SIDS INITIAL ASSESSMENT PROFILE

CAS No.	67-56-1
Chemical Name	Methanol
Structural Formula	CH_3OH

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Toxicokinetics, Metabolism, and Distribution: Methanol is readily absorbed by inhalation, ingestion and dermal contact and distributes rapidly throughout the body. Metabolism in humans, rodents, and monkeys contributes up to 98 percent of the clearance, with more than 90 percent of the administered dose exhaled as carbon dioxide. Renal and pulmonary excretion contributes only about 2 – 3 percent. The metabolism and toxicokinetics of methanol varies by species and dose. In humans, the half-life is approximately 2.5 – 3 hours at doses lower than 100 mg/kg bw. At higher doses, the half life can be 24 hours or more.

The mammalian metabolism of methanol occurs mainly in the liver, where methanol is initially converted to formaldehyde, which is in turn converted to formate. Formate is converted to carbon dioxide and water. In humans and monkeys, the conversion to formaldehyde is mediated by alcohol dehydrogenase. In rodents, the first reaction occurs mainly via a catalase-peroxidase pathway which is rate-limiting. Methanol in turn accumulates in the blood at high doses. In primates, the last reaction step, conversion of formate to carbon dioxide by the formyl-tetrahydrofolate synthetase, is rate-limiting, leading to a disproportionate increase of formate in the blood and sensitive target tissues (such as CNS and the retina).

In humans, when exposed via inhalation up to an air concentration of 0.065 mg/L, no increase of blood methanol is expected. Up to 0.26 mg/L (single or repeated exposure), the methanol blood level is likely to increase 2 to 4-fold above the endogenous methanol concentration in humans, but still remains significantly below 10 mg/L. Air concentrations up to 1.6 mg/L resulted in similar blood methanol among rats, monkeys, and humans. However, above 1.6 mg/L, a steep exponential increase occurs in rats, a smaller exponential increase occurs in monkeys, and humans exhibit a linear relationship between air concentrations and blood methanol levels.

Baseline levels of formate in blood are about 3 to 19 mg/L (0.07 – 0.4 mM) in humans. Toxic blood formate concentrations are reported to be 220 mg/L and higher ($\geq$5 mM formate). Inhalation of about 1.20 mg methanol/L for 2.5 hours contributed only insignificantly to the internal formate pool in monkeys (in the µM-range); this also held true for folate-deficient conditions. Also after repeated inhalation of 2.6 mg/L (2000 ml/m^3) for 6 hrs/day, 5 days/week, for 1 or 2 weeks, monkeys showed no discernible increase in formate concentration in blood [estimated body burden 200 to 300 mg/(kg bw$*$d)], whereas formate accumulation has been observed in primates at methanol doses greater than 500 mg/kg bw given as a bolus. The critical methanol dose that saturates the folate pathway in humans is estimated to be ≥200 mg/kg bw. Based on data produced in monkeys, metabolic saturation in humans is also less likely to happen during inhalation if the amount is divided over a prolonged time and not incorporated as a bolus.

Acute Toxicity: Formate is considered to be the ultimate toxicant in acute methanol intoxication in humans. Acidosis and ophthalmologic changes are typical primary effects. However, these effects do not occur in rodents or rabbits., which are able to remove formate more efficiently. In these animals, CNS depression is usually the cause of defects and finally death.

A blood level of 500 mg methanol/L in acutely poisoned patients generally is regarded as requiring hemodialysis. This blood concentration can transiently be achieved in an adult person (70 kg) by ingestion of 0.4 ml methanol/kg (approximately 0.32 mg/kg). Generally, in humans, transient central nervous system (CNS) effects appear above blood methanol levels of 200 mg/L and serious ocular symptoms appear above 500 mg/L.

The minimal acute methanol dose to humans that can result in death is considered to be 300 to 1000 mg/kg by ingestion, and fatalities have occurred in untreated patients with initial methanol blood levels in the range of 1500-2000 mg/L. However, such high blood methanol levels able to cause death are not .likely to be achieved through inhalation exposure. For example, 2.6 or 6.5 mg/L resulted in methanol blood levels that barely exceed 100 and 200 mg/L, respectively, after an 8-hour working shift. Exposure to 0.26 mg methanol/L for 4 hours was without significant physiologic effects in human volunteers.

