may develop following dermal exposure to trichloroethylene. After heavy skin contamination there is a risk of systemic poisoning with CNS and respiratory depression and elevation of liver enzymes (Balakrishnan *et al*., 1993).

Volunteers reported a burning sensation to the skin after contact with trichloroethylene. Five minutes after the onset the sensation was described as moderately severe by two of the three subjects. The pain became more intense for several minutes after exposure to trichloroethylene had ceased and for 30 minutes post exposure a tingling sensation was noted (Stewart and Dodd, 1964).

Eye

Splash contact of trichloroethylene in the eyes causes pain and may cause injury to the cornea but this usually resolves spontaneously. The most severe cases have occurred in patients who have become unconscious after inhaling trichloroethylene vapours and have fallen and remained exposed to high trichloroethylene concentrations of vapour or liquid. Loss of corneal epithelium may occur in these situations. The lids and conjunctivae may become oedematous and hyperaemic (Grant and Schuman, 1993).

Ingestion

Ingestion of trichloroethylene may cause nausea, vomiting and drowsiness progressing to deep coma in severe cases. Tachycardia and hypotension may also occur and there is a risk of cardiac arrhythmias. In severe cases respiratory depression, cyanosis and pulmonary oedema may occur.

Cardiac effects

Cardiac effects reported from ingestion of trichloroethylene include second degree AV and sino-atrial block (Hantson *et al*., 1990), bigeminy and junctional rhythm (Moritz *et al*., 2000).

Renal effects

Renal tubular damage has been reported following deliberate ingestion of trichloroethylene (Brüning *et al*., 1998).

Chronic exposure

Inhalation

Fatigue, weakness, headache, depression, loss of memory, impairment of judgement, emotional disorder, disturbed sleep, loss of appetite and autonomic disorders may occur in workers chronically exposed to trichloroethylene.

There was an increased incidence of fatigue, vertigo, dizziness, headache, memory loss and impaired concentration following exposure to 100-200 ppm trichloroethylene. Paraesthesia and muscular pains may also occur. Visual disturbances and feelings of inebriation may occur at exposures to 200-300 ppm trichloroethylene and exposures to 500-1,000 ppm have resulted in dizziness, light-headedness, lethargy and impairment in visual motor responses. Significant toxicity is unlikely from exposure to less than 300 ppm trichloroethylene (Hathaway *et al*., 1996). Loss of taste may occur (Mitchell and Parsons-Smith, 1969).

Following spillage of trichloroethylene at a pipe manufacturing plant, the mean time weighted occupational exposure to trichloroethylene of degreaser operators was 205 mg/m^3 (recommended exposure limit 135 mg/m^3). The mean short-term exposure was 1084 mg/m^3 (recommended limit 535 mg/m^3). Drowsiness, dizziness or mental confusion were reported in 7 of 9 workers exposed (Landrigan *et al.,* 1987).

Neurological effects

The association of clinically significant polyneuropathy with occupational exposure to trichloroethylene is controversial. In a study of thirty railroad workers who had an average 20 years of exposure to solvents including trichloroethylene, trichloroethane and tetrachloroethylene sufficient to produce acute intoxication on a regular basis, peripheral nervous system dysfunction was not found (Albers *et al*., 1999).

Severe cranial neuropathies affecting the trigeminal nerves have been reported with exposure to trichloroethylene. An increase incidence of trigeminal nerve impairment, asthenia, optic nerve impairment, headache and dizziness was reported in a group of workers chronically exposed to trichloroethylene (Barret *et al*., 1984). However, trigeminal neuropathy is more likely to be due to the breakdown products of trichloroethylene than exposure to trichloroethylene itself (Laureno, 1988; Grant and Schuman, 1993).

Other neurological effects have been reported with trichloroethylene. Distal paraesthesia, pain in the extremities, headache, and paraesthesia around the mouth were reported in a 51 year old woman who had been exposed to a high concentration of trichloroethylene at work for 12 years (Takeuchi *et al*., 1986). Parkinson's disease was reported in a 47 year old woman who had a 7 year occupational history of trichloroethylene exposure (Guehl *et al*., 1999). These authors also demonstrated nigral degeneration in mice treated with trichloroethylene.

Renal effects

Renal failure has been reported in a patient who intentionally abused shoe polish (containing trichloroethylene, methylene chloride, methylene ketone and dipropylene glycol) over a 5 year period (Mee and Wright, 1980).

Cardiac effects

Progressive heart failure and pulmonary oedema were reported in a 24 year old man who had a 5 year history of intentional sniffing of a shoe polish containing trichloroethylene, methylene chloride, methylene ketone and dipropylene glycol. Congestive cardiomyopathy was found on postmortem examination (Mee and Wright, 1980).

Hepatic effects

Occupational trichloroethylene exposure may affect liver function, particularly cholesterol metabolism. An increase in serum high-density lipoprotein cholesterol was found in workers exposed to concentrations of trichloroethylene below 50 ppm. These effects are likely to be subclinical and reversible (Nagaya *et al*., 1993).

Hepatitis from exposure to trichloroethylene in industrial settings is extremely rare but cases have been reported (McCunney, 1988; Schattner and Malnick, 1990). In addition, an increase in clinical liver impairment was seen among alcohol users exposed to trichloroethylene at work (Barret *et al*., 1984). An enlarged sclerotic liver was found on postmortem examination of a 24 year old man who had a 5 year history of intentional sniffing of a shoe polish containing trichloroethylene, methylene chloride, methylene ketone and dipropylene glycol (Mee and Wright, 1980).

Ototoxicity

Prolonged exposure to toxic concentrations of trichloroethylene may result in hearing defects (Hathaway *et al*., 1996).

Immunotoxicity

Scleroderma has been reported in a worker exposed to trichloroethylene. There were changes in the skin of the proximal digits consistent with scleroderma, and Raynaud's phenomenon with digital ulceration. Scaling erythema was found on the knuckles, elbows and knees. He also complained of exertional dyspnoea and proximal muscle weakness. He had been using trichloroethylene at work for 4 years to degrease metallic parts. Cases of scleroderma have also been reported following occupational exposure to mixtures of trichloroethylene and trichloroethane (Flindt-Hansen and Isager, 1987).

Diffuse fasciitis with eosinophilia has been reported following prolonged exposure to trichloroethylene. In one case the source of the exposure was thought to be contaminated drinking water from a well. This well water ran in close proximity to a holding pond used previously by a manufacturing facility to collect solvent runoff after degreasing metal equipment with trichloroethylene. Other chemicals may also have been present. The second case was associated with long-term occupational use of trichloroethylene (Waller *et al*., 1994). Eosinophilic fasciitis has also been reported in a patient with an 8 year exposure to trichloroethylene (Hayashi *et al.,* 2000).

A fatal hypersensitivity reaction to trichloroethylene (occupational exposure) has been reported and there have been reports of Stevens-Johnson syndrome (Goon *et al*., 2001).

Dermal

Dermatitis has been reported after chronic inhalation of trichloroethylene at work (Goh and Ng, 1988). Repeated skin contact may lead to drying and chapping (Hathaway *et al*., 1996).

Generalised dermatitis has been reported following occupational exposure to trichloroethylene for 2 weeks. There was exfoliative dermatitis with mucous membrane involvement, fever and severe liver dysfunction. Patch testing revealed positive results for trichloroethylene and trichloroethanol and the dermatitis was considered to have been mediated by a delayed-type hypersensitivity mechanism (Nakayama *et al*., 1988).

Eye

Trigeminal and oculomotor nerve paralysis, optic or retrobulbar neuritis and optic atrophy have been reported following trichloroethylene exposure (e.g., Abecia *et al*., 1996). However, it is more likely that decomposition products of trichloroethylene (on heating or mixing with other chemicals) are responsible for these effects, rather than trichloroethylene itself. Acute illness may occur after a latent period of a few hours or more (Grant and Schuman, 1993).

Bilateral uveitis has been reported in a 48 year old woman with a history of chronic occupational exposure to trichloroethylene. This patient also developed aniteric hepatitis (Schattner and Malnick 1990).

Ingestion

No information available.

Carcinogenicity

The IARC classifies trichloroethylene as probably carcinogenic (Group 2A). This is based on limited evidence for carcinogenicity in humans and sufficient evidence for carcinogenicity in experimental animals.

An association between trichloroethylene and cancer is controversial (Ramlow, 1995). An increased risk for malignant neoplasms was found in a study which examined 330 death certificates of workers in the dry cleaning industry (Blair *et al.*, 1979). At this time the most common chemicals used were carbon tetrachloride, trichloroethylene, tetrachloroethylene and petroleum solvents. An increased incidence of lung and cervical cancers were found with a slight excess in the incidence of leukaemia and liver cancer. An increased incidence of hepatocellular carcinoma has been reported in experimental animals, but it is unlikely that trichloroethylene causes increased hepatocellular cancer in humans (Elcombe, 1985).

Aircraft manufacturing workers routinely exposed to trichloroethylene (and other chemicals) did not have an increased incidence of lung cancer or total cancer. Slight to moderately increased rates of non-Hodgkin's lymphoma were found among workers exposed to trichloroethylene, but these differences were not significant (Boice *et al.*, 1999).

A retrospective study of workers in a cardboard factory was carried out to investigate the association between exposure to trichloroethylene and renal cancer (Henschler *et al.*, 1995). They found 5 cases of renal cancer in a group of 169 subjects. The authors concluded that exposure to high concentrations of trichloroethylene over prolonged periods of time may cause renal tumours in adults. However, this study was criticised for its methodology (Bloemen and Tomenson, 1995; Swaen, 1995) and other studies have failed to find a link between renal cancer and exposure to trichloroethylene (McLaughlin and Blot, 1997).

In a study examining the occupational history of white men who had died of brain cancer, an association of astrocytic brain cancer was observed in those possibly exposed to trichloroethylene (Heineman *et al.*, 1994).

Genotoxicity

There are conflicting results from the studies on the genotoxic effects of trichloroethylene. Some studies have identified genotoxic effects, while others have not. Conflicting results may in some cases be due to the mutagenicity of breakdown products of trichloroethylene rather than trichloroethylene itself (IPCS, 1985).

Sixteen halogenated aliphatic hydrocarbons were assayed for genotoxicity using the Ara mutagenicity assay with *Salmonella typhimurium* (Roldán-Arjona *et al.,* 1991). Trichloroethylene was non-mutagenic, both in the presence and absence of metabolic activation with a rat liver microsomal fraction (S9).

The frequency of sister chromatid exchanges in peripheral lymphocytes was studied in workers exposed to tetrachloroethylene and trichloroethylene. The groups included 38 men and women exposed to 7 ppm trichloroethylene and 19 men and women exposed to a mixture of 8 ppm trichloroethylene and 17 ppm tetrachloroethylene. There were no significant increases in the frequency of sister chromatid exchanges in association with exposure to trichloroethylene or trichloroethylene/tetrachloroethylene. However, the frequency of sister chromatid exchanges was significantly higher in the trichloroethylene and trichloroethylene/tetrachloroethylene exposed smoking men than in non-smoking controls. This indicates a possible synergism between solvent exposure and smoking (Seiji *et al.*, 1990).

Reproductive toxicity

There is limited information on the reproductive effects of trichloroethylene in humans. Experimental animal studies have shown that trichloroethylene does not adversely affect fertility, or embryo implantation and survival, and does not cause teratogenic effects. Trichloroethylene has, however, caused delayed development and decreased birth weight. In most studies, no neonatal mortality was observed unless maternal toxicity occurred (REPROTEXT document, 2001).

One study found that paternal occupational exposure to trichloroethylene was not associated with an increase in spontaneous abortion or congenital malformations (Taskinen *et al*., 1989). However studies have linked maternal occupational trichloroethylene exposure with an increase in spontaneous abortions (Hemminki *et al*., 1980; Windham *et al*., 1991). Epidemiological observations showed an increased number of congenital cardiac defects in children whose mothers resided in an area with drinking water contaminated by trichloroethylene and dichloroethylene as compared to mothers who did not live in a contaminated area (Goldberg *et al*., 1990).

Cardiac abnormalities have been described in chick embryos when eggs were injected with trichloroethylene. Experiments with rats showed that exposure to trichloroethylene or dichloroethylene in the period before pregnancy caused no increase in congenital cardiac defects. However, rats exposed to these agents both before and during pregnancy had a significantly greater number of fetuses with congenital cardiac malformations (Dawson *et al*., 1993; 1990). In another study, trichloroethylene did not cause significant maternal, embryonal or fetal toxicity and was not teratogenic in rats or mice (Schwetz *et al*., 1975).

RISK GROUPS

None identified.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Trichloroethylene is radiopaque (Dally *et al*., 1987) and an X-ray may confirm ingestion. Gastric lavage may be considered if ingestion was recent, however, because of the risk of aspiration due to CNS depression a cuffed endotracheal tube must be used to protect the airway. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing, the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive. See below for management of systemic effects.

Systemic effects

The ECG, renal and liver functions should be monitored. Oxygen may be given if required. Alveolar hyperventilation during the first 12 hours post ingestion increases the elimination of trichloroethylene from the body (Perbellini *et al*., 1991).

Antidotes

There is no specific antidote for trichloroethylene poisoning.

Chronic exposure

Monitor liver and renal function. Symptomatic and supportive care.

REFERENCES

Abecia E, Martinez-Jarreta B, Pinilla I, Larrosa M, Castellano M, Honrubia M. 1996 Bilateral optic neuritis in occupational exposure to trichloroethylene. *Med Lav* 87 (5):432-6.

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Albers JW, Wald JJ, Werner RA, Franzblau A, Berent S. 1999 Absence of polyneuropathy among workers previously diagnosed with solvent-induced toxic encephalopathy. *J Occup Environ Med* 41 (6):500-509.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals an air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Annau Z. 1981 The neurobehavioural toxicity of trichloroethylene. *Neurobehav Toxicol Teratol* 3:417-424.

Balakrishnan C, Leonard MW, Marson D. 1993 Trichloroethylene burn. *J Burn Care Rehabil* 14:461-462.

Barret L, Faure J, Guilland B, Didier B, Debru JL. 1984 Trichloroethylene occupational exposure: elements for better protection. *Int Arch Occup Environ Health* 53 (4):283-289.

Baselt RC. 2000 *Disposition of Toxic Drugs and Chemicals in Man,* fifth edition. Chemical Toxicology Institute, California.

Blair A, Decoufle P, Grauman D. 1979 Causes of death among laundry and dry cleaning workers. *Am J Pub Health* 69 (5): 508-511.

Bloemen LJ, Tomenson J. 1995 Increased incidence of renal cell tumours in a cohort of cardboard workers exposed to trichloroethylene. *Arch Toxicol* 70:129-130.

Boice JD Jr, Marano DE, Fryzek JP, Sadler CJ, McLaughlin JK. 1999 Mortality among aircraft manufacturing workers. *Occup Environ Med* 56:581-597.

Brüning T, Vamvakas S, Makropoulos V, Birner G. 1998 Acute intoxication with trichloroethene: Clinical symptoms, toxicokinetics, metabolism and development of biochemical parameters for renal damage. *Toxicol Sci* 41:157-165.

Charbonneau M, Perreault F, Greselin E, Brodeur J, Plaa GL. 1988 Assessment of the minimal effective dose of acetone for potentiation of the hepatotoxicity induced by trichloroethylene-carbon tetrachloride mixtures. *Fundam Appl Toxicol* 10 (3):431-438.

Condie LW. 1985 Target organ toxicity of halocarbons commonly found contaminating drinking water. *Sci Total Environ* 47:433-42.

Cornish HH, Adefuin J. 1966 Ethanol potentiation of halogenated aliphatic solvent toxicity. *Am Ind Hyg Assoc J* 27 (1):57-61.

Dally S, Garnier R, Bismuth C. 1987 Diagnosis of chlorinated hydrocarbon poisoning by x ray examination. *Br J Ind Med* 44:424.

David NJ, Wolman R, Milne FJ, Van Niekerk I. 1989 Acute renal failure due to trichloroethylene poisoning. *Br J Ind Med* 46: 347-349.

Dawson BV, Johnson PD, Goldberb SJ, Ulreich JB. 1993 Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. *J Am Coll Cardiol* 21 (6):1466-1472.

Dawson BV, Johnson PD, Goldberg SJ, Ulreich JB. 1990 Cardiac teratogenesis of trichloroethylene and dichloroethylene in a mammalian model. *J Am Coll Cardiol* 16 (5):1304-1309.

Dehon B, Humbert L, Devisme L, Stievenart M, Mathieu D, Houdret N, Lhermitte M. 2000 Tetrachloroethylene and trichloroethylene fatality: case report and simple headspace SPME-capillary gas chromatographic determination in tissues. *J Anal Toxicol* 24:22-26.

Droz PO, Fernández JG. 1978 Trichloroethylene exposure. Biological monitoring by breath and urine analyses. *Br J Ind Med* 35:35-42.

Elcombe CR. 1985 Species differences in carcinogenicity and peroxisome proliferation due to trichloroethylene: A biochemical human hazard assessment. *Arch Toxicol* Suppl 8:6-17.

Flindt-Hansen H, Isager H. 1987 Scleroderma after occupational exposure to trichloroethylene and trichloroethane. *Acta Derma Venereol* 67 (3):263-4.

Ford ES, Rhodes S, McDiarmid M, Schwartz SL, Brown J. 1995 Deaths from acute exposure to trichloroethylene. *J Occup Environ Med* 37 (6):749-754.

Goh CL, Ng SK. 1988 A cutaneous manifestation of trichloroethylene toxicity. *Contact Dermatitis* 18:59-61.

Goldberg SJ, Lebowitz MD, Graver EJ, Hicks S. 1990 An association of human congenital cardiac malformations and drinking water contaminants. *Pediatr Cardiol* 16 (1):155-164.

Goon AT, Lee LT, Tay YK, Yosopovitch G, Ng SK, Giam YC. 2001 A case of trichloroethylene hypersensivity syndrome. *Arch Dermat* 137:274-276.

Grant WM, Schuman JS. 1993 *Toxicology of the Eye,* fourth edition. Charles C Thomas, Springfield, Illinois.

Guehl D, Bezard E, Dovero S, Boraud T, Bioulac B, Gross C. 1999 Trichloroethylene and parkinsonism: a human and experimental observation. *Eur J Neurol* 6:609-611.

Hantson PH, Vandenplas O, Dive A, Mahieu P. 1990 Trichloroethylene and cardiac toxicity: report of two consecutive cases. *Acta Clin Belg* 45 (1):34-37.

Hathaway GJ, Proctor NH, Hughes JP. 1996 *Proctor & Hughes' Chemical Hazards of the Workplace,* fourth edition. John Wiley & Sons Inc, New York.

