



# HPA Compendium of Chemical Hazards

## Methanol

### Key Points

#### Fire

- Flammable; burns with a non-luminous, bluish flame.
- May explode upon mixing with air
- In the event of a fire involving methanol, use alcohol resistant foam or fine water spray and liquid-tight chemical protective suit with breathing apparatus

#### Health

- Absorbed via ingestion, inhalation and skin exposure
- Toxic
- Short-term exposure may result in drowsiness, headache, confusion, vomiting and abdominal pain, possibly within 30 minutes of exposure
- Coma, shock and renal failure may occur following substantial exposures
- Short-term exposure may be irritating to the eyes, causing burning, stinging and lacrimation
- Long-term effects may include blindness, and following more substantial exposures, permanent damage to the central nervous system may occur
- Long-term inhalation exposure to methanol may cause headaches and eye irritation
- Methanol is not considered to be mutagenic or carcinogenic in humans
- Methanol is not considered to affect human reproduction or cause damage to the unborn child

#### Environment

- Avoid release into the environment
- Inform the Environment Agency of substantial releases

## Contents

### GENERAL INFORMATION

Background .....	5
Frequently Asked Questions.....	6

### INCIDENT MANAGEMENT

Hazard Identification .....	9
Standard (UK) Dangerous Goods Emergency Action Codes	9
Chemical Hazard Information and Packaging for Supply Classification	10
Globally Harmonised System of Classification and Labelling of Chemicals (GHS)	11
Published Emergency Response Guidelines.....	14
Emergency Response Planning Guideline (ERPG) Values	14
Interim Acute Exposure Guideline Levels (AEGs)	14
Exposure Standards, Guidelines or Regulations .....	15
Occupational standards	15
Public health guidelines	15
Health Effects .....	16
Major routes of exposure	16
Immediate signs or symptoms of acute exposure	16
Decontamination and First Aid.....	17
Dermal exposure'	17
Ocular exposure	17
Inhalation	17
Ingestion	17

### TOXICOLOGICAL OVERVIEW

Toxicological Overview .....	20
Summary of Health Effects	20
Kinetics and metabolism	21
Sources and route of human exposure	21
Health Effects of Acute / Single Exposure .....	22
Human Data	22
General toxicity .....	22
Inhalation .....	22
Ingestion .....	23
Dermal / ocular exposure .....	23
Delayed effects following an acute exposure .....	23
Animal and In-Vitro Data	24

Inhalation .....	24
Ingestion .....	24
Dermal .....	25
Health Effects of Chronic / Repeated Exposure .....	26
Human Data .....	26
General toxicity .....	26
Inhalation .....	26
Dermal .....	26
Genotoxicity .....	26
Carcinogenicity .....	26
Reproductive and developmental toxicity.....	26
Animal and In-Vitro Data .....	27
Inhalation .....	27
Ingestion .....	27
Genotoxicity .....	27
Carcinogenicity .....	27
Reproductive and developmental toxicity.....	27
References .....	29

# Methanol

## General information

### Key Points

#### Fire

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- May explode upon mixing with air
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#### Health

- Absorbed via ingestion, inhalation and skin exposure
- Toxic
- Short-term exposure may result in drowsiness, headache, confusion, sickness and abdominal pain, possibly within 30 minutes of exposure
- Coma, shock and kidney failure may occur following substantial exposures
- Short-term exposure may be irritating to the eyes, causing burning, stinging and watering
- Long-term effects may include blindness, and following more substantial exposures, permanent damage to the central nervous system may occur
- Long-term inhalation exposure to methanol may cause headaches and eye irritation
- Methanol is not thought to cause cancer in humans
- Methanol is not considered to affect human reproduction or cause damage to the unborn child

#### Environment

- Avoid release into the environment
- Inform the Environment Agency of substantial releases

## Background

Methanol is a clear, colourless, flammable liquid with slightly alcoholic odour. Methanol can be made by reacting hydrogen with carbon monoxide or carbon dioxide. Historically, it was made from distilling wood, and has therefore also been called wood alcohol.

There are many uses for methanol including the manufacture of other chemicals and in the production of paints, solvents, varnishes, paint thinners, certain cleaning solutions such as windscreen wash and some antifreeze solutions. Methanol is also used in certain fuel blends with petrol, and may be more used more as new fuels are sought. Because it is widely used, exposure may occur in a number of situations.



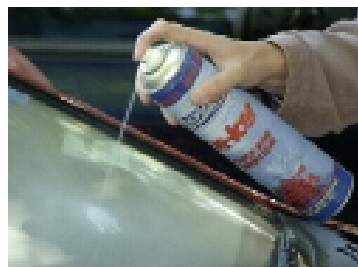
Exposure may occur in the workplace although safe limits are enforced to protect the employees. Such levels are below those that are thought to cause harmful effects.

In the home, methanol may be used in antifreeze and for powering small model engines. Methanol burns with a clear, almost invisible bluish flame. Methanol is also added in small quantities to alcohol to make methylated spirits or "meths"; this makes the alcohol unsuitable for human consumption.

