

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⁻¹ [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 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 (CO₂). 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 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 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
Central Nervous System depression	Onset of 30 min - 2 h; intoxication may be of shorter duration and less pronounced than that arising from ethanol ingestion
Asymptomatic latent period 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
Severe metabolic acidosis occurs after latent phase	Nausea, vomiting and headache may also occur and may be superimposed on the visual toxicity described below
Ocular toxicity 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⁻³ (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⁻¹ [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/m³ (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⁻¹ 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⁻¹ 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⁻¹ 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⁻¹ 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⁻³ [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 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 1300 mg m⁻³ (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/m³ (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⁻³) 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⁻³) 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⁻³) 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.