Hayashi N, Igarashi A, Matsuyama T, Harada S. 2000 Eosinophilic fasciitis following exposure to trichloroethylene: successful treatment with cyclosporin. *Br J Dermatol* 142:812-851.

Heineman EF, Cocco P, Gomez MR, Dosemeci M, Stewart PA, Hayes RB, Zahm SH, Thomas TL, Blair A. 1994 Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer. *Am J Ind Med* 26:155-169.

Hemminki K, Franssila E, Vainio H. 1980 Spontaneous abortion among female chemical workers in Finland. *Int Arch Occup Environ Health* 45:123-126.

Henschler D, Vamvakas S, Lammert M, Dekant W, Kraus B, Thomas B, Ulm K. 1995 Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene. *Arch Toxicol* 69:291-299.

Hills BW, Venable HL. 1982 The interaction of ethyl alcohol and industrial chemicals. *Am J Ind Med* 3:321-333.

Ikeda M, Ohtsuji H, Imamura T, Komoike Y. 1972 Urinary excretion of total trichloro-compounds, trichloroethanol, and trichloroacetic acid as a measure of exposure to trichloroethylene and tetrachloroethylene. *Br J Ind Med* 29:328-333.

Ikeda M. 1977 Metabolism of trichloroethylene and tetrachloroethylene in human subjects. *Environ Health Perspect* 21:219-245.

IPCS. 1985 *Environmental Health Criteria 50. Trichloroethylene*. World Health Organization, International Programme on Chemical Safety, Geneva.

Johnson HE, Shanor SP. 1968 Electrocardiographic findings in dogs inhaling the vapors of diverse chlorinated hydrocarbons [abstract]. *Toxicol Appl Pharmacol* 12:297.

King GS, Smialek JE, Troutman WG. 1985 Sudden death in adolescents resulting from the inhalation of typewriter correction fluid. *J Am Med Assoc* 253(11):1604-1606.

Köppel C, Lanz H-J, Ibe K. 1988 Acute trichloroethylene poisoning with additional ingestion of ethanol - concentrations of trichloroethylene and its metabolites during hyperventilation therapy. *Intensive Care Med* 14:74-76.

Kostrzewski P, Jakubowski M, Kolacinski Z. 1993 Kinetics of trichloroethylene elimination from venous blood after acute inhalation poisoning. *Clin Toxicol* 31 (2):353-363.

Landriault H, Sirois G, Chakrabati S, Cote MG. 1989 Effect of cimetidine on hepatic biochemical changes, liver toxicity and major urinary metabolite excretion of trichloroethylene in rats. *J Appl Toxicol* 9 (2):75-89.

Landrigan PJ, Stein GF, Kominsky JR, Ruhe RL, Watanabe AS. 1987 Common-source community and industrial exposure to trichloroethylene. *Arch Environ Health* 42 (6):327-332.

Laureno R. 1988 Trichloroethylene neurology [letter]. *Can J Neurol Sci* 15 (3):354.

Lemen RA. 2001 Unsaturated halogenated hydrocarbons. In: *Patty's Toxicology,* fifth edition, Volume 5. Bingham E, Cohrssen B, Powell CH (editors). John Wiley & Sons Inc, New York.

Maull EA, Cogliano VJ, Scott CS, Barton HA, Fisher JW, Greenberg M, Rhomberg L, Sorgen SP. 1997 Trichloroethylene health risk assessment: a new and improved process. *Drug Chem Toxicol* 20 (4):426-442.

McCarthy TB, Jones RD. 1983 Industrial gassing poisonings due to trichloroethylene, perchloroethylene, and 1,1,1-trichloroethane, 1961-80. *Br J Ind Med* 40:450-455.

McCunney RJ. 1988 Diverse manifestations of trichloroethylene. *Br J Ind Med* 45:122-126.

McLaughlin JK, Blot WJ. 1997 A critical review of epidemiology studies of trichloroethylene and perchloroethylene and risk of renal-cell cancer. *Int Arch Occup Environ Health* 70:222-231.

Mee AS, Wright PL. 1980 Congestive (dilated) cardiomyopathy in association with solvent abuse. *J R Soc Med* 73:671.

Mitchell ABS, Parsons-Smith BG. 1969 Trichloroethylene neuropathy. *Br Med J* 1:422-423.

Monster AC. 1979 Difference in uptake, elimination and metabolism in exposure to trichloroethylene, 1,1,1-trichloroethane and tetrachloroethylene. *Int Arch Occup Environ Health* 42:311-317.

Monster AC, Houtkooper JM. 1979 Estimation of individual uptake of trichloroethylene, 1,1,1-trichloroethane and tetrachloroethylene from biological parameters. *Int Arch Occup Environ Health* 42:319-323.

Monster AC, Boersma G, Duba WC. 1979 Kinetics of trichloroethylene in repeated exposure of volunteers. *Int Arch Occup Environ Health* 42:283-292.

Moritz F, de La Chapelle A, Bauer F, Leroy JP, Goullé JP, Bonmarchand G. 2000 Esmolol in the treatment of severe arrhythmia after acute trichloroethylene poisoning [letter]. *Intensive Care Med* 2:256.

Müller G, Spassowski M, Henschler. 1975 Metabolism of trichloroethylene in man. *Arch Toxicol* 33:173-189.

Mutti A, Franchini I. 1987 Toxicity of metabolites to dopaminergic systems and the behavioural effects of organic solvents. *Br J Ind Med* 44:721-723.

Nakajima T, Okino T, Ohuyama S, Kaneko T, Yonekura I, Sato A. 1988 Ethanol-induced enhancement of trichloroethylene metabolism and hepatotoxicity: difference from the effect of phenobarbital. *Toxicol Appl Pharmacol* 94:227-237.

Nagaya T, Ishikawa N, Hata H, Otobe T. 1993 Subclinical and reversible hepatic effects of occupational exposure to trichloroethylene. *Int Arch Occup Environ Health* 64: 561-563.

Nakayama H, Kobayashi M, Takahashi M, Ageishi Y, Takano T. 1988 Generalized eruption with severe liver dysfunction associated with occupational exposure to trichloroethylene. *Contact Dermatitis* 19:48-51.

Noseworthy JH, Rice GPA. 1988 Trichloroethylene poisoning mimicking multiple sclerosis [letter]. *Can J Neurol Sci* 15 (1):87-88.

Ogata M, Takatsuka Y, Tomokuni K, Muroi K. 1971 Excretion of organic chlorine compounds in the urine of persons exposed to vapours of trichloroethylene and tetrachloroethylene. *Br J Ind Med* 28:386-391.

Perbellini L, Olivato D, Zedde A, Miglioranzi R. 1991 Acute trichloroethylene poisoning by ingestion: clinical and pharmacokinetic aspects. *Intensive Care Med* 17:234-235.

Ramlow JM. 1995 Critique of review of chlorinated solvents epidemiology [letter]. *Am J Ind Med* 27:313-316.

REPROTEXT Document. 2001 *Trichloroethylene*. In: Heitland G, Hurlbut KM (editors): REPROTEXT® Database (electronic version), MICROMEDEX, Greenwood Village, Colorado, USA. Available at www.tomescps.com/DATA/RE/RE1405.HTM (site visited 01/08/01).

Roldán-Arjona T, García-Pedrajas M, Luque-Romero FL, Hera C, Pueyo C. 1991 An association between mutagenicity of the Ara test of *Salmonella typhimurium* and carcinogenicity in rodents for 16 halogenated aliphatic hydrocarbons. *Mutagenesis* 6 (3): 199-205.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Sato A, Nakajima T. 1978 Differences following skin or inhalation exposure in the absorption and excretion kinetics of trichloroethylene and toluene. *Br J Ind Med* 35:43-49.

Sato A, Endoh K, Kaneko T, Johanson G. 1991 Effects of consumption of ethanol on the biological monitoring of exposure to organic solvent vapours: a simulation study with trichloroethylene. *Br J Ind Med* 48:548-556.

Sato A, Nakajima T, Fujiwara Y, Murayama N. 1977 A pharmacokinetic model to study the excretion of trichloroethylene and its metabolites after an inhalation exposure. *Br J Ind Med* 34:56-63.

Schattner A, Malnick SDH. 1990 Anicteric hepatitis and uveitis in a worker exposed to trichloroethylene. *Postgrad Med J* 66:730-731.

Schwetz BA, Leong BKJ, Gehring PJ. 1975 The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform and methylene chloride on embryonal and fetal development in mice and rats. *Toxicol Appl Pharmacol* 32:84-96.

Seiji K, Jin C, Watanabe T, Nakatsuka H, Ikeda M. 1990 Sister chromatid exchanges in peripheral lymphocytes of workers exposed to benzene, trichloroethylene or terachloroethylene with reference to smoking habits. *Int Arch Occup Environ Health* 62:171-176.

Skender L, Karačić V. 1996 Assessment of environmental exposure to trichloroethylene and tetrachloroethylene. *Environ Manag Health* 7:14-16.

Stacey NH. 1989 Toxicity of mixtures of trichloroethylene, tetrachloroethylene and 1,1,1-trichloroethane: similarity of *in vitro* to *in vivo* responses. *Toxicol Ind Health* 5 (3):441-450.

Stewart RD, Dodd HC. 1964 Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride and 1,1,1-trichloroethane through the human skin. *Ind Hyg J* 25:439-446.

Stewart RD, Hake CL, Peterson JE. 1974 "Degreaser's Flush": Dermal response to trichloroethylene and ethanol. *Arch Environ Health* 29:1-5.

Swaen GMH. 1995 Increased incidence of renal cell tumours in a cohort of cardboard workers exposed to trichloroethylene. *Arch Toxicol* 70:127-128.

Takeuchi Y, Iwata M, Hisanaga N, Ono Y, Shibata E, Huang J, Takegami T, Okamoto S, Koike Y. 1986 Polyneuropathy caused by chronic exposure to trichloroethylene. *Ind Health* 24:243-247.

Taskinen H, Anttila A, Lindbohm ML, Sallmén M, Hemminki K. 1989 Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand J Work Environ Health* 15:345-352.

Thomas G, Baud FJ. 1987 Clinical and kinetic study of 4 cases of acute trichloroethylene intoxication. *Vet Hum Toxicol* 29 (Suppl 2):97-99.

Waller PA, Clauw D, Cupps T, Metcalf JS, Silver RM, Leroy EC. 1994 Fasciitis (not scleroderma) following prolonged exposure to an organic solvent (trichloroethylene). *J Rheumatol* 21:1567-1570S.

Windham GC, Shusterman D, Swan SH, Fenster L, Eskenazi B. 1991 Exposure to organic solvents and adverse pregnancy outcome. *Am J Ind Med* 20:241-259.

Wodka RM, Jeong EWS. 1989 Cardiac effects of inhaled typewriter correction fluid [letter]. *Ann Emerg Med* 110 (1):91-92.

Yoshida M, Fukabori S, Hara K, Yuasa H, Nakaaki K, Yamamura Y, Yoshida K. 1996 Concentrations of trichloroethylene and its metabolites in blood and urine after acute poisoning by ingestion. *Hum Exp Toxicol* 15:254-258.

24 White Spirit

Maeve McParland

SUMMARY

- White spirit is a mixture of many chemical components and study of its toxicokinetics is complex
- The main route of exposure to white spirit is via inhalation
- White spirit is poorly absorbed from the gastrointestinal tract and systemic toxicity is unlikely from ingestion
- The main risk from ingestion of white spirit is aspiration
- White spirit is irritant to skin and may cause dermatitis
- White spirit is possibly neurotoxic; long-term occupational exposure may lead to a chronic toxic encephalopathy, however studies on exposure to white spirit alone are limited
- Liver damage has been reported rarely
- Adverse reproductive effects have been reported for mixtures of solvents including white spirit, but the effects of the solvent alone remain unconfirmed
- White spirit is not classifiable as to its carcinogenicity in humans

DESCRIPTION

White spirit is a clear, colourless, non-viscous liquid. It is a complex mixture containing mainly C7-C12 hydrocarbons with a boiling range of 130-220 °C, and is produced by fractional distillation of the naphtha and kerosene components of crude petroleum. The exact content of white spirit can vary due to differences in production processes, but more significantly from variations in the raw material (crude oil).

There are four types of white spirit defined by the chemical processes that the crude substance undergoes during its production (IPCS, 1996):

1) 'Straight run white spirit' which has not been treated beyond the process of distillation (type 0)
2) Hydrodesulphurised (type 1)
3) Solvent extracted (type 2)
4) Hydrogenated (type 3)

Each type of white spirit is further sub-divided in to 3 technical grades: a) low flash grade, b) regular grade and c) high flash grade.

White spirit in Europe and Stoddard solvent in the USA are both type 1 white spirit. NIOSH (1977) considers Stoddard solvent to contain mainly C9-C11 hydrocarbons and the proportion of hydrocarbons to be: 30-50% straight and branched chain hydrocarbons, 30-40% naphthenes and 10-20% aromatics.

Synonyms

Stoddard solvent, turpentine substitute, solvent naphtha, varsol, 140 flash solvent, mineral turpentine, petroleum spirit, mineral spirit, petroleum ether, petroleum distillate.

Identification numbers

CAS 8052-41-3 (Stoddard solvent)
64742-88-7 (white spirit type 0)
64742-82-1 (white spirit type 1)
64741-92-0 (white spirit type 2)
64742-48-9 (white spirit type 3)

UN 1268 (petroleum distillates)

RTECS WJ8925000 (Stoddard solvent)
ZC3850000 (white spirit)

EINECS 2324893 (Stoddard solvent)
2651917 (white spirit type 0)
2651854 (white spirit type 1)
2650955 (white spirit type 2)
2651503 (white spirit type 3)

PHYSICAL AND CHEMICAL PROPERTIES (Table 24.1)

Table 24.1 Physical and chemical properties of white spirit

molecular formula	C_nH_{2n+2} (n-alkanes and isoalkanes) C_nH_{2n} (cycloalkanes) C_nH_{2n-6} (aromatics), n>6		
physical form	Clear colourless volatile liquid with kerosene-like odour		
white spirit grade	**low flash**	**regular**	**high flash**
molecular mass	140	150	160
relative vapour density (air=1)	4.5-5	4.5-5	4.5-5
flash point (°C)	21-30	31-54	≥55
boiling point (°C)	130-144	145-174	175-200
autoignition temperature (°C)	240	240	230
refractive index	1.41-1.44	1.41-1.44	1.41-1.44
explosive limits in air (%v/v)	0.6-6.5	0.6-6.5	0.6-8

Odour threshold

The odour threshold for white spirit is quite low at 0.5-5 mg/m^3 (0.085-0.85 ppm), however tolerance can develop (IPCS, 1996). Carpenter *et al.* (1975) reported the human odour threshold as below 0.005 mg/l (0.9 ppm), and although olfactory fatigue occurred in a short time, ten minutes in fresh air restored acuity.

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK and ACGIH): 100 ppm (425-600 mg/m^3 – based on the conversion range below)

Conversion factors

1 ppm = 5.25-6.0 mg/m^3
1 mg/l = 176.5 ppm
1 mg/m^3 = 0.17 - 0.19 ppm

Note: A range is used because of the complex nature of a white spirit mixture.

Biomonitoring

A biological exposure index (BEI) has not been established for white spirit by the ACGIH.

Dimethylbenzoic acid isomers have been used as a marker for exposure to white spirit (Verkkala *et al.,* 1984; Pfäffli *et al.,* 1985; Järnberg *et al.,* 1998). The aromatic component of white spirit contains a small percentage of trimethylbenzene isomers (1%), which are metabolised (by oxidation) to dimethylbenzoic acid isomers (Pfäffli *et al.,* 1985). In rats exposed dermally to white spirit, excretion of these acid isomers correlated well with the absorbed dose, even though trimethylbenzene isomers represented only a minor fraction of the mixture (Verkkala *et al.,* 1984). However, Järnberg *et al.* (1998), compared the metabolism of trimethylbenzene in volunteers exposed (by inhalation) to trimethylbenzene alone, with others exposed to white spirit, and concluded that components of white spirit interfere with the elimination of trimethylbenzene. This must be taken into consideration when using metabolites of trimethylbenzene as a biological marker for white spirit exposure.

TOXICITY

White spirit is commonly used in many industries as a solvent in varnishes and lacquers, inks, degreasers, wood preservatives, aerosols, asphalt products and dry cleaning agents. It is the most commonly used solvent in the paint industry, with 60% of total white spirit consumption in Western Europe being utilised in the manufacture of paint, varnish and lacquers (IPCS, 1996). It is widely used domestically to 'thin' paints and for cleaning paint and varnish from decorating tools.

When interpreting the literature on white spirit toxicity, a few uncertainties remain. There are many epidemiological studies on the effect of chronic exposure to solvents, where white spirit is only part of a more complex exposure. It is difficult to identify the causative agents of occupational diseases when such solvent mixtures are involved (Pedersen *et al.*, 1980). In addition, white spirit itself is a complex mixture of aliphatic, alicyclic and aromatic hydrocarbons, comprising over 200 compounds (Pfäffli *et al.,* 1985; IPCS, 1996) and this makes it very difficult to establish a cause/effect relationship. Furthermore, in many of the human and animal studies, and the limited case reports, it is often unclear which class of white spirit is being referred to. Some investigating authors do clarify the matter and present a breakdown of the aliphatic and aromatic hydrocarbon content of the solvent studied, but generally conclusions are ambiguous because of the wide range of hydrocarbons that the term white spirit encompasses. The various synonyms of white spirit (e.g., turpentine substitute, mineral spirits, Stoddard solvent) add to the confusion. They are sometimes used interchangeably, and in the older literature white spirit may be referred to simply as 'solvent' (e.g., in Braunstein, 1940).

House painters are an occupational group frequently investigated for possible toxic effects of mixed solvents (including white spirit), but in a report from the Commission of the European Communities investigating long-term neurotoxic effects in painters (CEC, 1990), one of the major limitations highlighted was the lack of exact knowledge about the nature and level of exposure. There are, however, a few studies where the dominant exposure is to white spirit (Arlien-Søborg *et al*., 1979, Seppäläinen and Lindström, 1982; Bazylewicz-Walczak *et al*., 1990), but the effect of long-term exposure to white spirit alone is still unresolved.