Methanol is not a persistent chemical and is broken down in the environment.

Methanol is more harmful than ethanol (alcohol) and drinking it can be very dangerous. Drinking methanol may cause serious health effects including blindness and can cause death. Methanol is an irritant and splashes in the eyes may cause

stinging. Children may be more sensitive to the effects of methanol due to their smaller size.



Methanol may cause harm to the unborn child if the mother is exposed to large amounts. Exposure to small amounts of methanol is unlikely to have effects on the unborn child.

Methanol or its solutions are not classified as carcinogens; methanol is not considered to be a cancer causing agent

## Frequently Asked Questions

### *What is methanol?*

Methanol is a clear, colourless, flammable liquid with a slightly alcoholic odour.

### *How does methanol get into the environment?*

Methanol may enter the environment from industrial sources, such as factory effluent.

### *How will I be exposed to methanol?*

Exposure to methanol may occur if it is used at your work or if you use methanol containing products at home. Low level exposure also occurs from the diet due to the small amount naturally present in fruit and vegetables.

### *If there is methanol in the environment will I have any adverse health effects?*

The presence of methanol in the environment does not always lead to exposure. Clearly, in order for it to cause any adverse health effects you must come into contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact. Following exposure to any chemical, the adverse health effects you may encounter depend on several factors, including the amount to which you are exposed (dose), the way you are exposed, the duration of exposure, the form of the chemical and if you were exposed to any other chemicals.

Methanol is not persistent and it is quickly broken down in the environment. It is unlikely that environmental contamination will have any adverse health effects.

### *Can methanol affect my health?*

Drinking even small amounts of methanol is dangerous and can cause serious health effects including coma, convulsions, and blindness and may even cause death. Methanol is also toxic by inhalation; deliberately inhaling methanol is dangerous, can permanently damage eyesight and could cause death. Methanol is an irritant and splashing it in the eyes could cause stinging, though this should not lead to permanent damage.

### *Can methanol cause cancer?*

Methanol or its solutions are not classified as carcinogens; they are not considered to be cancer-causing chemicals.

### *Does methanol affect children or damage the unborn child?*

Methanol may affect children in the same way as adults, but they may more sensitive due to their smaller size. Methanol stored at home should therefore be kept out of the reach of children and in an appropriate container.

Methanol can cause harm to the unborn child if the mother is exposed to large amounts. Exposure to low levels of methanol is unlikely to have effects on the unborn child.

### *What should I do if I am exposed to methanol?*

You should remove yourself from the source of exposure.

If you have got methanol on your skin, remove soiled clothing, wash the affected area with lukewarm water and soap for at least 10 – 15 minutes and seek medical advice.

If you have got methanol in your eyes, remove contact lenses, irrigate the affected eye with lukewarm water for at least 10 – 15 minutes and seek medical advice.

If you have inhaled or ingested methanol seek medical advice.

# Methanol

# Methanol

## Incident management

### Key Points

#### **Fire**

- Flammable; burns with a non-luminous, bluish flame.
- Methanol forms an explosive mixture with air due to its low flash point
- In the event of a fire involving methanol, use alcohol resistant foam or fine water spray and liquid-tight chemical protective suit with breathing apparatus

#### **Health**


- Ingestion, inhalation and skin absorption are the main routes of exposure
- Toxic
- Exposure causes headache, confusion, vertigo, ataxia, drowsiness, nausea, vomiting and abdominal pain. Convulsions and coma are seen in severe toxicity
- May be directly irritating to the eyes causing an immediate stinging and burning sensation with lacrimation, as well as blurred vision with the appearance of a 'snow field' and photophobia

#### **Environment**

- Avoid release into the environment
- Inform Environment Agency of substantial release incidents

## Hazard Identification

### Standard (UK) Dangerous Goods Emergency Action Codes<sup>(a)</sup>

<b>UN</b>		<b>1230</b>	Methanol	
<b>EAC</b>		<b>•2WE</b>	Use alcohol resistant foam but, if not available, fine water spray. Wear liquid-tight chemical protective clothing in combination with breathing apparatus*. Spillages and decontamination run-off should be prevented from entering drains and watercourses. Substance can be violently or explosively reactive. There may be a public safety hazard outside the immediate area of the incident**.	
<b>APP</b>		<b>A(fl)</b>	Gas-tight chemical protective suit with breathing apparatus***	
<b>Hazards</b>	<b>Class</b>	<b>3</b>	Flammable liquid	
	<b>Sub risks</b>	<b>6.1</b>	Toxic substance	
<b>HIN</b>		<b>336</b>	Highly flammable liquid, toxic	

UN – United Nations number; EAC – Emergency Action Code; APP – Additional Personal Protection; HIN - Hazard Identification Number



\* Liquid-tight chemical protective clothing (BS 8428) in combination self-containing open circuit positive pressure compressed air breathing apparatus (BS EN 137).

\*\* People should stay indoors with windows and doors closed, ignition sources should be eliminated and ventilation stopped. Non-essential personnel should move at least 250 m away from the incident.

