



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 by the lungs and in the urine

Health effects of acute exposure

- methanol is toxic following ingestion, inhalation or dermal 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 has resulted in headaches and eye irritation in workers
- methanol is considered not to be a mutagen or carcinogen in humans
- methanol is considered not to be a reproductive toxicant in humans

Summary of Health Effects

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

Acute methanol toxicity often follows a characteristic series of features; initially central nervous system (CNS) depression and gastrointestinal tract (GI) irritation may be observed. This is typically followed by a latent period of varying duration from 12–24 hours and occasionally up to 48 hours. Subsequently, a severe metabolic acidosis develops with nausea, vomiting and headache.

Ocular toxicity ranges from photophobia and misty or blurred vision to markedly reduced visual acuity and complete blindness following high levels of exposure. Ingestion of as little as 4–10 mL of methanol in adults may cause permanent damage.

Coma and death may occur after substantial exposures. The minimal lethal dose following ingestion is considered to be in the range of 300–1,000 mg/kg. Severe intoxication may cause permanent damage to the CNS, manifesting as a Parkinsonian-like condition and permanent blindness.

Chronic inhalation exposure to low concentrations of methanol has resulted in headache and eye irritation in workers.

Methanol has no structural alerts for mutagenicity and in-vitro animal studies are negative. The limited data on the mutagenicity of methanol in humans, suggests that methanol is non-genotoxic.

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; 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.

Kinetics and Metabolism

Methanol is readily absorbed by inhalation, ingestion and dermal exposure [1, 2]. Following ingestion, methanol is absorbed within 30–60 minutes depending upon the presence or absence of food in the GI tract [1]. Around 60–80% of inhaled methanol is absorbed in the lung of humans [2].

Distribution is rapid and occurs throughout body water as indicated by a volume of distribution of approximately 0.6 L/kg [2]. Individual tissue and organ concentrations are dependent on their water content [2]. There is no protein binding and methanol is poorly distributed to fatty tissues [3].

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 (CO₂). The majority of an ingested dose of methanol (96.9%) is converted to carbon dioxide by this route [1]. 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. In humans and primates, toxicity of methanol is mediated through metabolites and not the parent molecule. 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 a profound anion gap metabolic acidosis and neuronal toxicity [2, 4]. 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 [3].

As a moderate inhibitor of cytochrome-c oxidase, formate may cause tissue oxygen use to be impaired, leading to anaerobic respiration with subsequent increased lactate production, which may further contribute to the acidosis [3].

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 [5].

The majority of metabolised methanol is ultimately excreted as carbon dioxide [1]. A minor portion of methanol is excreted unchanged in the urine or in exhaled air. The half-life for the systemic clearance of methanol has been reported to be 2.5–3 hours for doses less than 100 mg/kg bodyweight (bw) methanol, increasing to 24 hours or longer for doses greater than 1,000 mg/kg bw methanol [1].

Sources and Route of Human Exposure

Methanol is produced endogenously, as a result of intermediary metabolism. It is also present in the diet, notably in fruit and vegetables and their juices. Exposure to methanol at levels found in the diet would not be expected to result in adverse effects [1]. Low concentrations of methanol may be found in alcoholic beverages, although concentrations in products of illegal distillation may be much higher [1]. Exposure may also occur by the intentional or accidental ingestion of consumer products containing methanol, such as antifreeze, brake fluid and window cleaning solutions [6].

Inhalant misuse of volatile methanol-containing products may be a significant source of exposure to methanol [7]. In some countries methanol is used as a denaturant for ethanol; methanol intoxication has occurred in individuals intentionally consuming such mixtures [8].

Methanol is produced in large quantities worldwide and is used extensively as a solvent. Other notable uses are as a chemical intermediate and as a denaturant. Individuals who work in industries in which methanol is used may be chronically exposed to methanol vapours [3]. Workplace exposure limits (WELs) are enforced to protect workers from the harmful effects of methanol; in the UK the long-term WEL is 266 mg/m^3 (200 ppm) and the short-term WEL is 333 mg/m^3 (250 ppm) [9].