White spirit has low acute toxicity by all routes of exposure. The main route of absorption and exposure is via inhalation. Systemic toxicity is rare and the main risk associated with exposure to white spirit is aspiration. Toxicity from white spirit predominantly affects the pulmonary system and less commonly the central nervous system, gastrointestinal, cardiac and dermatological systems. Ingestion of even small quantities can result in pulmonary aspiration of the liquid and subsequent chemical pneumonitis and pulmonary oedema (Gerade, 1963). There are rare reports of haematological (Scott *et al.*, 1959; Kegels, 1958; Prager and Peters, 1970) and hepatic effects (Braunstein, 1940, Døssing *et al.,* 1983). Workers with long-term white spirit exposure may gradually develop a chronic organic brain syndrome, often following a period of acute intoxication; this has been termed chronic painter's syndrome (Arlien-Søborg *et al.*, 1979).

Absorption

White spirit is well absorbed by inhalation. The aromatic components of white spirit are more efficiently absorbed and accumulate in the body more readily than the aliphatic components (Åstrand *et al.*, 1975). In a volunteer study where 15 subjects were exposed via inhalation (1,000 mg/m^3; 167-190 ppm, for 30 minutes) to white spirit (83% aliphatic and alicyclic hydrocarbons, 17% aromatic hydrocarbons), it was determined that 59% of the aliphatic and alicyclic components, and 70% of the aromatic hydrocarbon components were absorbed (Åstrand *et al.,* 1975). Pedersen *et al.*, (1987) exposed eight men to 100 ppm white spirit (99% aliphatics) for three hours and the calculated pulmonary uptake was 392 ± 38 mg. On further exposure of the same subjects to 100 ppm of white spirit for six hours daily on five consecutive days, pulmonary uptake was calculated at 3,464 ± 329 mg.

Blood concentrations of the aromatic components of inhaled white spirit have been shown to increase 2.0-fold during light to moderate exercise; for aliphatic components the increase was 2.5-fold (Åstrand *et al.*, 1975).

Petroleum distillates, including white spirit, are not well absorbed from the gastrointestinal tract, however, following large ingestions of white spirit signs of systemic toxicity have occurred (Jouet *et al.,* 1983).

There is no information available on the dermal absorption of white spirit in humans. In an animal study investigating the neurotoxicity of white spirit by percutaneous exposure, rats were exposed to three different types of white spirit:

(a) 60% aliphatics, 39.7% alicyclics, 0.3% aromatics;

(b) 61% aliphatics, 27.3% alicyclics, 11.7% aromatics;

(c) 83% alicyclics, 17% aromatics.

A tail skin area of 12 cm^3 was exposed for a three hour period. The total absorbed dose of the three mixtures was: (a) 260 ± 80 mg, (b) 210 ± 40 mg, and (c) 240 ± 20 mg (Verkkala *et al.*, 1984).

Distribution

White sprit is widely distributed throughout the body. The aromatic hydrocarbon components of white spirit are generally more soluble in blood than the aliphatic and alicyclic hydrocarbon components (IPCS, 1996).

In seven volunteers exposed to 100 ppm white spirit (99% aliphatics) for six hours daily on five consecutive days, mathematical modelling was used to calculate the tissue concentrations during repeated doses over an extended period. The fat:blood partition coefficient was calculated as 47. The redistribution phase in adipose tissue in white spirit was approximately 20 hours for the first 5 exposures and shorter for subsequent exposures (Pedersen *et al.,* 1987).

Wide distribution occurs from the blood to other tissues, mainly blood, brain and fat. Löf *et al.* (1999) found a fat:brain:blood tissue concentration coefficient of approximately 250:3:1 in rats after inhalation of de-aromatised white spirit. White spirit kinetics in all tissues were non-linear. The accumulation of both the individual aliphatic hydrocarbons and total de-aromatised white spirit in both brain and blood achieved steady state concentrations within the first week. However, concentrations of both individual hydrocarbons and total white spirit in fat increased throughout the three week period and steady state was not achieved.

Metabolism

White spirit is a complex mixture of aliphatic and aromatic hydrocarbons and information on its metabolism is limited. Metabolic pathways have been elucidated for only a small portion of the numerous chemicals in white spirit (Rothman and Emmet, 1988). It is impossible to extrapolate from these findings when attempting to predict the metabolic reactions of a mixture. The simultaneous metabolism of the different chemicals in the white spirit mixture introduces additional factors which will influence kinetics, e.g., inhibition or induction of the metabolising enzyme systems.

The aliphatic hydrocarbons primarily undergo oxidative conversion to alcohols catalysed by cytochrome P450 dependent monooxygenases in the liver. For *n*-alkanes with a carbon chain of 7 or less, oxidation to alcohol predominantly occurs at the penultimate carbon (ω-1 oxidation) giving secondary mono- or dialcohols. In higher alkanes, only oxidation at the terminal carbon has been observed (ω-oxidation), and branched alkanes are oxidised at either the ω or ω-1 position, resulting in secondary or tertiary alcohols. Monocyclic and polycyclic alkanes are oxidised at the CH_2-group in the ring structure. After these primary conversions, phase II conversion occurs with conjugation of the hydroxy groups to form excretable glucuronide or sulphatide conjugates (Bondy, 1995; IPCS, 1996).

Alkyl benzenes are mainly oxidised to alcohols via the cytochrome P450 enzyme system. Alternatively, direct hydroxylation of the aromatic structure can occur and the resultant hydroxy groups are either conjugated to glucuronic acid or sulphate, or further oxidised to ketone/aldehyde or carboxylic acid, and then conjugated to glucuronic acid, sulphate or glycine (IPCS, 1996).

The polyaromatic hydrocarbons (e.g., benzene, naphthalene) are oxidised by cytochrome P450 to form arene oxides. With further oxidation and hydration, the ring structure may break and in the case of benzene this results in the formation of very reactive benzoquinones (IPCS, 1996).

The aromatic component of white spirit contains a small percentage of trimethylbenzene isomers (1%), which are oxidised to dimethylbenzoic acid isomers (Pfäffli *et al.,* 1985), and these have been used as markers for exposure to white spirit (Verkkala *et al.,* 1984; Pfäffli *et al.,* 1985; Järnberg *et al.,* 1998).

Elimination

White spirit appears to undergo biphasic elimination. It has an initial, short distribution phase with rapid elimination from the blood, followed by a longer distribution phase with a slower elimination rate (half-life of approximately 46 hours) (IPCS, 1996). White spirit has been detected in blood 66 hours after a single inhalation exposure (IPCS, 1996).

Urinary excretion of metabolites and expiration of parent compounds are thought to be the major routes of elimination. In a human volunteer study, seven subjects were exposed to 100 ppm white spirit (99% paraffins C8-C12) 6 hours daily for 5 days. The mean concentration in fat was 41.1 mg/kg after 5 days and this fell to 31.7 mg/kg after two exposure free days. The estimated mean and median half-life in fat was 7 and 8 days respectively, and the time to reach steady state was 5-8 weeks. The concentration of white spirit in the brain at steady state was estimated to be 11 mg/kg maximum, while the half-life in the brain was estimated to be 18-19 hours maximum. It was concluded that, during exposure at the threshold limit value (100 ppm), white spirit accumulates in depot fat over weekends and in brain over working days. However, it is almost eliminated from the brain during weekends (Pedersen *et al*., 1984). In a subsequent study the same authors revised these values and calculated the half-life for white spirit in adipose tissue as 46-48 hours. This second value was considered more accurate as it took into account a redistribution phase (Pedersen *et al*., 1987). In rats elimination of white spirit in blood and brain was biphasic, and monophasic in fat tissue. The half-lives were: blood 1 and 8 hours; brain 2 and 15 hours; fat tissue 30 hours (Löf *et al.,* 1999*)*.

Löf *et al.* (1999) investigated the disposition of de-aromatised white spirit in male rats exposed to concentrations of 0, 400 ppm and 800 ppm, for 6 hours/day, 5 days/week for up to three weeks. Five rats from each group were sacrificed immediately after exposure and additionally at periods of one, two, or three weeks post exposure. After three weeks of exposure to 400 ppm or 800 ppm the concentration of total white spirit in blood was 1.5 mg/kg and 5.6 mg/kg, in brain 7.1 mg/kg and 17.1 mg/kg and in fat tissue 432 mg/kg and

1,452 mg/kg, respectively. The total white spirit concentrations in blood and brain were not affected by the duration of exposure. The fat concentration of white spirit decreased very slowly compared with the rate of decrease in blood and brain, suggesting that long lasting redistribution from fat to brain may occur. The blood and brain concentrations of individual components of white spirit (*n*-nonane, *n*-decane, and *n*-undecane) also decreased rapidly compared with the decrease in fat tissue. It was concluded that total white spirit behaved similarly to the *n*-alkanes in blood, brain and fat tissue, indicating that the non-*n*-alkane components of white spirit possess toxicokinetic properties similar to the *n*-alkanes.

Mode of action

White spirit is a complex mixture of aliphatic, alicyclic and aromatic hydrocarbons, comprising over 200 compounds (Pfäffli *et al.,* 1985; IPCS, 1996). With such solvent mixtures it is difficult to identify the causative agents of occupational diseases (Pedersen et al, 1980). From kinetic studies in humans, white spirit has a long redistribution phase, a large volume of distribution, slow total body clearance, and a long mean residence time (Pedersen *et al*., 1987). This means that even when exposure has ceased, adipose tissue continues to release white spirit into the blood, and hence the brain. Pedersen *et al*. (1987) suggested that this uninterrupted concentration of white spirit may be one of the explanations of the toxic encephalopathy reported after white spirit exposure (Arlien-Søborg *et al*., 1993).

All hydrocarbons may cause CNS depression, however the straight chain hydrocarbons that predominate in white spirit are poorly absorbed across the gastrointestinal tract. The aspiration toxicity of white spirit is due to the physical characteristics of the compound rather than any particular constituent. The risk of aspiration of a chemical depends upon its viscosity and surface tension. The lower the viscosity, the greater the penetration into the distal airway, and the lower the surface tension the more the product spreads across the lung tissue. White spirit has an extremely low viscosity that enables it to be easily aspirated into the lungs. Once in the lungs, small amounts of low viscosity material can spread over large portions of the pulmonary bed resulting in chemical pneumonitis.

Metabolism of the small percentage of polyaromatic hydrocarbons (e.g., benzene and naphthalene) in white spirit may produce active metabolites. Benzene is metabolised to reactive benzoquinones (IPCS, 1996) and 1,4-benzoquinone, for example, has been shown to inhibit topoisomerase II (Chen and Eastmond, 1995). Topoisomerase II is believed to play a role in genomic stability, and interference with topoisomerase II activity at critical stages of the cell cycle could cause chromosome breakage, aneuploidy or cell death (Chen and Eastmond, 1995).

Cumulative oxidative damage may be an underlying mechanism of white spirit induced neurotoxicity (Lam *et al*. 1994; Bondy *et al*., 1995). Following inhalation exposure of rats to white spirit (14-21% aromatic hydrocarbons) there was depression of glutamine synthetase concentrations in the P2 fraction of the liver and kidney. This suggested that prolonged inhalation of white spirit elevated pro-oxidant events in liver and kidney tissue (Bondy *et al*., 1995).

Metabolic interactions

The metabolism of white spirit involves many metabolic pathways, only a few of which are fully understood. Exposure to a white spirit mixture alone or simultaneous exposure to white spirit and other xenobiotics will involve many metabolic interactions, e.g., inhibition or induction of metabolic enzyme systems.

CASE REPORTS

Toxic reaction to white spirit fumes

A 60 year old man was admitted to hospital confused and pyrexial. Thirty hours prior to admission he had spent approximately one hour painting large surfaces with a polyurethane paint in a small non-ventilated room. Prior to this he had been well, with no history of recent drug or alcohol consumption, nor any other chemical exposure. He drank 30 units of alcohol weekly. Immediately after painting he appeared pale and unwell and complained of malaise and anorexia. He went to bed but spent a very restless night and was noted

to be coughing. He got up for a short while 19 hours later but returned to bed because he was unsteady on his feet. His cough continued and he was still restless, often shouting in his sleep. After a further six hours he got up again, but was very uncoordinated and complained of a headache. He subsequently fell down stairs and was unrousable for about five minutes, then became aggressive and confused.

On admission he had a temperature of 40°C, and a left periorbital haematoma. He was drowsy with no memory of recent events, but was well orientated and cardiovascular and neurological examinations were unremarkable. There were no signs of chronic liver disease or jaundice, but the liver and spleen were palpable and there were a few course crepitations in the right lung mid-zone. At this stage haematological investigations, urea, creatinine and electrolytes, chest X-ray and ECG were normal. Blood, urine and sputum cultures were negative. Three days after admission aspartate aminotransferase (AST) was raised, but bilirubin, alkaline phosphatase and gamma glutamyl transferase were normal. Viral titres and cultures, hepatitis B surface antigen, hepatitis B specific immunoglobulin and autoantibodies including antinuclear factor and smooth muscle antibody, were negative. The patient improved without any specific treatment, becoming lucid and apyrexial over the next three days. At this stage the spleen was barely palpable and by the next day could not be felt. The liver remained palpable. An ultrasound scan at this time showed normal appearances of liver and spleen. A blood count four days after admission showed thrombocytopenia; AST had risen further. Histological examination of a percutaneous needle biopsy of the liver showed changes of mitotic activity and thickening of liver cell plates. Necrosis and steatosis were not observed. There was no evidence of any chronic liver disease. The appearances were consistent with the sequelae of exposure to a toxic organic solvent. On discharge five days after admission the patient was well. At follow up one month later he had normal liver function tests, biochemical profile and haematological indices. The authors concluded that the patient had a reaction to white spirit fumes that caused reversible hepatic, bone marrow and nervous system toxicity. In response to the case study publication, however, the manufacturer's medical advisor expressed doubt as to whether the patient's symptoms were solely due to the paint exposure and suggested that other factors were involved (Atkinson *et al.,* 1989).

Aplastic anaemia from chronic exposure to white spirit

A 41 year old male had worked as a heavy equipment mechanic for 16 years, which involved frequent exposure to a chemical mixture containing Stoddard solvent. He had been well until three months prior to hospital admission, when he began to experience progressive tiredness, light-headedness, and increased bruising. Some ecchymotic areas and diffuse petechiae were noted on initial physical examination. There was no palpable hepatomegaly or splenomegaly. Initial investigations showed anaemia, thrombocytopenia and leucopenia. A sternal marrow biopsy was performed, but no marrow particles were found, and subsequent percutaneous bone biopsy of the iliac crest showed a markedly hypocellular bone marrow with a scarcity of all cellular components. The other investigations were normal. Eleven months after the initial diagnosis the patient was admitted to hospital in a coma and died. Postmortem examination revealed diffuse intracerebral haemorrhage involving the right occipital lobe. The bone marrow exhibited the previously noted hypocellularity with depression of all cellular components (Prager and Peters, 1970).

CLINICAL EFFECTS

Acute exposure

Inhalation

Inhalation of white spirit can cause nausea, vomiting, headache, dizziness, mild respiratory tract irritation, euphoria and CNS depression. Acute exposure to 470 ppm white spirit caused transient eye irritation and dizziness (Carpenter *et al.,* 1975). Nelson (1943) also observed that concentrations of >400 ppm were required to develop eye irritation, and in this study subjects also reported nose and throat irritation, but no effects below this exposure concentration.

Severe CNS depression is usually only associated with exposure to very high concentrations, particularly in enclosed spaces. At very high concentrations coma, convulsions and cardiac arrhythmias may occur. Such severe symptoms are usually only seen in patients who have been intentionally inhaling solvents, or as the result of an industrial accident, and not following a brief accidental exposure.

Atkinson *et al.* (1989) attributed reversible hepatic, bone marrow and nervous system toxicity to an acute one hour exposure to a paint containing white spirit. However, the causal relationship between the patient's clinical effects and the white spirit exposure was questioned.

Cohr *et al.* (1980) investigated the acute effects of white spirit on the human nervous system. They conducted a series of seven hour exposures to different concentrations (range 0-400 ppm) of white spirit (17% aromatic hydrocarbons) on healthy men. The subjects were divided into two groups, group one consisted of students (no previous exposure) with a mean age of 23 years and group two consisted of house painters with a mean age of 49 years (with at least 10 years occupational exposure). From neurological assessment and the symptoms reported, the authors concluded that white spirit stimulates the trigeminal nerve and affects the central nervous system. The effects occurred at lower concentrations in the house painters than the students, but it is unclear whether this difference in sensitivity was occupation dependent or due to age differences.

Eight volunteers exposed to 4,000 mg/m^3 (667-760 ppm) for 35-40 minutes had some changes in simple reaction time tests and possible impaired short-term memory for visual stimuli, however, there was no effect on manual dexterity when compared to pre- and post-exposure self-controls (Gamberale *et al.,* 1975).

Cardiac effects

White spirit exposure may increase the risk of cardiac arrhythmias (due to sensitisation of the myocardium to catecholamines, e.g., epinephrine (adrenaline)). In a volunteer study investigating the white spirit concentration of alveolar air and blood during rest and exercise, one subject displayed gradual flattening and ultimately, inversion of the T-wave during exposure, indicating possible action on the myocardium. When an ECG was checked a few days later, in conjunction with exercise, it was normal (Åstrand *et al.,* 1975).

Chest pain, cyanosis, apnoea and cardiac arrest with ventricular fibrillation occurred in a 42 year old woman who had worked for the majority of a day using 'mineral spirits' in a confined space. Whilst in hospital, amnesia, haemolytic anaemia, rhabdomyolysis and other metabolic abnormalities were observed (Nierenberg *et al.,* 1991).

Dermal

White spirit has a mild drying and defatting effect on skin that is unlikely to need treatment after acute exposure. White spirit was given a high irritant ranking in skin irritancy testing of various organic solvents on guinea pigs (Anderson *et al.,* 1986).

Eye

In a 15 minute inhalation period only slight eye irritation was reported by one of six persons exposed to 0.85 mg/l (150 ppm) of white spirit (Carpenter *et al.,* 1975). A concentration above 400 ppm is usually required to develop eye irritation (Nelson, 1943).

Liquid petroleum hydrocarbons, including Stoddard solvent, cause little or no injury on direct contact with the eye (Grant and Schuman, 1993).

Ingestion

White spirit is poorly absorbed from the gastrointestinal tract and does not cause appreciable systemic toxicity by this route unless aspiration occurs. Hydrocarbons (including white spirit) defat mucous membranes, and thus when they are ingested buccal and gastrointestinal irritation occurs, leading to nausea, vomiting and abdominal pain. Even if very large quantities are ingested minimal absorption occurs. There may be drowsiness, but other systemic effects would not be anticipated.

Signs indicative of aspiration include respiratory distress with coughing, choking and tachypnoea. Respiratory tract irritation following aspiration leads to a chemical pneumonitis and in severe cases can progress to pulmonary oedema that may be delayed in onset up to 24 to 72 hours after exposure. Pyrexia may occur and the white blood cell count may be raised.