\*\*\* Gas-tight chemical protective clothing conforming to BS EN 943 part 2 in combination with self-contained open circuit positive pressure compressed air breathing apparatus to BS EN 137.

<sup>a</sup> Dangerous Goods Emergency Action Code List, HM Fire Service Inspectorate, Publications Section, The Stationery Office, 2009.

*Chemical Hazard Information and Packaging for Supply Classification<sup>(a)</sup>*

<b>Classification</b>	<b>F</b>	Highly flammable	
	<b>T</b>	Toxic	
<b>Risk phrases</b>	<b>R11</b>	Highly flammable	
	<b>R23/24/25</b>	Toxic by inhalation, in contact with skin and if swallowed	
	<b>R39/23/24/25</b>	Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed	
<b>Safety phrases</b>	<b>S1/2</b>	Keep locked up and out of reach of children	
	<b>S7</b>	Keep container tightly closed	
	<b>S16</b>	Keep away from sources of ignition – No smoking	
	<b>S36/37</b>	Wear suitable protective clothing and gloves	
	<b>S45</b>	In case of accident or if you feel unwell seek medical advice immediately (show the label where possible)	




*Specific concentration limits*

Concentration	Classification
<b>C ≥ 20 %</b>	T; R23/24/25
<b>3 % ≤ C &lt; 20 %</b>	Xn; R20/21/22
<b>C ≥ 10 %</b>	T; R39/23/24/25
<b>3 % ≤ C &lt; 10 %</b>	Xn; R68/20/21/22

<sup>a</sup> Annex VI to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures- Table 3.2.

<http://esis.jrc.ec.europa.eu/index.php?PGM=cla> (accessed 11/2011)

*Globally Harmonised System of Classification and Labelling of Chemicals (GHS)<sup>(a)\*</sup>*

<b>Hazard Class and Category</b>	Flam. Liq. 2	Flammable liquid, category 2	
	Acute Tox. 3	Acute toxicity (oral, dermal, inhalation), category 3	
	STOT SE 1	Specific target organ toxicity following single exposure, category 1	
<b>Hazard Statement</b>	<b>H225</b>	Highly flammable liquid and vapour	
	<b>H331</b>	Toxic if inhaled	
	<b>H311</b>	Toxic in contact with skin	
	<b>H301</b>	Toxic if swallowed	
	<b>H370**</b>	Causes damage to organs	
<b>Signal Words</b>	DANGER		

\* Implemented in the EU on 20 January 2009.

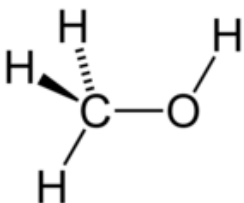
*Specific concentration limits and M factors*

Concentration	Hazard Class and Category	Hazard Statement	
C ≥ 10 %	STOT SE 1	<b>H370</b>	Causes damage to organs
3 % ≤ C < 10 %	STOT SE 2	<b>H371</b>	May cause damage to organs

<sup>a</sup> Annex VI to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures- Table 3.1.

<http://esis.jrc.ec.europa.eu/index.php?PGM=cla> (accessed 11/2011)

## Physicochemical Properties

<b>CAS number</b>	67-56-1
<b>Molecular weight</b>	32
<b>Empirical formula</b>	CH <sub>3</sub> OH
<b>Common synonyms</b>	Methyl alcohol; Wood alcohol; Carbinol
<b>State at room temperature</b>	Liquid
<b>Volatility</b>	Vapour pressure = 100 mm Hg at 21.2 °C
<b>Specific gravity</b>	0.8 at 20 °C (water = 1); vapours are lighter than air at room temperature
<b>Flammability</b>	Flammable: burns with a non-luminous, bluish flame.
<b>Lower explosive limit</b>	6%
<b>Upper explosive limit</b>	36.5%
<b>Water solubility</b>	Fully soluble in water
<b>Reactivity</b>	Methanol forms an explosive mixture with air due to its low flash point. Methanol is incompatible with beryllium dihydride, metals (such as potassium and magnesium), oxidants (such as barium perchlorate, bromine, sodium hypochlorite, chlorine, and hydrogen peroxide), potassium tert-butoxide, carbon tetrachloride + metals (such as aluminum, magnesium, and zinc), and dichloromethane. Attacks some plastics, rubber, and coatings.
<b>Reaction or degradation products</b>	Data not available
<b>Odour</b>	Slight alcoholic odour
<b>Structure</b>	

References<sup>(a,b,c)</sup>

<sup>a</sup> Methanol (HAZARDTEXT® Hazard Management). In: Klasco RK (Ed): TOMES® System. Thomson Micromedex, Greenwood Village, Colorado (accessed 02/2010).

<sup>b</sup> The Merck Index (14<sup>th</sup> Edition). Entry 5957, 2006.

<sup>c</sup> The Dictionary of Substances and their Effects. Ed. S Gangolli. Second Edition, Volume 5, 1999.