Health Effects of Acute/Single Exposure

Human data

General toxicity

Humans (and primates) are particularly sensitive to methanol toxicity 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 [3]. This is due to toxicity being determined primarily by the rate of formic acid formation and hepatic folate status which governs its detoxification. The key features include metabolic acidosis, ocular toxicity, CNS depression and coma (see table 1). Convulsions, coma, shock, persistent acidosis, bradycardia and renal failure are indicators of a poor prognosis [5]. Morbidity and mortality are high in methanol intoxication [4].

Table 1: Key features of methanol toxicity

Features	Comments
Initial CNS depression	Initial intoxication may resemble that arising from ethanol ingestion but of shorter duration and less pronounced. GI irritation may also occur
Asymptomatic latent period	May last 12–24 hours following ingestion, but occasionally up to 48 hours. Patients describe no overt signs or symptoms during this period
Severe metabolic acidosis	Nausea, vomiting and headaches may occur with acidosis
Ocular toxicity	Visual disturbances ranging from mild photophobia and “snowfield” vision to markedly reduced visual acuity and blindness may develop 12–48 hours after ingestion. Visual impairment usually takes the form of central scotoma or complete blindness secondary to optic atrophy
Delayed onset neuropathy	Symptoms occur 12–24 hours after exposure and include seizures, coma or cerebral oedema that may develop as a result of metabolic acidosis. Tremor, dementia, rigidity and bradykinesia have been observed
References [2-5, 10]	

Inhalation

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

Toxicity has been associated with the inhalation of methanol vapour at concentrations greater than 400 mg/m³ [2].

Deliberate inhalation of volatile preparations containing methanol may cause toxicity, in a series of four case reports, one patient was found on ophthalmic examination to have hyperaemic discs and decreased visual acuity [2, 11].

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 300–1,000 mg/kg [2]. In one review, the minimum lethal dose following ingestion has been reported at 15 mL of a 40% volume/volume (v/v) methanol solution [10]. Another individual is reported to have survived ingestion of 500 mL of the same solution. A significant confounding factor may be the concomitant ingestion of ethanol, which may have mitigated some of the methanol toxicity. Ingestion of as little as 4–10 mL methanol in adults may cause permanent blindness [3, 5]. CNS effects may occur from doses as low as 3–20 mL of methanol [12]. Other effects reported include acute pancreatitis and renal failure [5].

In one clinical case, a pregnant women (at 35 weeks' gestation) was reported to have ingested 250–500 mL of methanol [13]. 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 minute and 10/10 after 5 minutes. 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 [13]. 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 [14].

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 and 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) [15].

Contact of methanol with the eyes may result in irritation only; the ocular toxicity described previously is mediated by systemic and not local ocular exposure [3].

Delayed effects following acute exposure

Signs and symptoms of methanol poisoning may be delayed for up to 12–24 hours post-exposure. Ocular effects generally develop 12 – 48 hours following methanol ingestion [1]. Visual impairment or blindness 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, 16-18]. Long-term effects of methanol exposure may be reversible; in one case of acute intoxication, a follow up at 1 month showed increased cognitive function and only a mild lower extremity tremor [17].

Ethanol co-ingestion may lead to a delay in the onset of the metabolic toxic features due to competitive co-inhibition of alcohol dehydrogenase (please refer to the kinetics and metabolism section for more detail) [5].

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 – is 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 (*Macaca mulatta*), are sensitive to methanol and acidosis, 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 through 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, rabbits and monkeys [2]. In one early study using primates, death was reported following exposure to 1,310 mg/m³ (1,000 ppm); however, the duration of exposure was not cited [19]. This is at odds with a more recent study which did not report any ocular toxicity by ophthalmic examination in monkeys exposed to 6,500 mg/m³ for 6 hours a 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 1,310 mg/m³ (1,000 ppm) have been tolerated by monkeys in other studies.

Most animal and in-vitro data in the literature concerns chronic exposure to methanol.