Spontaneous vomiting occurred in 39% of paediatric cases hospitalised for ingestion of products which contained petroleum distillates (Anas *et al.,* 1981). A 63 year old man ingested approximately 500 ml of white spirit in a suicide attempt. Ten days later a gastrointestinal endoscopy showed moderate oesophagitis and a necrotic gastritis covering the entire stomach, which was most severe at the fundus but not affecting the duodenum or pyloric sphincter (Paris *et al.,* 1978).

Injection

Injection of white spirit and other hydrocarbons may occur from occupational accidents with high pressure injection equipment, e.g., airless paint sprayers and high pressure grease guns (Kaufman, 1970; Dickson, 1976; Booth, 1977; LeBlanc, 1977; Mrvos *et al*, 1987). In these cases injury is usually to the digits and penetration is limited to subcutaneous injection. Although not significant occupationally, intentional injection of hydrocarbons has also been reported. Injection of hydrocarbons poses a variety of risks depending on the route of injection.

Injected subcutaneously, hydrocarbons do not appear to dissipate from the injection site or to be absorbed systemically. Local toxic effects occur and development may be delayed and progressive. Local effects can be severe and include cellulitis (Wedin and Jones, 1984), sterile abscess formation and necrosis (Goldberg, 1982; Geoffray *et al.,* 1992). Systemic toxicity is not usually observed.

Pneumonitis may occur following intravenous injection of hydrocarbons (Beck *et al.,* 1981; Shusterman, 1999). This is thought to develop as a result of a direct action of the hydrocarbon on the lungs. Hydrocarbons may interact with the pulmonary surfactant, probably causing damage to the alveolar walls. Initial effects include cough, dyspnoea, tachypnoea and potentially cyanosis. Chest X-ray changes may be delayed.

Four cases of white spirit injection have been reported to the Medical Toxicology Unit (NPIS London, 1996 and 1997), involving the subcutaneous injection of white spirit, all were cases of deliberate self-harm. Immediate pain, local oedema and redness occurred in all cases. In all but one case, cellulitis, sterile abscess formation and/or necrosis developed, requiring excision and debridement. Compartment syndrome developed in two of these cases and fasciotomies and plastic surgery were performed.

Chronic exposure

Inhalation

Neurological effects

Neurotoxicity has been reported in workers exposed to mixtures of solvents including white spirit, but data for the neurotoxic effects of white spirit alone are limited and inconclusive.

Arlien-Søborg *et al*. (1979) propose that long-term exposure to turpentine substitute (i.e., white spirit) may gradually lead to the development of chronic CNS symptoms, which they termed 'chronic painters' syndrome'. After studying 70 house painters referred for neurological examination because of suspected organic solvent intoxication, they described a syndrome characterised by the presence of acute intoxication symptoms that resolve at weekends and holidays, and precede the chronic symptoms of memory impairment, fatigue, personality changes, headache and dizziness.

A group of rubber industry workers were assessed in an attempt to determine the effect of chronic occupational exposure to white spirit (Bazylewicz-Walczak *et al.,* 1990). The investigations were aimed at determining the effect of the solvent on selected mental and psychomotor functions of workers chronically using a white spirit based glue in rubber footwear production. Results showed that chronic exposure to levels of approximately 500 mg/m^3 (85-95 ppm) caused deterioration in some intellectual and psychomotor functions.

When Seppäläinen and Lindström (1982) compared 72 house painters with a control group, using a questionnaire and neurophysiological examinations, they found no differences in electroencephalographic (EEG) and nerve conduction velocity (NCV) measurements between the two groups. However, significantly more painters reported nausea, a feeling of drunkenness, mucous membrane irritation, paraesthesia, vertigo and an impaired sense of smell. The average long-term exposure concentration of the painters corresponded to 40 ppm, and the authors concluded this to be a no-effect level for sensitive neurophysiological methods.

Haematological effects

Aplastic anaemia has been reported from occupational exposure to white spirit (Kegels, 1958; Scott *et al.*, 1959; Prager and Peters, 1970). Scott *et al.* (1959) reviewed 39 cases of acquired aplastic anaemia and implicated Stoddard solvent as the causal agent in four of the cases. Two cases involved women who had used the solvent at home for dry cleaning. The first had been using it a few times a month for 2 years whilst the second had used it for 20 years. The 2 other patients were both male. The first, a student, had used the solvent as a hand cleanser 4 or 5 times weekly whilst on a 6 month car mechanics course and became unwell 2 months after finishing the course. The second man had also used white spirit as a hand cleanser after painting and was exposed periodically over 2 years.

Aplastic anaemia was reported in a man with a history of 16 years of occupational exposure to Stoddard solvent (Prager and Peters, 1970). A sternal bone marrow sample revealed no marrow particles and a subsequent percutaneous bone biopsy of the iliac crest revealed a marked decrease in cellular elements. These findings were confirmed on postmortem examination when the patient died 11 months post-diagnosis.

Hepatic effects

Liver damage has been ascribed to exposure to Stoddard solvent (Braunstein, 1940). A man whose arms and hands were wet with the solvent during most of his working day developed, over a three month period, dermatitis, anaemia, swelling of the liver and jaundice. The patient made a gradual, complete recovery.

Of 156 patients admitted to hospital because of suspected solvent intoxication, 13 subjects had elevated serum aminotransferases. No other factors (e.g., exposure to hepatotoxic drugs) except occupational exposure could be found to explain these elevations. Liver histology revealed 11 cases of steatosis, six of which had focal necrosis. In addition, six of the liver biopsies showed enlarged portal tracts with fibrosis. The workers had a history of exposure to white spirit, xylene, toluene and styrene. However, of the 13 cases, 10 were house painters who over a period of time (range 6-39 years) had been predominantly exposed to white spirit (Døssing *et al.,* 1983).

Immunotoxicity

In a controlled study, no changes in the concentration of immunoglobulins were observed in volunteers undergoing repeated exposures (100 ppm, 6 hours daily for 5 days) to white spirit (Pedersen and Cohr, 1984).

Dermal

Petroleum distillates (such as white spirit) have a defatting action on the skin, and prolonged or repeated contact may result in erythema, oedema, necrosis and scarring (MacFarland and Holdsworth, 1987). Dermatitis may occur (Braunstein, 1940; Larsen, 1974; Nethercott *et al.,* 1980). Five workers developed irritant contact dermatitis (redness and ulceration) from exposure to Stoddard solvent residue in their work overalls after dry cleaning (Nethercott *et al.,* 1980). In all cases, skin improvement was rapid after topical steroid therapy. Follicular dermatitis, with redness, roughness of the skin and dehydration with desquamation around the hair follicles, was noted in a male occupationally exposed to Stoddard solvent. During most of his working day, his hands and forearms were wet with the solvent (Braunstein, 1940).

Larsen (1974) described a patient with a papular erythematous rash on her forearms after using Stoddard solvent without gloves whilst operating a polisher at work. Another worker had mild folliculitis on the interior of his thighs after exposure to Stoddard solvent, which had soaked the front of his trousers during the working day.

Eye

No information available.

Ingestion

No information available.

Carcinogenicity

There is inadequate evidence in both humans and experimental animals on the carcinogenic potential of petroleum solvents (including white spirit). Consequently, white spirit has been classified by the IARC in Group 3, i.e., not classifiable as to its carcinogenicity in humans (IARC, 1989).

White spirit is not generally considered to be carcinogenic. However, epidemiological studies have suggested that respiratory tract, kidney and bladder cancers may be related to chronic white spirit exposure (Rothman and Emmett, 1988). Siemiatycki *et al.* (1987) investigated the possible association between exposure to petroleum derived liquids and cancer. They concluded that exposure to mineral spirits was significantly associated with squamous cell lung cancer, particularly among workers with long exposure to high concentrations. In addition, both prostate cancer and Hodgkin's lymphoma showed signs of association with exposure to mineral spirits.

Genotoxicity

White spirit was not mutagenic in human lymphocytes *in vitro*, mouse bone marrow studies, or bacterial assays (Gochet *et al.*, 1984) including the Salmonella/microsome assay (Ames test) (Conaway *et al.*, 1984).

Reproductive toxicity

White spirit is categorised in Class A, unconfirmed reproductive effects (REPROTEXT® 2001), as adverse effects have been reported in women with exposure to mixed solvents including white spirit. However, the reproductive risk to humans of white spirit alone is not known.

Female painters exposed to a mixture of solvents including white spirit had a higher incidence of complications in pregnancy including spontaneous abortions and stillbirths (Tikhonova *et al.*, 1997). Syrovadko *et al.* (1973) investigated menstrual disturbances and menstrual function in women exposed occupationally to white spirit and compared them with a control group of non-exposed office workers. The white spirit contained 16% toluene and xylene, and the other components were unknown. The women may also have been exposed to other varnishes during the course of their work. Compared to the control group, the exposed workers had decreased haemoglobin concentrations and total red blood cell counts, a higher incidence of prolapse of the uterus and vaginal wall, and a greater occurrence of menstrual disturbances (polyhypermenorrhoea, dysmenorrhoea and changes in cycle patterns). However, Barlow and Sullivan (1982) highlight the fact that it is not possible from this study to ascertain which, if any of the various chemicals, might be responsible for the observed effects.

White spirit did not affect reproduction data or the incidence of skeletal or visceral anomalies and malformations in rats. It was fetotoxic only at maternally toxic doses (Jakobsen *et al.* 1986).

RISK GROUPS

None identified for white spirit. However, owing to the complex nature of white spirit some individuals may be more at risk of toxicity from the individual components.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The patient should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Emesis is not recommended because of the risk of aspiration. Activated charcoal may cause vomiting which may be hazardous to patients who have ingested hydrocarbons.

Injection

The management of patients with injection injury from white spirit depends on the route of injection. Immediate pain, local oedema and redness would be expected in all cases.

Subcutaneous injection

In cases of subcutaneous injection of hydrocarbons, early and aggressive management has been shown to reduce morbidity and prevent long-term sequelae. Cellulitis, sterile abscess formation and/or necrosis may develop, requiring excision, drainage and debridement. Analgesics and antibiotics should be given if indicated, and anti-tetanus status should be checked. Compartment syndrome has been reported following subcutaneous injection of white spirit, where fasciotomy and plastic surgery were necessary.

Intravenous injection

Conventional supportive management is recommended for patients with respiratory effects and/or pneumonitis following intravenous hydrocarbon injection.

Systemic effects

Treatment is primarily symptomatic, with support of the cardiovascular and respiratory systems. Use of epinephrine (adrenaline) or related sympathomimetic stimulants is contraindicated due to the risk of inducing ventricular fibrillation.

The level of consciousness, ECG and respiratory rate should be monitored, along with liver and kidney function in severe cases. A chest X-ray is indicated in patients with respiratory symptoms and in cases of suspected aspiration.

The efficacy of enhanced elimination techniques (e.g., haemodialysis, haemoperfusion, etc.) has not been established, but on theoretical grounds they are unlikely to be effective.

Antidotes

There is no specific antidote for white spirit.

Chronic exposure

Emphasis should be placed on examination of the central nervous system. Liver and kidney function should also be checked and a complete blood count performed. Effects from chronic dermal exposure will gradually resolve once exposure has ceased.

REFERENCES

Anas N, Namasonthi V, Ginsburg CM. 1981 Criteria for hospitalising children who have ingested products containing hydrocarbons. *J Am Med Assoc* 246:840-843.

Anderson C, Sundberg K, Groth O. 1986 Animal model for assessment of skin irritancy. *Contact Dermatitis* 15:143-151.

Arlien-Søborg P, Bruhn P, Glydensted C, Melgaard B. 1979 Chronic painters' syndrome: Chronic toxic encephalopathy in house painters. *Acta Neurol Scand* 60:149-156.

Åstrand I, Kilbom Å, Övrum P 1975 Exposure to white spirit. I. Concentration in alveolar air and blood during rest and exercise. *Scand J Work Environ Health* 1:15-30.

Atkinson L, Ince P, Smith NM, Taylor R 1989 Toxic reaction to inhaled paint fumes. *Postgrad Med J* 65:559-562.

Barlow SM, Sullivan FM. 1982 *Reproductive Hazards of Industrial Chemicals. An evaluation of animal and human data*. Academic Press, London.

Bazylewicz-Walczak B, Marszal-Wisniewska M, Siuda A. 1990 The psychological effects of chronic exposure to white spirit in rubber industry workers. *Polish J Occup Med* 3 (1):117-127.

Beck DE, Freeman B, Moore CR. 1981 Toxicities with intravenous and subcutaneous administration of a petroleum distillate. *Drug Intell Clin Pharm* 15:693-694.

Bondy SC, Lam HR, Østergaard G, Guo SX, Ladefoged Ø. 1995 Changes in markers of oxidative status in brain, liver, and kidney of young and aged rats following exposure to aromatic white spirit. *Arch Toxicol* 69:410-414.

Booth CM. 1977 High pressure paint gun injuries. *Br Med J* 2:1333-1335.

Braunstein LE. 1940 Subacute yellow atrophy of the liver due to "solvent". *J Am Med Assoc* 114:136-138.

Carpenter CP, Kinkead ER, Geary DL, Sullivan LJ, King JM. 1975 Petroleum hydrocarbon toxicity studies. III. Animal and human response to vapours of Stoddard solvent. *Toxicol Appl Pharmacol* 32: 282-297.

CEC. 1990 Long-term neurotoxic effects of paint solvents. Luxembourg, Commission of the European Communities (Publication No. EUR 13020). Cited in: IPCS. 1996 *Environmental Health Criteria 187. White Spirit*. World Health Organization, International Programme on Chemical Safety, Geneva.

Chen H, Eastmond DA. 1995 Topoisomerase inhibition by phenolic metabolites: a potential mechanism for benzene's clastogenic effects. *Carcinogenesis* 16 (10):2301-2307.

Cohr K, Stokholm J, Bruhn P. 1980 Neurological response to white spirit exposure. *Dev Toxicol Environ Sci* 8:95-102.

Conaway CC, Schreiner CA, Cragg ST. 1984 Mutagenicity evaluation of petroleum hydrocarbons. In: MacFarland HN, Holdsworth CE, MacGregor JA *et al.* (editors), *Advances in Modern Environmental Toxicology, Vol. 6, Applied Toxicology of Petroleum Hydrocarbons*. Princeton Scientific Publishers, New Jersey, pp 89-107. Cited in: Rothman N, Emmet EA. 1988 The carcinogenic potential of selected petroleum derived products. *Occup Med* 3 (3):475-495.

Dickson RA. 1976 High pressure injection injuries of the hand a clinical, chemical and histological study. *Hand* 8 (2):189-193.

Døssing M, Arlien-Søborg P, Petersen LM, Ranek L. 1983 Liver damage associated with occupational exposure to organic solvents in house painters. *Eur J Clin Invest* 13:151-157.

Gamberale F, Annwall G, Hultengren M. 1975 Exposure to white spirit. II. Psychological functions. *Scand J Work Environ Health* 1:31-39.

Geoffray C, Choisidow O, Reygagne A, Poli F, Revuz J, Bagot M. 1992 Cutaneous necrosis induced by injection of hydrocarbons. *Arch Dermatol* 128:997-998.

Gerade H. 1963 Toxicological studies on hydrocarbons: IX The aspiration hazard and toxicity of hydrocarbons and hydrocarbon mixtures. *Arch Toxicol* 6:329-341.

Gochet B, de Meester C, Léonard A, Deknudt G. 1984 Lack of mutagenic activity of white spirit. *Int Arch Occup Environ Health* 53:359-364.

Goldberg LH, Shupp D, Weitz HH, Zeccardi JA. 1982 Injection of household spray insecticide. *Ann Emerg Med* 11:626-629.

Grant WM, Schuman JS. 1993 *Toxicology of the Eye,* fourth edition, Charles C Thomas, Springfield, Illinois.

IARC (International Agency for Research on Cancer). 1989 *Occupational Exposures in Petroleum Refining; Crude Oil and Major Petroleum Fuels*. IARC Monograph 45.

IPCS. 1996 *Environmental Health Criteria 187. White Spirit*. World Health Organization, International Programme on Chemical Safety, Geneva.

Jakobsen BM, Hass U, Juul F, Kjaergaard S. 1986 Prenatal toxicity of white spirit inhalation in the rat [abstract]. *Teratology* 34: 415.

Järnberg J, Johanson G, Löf A, Ståhlbom B. 1998 Toxicokinetics of 1,2,4-trimethylbenzene in humans exposed to vapours of white spirit: comparison with exposure to 1,2,4-trimethylbenzene alone. *Arch Toxicol* 72: 483-491.

Jouet JB, Ferand O, Grimbert D. 1983 Accidental poisoning by volatile hydrocarbons in children. *Toxicol Eur Res* 5 (5):11-216.

Kaufman HD. 1970 High pressure injection injuries, the problems, pathogenesis and management. *Hand* 2 (1):6-67.

Kegels DR. 1958 Un cas d'anémie aplastique d'origine professionnelle probable par le white spirit [A case of aplastic anaemia probably due to occupational exposure to white spirit]. *Arch Belg Méd Soc Hyg Méd* 16 (4):161-174.

Lam HR, Østergaard, Guo SX, Ladefoged, Bondy SC. 1994 Three weeks' exposure of rats to dearomatised white spirit modifies indices of oxidative stress in brain, kidney and liver. *Biochem Pharmacol* 47 (4):651-657.

Larsen LB. 1974 Occupational health case report No. 6. Stoddard Solvent. *J Occup Med* 16 (4):276-278.

LeBlanc JV. 1977 High pressure petroleum injection injuries. *J Occup Med* 19 (4):276-277.

Löf A, Lam HR, Gullstrand E, Østergaard G, Ladefoged O. 1999 Distribution of dearomatised white spirit in brain, blood and fat tissue after repeated exposure of rats. *Pharmacol Toxicol* 85 (2):92-97.

MacFarland HN, Holdsworth CE. 1987 The toxicology of petroleum solvents. In: *Ethel Browning's Toxicity and Metabolism of Industrial Solvents*, second edition, Volume 1: Hydrocarbons. R Snyder (editor). Elsevier Science, Amsterdam.

Mvros R, Dean BS, Krenzelok EP 1987 High pressure injection injuries: a serious occupational hazard. *Clin Toxicol* 25 (4):297-304

Nelson KW, Ege JF, Ross M, Woodman LE, Silverman L. 1943 Sensory response to certain industrial solvent vapours. *J Ind Hyg Toxicol* 25:282-285.

Nethercott JR, Pierce JM, Likwornick G, Murray AH. 1980 Genital ulceration due to Stoddard solvent. *J Occup Med* 22 (8):549-552.