**Threshold Toxicity Values**

<b>EXPOSURE VIA INHALATION</b>		
<b>ppm</b>	<b>mg m<sup>-3</sup></b>	<b>SIGNS AND SYMPTOMS</b>
<b>300</b>	<b>393</b>	Visual changes, headache; lung, thorax or respiration changes
<b>65627</b>	<b>86000</b>	Lacrimation, cough, changes of the lung, thorax, or respiration

Reference<sup>(a)</sup>

<sup>a</sup> Methanol (MEDITEXT® Medical Management). In: Klasco RK (Ed): TOMES® System. Thomson Micromedex, Greenwood Village, Colorado (accessed 02/2010).

## Published Emergency Response Guidelines

### Emergency Response Planning Guideline (ERPG) Values<sup>(a)</sup>

	Listed value (ppm)	Calculated value (mg m <sup>-3</sup> )
<b>ERPG-1*</b>	200	262
<b>ERPG-2**</b>	1000	1310
<b>ERPG-3***</b>	5000	6552

\* Maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hr without experiencing other than mild transient adverse health effects or perceiving a clearly defined, objectionable odour.

\*\* Maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hr without experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action.

\*\*\* Maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hr without experiencing or developing life-threatening health effects.

### Interim Acute Exposure Guideline Levels (AEGs)<sup>(b)</sup>

	ppm				
	10 min	30 min	60 min	4 hr	8 hr
<b>AEGL-1<sup>†</sup></b>	670	670	530	340	270
<b>AEGL-2<sup>††</sup></b>	11000 <sup>◇</sup>	4000	2100	730	520
<b>AEGL-3<sup>†††</sup></b>	◇◇	14000 <sup>◇</sup>	7200 <sup>◇</sup>	2400	1600

<sup>†</sup> The level of the chemical in air at or above which the general population could experience notable discomfort.

<sup>††</sup> The level of the chemical in air at or above which there may be irreversible or other serious long-lasting effects or impaired ability to escape.

<sup>†††</sup> The level of the chemical in air at or above which the general population could experience life-threatening health effects or death.

Lower explosion Limit (LEL) = 55000 ppm

◇ ≥ 10 % LEL; > 50 % LEL

◇◇ 3 – 10 min = 40000ppm

<sup>a</sup> American Industrial Hygiene Association (AIHA). 2010 Emergency Response Planning Guideline Values and Workplace Environmental Exposure Level Guides Handbook, Fairfax, VA (accessed 01/2011).

<sup>b</sup> U.S. Environmental Protection Agency. Acute Exposure Guideline Levels, <http://www.epa.gov/oppt/aegl/pubs/chemlist.htm> (accessed 01/2011)..

## Exposure Standards, Guidelines or Regulations

### *Occupational standards*

<b>WEL<sup>(a)</sup></b>	LTEL (8 hour reference period): 200 ppm (266 mg m <sup>-3</sup> )
	STEL (15 min reference period): 250 ppm (333 mg m <sup>-3</sup> )

### *Public health guidelines*

<b>DRINKING WATER QUALITY GUIDELINE</b>	No guideline value specified
<b>AIR QUALITY GUIDELINE</b>	No guideline value specified
<b>SOIL GUIDELINE VALUE AND HEALTH CRITERIA VALUES</b>	No guideline value specified

WEL – Workplace exposure limit; LTEL - Long-term exposure limit; STEL – Short-term exposure limit

<sup>a</sup> List of approved workplace exposure limits (as consolidated with amendments October 2007). <http://www.hse.gov.uk/cosHH/table1.pdf> (An update to EH40/2005: Workplace Exposure Limits 2005. The Stationery Office, London) (accessed 01/2011).

## Health Effects

### *Major routes of exposure<sup>(a)</sup>*

- Toxic by ingestion, inhalation and skin absorption.

### *Immediate signs or symptoms of acute exposure<sup>(b,c)</sup>*

- Methanol is an alcohol and will cause features of intoxication.
- Ingestion causes ataxia, drowsiness, dysarthria, nystagmus within 30 minutes, followed by a latent period of 12 – 24 hours before metabolic toxicity becomes apparent. Poor prognostic features include convulsions, coma, shock, persistent acidosis, bradycardia and renal failure.
- Central nervous system effects include headache, confusion and vertigo occur with mild to moderate toxicity. Convulsions and coma are seen in severe toxicity.
- Common gastrointestinal features include nausea, vomiting and abdominal pain. Acute pancreatitis can occur.
- Other common features include blurred vision, with the appearance of a "snow field", and photophobia. Optic disc and retinal oedema occur with diminished pupillary light response.
- A severe metabolic acidosis with an increased anion and osmolal gap is usually seen. Tachypnoea is common. Hyperglycaemia may occur. Renal failure may develop in severe cases.
- Eye exposure may cause eye irritation and immediate stinging and burning sensation with lacrimation.

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TOXBASE - <http://www.toxbase.org> (accessed 01/2011)

<sup>a</sup> TOXBASE: Methanol, 12/2009.

<sup>b</sup> TOXBASE: Methanol – features and management, 07/2010.

<sup>c</sup> TOXBASE: Eye irritants, 05/2002.