In rats, LC_{50} values have been calculated to be 83.2 and 128.8 mg/L after 4 hours. In cats, the LC_{50} was 85.4 mg/L after four hours. In monkeys, air concentrations of 52 mg/L after 1-4 hours and 13 mg/L after 18 hours led to an unspecified level of mortality. Dermal LD_{50}s in rabbits range from 15800 to 20000 mg/kg bw. In rats, the dermal LD_{50} is greater than 45,000 mg/kg bw. In monkeys, four daily dermal doses of 400 mg/kg bw eventually resulted in death. Oral LD_{50}s in rats range from < 790 to 13,000 mg/kg bw; in mice, the values range from 7,300 to 10,000 mg/kg bw; in rabbits, the LD_{50} was approximately 14,200 to 14,400 mg/kg bw; and in monkeys, the values range from 7000 to 9000 mg/kg. Although most of the references for these values provided only limited details, the values are consistent within species and route of exposure.

Irritation/Sensitisation: Methanol exhibited no skin irritation in one study in which the chemical was administered under occluded conditions as a 100 percent concentration. Limited information from another study showed moderate irritation with 500 mg. Available studies show that methanol is a slight eye irritant with doses of 0.05 to 0.1 mL. Some reversibility of effects was observed. High concentration of methanol vapours may be irritating to mucous membranes. A guinea pig maximization assay gave no evidence of contact sensitisation after induction and challenge doses of 50 percent.

Repeated-Dose Toxicity: In a whole body inhalation study in monkeys exposed to 0.013, 0.13, and 1.3 mg/L 21 hours per day 7 days per week for 7, 19, and 29 months, several general clinical signs as well as degenerative effects in the brain (at 0.13 and 1.3 mg/L), slight peripheral nerve damage (at 0.13 and 1.3 mg/L), very slight degeneration of the optic nerve (concentrations not noted), increased fat granules and slight fibrosis in the liver (all concentrations), and Sudan positive granules in the kidney were observed (at 0.13 and 1.3 mg/L). Also, a slight myocardial disorder (at 0.13 and 1.3 mg/L) and localized effects in the trachea and possible slight fibrosis in the lungs (concentrations not noted) were observed. Although the statistical significance of the effects cannot be verified from the study report, the number of effects and systems affected indicate a relationship with methanol.

In another whole body inhalation study in monkeys exposed up to 20 days for 21 hours per day, coma and lethality were observed at concentrations $\geq$ 9.1 mg/(L$*$d). In the brain, necrosis of the basal ganglia and cerebral edema were observed at 6.5 mg/(L$*$d) and at 3.9 mg/(L$*$d), hyperplasia and fibrosis around myelin sheaths of the basal ganglia as well as a slight to moderate increase in astroglia cells were observed. The optic nerve showed atrophy at >3.9 mg/(L$*$d), along with reduction in myelin fibers. In the liver, fibrosis was observed at 6.5 mg/(L$*$d) and mild fatty degeneration was observed at 3.9 mg/(L$*$d). In the kidney, partly vacuolated hyaline degeneration was observed at 6.5 mg/(L$*$d).

In rats exposed to methanol up to 6.5 mg/L for 6 hours per day, five days per week for 28 days, no adverse effects were observed except local nasal irritation and increased relative spleen weights, which were observed only at the middle dose. The estimated blood level of methanol was about 250 mg/L under this condition.

In a whole body inhalation study in mice exposed for 12 months to concentrations of 0.013, 0.13, and 1.3 mg/L 20 hours per day, slight changes in clinical signs, body and organ weights, and some changes in histopathology were observed. In rats exposed in the same manner, slight changes in body weight and organ weights were observed at the highest dose. The NOEL is 0.13 mg/L. In rats, gavage doses of 100, 500, and 2,500 mg/(kg bw$*$d) for 90 days

resulted in increased liver enzymes and reduced brain weights at the highest dose resulting in a NOAEL of 500 mg/(kg bw*d).

Mutagenicity: Numerous *in vitro* assays (including seven Ames assays, four micronucleus/cytogenetic assays, a mammalian gene mutation assay, a yeast gene mutation assay, a mouse lymphoma test, three cell transformation assays, and a DNA damage and repair assay) were conducted on methanol. The majority of these assays are negative, with the exception of positive results in the mouse lymphoma test and a mitotic recombination assay in Aspergillus, and ambiguous results in an Ames assay for strain TA102 and in the DNA damage and repair assay. Only limited details were available for the mouse lymphoma test. Of the eleven *in vivo* assays (all micronucleus and cytogenicity assays plus a *Drosophila* SLRL assay), all are negative except one cytogenetic assay, which was positive for aneuploidy, sister chromatid exchange, and micronuclei. Limited information was available regarding this positive result. Thus, although most studies indicate that methanol does not have the potential to be mutagenic, not all studies lead to that conclusion.