NIOSH. 1977 Criteria for a recommended standard: Occupational exposure to refined petroleum solvents. Publication No. (NIOSH) 77-192. Cited in: MacFarland HN, Holdsworth CE. 1987 In: *Ethel Browning's*

Toxicity and Metabolism of Industrial Solvents, second edition, Volume 1: Hydrocarbons. R Snyder (editor). Elsevier Science, Amsterdam.

Nierenberg DW, Horowitz MB, Harris KM, James DH. 1991 Mineral salts inhalation associated with haemolysis, pulmonary oedema, and ventricular fibrillation. *Arch Intern Med* 151:1437-1440.

NPIS (National Poisons Information Service (London)). 1996 and 1997 Injection of white spirit: Case report numbers 96/087198, 96/105914, 97/088636, 97/172716. In-house data, Medical Toxicology Unit, London.

Paris J, Ribet M, Busi P. 1978 Lesions oeso-gastriques après absorption de white spirit [Oesophago-gastric lesions after absorption of white spirit]. *Sem Hop Paris* 54 (3):151-153.

Pedersen LM, Nygaard E, Nielsen OS, Saltin B. 1980 Solvent induced occupational myopathy. *J Occup Med* 22 (9):603-606.

Pedersen LM, Cohr K. 1984 Biochemical pattern in experimental exposure of humans to white spirit. II. The effects of repetitive exposures. *Acta Pharmacol Toxicol* 55:325-330.

Pedersen LM, Larsen K, Cohr K. 1984 Kinetics of white spirit in human fat and blood during short-term experimental exposure. *Acta Pharmacol Toxicol* 55:308-316.

Pedersen LM, Rasmussen S, Cohr C. 1987 Further evaluation of the kinetics of white spirit in human volunteers. *Pharmacol Toxicol* 60:135-139.

Pfäffli P, Härkönen H, Savolainen H. 1985 Urinary dimethylbenzoic acid excretion as an indicator of occupational exposure to white spirit. *J Chromatog* 337:146-150.

Prager D, Peters C. 1970 Development of aplastic anaemia and the exposure to Stoddard solvent. *Blood* 35 (3):286-287.

REPROTEXT® Document. 2001 *White spirit* In: Heitland G & Hurlbut KM (editors): REPROTEXT® Database (electronic version) MICROMEDEX, Greenwood Village, Colorado, USA. Available at www.tomescps.com/DATA/RE/RE1405.HTM (24/07/01).

Rothman N, Emmet EA. 1988 The carcinogenic potential of selected petroleum derived products. *Occup Med* 3 (3):475-495.

Seppäläinen AM, Lindström K. 1982 Neurological findings among house painters exposed to solvents. *Scand J Work Environ Health* 8 (Suppl 1):131-135.

Scott JL, Cartwright GE, Wintrobe MM. 1959 Acquired aplastic anaemia: An analysis of thirty-nine cases and review of the pertinent literature. *Medicine* 38:119-172.

Siemiatycki J, Dewar R, Nadon R, Gérin M, Richardson L, Wacholder S. 1987 Associations between several sites of cancer and twelve petroleum-derived liquids. *Scand J Work Environ Health* 13:494-504.

Shusterman EM, Williams SR, Childers BJ. 1999 Soft tissue injection of hydrocarbons: a case report and review of the literature. *J Emerg Med* 17(1):63-65.

Syrovadko ON, Skornin VF, Pronkova EN, Sorkina NS, Izyumova AS, Gribova IA, Popova AF. 1973 [Effect of working conditions on the health status and some specific functions of women handling white spirit]. *Gig Tr Prof Zabol* 1973 17:5-8 (in Russian). Cited in: Barlow SM, Sullivan FM. 1982 *Reproductive Hazards of Industrial Chemicals. An evaluation of animal and human data*. Academic Press, London.

Tikhonova GI, Lebedeva NV, Federova BV. 1997 [The effect of organic solvents on the child-bearing function of women painters (an epidemiological hygiene study)]. *Med Tr Prom Ekol* 3:20-24 (in Russian, abstract only used].

Verkkala, E, Pfäffli, P, Savolainen H. 1984 Comparison of local neurotoxicity of three white spirit formulations by percutaneous exposure of rat tail nerve. *Toxicol Lett* 21:293-299.

Wedin GP, Jones RR. 1984 Parenteral administration of hydrocarbons. *Clin Toxicol* 22 (5):485-492.

25 Xylenes

Nicola Bates

SUMMARY

- Xylenes are of relatively low acute toxicity
- They are irritant and cause CNS depression
- Effects from a short exposure resolve rapidly due to rapid metabolism and elimination
- Prolonged or repeated exposure may result in accumulation in adipose tissue
- Human data on chronic exposure is limited
- Xylenes do not appear to be genotoxic
- Xylenes are not classifiable as to their carcinogenicity in humans
- Embryotoxicity and fetotoxicity have been reported in animal experiments; teratogenicity has been demonstrated but only at near lethal concentrations

DESCRIPTION

Xylene is a mixture of three isomers, *ortho*-, *meta*- and *para*-xylene. Commercial xylene is a mixture of these isomers, with *meta*-xylene making up the main component (up to 75-80%) and up to 5% *para*-xylene (Caperos and Fernàndez, 1977). The technical product 'mixed xylenes' contains approximately 40% *m*-xylene and 20% each of ethylbenzene, *o*-xylene and *p*-xylene (IPCS, 1997). There may also be traces of toluene and benzene.

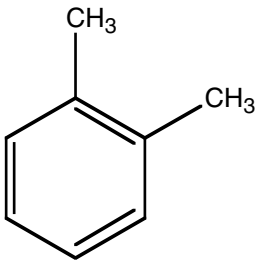
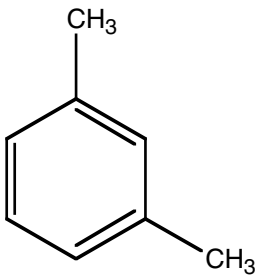
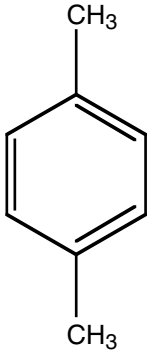
Synonyms

xylene	***o*-xylene**	***m*-xylene**	***p*-xylene**
dimethylbenzene	1,2-dimethylbenzene	1,3-dimethylbenzene	1,4-dimethylbenzene
xylol	1,2-xylene *o*-xylol	1,3-xylene *m*-xylol	1,4-xylene *p*-xylol

Identification numbers

	xylene (mixed)	***o*-xylene**	***m*-xylene**	***p*-xylene**
CAS	1330-20-7	108-38-3	95-47-6	106-42-3
UN	1307	1307	1307	1307
RTECS	ZE 210000	ZE 2450000	ZE 2275000	ZE 2625000
EINECS	2155357	2024222	2635763	2033965

PHYSICAL AND CHEMICAL PROPERTIES (Table 25.1)

Table 25.1 Physical and chemical properties of xylenes			
	***o*-xylene**	***m*-xylene**	***p*-xylene**
chemical formula	C_8H_{10}	C_8H_{10}	C_8H_{10}
molecular formula			
molecular mass	106.16	106.16	106.16
physical form	colourless liquid	colourless liquid	colourless liquid
relative vapour density	0.876	0.860	0.857
flash point (closed cup) (°C)	30	25	25
boiling point (°C)	144.4	139.1	138.3
autoignition temperature (°C)	465	525	525
refractive index	1.503	1.494	1.493
explosive limits (% v/v)	1.0-6.0	1.1-7.0	1.1-9.0

Odour threshold

Mixed xylenes 1 ppm (Carpenter *et al.*, 1975), 0.8-40 ppm (Ruth, 1986).
m-Xylene 1.1 ppm (Amoore and Hautala, 1983), 0.14-0.44 ppm (Gusev, 1965).
o-Xylene 0.17 ppm (Gerarde, 1960).

OCCUPATIONAL EXPOSURE

Exposure limits

TWA (UK and ACGIH): 100 ppm (441 mg/m^3)

Conversion factors

1 ppm = 4.35 mg/m^3 = 0.00435 mg/l
1 mg/m^3 = 0.23 ppm
1 mg/l = 230 ppm

Biomonitoring

The biological exposure index (BEI) for xylenes set by the ACGIH is an end of shift urinary concentration of methylhippuric acids, 1.5 g/g creatinine (ACGIH, 2000).

TOXICITY

Chronic exposure to a low concentration of xylene is usually not associated with toxicity. Most cases of occupational xylene poisoning are due to accidental high exposure (Uchida *et al.*, 1993). Xylene poisoning has also been reported following abuse (Sarmiento Martinez *et al.*, 1989; Kaneko *et al.,* 1992) and use of a xylene containing product in an enclosed space (Morley *et al.*, 1970; Roberts *et al.,* 1988). Xylene has been used as a means of suicide (Abu Al Ragheb *et al.*, 1986). Occasionally xylene abuse may occur following occupational exposure (Bakinson and Jones, 1985). Poisoning has also been reported in a hospital where xylene was discarded down a sink in the pathology laboratory, and, through a combination of events, became drawn into the room containing the fan of the main ventilation system. Fifteen members of staff became unwell as a result (Klaucke *et al.*, 1982).

Most studies on the effects of xylene have been conducted using *m*-xylene, the most abundant isomer in commercial xylene (Low *et al.,* 1989). Many studies linking adverse effects and xylene exposure have involved workers who have been exposed to other solvents, and individual exposure is ill defined. Consequently the role of xylene toxicity in these cases has not been fully established. It is unclear whether long-term exposure to xylene causes permanent CNS damage (ECETOC, 1986).

Absorption

The respiratory tract is the main route of exposure. Xylene is rapidly absorbed and very soluble in blood and tissues (Åstrand *et al.*, 1978). Pulmonary retention of xylene is approximately 60-65% (Sedivec and Flek, 1976; Åstrand *et al.*, 1978; Riihimäki *et al.*, 1979; Riihimäki and Savolainen, 1980; Liira *et al.*, 1988; Laine *et al.*, 1993). Uptake remains constant even after tissue equilibrium is reached (Riihimäki and Savolainen, 1980). The magnitude of uptake has been found to correlate with the amount of body fat (Engström and Bjurström, 1978).

Uptake of xylene is increased with exercise (Åstrand *et al.*, 1978; Gamberale *et al.*, 1978; Riihimäki and Savolainen, 1980; Savolainen *et al.*, 1980; Laine *et al.*, 1993) due to increased respiration and heart rate. Increased uptake of 30-50% has been reported during exercise (Riihimäki and Savolainen, 1980).

The concentration of xylene in the air correlates with the concentration of xylene in the blood (Krämer *et al.*, 1999) and the urinary concentration of methylhippuric acids (Engström *et al.*, 1978; Lundberg and Sollenberg, 1986; Kawai *et al.*, 1991; Krämer *et al.*, 1999). This is true whether the isomers are considered separately or together (Kawai *et al.*, 1991). Fluctuations in the air concentration of xylene result in relatively rapid changes in the tissue, and particularly the blood, concentration (Riihimäki and Savolainen, 1980; Riihimäki and Hänninen, 1987); this has implications for biological monitoring.

Xylene is absorbed through the skin. In a volunteer study where both hands were immersed in xylene for 20 minutes, xylene was detectable in expired air about 10 minutes after the start of exposure. The peak concentration occurred at 30 minutes (i.e., 10 minutes after exposure ceased). Use of a barrier cream did not influence the dermal absorption of xylene (Lauwreys *et al.*, 1978). In a similar experiment where volunteers placed a hand in *m*-xylene for 15 minutes the blood concentration was fifty times greater in the sample from the exposed arm than from the non-exposed arm. This difference persisted for five hours suggesting a reservoir of xylene and continued absorption (Engström *et al.*, 1977).

Xylene is readily absorbed from the gastrointestinal tract. Death has occurred from ingestion of xylene (Abu Al Ragheb *et al.*, 1986).

Distribution

Xylene is taken up quickly by the blood and then rapidly redistributed to tissues. Well perfused tissues such as the brain rapidly reach an equilibrium xylene concentration. The concentration in the brain probably closely follows that in the blood (Riihimäki and Savolainen, 1980).

In prolonged exposure xylene accumulates in adipose tissue. However, the distribution is low compared to other solvents; only about 4-8% of absorbed xylene is retained in fat (Engström and Bjurström, 1978; Engström and Riihimäki, 1979). In a volunteer study, distribution to adipose tissue was affected by exposure pattern. When exercise was performed during exposure a proportionally greater distribution to adipose tissue occurred (Engström and Riihimäki, 1979).

In a suicidal case of xylene ingestion the highest concentration was found in the duodenum (3,300 mg/dl), followed by the gastric contents (880 mg/dl) and the blood (11 mg/dl). Postmortem examination revealed no significant changes except pulmonary oedema. The time between ingestion and death was not stated (Abu Al Ragheb *et al.*, 1986).

Metabolism

The xylene isomers are metabolised by oxidation of the methyl groups. The initial products of biotransformation are methylbenzyl alcohols, which are metabolised to methylbenzaldehydes by alcohol dehydrogenase. Then aldehyde dehydrogenase is involved in the conversion to methylbenzoic acids (toluic acids) (Miller and Edwards, 1999). These are then conjugated with glycine and excreted as methylhippuric acids (MHA, toluric acids) (Sedivec and Flek, 1976). The isomer of methylhippuric acid excreted depends on the isomer of xylene to which an individual has been exposed; *o*-xylene is metabolised to *o*-methylhippuric acid, *m*-xylene to *m*-methylhippuric acid and *p*-xylene to *p*-methylhippuric acid. The urinary concentrations of methylhippuric acids correlate with the exposure concentration of xylene isomers (Inoue *et al.*, 1993).

Metabolism of xylene is rapid (Senczuk and Orlowski, 1978) with methylhippuric acid detectable in urine within 2 hours of exposure (Sedivec and Flek, 1976). The different isomers of xylene may be metabolised at slightly different rates; *p*-xylene may be metabolised more quickly than *m*- and *o*-xylene (Sedivec and Flek, 1976; Kawai *et al.*, 1991). In volunteers exposed to a 1:1:1 mixture of the 3 isomers the concentration of the methylhippuric acids in the initial urine sample were: *p*-methylhippuric acid 41.5%, *o*-methylhippuric acid 23.8% and *m*-methylhippuric acid 34.7%. When the hippuric acid concentrations were calculated for all urine samples the percentages evened out at 33% each (Sedivec and Flek, 1976). However, in a more recent study in exposed workers metabolism of *m*-xylene appeared to be favoured over that of the other isomers. This was independent of the concentrations of the isomers in the mixture to which the workers were exposed (Miller and Edwards, 1999).

Xylenols are formed by hydroxylation of the aromatic ring. In volunteers exposed to the different isomers, 2,3-xylenol and 3,4-xylenol were found after exposure to *o*-xylene; 2,4-xylenol and 2,6-xylenol after exposure to *m*-xylene; and 2,5-xylenol after *p*-xylenol exposure. The highest concentration of xylenols is observed just after cessation of exposure (Sedivec and Flek, 1976; Riihimäki *et al.*, 1979). This is also the case with the methylhippuric acid metabolites (Riihimäki *et al.*, 1979).

Elimination

Over 95% of absorbed xylene is metabolised. Approximately 5% is eliminated unchanged from the lungs (Sedivec and Flek, 1976; Åstrand *et al.*, 1978; Riihimäki *et al.*, 1979). After cessation of exposure the concentration in expired air initially falls rapidly (half-life in the range 0.5-1.0 hours) and then the rate of decline decreases. The last phase of elimination has a half-life of approximately 20-30 hours (Riihimäki *et al.*, 1979; Riihimäki and Savolainen, 1980). Trace quantities of xylene may be detected in expired air 48 hours after cessation of exposure (Sedivec and Flek, 1976).

Xylene can be detected in the urine within two hours of exposure. However, only trace amounts of xylene are excreted by this route (Sedivec and Flek, 1976). Excretion of the xylenol metabolites appears to be slower than that of the methylhippuric acids (Sedivec and Flek, 1976; Riihimäki *et al.*, 1979). The methylhippuric

acid metabolites can be detected in the urine within two hours of exposure (Sedivec and Flek, 1976). The concentration has been reported to peak in the last two hours of exposure (Senczuk and Orlowski, 1978) and two hours after cessation of exposure (Sedivec and Flek, 1976). Trace quantities can still be detected 4-5 days after cessation of exposure (Sedivec and Flek, 1976). The urinary metabolites in a volunteer study (*m*-xylene 150 ppm for four hours) were found in the following concentrations: *m*-methylhippuric acid 97.4%, 2,4-dimethylphenol 2.5%, 3-methylbenzylalcohol 0.05% (Engström *et al*., 1984). Most absorbed xylene is excreted as methylhippuric acids (Lauwerys *et al*., 1978) and only 1-2% as the xylenol metabolites (Sedivec and Flek, 1976; Riihimäki *et al*., 1979; Riihimäki and Hänninen, 1987).

Elimination of xylene from adipose tissue is slow with an average elimination half-life of 58 hours with a range of 25-128 hours (Engström and Riihimäki, 1979; Riihimäki *et al*., 1979).

Metabolism and excretion of xylene is efficient and rapid, consequently the effects following a short exposure are expected to resolve rapidly. However, following prolonged or repeated exposure, elimination will be governed by the rate of release from adipose tissues (Riihimäki and Hänninen, 1987).

Mode of action

The brain is the main target organ in xylene toxicity but the mechanism of action is not known. At high concentrations it causes local irritation and CNS depression but these effects are probably due to non-specific mechanisms (Riihimäki and Hänninen, 1987).

Metabolic interactions

Benzene, styrene, xylene and toluene are metabolised by the same enzyme systems and may competitively inhibit the metabolism of each other (Cohr and Stokholm, 1979; Tardif *et al.,* 1992). Consequently, there may be an increased concentration of unchanged solvent in the blood and decreased or delayed urinary excretion of metabolites (Tardif *et al.,* 1991; Tardif *et al.,* 1992). This may result in overestimation of the toxic risk where blood concentrations are used for monitoring, or underestimation where the urinary metabolites are used (Tardif *et al.,* 1992).

Xylene exposure can result in enzyme induction. This causes enhanced microsomal drug metabolising enzyme activities and increased cytochrome P450 concentrations in the liver and kidneys of rats. It has been shown to resemble the type of induction caused by the drug phenobarbital (Toftgård and Nilsen, 1982; Toftgård *et al.,* 1983). This may result in synergistic toxic effects following simultaneous exposure to xylene and other chemicals metabolised by cytochrome P450. For example, rats pretreated with xylene and then exposed to n-hexane had higher serum concentrations of 2,4-hexanedione, the neurotoxic metabolite of n-hexane (Toftgård *et al*., 1983). Induction is thought to be an adaptive process for increasing the metabolism of xylene (Riihimäki and Hänninen, 1987).