## Decontamination and First Aid

### Important Notes

- Ambulance staff, paramedics and emergency department staff treating chemically-contaminated casualties should be equipped with Department of Health approved, gas-tight (Respirex) decontamination suits based on EN466:1995, EN12941:1998 and prEN943-1:2001, where appropriate.
- Decontamination should be performed using local protocols in designated areas such as a decontamination cubicle with adequate ventilation.
- Flammability warning: prevent exposure to all sources of ignition such as naked flames, electrical equipment, oxidising chemicals and the smoking of tobacco products.

### Dermal exposure<sup>(a,b)</sup>

- Remove patient from exposure.
- The patient should remove all clothing and personal effects.
- Double-bag soiled clothing and place in a sealed container clearly labelled as a biohazard.
- Gently blot away any adherent liquid from the patient.
- Wash hair and all contaminated skin with copious amounts of water (preferably warm) and soap for at least 10-15 minutes. Decontaminate open wounds first and avoid contamination of unexposed skin.
- Pay special attention to skin folds, axillae, ears, fingernails, genital areas and feet.
- Ensure clear airway and adequate ventilation, particularly if there is depression of conscious level.

### Ocular exposure<sup>(c)</sup>

- Remove patient from exposure.
- Remove contact lenses if necessary and immediately irrigate the affected eye thoroughly with water or 0.9% saline for at least 10-15 minutes.
- Patients with corneal damage or those whose symptoms do not resolve rapidly should be referred for urgent ophthalmological assessment.

### Inhalation<sup>(a)</sup>

- Ensure a clear airway and adequate ventilation,
- Monitor pulse, blood pressure, respiratory rate, cardiac rhythm and urine output. Perform a 12 lead ECG.
- Apply other measures as indicated by the patient's clinical condition.

### Ingestion<sup>(d)</sup>

- Ensure a clear airway and adequate ventilation,

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TOXBASE - <http://www.toxbase.org> (accessed 01/2011)

<sup>a</sup> TOXBASE: Methanol 12/2009.

<sup>b</sup> TOXBASE: Methanol – features and management, 07/2010.

<sup>c</sup> TOXBASE: Eye irritants, 05/2002.

<sup>d</sup> TOXBASE: Methanol – features and management, 07/2010.

- Consider gastric aspiration if the patient presents within 1 hour of ingestion. Charcoal is of no use since it does not adsorb significant quantities of methanol.
- Monitor pulse, blood pressure, respiratory rate, cardiac rhythm and urine output. Perform a 12 lead ECG.
- For patients with methanol intoxication, early administration of [fomepizole](#) or [ethanol](#) will minimise the further metabolism of methanol and the development of clinical and metabolic complications. This means that treatment usually needs to be started before the diagnosis has been confirmed.
- Apply other measures as indicated by the patient's clinical condition.

# Methanol

## Toxicological overview

### Key Points

#### *Kinetics and metabolism*

- Readily absorbed by all routes and distributed in the body water
- Undergoes extensive metabolism, but small quantities are excreted unchanged in the lungs and in the kidneys
- Excretion of methanol is relatively slow ( $t_{1/2}$  is about 24 h) and is primarily as formic acid in the urine

#### *Health effects of acute exposure*

- Methanol is toxic following ingestion, inhalation or percutaneous exposure
- Exposure may initially result in CNS depression, followed by an asymptomatic latent period
- Metabolic acidosis and ocular toxicity, which may result in blindness are subsequent manifestations of toxicity
- Coma and death may occur following substantial exposures
- Long term effects may include blindness and following more substantial exposures, permanent damage to the CNS.

#### *Health effects of chronic exposure*

- Long term inhalation exposure to methanol may cause headaches and eye irritation
- Methanol is considered not to be a mutagen or carcinogen in humans
- Methanol is considered not to be a reproductive toxicant in humans

## Toxicological Overview

### Summary of Health Effects

Methanol may be acutely toxic following inhalation, oral or percutaneous exposure.

Acute toxicity from methanol manifests as CNS depression, followed by a latent period of varying duration from 8-36 h and occasionally up to 48 h. Subsequently, metabolic acidosis develops, superimposed with headache, nausea and features of ocular toxicity. Ocular toxicity may range from photophobia and misty or blurred vision to markedly reduced visual acuity and complete blindness; ingestion of as little as 4-10 mL methanol in adults may cause permanent damage [1].

Coma and death may occur after substantial exposures. The minimal lethal dose following ingestion is considered to be in the range of 300-1000 mg kg<sup>-1</sup> [2]. Severe intoxication, if survived, may cause permanent damage to the CNS, manifest as a Parkinsonian-like condition and permanent blindness [2].

There is limited data on the effects of chronic effects of methanol exposure in humans. However, chronic inhalation exposure to low concentrations of methanol may result in headache and eye irritation.

There are no data on the mutagenicity of methanol in humans. However, methanol has no structural alerts for mutagenicity and *in-vitro* animal studies are negative [2], which indicate that methanol is unlikely to be a human mutagen.

Methanol is not classified as a mutagen or carcinogen in humans.