Ingestion

A minimum lethal dose of methanol of 3 g/kg bw has been reported for the rhesus monkey [20]. 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, although approximate, the primate data would suggest that the single oral lethal dose is of the same order of magnitude as that 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 out of four

monkeys receiving lethal doses of methanol had ocular changes. In one animal, receiving a dose of methanol of 6 g/kg bw, a small monocular retinal haemorrhage was noted prior to death and 29 hours after dosing. The other animal, receiving 3 g/kg bw, had slight but definite blurring of the temporal disc margins which were blurred everywhere except nasally at 31.5 hours 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 hours [20].

Dermal/ocular exposure

Methanol has been demonstrated to be toxic through 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 bw applied four times daily, toxicity was noted on the first day, with death occurring on the second day [19]. The exposure model used minimised concomitant inhalation exposure [19].

Health Effects of Chronic/Repeated Exposure

Human data

General toxicology

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

Inhalation

Data on chronic exposure to methanol is limited. There have been reports of dizziness, headaches, GI and visual disturbance in individuals exposed to methanol above the WEL of 260 mg/m³ (200 ppm) but not in those exposed to lower levels [1].

In one study, blurred vision, headache, nausea, dizziness and eye irritation were experienced by workers using “spirit duplicators” (early document copying machines) at concentrations greater than the WEL [2]. The duration of exposure and the number of individuals exposed were not reported [2].

Dermal/ocular exposure

Long-term or repeated dermal exposures to methanol may cause dermatitis [14].

There is insufficient data on chronic ocular exposure.

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 the next section on animal and in-vitro data). The European Food Safety Authority (EFSA) recently evaluated the limited available evidence and concluded that methanol was not genotoxic [21].

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 [22]. 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 that of humans as indicated previously. It is unlikely that exposure to low concentrations of methanol would result in adverse effects in the fetus.

Animal and in-vitro data

Inhalation

In a chronic inhalation study, monkeys were exposed to methanol concentrations of 13, 130 or 1,300 mg/m³ (10, 100 and 1,000 ppm, respectively) for 22 hours a day for up to 29 months. Bodyweight 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; the data indicates that it does not damage genetic material [2].

Methanol gave negative results for mutagenicity in a series of Ames tests in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and in *Escherichia coli* strain WP2uvrA [23].

Mice exposed by inhalation to methanol at 1,050 or 5,200 mg/m³ had no increase in the frequency of micronuclei in red blood cells or sister chromosome exchanges (SCEs), chromosomal aberrations or micronuclei in lung cells [2].

In a study designed to measure DNA adducts from exogenous sources, isotope-labelled methanol was administered orally to rats at doses of 500 or 2,000 mg/kg bw/day for 5 days [21]. An increasing number of adducts in all tissues was observed with an increase in administered dose [21]. In a recent evaluation EFSA considered that no conclusions could be drawn from this and similar studies, noting that the method was not suitably robust and that DNA adducts are biomarkers of exposure of organs and tissues to methanol and not direct indicators of mutagenic effect. EFSA concluded that the reliable in-vivo and in-vitro data did not suggest that methanol is genotoxic [21].

Carcinogenicity

There is no evidence from animal studies to suggest that methanol is a carcinogen, although because of major differences in the metabolism of methanol between rodents and humans the lack of an appropriate animal model is recognised [2]. In a recent evaluation EFSA concluded that the available evidence is inadequate to determine the carcinogenic potential of methanol [21].

Reproductive and developmental toxicity

Developmental effects have been reported in rodents exposed to high concentrations (> 2 g/kg bw) of methanol through inhalation and ingestion [1, 2, 21, 22, 24]. 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.

There is little data available on the reproductive and developmental effects of exposure to methanol in non-human primates. In the only reported study macaque monkeys were exposed to 0, 260, 780 or 2,340 mg/m³ (0, 200, 600 or 1,800 ppm) methanol vapour for 2.5 hours a day for 7 days a week prior to breeding and throughout pregnancy (approximately 120 days). The mothers remained healthy throughout the study and the methanol exposure did not affect menstrual cycles, number of matings to conception or conception rate. There was a significant reduction in the length of pregnancy in treated animals (6–8 days less than in the controls); however, the reduction was not dose related. The maternal methanol exposure did not have an apparent effect on the birthweight or health of the offspring [1, 21].

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