- **Aspirin**

  Exposure to *m*-xylene and administration of acetylsalicylic acid (aspirin) in volunteers caused a significant reduction in the urinary concentration of the metabolites (*m*-methylhippuric acid and salicyluric acid) of both substances. Both these metabolites are glycine conjugates and it is likely that there is mutual inhibition of conjugate formation. Any worker exposed to xylene who has taken aspirin may have an artificially low urinary methylhippuric acid concentration (Campbell *et al*., 1988).

- **Ethanol**

  The metabolism of both ethanol and xylene involves the enzymes alcohol dehydrogenase and aldehyde dehydrogenase. In an experimental study of the metabolic interaction of ethanol and *m*-xylene, ingestion of a moderate dose of ethanol (0.8 g/kg) before exposure to xylene (6 or 11.5 mmol/m^3 (145 or 280 ppm) for four hours) raised the blood xylene concentration by 1.5-2 fold. The urinary concentration of methylhippuric acid decreased by about 50%, whereas the excretion of the minor metabolite 2,4-xylenol was unchanged or increased. Some individuals had a transiently raised

acetaldehyde concentration and this may have been the cause of their dizziness and nausea (Riihimäki *et al.*, 1982). Another volunteer study found that ethanol is only likely to affect *m*-xylene kinetics at high concentrations, i.e., above the occupational exposure limit. Ingestion of ethanol (the night before) and then inhalation of *m*-xylene at 400 ppm for two hours, resulted in lower *m*-xylene concentrations in blood and alveolar air compared to exposure at 100 ppm. Urinary excretion of *m*-methylhippuric acid was increased at 400 ppm. This study showed that ingestion of ethanol for two days prior to xylene exposure was enough to alter the kinetics of xylene, but only at a high xylene concentration (Tardif *et al.*, 1994). Ethanol exposure has also been shown to modify xylene kinetics in animal studies (Savolainen *et al.,* 1978).

- **Ethylbenzene**

  In a volunteer study, concomitant exposure to ethylbenzene and *m*-xylene (both at 150 ppm for four hours) resulted in a significant decrease in urinary metabolites of both solvents (Engström *et al.*, 1984).

- **Methylene chloride**

  Studies in rats have shown that a single oral administration of an aromatic hydrocarbon (benzene, toluene or *m*-xylene) 16-24 hours before the administration of methylene chloride increases the peak concentration of carboxyhaemoglobin (carbon monoxide is a metabolite of methylene chloride). The half-life of methylene chloride in blood was shorter, indicating that the metabolic degradation of methylene chloride is enhanced by the aromatic hydrocarbons. This effect on the peak carboxyhaemoglobin concentration was dependent on the time interval between aromatic hydrocarbon and methylene chloride treatment, since earlier administration of toluene or *m*-xylene decreased the carboxyhaemoglobin elevation. Disulfiram treatment blocked the carboxyhaemoglobin elevation completely and corresponding increases in the concentration and half-life of methylene chloride were observed (Kim and Kim, 1996).

- **Methyl ethyl ketone (MEK)**

  MEK appears to inhibit the metabolism of xylene, possibly by interaction with the initial monooxygenase catalysed step of biotransformation. In volunteers exposed to *m*-xylene and MEK the blood xylene concentration increased almost 2-fold compared to the concentration following exposure to xylene alone. Although the clearance of *m*-xylene and excretion of its metabolite, methylhippuric acid, were reduced, there appeared to be no effect on the biotransformation of MEK. Exposure to MEK 20 hours before exposure to *m*-xylene did not affect xylene metabolism (Liira *et al.*, 1988).

- **Smoking and drinking**

  Male workers who both smoked and drank ethanol were found to have decreased metabolism of xylene isomers and therefore lower urinary concentrations of methylhippuric acids (Inoue *et al.*, 1993).

- **Toluene**

  In a volunteer study, co-exposure to xylene (40 ppm) and toluene (50 ppm) did not affect the concentration of solvent in blood or inhaled air; the urinary excretion of metabolites was unchanged. However, exposure to higher concentrations (80 ppm and 95 ppm respectively) resulted in an increase in the blood and end-exhaled air concentration of these solvents. Excretion of the toluene metabolite (hippuric acid) was affected, but excretion of methylhippuric acid was unchanged (Tardif *et al.*, 1991). Animal studies suggest metabolic interaction of xylene and toluene is only likely to occur when the concentration of both solvents exceeds 50 ppm (Tardif *et al.*, 1993).

- **1,1,1-Trichloroethane**

  The time to peak *m*-xylene concentration was not affected by co-exposure to 1,1,1-trichloroethane (Savolainen *et al.*, 1982).

CASE REPORTS

Acute inhalation exposure

Three men (aged 54, 52 and 24) were employed to paint a double-bottomed tank in the engine room of a ship. Access to the tank was via two manholes at the end. Work began at 10.30 am and the men were due to finish at 4.30 pm but were found at 5 am (16.5 hours after starting work). All three were unconscious and, although there was a strong odour of solvent fumes in the tank, the rescuers were able to work without breathing apparatus.

The first victim was dead on arrival at hospital. Postmortem examination showed congestion of the liver and lungs with histological evidence of focal intra-alveolar haemorrhage and pulmonary oedema. There was swelling and vacuolation of liver cells. The brain showed microscopic petechial haemorrhage and there was evidence of anoxic neuronal damage.

The second victim was unconscious on arrival with hypothermia and peripheral cyanosis. There were medium grade moist sounds audible over the lung fields and a chest X-ray demonstrated patchy diffuse opacity over both fields. He was managed supportively and began to regain consciousness over the next five hours. He was confused and amnesic about the events which occurred 24 hours prior to his collapse. The confusion resolved over the next 2-3 days. He developed renal impairment and raised liver enzymes but these resolved.

The third victim began to regain consciousness soon after arrival but was also confused and amnesic for events. He had slurred speech and ataxia. He recovered slowly over the next 24-48 hours. He had no renal impairment but liver enzymes were raised. The breath of these victims had a strong odour of solvent. The paint used was found to contain over 90% xylene and it was estimated that the amount applied represented only about 1 hour's work. The estimated air concentration of xylene in the tank was 10,000 ppm (Morley *et al*., 1970).

Neurological effects following heavy exposure

A 57 year old male worked repairing boat hulls from 1977-1985 and from mid-1983 began using xylene. For the first seven months of 1985 his workload increased and, consequently, his exposure. He applied xylene (99.7% pure) with a brush dipped in an open bucket for four hours a day. The concentration of xylene over the half-filled bucket he used was 7,000 ppm. There was insidious onset of neuropsychiatric effects with irritability, headaches, dizziness and tiredness; in July 1985 he was admitted to hospital. He complained of agitation, breathlessness, light-headedness, confusion, impaired concentration and short-term memory. He was found to have dysphasia, tremor, ataxia and hyperreflexia. Routine investigations and nerve conduction studies were normal. He gradually improved but by December he still had transient lightheadedness and unsteadiness in crowds. By February 1986 he experienced only occasional imbalance (Roberts *et al*., 1988).

CLINICAL EFFECTS

Acute exposure

Inhalation

Nausea, vomiting, headache, dizziness, drowsiness, ataxia and slurred speech may result from acute inhalation of xylene (Morley *et al*., 1970; Klaucke *et al*., 1982; Bakinson and Jones, 1985; Low *et al*., 1989). There may also be nasal and throat irritation (Carpenter *et al.,* 1975; Riihimäki and Savolainen, 1980; Klaucke *et al*., 1982). In severe cases there may be coma (Bakinson and Jones, 1985), renal impairment and raised liver enzymes (Morley *et al*., 1970). Coma may be prolonged and complete resolution of CNS depression may take up to 48 hours (Morley *et al*., 1970; Klaucke *et al*., 1982). Confusion and retrograde amnesia may occur during recovery (Morley *et al*., 1970). Concentrations of up to 110 ppm should not be objectionable in most cases (Carpenter *et al.,* 1975).

Convulsions have been reported from accidental exposure to a xylene containing glue (while making model aircraft). There were no convulsions when a different glue was used (Arthur and Curnock, 1982).

Arrhythmias have been reported following acute xylene exposure (Sikora and Gala, 1967; Tomaszewski *et al*., 1978) but hypoxia may have been a contributing factor in these two cases (Riihimäki and Hänninen, 1987). Acute inhalation of xylene in volunteers caused a decrease in pulse rate and systolic blood pressure, but these changes were not significant (Ogata *et al*., 1970).

There were no changes in performance tests (e.g., numerical ability, reaction time and short-term memory) in volunteers exposed for 70 minutes to 100 or 300 ppm mixed xylenes (*p*-xylene 12.8%, *o*-xylene 12.1%, *m*-xylene 54.4%, ethylbenzene 20.7%). However, exposure to 300 ppm with exercise (which increased uptake) resulted in impairment in all tests (Gamberale *et al*., 1978).

An electroencephalographic (EEG) study on volunteers exposed to *m*-xylene showed only minor changes. The increased alpha activity and decreased theta and delta activity may be indicative of the stimulatory and excitatory effects of xylene (Seppäläinen *et al.,* 1991). There were EEG changes in non-adapted volunteers following inhalation of *m*-xylene which were suggestive of lowered vigilance (Savolainen *et al*., 1980).

Experimental exposure to 200 ppm *m*-xylene did not affect body balance (as measured by body sway) even after periods of exercise, which were used to increase xylene uptake and blood concentration. There were no unequivocal effects on the quality of sleep or on psychophysiological function (as measured by reaction time tests). However, there was a tendency to stay in bed longer with decreased body movements suggesting a relaxing or tiring effect of exposure (Laine *et al*., 1993). Another study investigated the effects of *m*-xylene on the CNS following exposure to 8.2 µmol/l (200 ppm) for 4 hours a day with peaks of 16.4 µmol/l (400 ppm). Volunteers were either sedentary or had a 10 minute period of exercise. Body balance was affected in the anterioposterior direction, but was improved in individuals who had exercised, despite a higher blood xylene concentration. This was probably because individuals who had exercised were more alert. However, the situation was reversed for body sway in the lateral direction (Savolainen *et al*., 1984). In another volunteer study there was significant impairment of body sway at 90 ppm *m*-xylene. However, the effects were reduced over a simulated working week, i.e., two 3 hour periods with a 1 hour break daily for 5 days. The effect on reaction time and manual co-ordination was about the same (Savolainen *et al*., 1980).

Volunteers exposed to toluene (3.25 mmol/m^3, 80 ppm), *p*-xylene (2.84 mmol/m^3, 70 ppm) or a mixture (2.20 mmol/m^3 toluene, 54 ppm; 0.94 mmol/m^3 xylene, 23 ppm) performed tests of reaction time and short-term memory. The tests were performed immediately after exposure started and then repeated at 2 and 4 hours. They also performed the tests in control conditions without solvent exposure. Performance was unaffected by the solvent exposure (Anshelm Olson *et al*., 1985).

Dermal

Xylene is irritant to the skin and may cause a burning sensation, drying and erythema (Gerarde, 1960; Lauwerys *et al*., 1978; Riihimäki and Hänninen, 1987; Harbison, 1998). Erythema usually resolves within a few hours (Lauwerys *et al*., 1978). In a volunteer study where hands were immersed in xylene, there were no differences in dermal changes with use of a barrier cream (Lauwreys *et al*., 1978). Vasodilation has been observed following immersion of hands in xylene (Engström *et al*., 1977). Blistering may occur, particularly following prolonged contact (ECETOC, 1986).

Eye

Xylene is a mild eye irritant (Carpenter *et al.,* 1975; Klaucke *et al*., 1982), which can cause transient corneal injury (Wolf *et al*., 1956). Liquid xylene in the eye may cause immediate discomfort and blepharospasm, with conjunctival hyperaemia and transient injury to the corneal epithelium. Recovery is usually rapid (Grant and Schuman, 1993).

Ingestion

Coma, hypotonia (general flaccidity), cyanosis and death have been reported following ingestion of xylene (Abu Al Ragheb *et al*., 1986).

Xylene may be an aspiration hazard (Gerade, 1960) and could cause chemical pneumonitis and pulmonary oedema if aspirated into the lung. However, there are no human cases (ECETOC, 1986).

Other routes

Drowsiness, mild tachycardia, tachypnoea, acrocyanosis and hypotension occurred within a few minutes of intravenous injection of 8 ml of xylene (0.1 mg/kg). Acute respiratory failure occurred within 10 minutes. On admission the patient had severe pulmonary oedema, cyanosis, coma and tonic-clonic movements. A chest X-ray showed opacities over both lungs. There was mild coagulopathy and liver damage and xylene was detected in the blood. He survived with supportive care and required ventilation for eight days (Sevcik *et al.*, 1992).

Chronic exposure

Inhalation

Nausea, vomiting, loss of appetite and ataxia may occur (Glass, 1961). Headaches, irritability, tiredness, dizziness, agitation, breathlessness, impaired concentration and short-term memory, confusion, dysphasia, nasal irritation and sore throat, tremor, ataxia and hyperreflexia have been reported (Hipolito, 1980; Roberts *et al.*, 1988; Uchida *et al.*, 1993). A sensation of floating (Uchida *et al.*, 1993), chest pain, ECG abnormalities, pyrexia and dyspnoea have also been reported (Hipolito, 1980).

Some tolerance to the CNS depressant effects of xylene may occur in individuals with repeated daily exposure (Riihimäki and Savolainen, 1980; Savolainen *et al.*, 1980). However, tolerance of the CNS depressant effects of xylene, which developed over a simulated working week in volunteers, did not last long. Impairment of pyschophysiological functions was observed after a 2 day (i.e., a weekend) period of non-exposure (Savolainen *et al.*, 1980).

There is little information on the chronic neurological effects of xylene. There is far less information on xylene abuse than there is on toluene. In addition, exposure during solvent abuse involves very high concentrations and does not reflect the pattern of occupational exposure. Animal studies have demonstrated irreversible brain damage following exposure to xylene. The findings were in agreement with the impairment of the cerebellum observed as a consequence of toluene abuse (Rosengren *et al.,* 1986).

Mood changes, complaints about equilibrium and fatigue were reported more commonly in spray painters than in control workers. The painters were exposed to a number of solvents (xylene, trimethylbenzene and butanol), however, xylene made up >50% of the total weight of solvents. In addition, neurophysical examination revealed decreased peripheral nerve function in the leg nerves (peroneal and sural nerves). There was a similar tendency in the arm nerves, but only the motor nerve conduction velocity (MCNV) of the median nerve was significantly reduced. The refractory period appeared to be to a sensitive parameter to detect damage in motor nerves. Performance in solvent exposed painters was also poorer in neurobehavioural tests and the number of missed relevant responses and false positive stimuli were significantly correlated with the calculated exposure index (Ruijten *et al.*, 1994).

Renal effects

Renal tubular acidosis has been reported from xylene abuse (Sarmiento Martinez *et al.*, 1989). There may be metabolic hyperchloraemic acidosis, hypokalaemia, hyponatraemia, hypocalcaemia and an elevated anion gap. Severe muscle weakness with paralysis may occur, due to electrolyte imbalance. Urinary calculi, proteinuria and haematuria have also been reported following xylene abuse (Kaneko *et al.,* 1992). These effects are also observed with toluene (see Chapter 21), which is more commonly abused than xylene.

The creatinine concentration was normal in 175 workers predominately exposed to xylene isomers (up to 175 ppm) (Uchida *et al.*, 1993).

Haematological effects

There are no reports of bone marrow toxicity following exposure to xylene alone (Riihimäki and Hänninen, 1987; Harbison, 1998). Haematological effects reported in the older literature may have been due to the presence of benzene, which was a common contaminant of xylene before the 1940s (Von Burg, 1982; ECETOC, 1986). In a study of 175 workers predominately exposed to xylene isomers (up to 175 ppm), there was no significant difference in the haematological parameters compared to controls (Uchida *et al.*, 1993).

Red blood cell counts and haemoglobin were significantly reduced in 35 workers exposed for 2-24 years (average 8.2 years) to xylene. However, these changes were found to be small. Average concentrations for *o*-, *m*-, *p*-xylene and ethylbenzene were 2.1, 7.9, 2.8 and 4.0 ppm and were well below recommended exposure limits. Benzene was not detected. Leucocyte counts did not differ from controls (Angerer and Wulf, 1985).

Leucopenia has been reported in laboratory workers chronically exposed to xylene (up to 18 years). However, the concentrations of xylene or other solvents in the air and urinary metabolites were not measured (Hipolito, 1980). A study of workers involved in the manufacture of xylene from gasoline found no decrease in leucocyte count compared to controls. However, there was evidence of reduced functional capacity of leucocytes with a decrease in glycogen and peroxidase in neutrophils. Exposure time varied from five months to five years. About one-third of workers complained of occasional headaches, irritability, insomnia, dyspepsia and tachycardia. The concentration of xylene exceeded the maximum permissible concentration (not stated) on 1.5-4 times in 35-40% of air samples. Concentrations of other hydrocarbons did not exceed permissible concentrations (Sukhanova *et al.*, 1969).

Hepatic effects

Hepatotoxicity from xylene is rare (Riihimäki and Hänninen, 1987). In a study of 175 workers predominately exposed to xylene isomers (up to 175 ppm), liver function parameters were considered normal. Although the AST/ALT ratio was significantly higher in the exposed group than the controls, none of these individuals had >100 IU/l AST and >100 IU/l ALT in combination (Uchida *et al.*, 1993).

Immunotoxicity

A study of 35 painters exposed to benzene, toluene and xylene found that they had significantly lower immunoglobulin A (IgA) and IgG concentrations, but increased IgM. This was thought to be due to a suppressive action of benzene on immunoglobulin producing cells, resulting in inhibition of DNA synthesis (Lange *et al.,* 1973). Serum complement concentrations were decreased in 62 of 79 workers exposed to benzene, toluene and xylene for 0.25 to 18 years (Smolik *et al.*, 1973).

Dermal

Urticaria, facial redness and peeling have been reported following chronic exposure to xylene vapour (Palmer and Rycroft, 1993). Dermatitis may occur from chronic exposure to xylene (Gerarde, 1960). Repeated application of xylene to rabbit skin caused erythema, oedema, exfoliation, blistering and moderate necrosis (Wolf *et al.*, 1956).

Eye

Irritation of eyes may occur following chronic exposure (Uchida *et al.*, 1993). Vacuoles in the corneal epithelium have been reported in workers exposed to solvent mixtures including xylene (Schmid, 1956). The vacuoles resolved spontaneously within 2-4 weeks without scarring (Matthäus, 1964).