Methanol is not classified as a human reproductive toxicant. However, fetal toxicity may arise secondary to maternal toxicity. Findings from animal studies may indicate possible risks to the human fetus at early stages of development due to the similarity of early embryonic processes [3]; however, non-primate metabolism of methanol is distinct from human metabolism and this should be considered when determining risks to humans. It is unlikely that exposure to low concentrations of methanol would result in adverse effects in the fetus, though exposure should be minimised.

## ***Kinetics and metabolism***

Methanol is readily absorbed by inhalation, ingestion and dermal exposure [2]. Around 60-80% of inhaled methanol is absorbed in the lung of humans.

Distribution is rapid and occurs throughout body water as indicated by a volume of distribution of approximately  $0.6 \text{ L kg}^{-1}$  [2]; individual tissue and organ concentrations are dependent on their water content. Following ingestion, peak serum concentrations are obtained within 30-90 min [2]. There is no protein binding and methanol is poorly distributed to fatty tissues [1].

In humans and primates, toxicity of methanol is mediated via metabolites and not the parent molecule. The liver is the primary site of metabolism for methanol. Through a series of oxidative steps methanol is oxidised to methanal (HCHO, formaldehyde), methanoic acid (H•COOH, formic acid) and finally detoxified to carbon dioxide (CO<sub>2</sub>). The main enzyme groups involved in each step are alcohol dehydrogenase, aldehyde dehydrogenase, and folate dependent mechanisms, respectively. Methanoate (formate) or methanoic acid (formic acid) may be formed, dependent on pH [2]. The term “formic acid” and not methanoic acid persists in the literature and will therefore be used in this text for compatibility. Formic acid is considered to be the key toxicant; and in animal species with a poor ability to metabolise this product (primates and humans) fatal toxicity may occur from metabolic acidosis and neuronal toxicity [2]. Un-dissociated formic acid readily crosses the blood brain barrier leading to CNS toxicity, aggressive alkaline therapy is required to maintain formic acid in the dissociated form [1].

As a moderate inhibitor of cytochrome c oxidase, formate may cause tissue oxygen utilisation to be impaired leading to anaerobic respiration with subsequent increased lactate production, which may further contribute to the acidosis [1].

The relative affinity of alcohol dehydrogenase for ethanol is much greater than for methanol (20:1) [2]. This difference has been exploited therapeutically in cases of poisoning, where alcohol is administered under medical supervision to reduce the formation of formic acid. A selective enzyme inhibitor such as Fomepizole may also be used to block the metabolism of methanol.

Elimination of methanol as formic acid occurs primarily via urinary excretion. At high concentrations, methanol elimination is saturated and is zero order with a rate of approximately  $85 \text{ mg L}^{-1}$ , about half the elimination rate of ethanol. Maximum excretion of formic acid may be as late as the second or third day following ingestion [2]. Small quantities of methanol are excreted unchanged in the lung and the kidneys (2% of a dose of  $50 \text{ mg kg}^{-1}$ ). Concentration of methanol in the urine may be 20-30% higher than in the blood [2].

## ***Sources and route of human exposure***

Inhalation and dermal exposure are the major routes of exposure to methanol. Accidental or deliberate ingestion of methanol is less common.

## Health Effects of Acute / Single Exposure

### Human Data

#### General toxicity

Humans (and primates) are particularly sensitive to toxicity from methanol when compared to non-primates. The severity of toxicity following exposure has been correlated with the degree of metabolic acidosis rather than to the concentration of methanol [1]. This is due to toxicity being determined primarily by the rate of formic acid formation and hepatic folate status which governs its detoxification. Key features include metabolic acidosis, ocular toxicity, central nervous system depression and coma: methanol intoxication may be fatal.

Key phases of methanol toxicity are summarised below [1, 2, 4]:

Phase	Comments
<b>Central Nervous System depression</b>	Onset of 30 min - 2 h; intoxication may be of shorter duration and less pronounced than that arising from ethanol ingestion
<b>Asymptomatic latent period</b> following central depression	This period of varying duration: may last 8-24 h following ingestion, but occasionally up to 48 h. Patients describe no overt symptoms or have signs during this period
<b>Severe metabolic acidosis</b> occurs after latent phase	Nausea, vomiting and headache may also occur and may be superimposed on the visual toxicity described below
<b>Ocular toxicity</b> followed by blindness, coma and in extreme cases death.	Visual disturbances generally develop 12-48 h after ingestion and range from mild photophobia and misty or blurred vision to markedly reduced visual acuity and complete blindness. Visual impairment usually takes the form of central scotoma or complete blindness secondary to optic atrophy.

Both Industrial Methylated Spirit (IMS or “meths”) and surgical spirit contain primarily ethanol and only small percentages of methanol (ca 5%). Unless exposure occurs to large volumes, e.g. from a substantial deliberate ingestion of methylated spirits, for instance, ocular findings are unlikely [5].

#### Inhalation

Inhalation of high concentrations of methanol vapour can cause acute toxicity, as described in the general toxicity section.

Toxicity has been associated with the inhalation of methanol concentrations greater than 400 mg m<sup>-3</sup> (300 ppm). Deliberate inhalation of volatile preparations containing methanol may cause toxicity, in a series of four such cases, one patient was found on ophthalmic examination to have hyperaemic discs and decreased visual acuity [2, 6].

## **Ingestion**

Ingestion of methanol can cause severe acute toxicity, as described in the general toxicity section.

There is significant variability within humans on the reported oral toxicity and lethality of methanol. The minimal lethal dose following ingestion is considered to be in the range of 300-1000 mg kg<sup>-1</sup> [2]. In one review, the minimum lethal dose following ingestion has been reported at 15 mL of a 40% v/v methanol solution [4]. Another individual is reported to have survived ingestion of 500 mL of the same solution. A significant confounding matter may be the concomitant ingestion of ethanol, which may have mitigated some of the methanol toxicity, as understood from its use as an antidote in methanol intoxication. Ingestion of as little as 4-10 mL methanol in adults may cause permanent blindness [1].

In one clinical case; a pregnant women (35 weeks gestation) was reported to have ingested 250-500 mL of methanol [7]. After 1 hour of uncomplicated labour on day 6 of admission and treatment, the patient delivered a child who had no signs of distress and with Apgar scores of 9/10 at 1 min and 10/10 after 5 min. The clinical course was uneventful in both the child and mother and no visual disturbances developed in the child within a follow up of 10 years [7]. This case highlights the potential for a positive outcome following acute maternal intoxication with methanol where interventions are initiated rapidly.

## **Dermal / ocular exposure**

Methanol may be absorbed across the skin and can result in systemic toxicity. Methanol is also irritating to skin and may cause dry skin and redness [8].

Percutaneous absorption has been noted to cause toxicity in children. In a case series of 48 intoxicated patients; 30 had severe respiratory depression, 14 were comatose, 11 had seizures, 7 had anuria or severe oligouria; there were 12 deaths [2]. In Egypt, a number of neonates died of severe metabolic acidosis following dermal exposure to methanol which was the main constituent of a compress used to relieve fever. The compresses were made using a local product termed “red-alcohol” which on analysis was found to have contained methanol (70-90% v/v) [9].

Contact of methanol with the eyes may result in irritation only [2]: the ocular toxicity described previously is mediated by systemic and not local ocular exposure.

## **Delayed effects following an acute exposure**

The latent periods reported are of widely varying duration. The delayed onset of ocular toxicity and acidosis thereafter is also variable. Visual impairment or blindness arising may be permanent. Damage to the CNS is often in the form of lesions in basal ganglia especially the putamen, which may result in long term neurological deficits ranging from moderate polyneuropathy to tremors, rigidity, spasticity and hypokinesia as well as Parkinsonian-like extrapyramidal syndrome with mild dementia. [2, 10-12]. Some of these effects may be reversible; in one case of acute intoxication, a follow up at one month showed increased cognitive function and only a mild lower extremity tremor [11].

## ***Animal and In-Vitro Data***

Due in part to metabolic differences, lower-order animal species such as the rat exhibit different responses to methanol than humans. Methanol and not its metabolites predominates as the key toxicant; with features of CNS depression a common finding. The key findings in humans of metabolic acidosis and ocular toxicity are normally not seen. Thus, extrapolation from animal studies to human findings must be performed with caution.

Non-human primates, such as rhesus monkeys, are sensitive to methanol and acidosis and ocular findings have been reported. Consequently, primate data is the focus of much of the animal toxicology section.

### **Inhalation**

Methanol has been demonstrated as toxic via inhalation exposure in a number of animal species. Acute inhalation exposure has been associated with degeneration and necrosis of parenchymal tissues and neurons, accompanied by capillary congestion and oedema in rats, a rabbits and monkeys [2]. In one early study using primates, death was reported following exposure to 1000 ppm; however, the duration of exposure was not cited [13]. This is at odds with a more recent study which did not report any ocular toxicity by ophthalmic examination in monkeys exposed to 6500 mg/m<sup>3</sup> (5000 ppm) for 6 h/day, 5 days a week for a total of 4 weeks [2]. Considering the chronic exposures (described below) the results from the former study need to be considered with some caution as exposures in excess of 1000 ppm have been tolerated by monkeys in other studies.

Most data in the literature concerns chronic exposure to methanol.

### **Ingestion**

A minimum lethal dose of 3 g kg<sup>-1</sup> has been reported for the rhesus monkey (*Macaca mulatta*) [14]. The authors note, however, that the series of experiments was too small to give more than an approximate lethal dose, especially since there is likely to be considerable inter-individual variation in their response to methanol. The authors conclude that though approximate, the primate data would suggest that single oral lethal dose is of the same order of magnitude as those for humans. Clinical observations in the animals were considered to have been akin to those in humans. Inebriation was not observed below lethal doses but CNS depression was apparent at higher dose levels. This was followed by a latent period and progressive weakness, coma and death from respiratory failure. Two animals of four monkeys receiving lethal doses of methanol had ocular changes. In one animal, receiving 6 g kg<sup>-1</sup> bodyweight of methanol, a small monocular retinal haemorrhage was noted prior to death and 29 h after dosing. The other animal, receiving 3 g kg<sup>-1</sup> bodyweight, had slight but definite blurring of the temporal disc margins which were blurred everywhere except nasally at 31½ h after dosing. At the time of assessment, both animals were apparently too weak to resist handling; suggesting vascular changes did not arise from neck stricture. Animals receiving lethal doses were noted as severely acidotic within 24 h [14].