Carcinogenicity

There is inadequate evidence in both humans and experimental animals that xylenes are carcinogenic. Consequently, xylenes have been placed in Group 3 by IARC and are not classifiable as to their carcinogenicity in humans (IARC, 1999).

Genotoxicity

Xylene does not appear to cause genotoxicity (Von Burg, 1982; Dean, 1985; Fishbein, 1985; Riihimäki and Hänninen, 1987)

There was no significant difference in sister chromatid exchanges (SCEs) of peripheral lymphocytes in two groups of workers exposed to xylene (average concentration 10.9 ppm and 12.9 ppm) compared to controls (Pap and Varga, 1987).

A study of 17 workers (employed 0.8-44 years, average 22.8 years) exposed to several solvents but particularly toluene (1-1257 mg/m^3; 0.27-334 ppm) and xylene (14-6,074 mg/m^3; 3.2-1,396 ppm) found no differences in SCEs or chromosome aberrations compared to controls (Haglund *et al.*, 1980).

An experimental study of exposure to toluene, xylene or their mixture (toluene 50 ppm, xylene 40 ppm, for 7 hours a day for 3 consecutive days, on three occasions, two weeks apart) in five individuals, found no significant effect on SCEs, cell cycle delay or cell mortality. Also, exposure of human lymphocytes *in vitro* to toluene (0-2.5 mM), xylene (0-2 mM) or their mixture had no observable effect at low concentrations, with only increased cell mortality occurring at higher concentrations (Richer *et al.*, 1993).

In vitro studies on human lymphocytes exposed to various xylene concentrations found no increase in SCEs or the number of chromosome aberrations. However, at the higher concentrations there was significant inhibition of cell growth (Gerner-Smidt and Friedrich, 1978).

Reproductive toxicity

There are studies involving mixed solvents which have shown adverse reproductive effects, but none have involved exposure to xylene alone. Consequently, no definite conclusion can be reached about the reproductive toxicity of xylene in humans.

In a study of laboratory workers exposed to various chemicals, exposure to xylene was associated with an increased risk of spontaneous abortion (Taskinen *et al.*, 1994). A study of men exposed to a mixture of solvents found that spontaneous abortion in their partners was significantly associated with paternal exposure to organic solvents in general, high/frequent exposure to toluene and miscellaneous organic solvents. There was also greater risk with xylene exposure but the increase was not statistically significant (Taskinen *et al.*, 1989).

A woman exposed to xylenes and a number of other solvents during pregnancy gave birth to a child with hydranencephaly. However, she had previously had another child born with a brain abnormality and the author concluded that the defect was due to predisposition and parental age rather than solvent exposure (Holmberg, 1979).

Xylene has been shown to be embryotoxic and fetotoxic in animal experiments. Teratogenicity has been demonstrated with mixed and individual isomers but only at concentrations causing maternal toxicity (reviewed in Barlow and Sullivan, 1982; Hood and Ottley, 1985; Riihimäki and Hänninen, 1987). The *o*- and *p*-isomers appear to be more hazardous to offspring than *m*-xylene (Hood and Ottley, 1985).

RISK GROUPS

Individuals may differ in the metabolism of chemicals depending on their ethnic group owing, for example, to physiological differences in renal function, body size and composition and genetic differences. However, this is a comparatively new area of research and the significance of these differences, particularly in terms of biological monitoring, has not been fully elucidated.

Jang *et al.* (1997) compared the differences in pharmacokinetics and urinary metabolite concentrations of several solvents in a small group of Caucasian and Oriental volunteers. In the case of *m*-xylene exposure (100 ppm for six hours) the Caucasian group had a higher average concentration of xylene in exhaled air than the Oriental group, but variation between the subjects in each group was so high that the difference was not significant. The Caucasian group had a higher urinary concentration of methylhippuric acid than the Oriental

group until three hours after exposure, but after six hours there was no difference. The average peak concentration was also significantly higher in the Caucasian group. Immediately after cessation of exposure, the urinary concentration of methylhippuric acid was about 30% higher in the Caucasian group.

HOSPITAL MANAGEMENT

Acute exposure

Inhalation

The victim should be removed from exposure and all contaminated clothing removed. The respiratory function should be assessed. Further treatment is symptomatic and supportive. See below for management of systemic effects.

Dermal

Contaminated clothing should be removed and the skin thoroughly irrigated with water or saline. Further treatment is symptomatic and supportive.

Eye

The eyes should be thoroughly irrigated with water or saline for 15 minutes and then stained with fluorescein. Referral to an ophthalmologist is recommended if there is any uptake of fluorescein.

Ingestion

Gastric lavage may be considered if ingestion was recent, however, because of the risk of aspiration a cuffed endotracheal tube must be used to protect the airway. Activated charcoal is unlikely to be of benefit. If there has been any vomiting, coughing or wheezing then the patient will need to be assessed to determine if aspiration has occurred. Treatment is supportive. See below for management of systemic effects.

Systemic effects

It is essential to check electrolytes, blood gases, renal and hepatic function, urinalysis and CPK particularly in patients with generalised weakness. Monitor ECG in symptomatic patients.

Renal tubular acidosis is treated conventionally with correction of hypokalaemia then acidosis. It is essential to correct the hypokalaemia before giving sodium bicarbonate as bicarbonate worsens hypokalaemia and hypocalcaemia. This can result in arrhythmias and rhabdomyolysis. No attempt should be made to correct acidosis until the potassium concentration is above 3 mmol/l (Kroeger *et al*., 1980). Potassium chloride should not be used since patients usually have hyperchloraemic acidosis. Regular monitoring of electrolytes, blood gases and ECG is essential. Hypocalcaemia (resulting in tetany) may occur during fluid and electrolyte repletion and should be managed with calcium supplementation if necessary.

Antidotes

There is no specific antidote for xylene.

Chronic exposure

In most cases of chronic poisoning clinical effects resolve gradually once exposure has ceased. Symptomatic and supportive care.

REFERENCES

Abu Al Ragheb S, Salhab AS, Amr SS. 1986 Suicide by xylene ingestion. A case report and review of literature. *Am J Forensic Med Pathol* 7 (4):327-329.

ACGIH. 2000 *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Limits*. American Conference of Governmental Industrial Hygienists.

Amoore JE, Hautala E. 1983 Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3 (6):272-290.

Angerer J, Wulf H. 1985 Occupational chronic exposure to organic solvents XI. Alkylbenzene exposure of varnish workers: effects on hematopoietic system. *Int Arch Occup Environ Health* 56:307-321.

Anshelm Olson B, Gamberale F, Iregren A. 1985 Co-exposure to toluene and *p*-xylene in man: central nervous functions. *Br J Ind Med* 42:117-122.

Arthur LJH, Curnock DA. 1982 Xylene-induced epilepsy following innocent glue sniffing [letter]. *Br Med J* 284:1787.

Åstrand I, Engström J, Övrum P. 1978 Exposure to xylene and ethylbenzene I: Uptake, distribution and elimination in man. *Scand J Work Environ Health* 4:185-194.

Bakinson MA, Jones RD. 1985 Gassings due to methylene chloride, xylene, toluene, and styrene reported to Her Majesty's Factory Inspectorate 1961-80. *Br J Ind Med* 42:184-190.

Barlow SM, Sullivan FM. 1982 *Reproductive Hazards of Industrial Chemicals. An evaluation of animal and human data*. Academic Press, London.

Campbell L, Wilson HK, Samuel AM, Gompertz D. 1988 Interactions of *m*-xylene and aspirin metabolism in man. *Br J Ind Med* 45:127-132.

Caperos JR, Fernàndez JG. 1977 Simultaneous determination of toluene and xylene metabolites in urine by gas chromatography. *Br J Ind Med* 34:229-233.

Carpenter CP, Kinkead ER, Geary DL Jr, Sullivan LJ, King JM. 1975 Petroleum hydrocarbon toxicity studies. V. Animal and human responses to vapors of mixed xylenes. *Toxicol Appl Pharmacol* 33:543-558.

Cohr K-H, Skokholm J. 1979 Toluene. A toxicologic review. *Scan J Work Environ Health* 5 (2):71-90.

Dean BJ. 1985 Recent findings on the genetic toxicology of benzene, toluene and xylene. *Mutat Res* 154:153-181.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 1986 Xylenes. *Joint Assessment of Commodity Chemicals No. 6*.

Engström K, Husman K, Riihimäki V. 1977 Percutaneous absorption of *m*-xylene in man. *Int Arch Occup Environ Health* 39:181-189.

Engström J, Bjurström R. 1978 Exposure to xylene and ethylbenzene II: Concentration in subcutaneous adipose tissue. *Scand J Work Environ Health* 4:195-203.

Engström K, Husman K, Pfäffli P, Riihimäki V. 1978 Evaluation of occupational exposure to xylene by blood, exhaled air and urine analysis. *Scand J Work Environ Health* 4:114-121.

Engström J, Riihimäki V. 1979 Distribution of *m*-xylene to subcutaneous adipose tissue in short-term experimental human exposure. *Scand J Work Environ Health* 5:126-134.

Engström K, Riihimäki V, Laine A. 1984 Urinary deposition of ethylbenzene and *m*-xylene in man following separate and combined exposure. *Int Arch Occup Environ Health* 54:355-363.

Fishbein L. 1985 An overview of environmental and toxicological aspects of aromatic hydrocarbons. III Xylene. *Sci Totol Environ* 43:165-183.

Gamberale F, Annwall G, Hultengren M. 1978 Exposure to xylene and ethylbenzene III: Effects on central nervous functions. *Scand J Work Environ Health* 4:204-211.

Gerade HW. 1960 *Toxicology and Biochemistry of Aromatic Hydrocarbons*. Elsevier, Amsterdam.

Gerner-Schmit P, Friedrich U. 1978 The mutagenic effects of benzene, toluene and xylene studied by the SCE technique. *Mutat Res* 58:313-316.

Glass WI. 1961 A case of suspected xylol poisoning. *NZ J Med* 60:113.

Grant WM, Schuman, JH. 1993 *Toxicology of the Eye,* 4th edition. Charles C Thomas, Springfield, Illinois.

Gusev IS. 1965. Reflective effects of microconcentrations of benzene, toluene and xylene and their comparative assessment. *Hyg Sanit* 30:331-336.

Haglund U, Lundberg I, Zech L. 1980 Chromosome aberrations and sister chromatid exchanges in Swedish paint industry workers. *Scand J Work Environ Health* 6:291-298.

Harbison RD. 1998 Aromatic hydrocarbons. In: *Hamilton and Hardy's Industrial Toxicology*, fifth edition. Harbison RD (editor). Mosby, St Louis.

Hipolito RN. 1980 Xylene poisoning in laboratory workers: case reports and discussion. *Lab Med* 11:593-595.

Holmberg PC. 1979 Central-nervous-system defects in children born to mothers exposed to organic solvents during pregnancy. *Lancet* 2:177-179.

Hood RD, Ottley MS. 1985 Development effects associated with exposure to xylene: a review. *Drug Chem Toxicol* 8 (4):281-297.

IARC (International Agency for Research on Cancer). 1999 *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*. IARC Monograph 71, p 1189.

Inoue O, Seiji K, Kawai T, Watanabe T, Jin C, Cai S-X, Chen Z, Qu Q-S, Zhang T, Ikeda M. 1993 Excretion of methylhippuric acids in urine of workers exposed to a xylene mixture: comparison among three xylene isomers and toluene. *Int Arch Occup Environ Health* 64:533-539.

IPCS. 1997 *Environmental Health Criteria 190. Xylenes*. World Health Organization, International Programme on Chemical Safety, Geneva.

Jang J-Y, Droz PO, Berode M. 1997 Ethnic differences in biological monitoring of several organic solvents I. Human exposure experiment. *Int Arch Occup Environ Health* 69:343-349.

Kaneko T, Koizumi T, Takezaki T, Sato A. 1992 Urinary calculi associated with solvent abuse. *J Urol* 147:1365-1366.

Kawai T, Mizunuma K, Yasgui T, Horiguchi S, Uchida Y, Iwami O, Iguchi H, Ikeda M. 1991 Urinary methylhippuric isomer levels after occupational exposure to a xylene mixture. *Int Arch Occup Environ Health* 63:69-75.

Kim SK, Kim YC. 1996 Effect of a single administration of benzene, toluene or *m*-xylene on carboxyhaemoglobin elevation and metabolism in rats. *J Appl Toxicol* 16(5):437-444.

Klaucke DN, Johansen M, Vogt RL. 1982 An outbreak of xylene intoxication in a hospital. *Am J Ind Med* 3:173-178.

Krämer A, Linnert M, Wrbitsky R, Angerer J. 1999 Occupational chronic exposure to organic solvents XVII. Ambient and biological monitoring of workers exposed to xylenes. *Int Arch Occup Environ Health* 72:52-55.

Kroeger RM, Moore RJ, Lehman TH, Giesy JG, Skeeters CE. 1980 Recurrent urinary calculi associated with toluene sniffing. *J Urol* 123:89-91.

Laine A, Savolainen K, Riihimäki V, Matikainen E, Salmi T, Juntunen J. 1993 Acute effects of *m*-xylene inhalation on body sway, reaction times, and sleep in man. *Int Arch Occup Environ Health* 65:197-188.

Lange A, Smolik R, Zatonski W, Szymanska J. 1973 Serum immunoglobulin levels in workers exposed to benzene, toluene and xylene. *Int Arch Arbeitsmed* 31:37-44.

Lauwerys RR, Dath T, Lachapelle J-M, Buchet J-P, Roels H. 1978 The influence of two barrier creams on the percutaneous absorption of *m*-xylene in man. *J Occup Med* 20 (1):17-20.

Liira J, Riihimäki V, Engström K, Pfäffli P. 1988 Coexposure of man to *m*-xylene and methyl ethyl ketone. Kinetics and metabolism. *Scand J Work Environ Health* 14 (5):322-327.

Low LK, Meeks JR, Mackerer CR. 1989 Health effects of the alkylbenzenes. II. Xylenes. *Toxicol Ind Health* 5 (1):85-97.

Lundberg I, Sollenberg J. 1986 Correlation of xylene exposure and methyl hippuric acid excretion in urine among paint industry workers. *Scand J Work Environ Health* 12:149-153.

Matthäus W. 1964 Beitrag zur Hornhauterkrankung von Oberflächenbearbeitern in der Möbelindustrie [Report of corneal disturbance of finish-workers in the furniture industry]. *Klin Monatsbl Augenheilkd* 144:713-717.

Miller MJ, Edwards JW. 1999 Possible preferential metabolism of xylene isomers following occupational exposure to mixed xylenes. *Int Arch Occup Environ Health* 72:89-97.

Morley R, Eccleston DW, Douglas CP, Greville WEJ, Scott DJ, Anderson J. 1970 Xylene poisoning: a report on one fatal case and two cases of recovery after prolonged unconsciousness. *Br Med J* 3:442-443.

Ogata M, Tomokuni K, Takatsuka Y. 1970 Urinary excretion of hippuric acid and *m*- or *p*-methylhippuric acid in the urine of persons exposed to vapours of toluene and *m*- or *p*-xylene as a test of exposure. *Br J Ind Med* 27:43-50.

Palmer KT, Rycroft RJG. 1993 Occupational airborne contact urticaria due to xylene. *Contact Dermatitis* 28:44.

Pap M, Varga C. 1987 Sister-chromatid exchanges in peripheral lymphocytes of workers occupationally exposed to xylenes. *Mutat Res* 187:223-225.

Richer C-L, Chakrabarti S, Senécal-Quevillon M, Duhr MA, Zhang XX, Tardif R. 1993 Cytogenetic effects of low-level exposure to toluene, xylene and their mixture on human blood lymphocytes. *Int Arch Occup Environ Health* 64:581-585.

Riihimäki V, Pfäffli P, Savolainen K, Pekari K. 1979 Kinetics of *m*-xylene in man. General features of absorption, distribution, biotransformation and excretion in repetitive inhalation exposure. *Scand J Work Environ Health* 5:217-231.

Riihimäki V, Savolainen K. 1980 Human exposure to *m*-xylene, kinetics and acute effects on the central nervous system. *Ann Occup Med* 23:411-422.

Riihimäki V, Savolainen K, Pfäffli P, Pekari K, Sippel HW, Laine A. 1982 Metabolic interaction between *m*-xylene and ethanol. *Arch Toxicol* 49:253-263.

Riihimäki V, Hänninen O. 1987 Xylenes. In: *Ethel Browning's Toxicity and Metabolism of Industrial Solvents*, 2nd edition, Volume 1: Hydrocarbons. R Snyder (editor). Elsevier, Amsterdam.

Roberts FP, Lucas EG, Marsden CD, Trauer T. 1988 Near-pure xylene causing reversible neuropsychiatric disturbance [letter]. *Lancet* 2:273.

Rosengren LE, Kiellstrand P, Aurell A, Haglid KG. 1986 Irreversible effects of xylene on the brain after long term exposure: a quantitative study of DNA and the glial cell marker proteins S-100 and GFA. *Neurotoxicology* 7 (3):121-136.

Ruijten MWMM, Hooisma J, Brons JT, Habets CEP, Emmen HH, Muijser H. 1994 Neurobehavioral effects of long-term exposure to xylene and mixed organic solvents in shipyard spray painters. *Neurotoxicology* 15 (3):613-620.

Ruth JH. 1986 Odor threshold and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47:A142-A151.

Sarmiento Martinez J, Guardiola Sala JJ, Campãna Casals E. 1989 Renal tubular acidosis with an elevated anion gap in a 'glue sniffer'. *Hum Toxicol* 8:139-140.

Savolainen K, Vainio H, Helojoki M, Elovaara E. 1978 Biochemical and toxicological effects of short-term, intermittent *m*-xylene inhalation exposure and combined ethanol intake. *Arch Toxicol* 41:195-205.

Savolainen K, Riihimäki V, Seppäläinen AM, Linnoila M. 1980 Effects of short-term *m*-xylene exposure and physical exercise on the central nervous system. *Int Arch Occup Environ Health* 45:105-121.

Savolainen K, Riihimäki V, Laine A, Kekoni J. 1982 Short-term exposure of human subjects to *m*-xylene and 1,1,1-trichloroethane. *Arch Toxicol* 5:96-99.

Savolainen K, Kekoni J, Riihimäki V, Laine A. 1984 Immediate effects of *m*-xylene on the human central nervous system. *Arch Toxicol* 7:412-417.

Schmid E. 1956 Die Augenhornhauterkrankung der Möbelpolierer [Corneal damage due to furniture polishes]. *Arch Gewerbepathol Gewerbehgy* 15:37-44.