### Dermal

Methanol has been demonstrated to be toxic via dermal exposure in a number of animal species. In one early study using primates, following dosing with either 0.5 or 1.3 mL kg<sup>-1</sup> bodyweight applied four times daily toxicity was noted on the first day with death occurring on the second day [13]. The exposure model used minimised concomitant inhalation exposure [13].

## Health Effects of Chronic / Repeated Exposure

### Human Data

#### General toxicity

In contrast to the widely reported toxicity of acute intoxication, reports of effect following chronic exposure are infrequently reported [2].

#### Inhalation

Chronic exposure to methanol may cause persistent or recurring headaches and impaired vision [8].

In one study, blurred vision, headache, nausea, dizziness and eye irritation was experienced by workers using “spirit duplicators” (early document copying machines) at concentrations greater than 260 mg m<sup>-3</sup> [2]. The duration of exposures was, however, not quantified.

#### Dermal

Long term or repeated dermal exposures to methanol may cause dermatitis [8].

#### Genotoxicity

There are no studies in the literature that describe mutagenic or chromosomal effects of methanol in humans. There are no structural alerts for methanol and *in vitro* studies are negative (see next section on animal and in vitro data). Consequently, methanol is considered not to be a mutagen in humans.

#### Carcinogenicity

There is no data in the literature to indicate that methanol is carcinogenic in humans. Based on limited animal data, the lack of structural alerts and the lack of genotoxicity, methanol is not considered to be a carcinogen.

#### Reproductive and developmental toxicity

There is insufficient human data upon which to evaluate the developmental toxicity of methanol [3]. Methanol is not classified on the basis of its reproductive toxicity and is not considered to be a reproductive or developmental toxicant in humans. However, fetal toxicity may arise secondary to maternal toxicity. Findings from animal studies may indicate possible risks to the fetus at early stages of development but non-primate metabolism of methanol is distinct from human as indicated previously. It is unlikely that exposure to low concentrations of methanol would result in adverse affects in the fetus.

## ***Animal and In-Vitro Data***

### **Inhalation**

In a chronic inhalation study, monkeys were exposed to methanol concentrations of 13, 130 or 1300 mg m<sup>-3</sup> (10, 100 and 1000 ppm, respectively) for 22 h per day for up to 29 months. Body weight values and haematological and pathological examinations did not reveal any dose dependent effects except for hyperplasia of reactive astroglia in the nervous system. This effect was not correlated with dose or exposure time and was found to be a reversible effect within a recovery test [2].

### **Ingestion**

There is insufficient data on the toxicity of methanol *in vivo* following chronic ingestion of methanol.

### **Genotoxicity**

Methanol is not classified as a mutagenic compound; data indicate that it does not damage genetic material [2].

Methanol gave negative results for mutagenicity in a series of Ames tests in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and in *E. Coli* strain WP2uvrA [15].

Mice exposed by inhalation to methanol at 1050 or 5200 mg/m<sup>3</sup> (800 or 4000 ppm) had no increase in the frequency of micronuclei in red blood cells or sister chromosome exchanges (SCEs), chromosome aberrations or micronuclei in lung cells [2].

### **Carcinogenicity**

There is no evidence from animal studies to suggest that methanol is a carcinogen, although the lack of an appropriate animal model because of major differences in the metabolism of methanol between rodents and humans is recognised [2].

### **Reproductive and developmental toxicity**

With exposure to high concentrations, methanol is considered to be a developmental toxicant in rats and mice following both oral and inhalation exposure [2, 3]. The differences in metabolism in rodents when compared with primates must be considered when relating these findings to possible human exposures, as must the high dose levels used in these studies.

In one developmental toxicity study, prenatal exposure of pregnant mice on gestational days 6-15 to methanol vapour concentrations of 2000 ppm (ca 2600 mg m<sup>-3</sup>) or more caused an increased incidence of abnormalities including cleft palate, exencephaly and skeletal malformations [3]. In another developmental toxicity study using pregnant rats, exposure to 20,000 ppm (ca 26000 mg m<sup>-3</sup>) of methanol resulted in slight maternal toxicity and a high incidence of congenital malformations [16]. However, no adverse effects were noted in the

offspring of pregnant animals exposed to 5000 ppm (ca 6500 mg m<sup>-3</sup>) of methanol for the duration of gestation [16].

Methanol is developmentally toxic to both mouse and rat embryos during organogenesis in whole embryo culture (WEC) [2].

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This document will be reviewed not later than 3 years or sooner if substantive evidence becomes available.