Sedivec V, Flek J. 1976 The absorption, metabolism and excretion of xylenes in man. *Int Arch Occup Environ Health* 37:205-217.

Senczuk W, Orlowski J. 1978 Absorption of *m*-xylene vapours through the respiratory tract and excretion of *m*-methylhippuric acid in urine. *Br J Ind Med* 35:50-55.

Seppäläinen AM, Laine A, Salmi T, Verkkala E, Riihimäki V, Luukkonen R. 1991 Electroencephalographic findings during experimental human exposure to *m*-xylene. *Arch Environ Health* 46 (1):16-24.

Ševčik P, Hep A, Peslová M. 1992 Intravenous xylene poisoning. *Intensive Care Med* 18:377-378.

Sikora H, Gala J. 1967 Uszkodzenie miesnia sercowego w przebiegu ostrego zatrucia ksylenem [Damage of cardiac muscle in the course of acute xylene poisoning]. *Med Pracy* 18 (1):75-77

Smolik R, Grzybek-Hryncewicz K, Lange A, Zatonski W. 1973 Serum complement level in workers exposed to benzene, toluene and xylene. *Int Arch Arbeitsmed* 31:243-247.

Sukhanova VA, Makar'eva LM, Boiko VI. 1969 Investigation of functional properties of leukocytes of workers engaged in manufacture of xylene. *Hyg Sanit* 34:448-450.

Tardif R, Laparé S, Plaa GL, Brodeur J. 1991 Effects of simultaneous exposure to toluene and xylene on their respective biological exposure indices in humans. *Int Arch Occup Environ Health* 63:279-284.

Tardif R, Goyal R, Brodeur J. 1992 Assessment of occupational health risk from multiple exposure: review of industrial solvent interaction and implication for biological monitoring of exposure. *Toxicol Ind Health* 8 (1/2):37-52.

Tardif R, Laparé S, Krishnan K, Brodeur J. 1993 A descriptive and mechanistic study of the interaction between toluene and xylene in humans. *Int Arch Occup Environ Health* 65:S135-S137.

Tardif R, Sato A, Laparé S, Brodeur J. 1994 Ethanol induced modification of *m*-xylene toxicokinetics in humans. *Occup Environ Med* 51:187-191.

Taskinen H, Anttila A, Lindbohm M-L, Sallmén M, Hemminki K. 1989 Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand J Work Environ Health* 15:345-352.

Taskinen H, Kyyrönen P, Hemminiki K, Hoikkala M, Lajunen K, Lindbohm M-L. 1994 Laboratory work and pregnancy outcome. *J Occup Med* 36 (3):311-319.

Toftgård R, Nilsen OG. 1982 Effects of xylene and xylene isomers on cytochrome P-450 and *in vitro* enzymatic activities in rat liver, kidney and lung. *Toxicology* 23:197-212.

Toftgård R, Halpert J, Gustafsson J-Å. 1983 Xylene induces a cytochrome P-450 isozyme in rat liver similar to the major isozyme induced by phenobarbital. *Mol Pharmacol* 23:265-271.

Tomaszewski R, Gandurski P, Chmielewski J. 1978 Rytm wezlowy w zatruciu ksylenem [Nodal rhythm in xylene intoxication]. *Wiad Lek* 31 (3):193-194.

Uchida Y, Natasuka H, Ukai H, Watanabe T, Liu Y-T, Huang M-Y, Wang Y-L, Zhu F-Z, Yin H, Ikeda M. 1993 Symptoms and signs in workers exposed predominantly to xylenes. *Int Arch Occup Environ Health* 64:597-605.

Von Burg R. 1982 Xylene. *J Appl Toxicol* 2 (5):269-271.

Wolf MA, Rowe VK, McCollister DD, Hollingsworth RL, Oyen F. 1956 Toxicological studies of certain alkylated benzenes and benzene. *Arch Ind Health* 14:387-398.

Abbreviations and Acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
ADH	alcohol dehydrogenase
AG	anion gap
ALDH	aldehyde dehydrogenase
ALL	acute lymphoblastic leukaemia
ALT	alanine aminotransferase (formerly SGPT)
AMCC	*N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine
AML	acute myelogenous leukaemia
ANA	anti-nuclear antibodies
AST	aspartate aminotransferase (formerly SGOT)
atm	atmosphere
ATP	adenosine triphosphate
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
BAA	butoxyacetic acid
BAC	blood alcohol concentration
BEI	biological exposure index
BUA	Beratergremium für umweltrelevante Altstoffe (Committee on Existing Chemicals of Environmental Relevance)
CAHD	Coronary atherosclerotic heart disease
CAS	Chemical Abstracts Service
CMAP	compound muscle action potential
CML	chronic myelogenous leukaemia
CNS	central nervous system
CPK	creatine phosphokinase
CSF	cerebrospinal fluid
CT	computerised tomography
CVS	cardiovascular system
DCVG	*S*-(dichlorovinyl)glutathione
DEGDME	diethylene glycol dimethyl ether
DIC	disseminated intravascular coagulation
DL	distal latency
DMF	dimethylformamide
DMFA	dimethylformamide
DNA	deoxyribonucleic acid
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECG	electrocardiograph
EE	ethoxyethanol
EEA	ethoxyacetic acid

EEAc	ethoxyethyl acetate
EEG	electroencephalograph
EGBE	ethylene glycol monobutyl ether
EGBEA	ethylene glycol monobutyl ether acetate
EGDEE	ethylene glycol diethyl ether
EGDME	ethylene glycol dimethyl ether
EGEE	ethylene glycol monoethyl ether
EGEEA	ethylene glycol monoethyl ether acetate
EGEEAc	ethylene glycol monoethyl ether acetate
EGME	ethylene glycol monomethyl ether
EGMEA	ethylene glycol monomethyl ether acetate
EINECS	European Inventory of Existing Chemical Substances
EMC	ethyl-*N*-methylcarbamate
EP	evoked potential
EPA	Environmental Protection Agency (USA)
ERG	electroretinogram
ESRD	end-stage renal disease
FSGS	focal segmental glomerulosclerosis
FSH	follicle stimulating hormone
g	gram
GABA	gamma aminobutryic acid
GBM	glomerular basement membrane
GCS	Glasgow coma scale
GnRH	gonadotrophin releasing hormone
GPA	glycophorin A
GSH	glutathione
GTP	guanosine triphosphate
h	hour
HAZMAT	hazardous materials (USA)
HMMF	*N*-(hydroxymethyl)-*N*-methylformamide
2-HMSI	2-hydroxy-*N*-methylsuccinimide
5-HNMP	5-hydroxy-*N*-methylpyrrolidone
HPLC	high performance liquid chromatography
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer (WHO)
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	International Normalised Ratio
IPCS	International Programme on Chemical Safety (WHO)
ITU	intensive therapy unit
IU	international units
IV	intravenous
l	litre
LFT	liver function test

LH	luteinising hormone
m-	meta-
MAA	methoxyacetic acid
MAC	maximum allowable concentration
MBK	methyl *n*-butyl ketone
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
MEK	methyl ethyl ketone
mg	milligram
mg/l	milligrams per litre
mg/m^3	milligrams per cubic metre
MHA	methylhippuric acid
MIBK	methyl isobutyl ketone
min	minute
ml	millilitre
MM	multiple myeloma
mM	millimolar
MMF	mono-*N*-methylformamide
MnBK	methyl *n*-butyl ketone
MNCV	motor nerve conduction velocity
MO	measured osmolality
mOsm/kg H_2O	milliosmoles per kilogram of water
MPO	myeloperoxidase
MRI	magnetic resonance image
MSI	*N*-methyl succinimide
na	not analysed
NAD	nicotinamide adenine dinucleotide
NADH	reduced form of nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
NADPH	reduced form of nicotinamide adenine dinucleotide phosphate
NCI	National Cancer Institute (USA)
NCV	nerve conduction velocity
NHL	non-Hodgkin's lymphoma
NHS	National Health Service (UK)
NIOSH	National Institute for Occupational Safety and Health (USA)
NK	not known
nm	nanometers
NMF	mono-*N*-methylformamide
NMG	*S*-(*N*-methylcarbamoyl)glutathione
NMP	*N*-methyl-2-pyrrolidone
NQO1	NAD(P)H:quinone oxidoreductase 1
NTP	National Toxicology Program (USA)
o-	ortho-
OG	osmolal gap
OSHA	Occupational Safety and Health Administration (USA)

oz	ounce
p-	para-
PAA	*n*-propoxyacetic acid
PAS	periodic acid-Schiff
PBPK	physiological-based pharmacokinetic
PCE	perchloroethylene (tetrachloroethylene)
PEEP	positive expiratory end pressure
PGBE	2-propylene glycol 1-*n*-butyl ether
PGME	propylene glycol monomethyl ether
PGMEA	propylene glycol monomethyl ether acetate
PGMEAc	2-propylene glycol 1-methyl ether 2-acetate
PHA	phytohaemagglutinins
ppm	parts per million
PTR	prothrombin time ratio
PVC	polyvinyl chloride
®	registered trade name
RBC	red blood cell count
RTECS	Registry of the Toxic Effects of Chemical Substances (produced by NIOSH)
SCE	sister chromatid exchange
SDH	sorbitol dehydrogenase
SGOT	serum glutamic oxalacetic transaminase (now AST)
SGPT	serum glutamic pyruvic transaminase (now ALT)
SMG	*S*-(*N*-methylcarbamoyl)glutathione
SNAP	sensory nerve action potential
SNCV	sensory nerve conduction velocity
TCA	trichloroacetic acid
TCE	trichloroethanol
1,1,1-TCE	1,1,1-trichloroethane
THF	tetrahydrofolic acid
TLV	threshold limit value
TPN	total parenteral nutrition
TRI	trichloroethylene
TTCA	2-thiothiazolidine-4-carboxylic acid
TWA	time-weighted average
UK	United Kingdom
UN	United Nations
UV	ultraviolet
VEP	visual evoked potential
VSA	volatile solvent abuse
WBC	white cell count
WHO	World Health Organization
µg	microgram
µl	microlitre
µM	micromolar

Glossary

ACGIH	American Conference of Governmental Industrial Hygienists. A professional organisation (not a government agency) working on the administrative and technical aspects of occupational and environmental health in the USA.
acidosis	A high concentration of hydrogen ions in the blood, resulting in a decreased blood pH.
activated charcoal	Superheated charcoal produces porous material with a huge surface area, which is capable of binding a variety of drugs and chemicals.
adipsia	Absence of thirst.
agglutinin	Antibodies which agglutinate (clump) particles together.
Ames test	An *in vitro* test using strains of the bacterium *Salmonella typhimurium* to evaluate the capacity of chemicals to cause mutations.
aneuploidy	The loss or gain of whole chromosomes.
angioma	A tumour arising from the cells of blood vessels.
anion gap	A blood biochemistry parameter. The anion gap measures the extra anions produced from the metabolism of exogenous substances (e.g., alcohols). It is calculated as the sodium concentration minus the total of the bicarbonate plus the chloride concentrations in the blood.
anuria	No output of urine in a 24 hour period.
aplastic anaemia	A type of anaemia where the bone marrow fails to produce an adequate number of blood elements.
apnoea	Cessation of breathing (no respiratory effort).
atrophy	A decrease in the mass of body tissue.
axon	An extension of a nerve cell along which electrical impulses pass.
azoospermia	The finding of no sperm in the semen.
BEI	Biological Exposure Index. BEIs are guidance values for assessing biological monitoring results. The BEI generally indicates a concentration below which nearly all workers should not experience adverse health effects.
biological monitoring	Biological monitoring indirectly reflects the dose to which a worker has been exposed.
carboxyhaemoglobin	Haemoglobin combined with carbon monoxide, given as a percentage.
carcinogen	Any cancer producing substance or agent.
carcinogenicity	The ability to produce cancer.

CAS	Chemical Abstracts Service, an organisation that indexes information published in Chemical Abstracts by the American Chemical Society and provides index guides by which information about particular substances may be located in the abstracts. The CAS number is an assigned number used to identify specific chemicals. They are assigned sequentially and are useful as a concise, unique means of identification. The numbers have no chemical significance.
catecholamine	A group of compounds including epinephrine (adrenaline) and norepinephrine (noradrenaline).
choleostasis	Reduction or cessation of the flow of bile.
chromatid	One of the two filaments of the chromosome joined at the centromere.
clastogenic	Causing disruption or breakage of chromosomes.
CNS depression	Central nervous system depression. A decrease in function of the central nervous system resulting in a state ranging from drowsiness to coma.
coagulopathy	Any disorder of blood clotting.
creatinine	A compound produced in the body and excreted in urine.
cytochrome P450	An important group of enzymes involved in the metabolism of many different substances, including ethanol, and some drugs and solvents.
diplopia	Double vision.
distal	Furthest from the head.
disulfiram	A substance which produces unpleasant effects if ethanol is also taken. These effects include flushing, nausea and headache. Disulfiram is used to produce an aversion to alcohol in the treatment of chronic alcoholism.
DNA	Deoxyribonucleic acid; a compound which occurs mainly in the chromosomes and carries, in coded form, genetic information.
dysarthria	Imperfect articulation of speech.
dysgeusia	Abnormal sensation of taste.
dysplasia	Abnormality of cellular development.
dyspnoea	Difficult or laboured breathing.
ECG	Electrocardiogram; an instrument that measures the electrical activity of the heart.
EEG	Electroencephalogram; an instrument that measures the electrical activity of the brain.
EINECS	The European Inventory of Existing Commercial Chemical Substances is a system classifying and labelling existing chemical substances. It was published in the Annex to the Official Journal of the European Communities, No. C 146 A, 15 June 1990. It lists and defines those chemical substances that were on the European Community market between 1 January 1971 and 18 September 1981.
electromyography	The recording and study of electrical properties of skeletal muscle.
enzyme-induction	Increased synthesis of an enzyme induced by some chemicals. This results in an increased rate of metabolism.

erythema	Redness.
erythrocyte	Red blood cell.
erythroleukaemia	A malignant blood disorder.
erythromyelosis	A malignant blood disorder.
first-pass metabolism	Inactivation of a significant proportion of a substance by metabolism in the liver or gastrointestinal tract before it reaches the systemic circulation.
gastritis	Inflammation of the lining of the stomach.
genotoxicity	The ability to alter the structure, information content or segregation of DNA, or to inhibit its replication.
Glasgow coma scale	A numerical score for assessing the conscious level of an individual. The score is from 3 to 15, where 15 is normal.
haematocrit	The volume percentage of red blood cells in whole blood.
haptoglobin	A group of glycoproteins in serum which bind free haemoglobin.
HSE	The Health and Safety Executive (HSE) is a government body in the UK with responsibility for enforcing health and safety legislation and investigation of accidents.
hypercalcaemia	Abnormally increased concentration of calcium in the blood.
hypercapnia	Excess of carbon dioxide in the blood.
hyperdiploidy	A gain in chromosome number.
hyperkalaemia	Abnormally increased concentration of potassium in the blood.
hypernatraemia	Abnormally increased concentration of sodium in the blood
hypoglycaemia	Abnormally decreased glucose concentration in the blood.
IARC	International Agency for Research on Cancer (IARC) is part of the World Health Organization. The IARC coordinates and conducts research on the causes of human cancer, the mechanisms of carcinogenesis, and develops scientific strategies for cancer control.
in vitro	Literally in glass; in an artificial environment.
in vivo	Within the living body.
leucocytosis	An increased number of white blood cells in the blood.
leucopenia	A decreased number of white blood cells in the blood.
mutagenic	The ability to increase the occurrence of mutations.
mutation	An alteration in genes or chromosomes of a living cell giving rise to genetic change.
mydriasis	Dilated pupils.
myelin	White, fatty substance acting as an electrical insulator around nerves.
myelofibrosis	Replacement of the bone marrow by fibrous tissue.
myocardium	The muscular component of the heart.

necrosis	Localised death of tissue.
neoplasm	Abnormal and uncontrolled proliferation of a group of cells within the body.
neoplastic	Pertaining to or like a neoplasm.
neuropathy	A decrease in the function of a nerve.
NIOSH	The National Institute for Occupational Safety and Health (NIOSH) is the Federal agency in the USA responsible for conducting research and making recommendations for the prevention of work-related disease and injury.
nystagmus	An involuntary, rapid, repetitive, to and fro movement of the eyes.
occluded	To fit close together, to obstruct or close off.
occupational exposure limit	The concentration in air of a chemical in the workplace that is thought to be safe. This means that most workers can be exposed at the given concentration or lower without harmful effects.
oligospermia	Reduction in the number of sperm in the semen.
oliguria	Excretion of a reduced amount of urine (less than 400 ml per day).
pancytopenia	Reduction in the number of platelets, red blood cells and white blood cells (i.e. a reduction in all blood cell types).
paraesthesia	Any abnormality of sensation, usually in the form of 'pins and needles'.
peripheral neuropathy	Any disease of the peripheral nerves.
petechiae	Small, pinpoint purplish spots caused by haemorrhage.
phenobarbital pretreatment	Prior dosing with the enzyme-inducing drug phenobarbital.
platelets	A disc shaped blood component involved in the blood clotting process.
poikilothermia	The variation of body temperature with environmental temperature.
polycythaemia	An absolute increase in the number of red blood cells.
polyneuropathy	Disease which involves several nerves.
prothrombin time	A laboratory measurement of the time taken for blood to clot.
proximal	Nearest to the head.
pyrexia	Fever.
rhabdomyolysis	Disintegration of the muscle.
rhinorrhoea	Nasal discharge.
RTECS	The Registry of Toxic Effects of Chemical Substances (RTECS®) is a database of toxicological information compiled, maintained, and updated by the National Institute for Occupational Safety and Health (NIOSH) in the USA. The RTECS® database was mandated by the Occupational Safety and Health Act of 1970.
sister chromatid	The two chromatids of a chromosome held together by a centromere.
sister chromatid exchange	The reciprocal exchange of genetic material between sister chromatids resulting in a change in the morphology of the chromosome.

steatosis	Fatty degeneration.
tachypnoea	Increased frequency of respiration (breathing).
taurolithocholate	A bile salt.
teratogen	A substance which causes physical defects in the developing embryo.
threshold limit value	A term used by ACGIH to express the airborne concentration of a material to which nearly all workers can be exposed day after day without adverse effects. 'Workers' means healthy individuals.
time-weighted average	The Threshold Limit Value-Time Weighted Average is the concentration that could be tolerated by an average worker for a 40 hour work week (8 hours a day, 5 days a week). Workers could be expected to tolerate such exposures repeatedly, day after day, without adverse symptoms.
toxicity	The ability of a substance to cause damage to living tissue.
UN number	A number assigned to chemicals by the United Nations.
vesiculation	The process of blistering.

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