Carcinogenicity: Methanol was tested in two long-term whole body inhalation studies (24 months in rats and 18 months in mice for 20 and 19 hours per day, respectively). There was no evidence of a carcinogenic potential in rats and mice exposed to air concentrations of up to 1.3 mg/L.

Reproductive/Developmental Toxicity: ***Monkeys.*** In monkeys, parents were exposed via inhalation prior to and during breeding as well as during pregnancy to doses of 0.26, 0.78, and 2.34 mg/L. A late wasting syndrome was observed at the highest dose in 2 out of 7 female descendants, associated with signs of severe malnutrition and gastroenteritis noted at autopsy. Mild neurobehavioral effects in offspring and some vaginal bleeding in mothers were observed at all concentrations. However, due to the normal variance in and the low number of animals, along with pre-term delivery of several mothers, the observed findings are difficult to interpret.

Rats. Several inhalation studies in rats resulted in a variety of effects in offspring due to prenatal and/or postnatal dosing. In a 2-generation whole body inhalation reproductive study in which rats were exposed for 19-20 hours/day, decreased brain weights in the first and second generation offspring (F1, F2) resulted in a NOAEL of 0.13 mg/L. In a developmental study in which rats were exposed by whole body inhalation on gestation days 1 to 19 at the two lowest doses and days 7 to 15 at the highest dose for 7 hours/day, malformations and fetal weight changes resulted in a NOAEL of 6.5 mg/(L*d) (the lowest dose tested). A second whole-body inhalation developmental study in which rats were exposed on gestation days 7 to 17 for 23 hours/day, malformations, increased fetal resorptions, and decreased numbers of live fetuses were observed, resulting in a NOAEL of 1.3 mg/(L*d).

Mice. In a study of reproductive effects, there was an insignificant increase in morphological anomalies in spermatozoa in male mice at 1000 mg/(kg bw*d) after oral dosing for five weeks. A developmental whole body inhalation study in mice exposed on gestation days 6 to 15 for 7 hrs/day resulted in developmental effects including increased exencephaly and cleft palate, fully resorbed fetuses, decreased numbers of live pups, and decreased body weights; this study resulted in a NOAEL of 1.3 mg/(L*d). Oral studies in mice resulted in various malformations at 4000 mg/(kg bw*d) (the LOAEL) and higher; no NOAELs could be established from these studies.

Humans. No epidemiological studies in humans have been located to demonstrate that there is a link between methanol exposure and an increased incidence of fetal malformations or developmental impairment.

Rodent data on reproductive and developmental toxicity are relevant for humans despite the known differences in methanol metabolism between rodents and humans. Rodents are adequate models for human exposure to methanol at levels where formate does not accumulate. However, blood methanol concentrations associated with serious teratogenic effects and reproductive toxicity observed in the rodent studies are in the range of 1000 – 2000 mg methanol/L blood, associated with formate accumulation in humans, which is likely to result in metabolic acidosis and visual and clinical effects in humans. In humans, generally, transient central nervous system (CNS) effects appear above blood methanol levels of 200 mg/L, ocular symptoms appear above 500 mg/L, and fatalities have often occurred in untreated patients with initial methanol levels in the range of 1500-2000 mg/L. Other effects (e.g., subtle, not yet definitive neurological effects observed in primates) may be exhibited at lower inhalation concentrations and lower methanol blood levels.

Environment

Methanol is a colorless, clear, highly flammable liquid with a mild alcoholic odor. Physicochemical property values for methanol are: melting point –97.8 ^{0}C, boiling point 65 ^{0}C, density 0.79 g/m^3, vapor pressure 128 hPa, and log Kow –0.74. Methanol is miscible with water at 20 °C. It does not undergo hydrolysis. A value of 0.461 Pa m³/mol for the Henry's Law constant indicates that volatilization is not a significant removal process from the aquatic compartment.

Air is the main target compartment, based on a fugacity model calculation (Mackay Level III) with about 73 % of environmental methanol distributing to air and 16 % to water. Methanol is degraded in the atmosphere by photochemical, hydroxyl-radical dependent reactions. The estimated elimination half-life is calculated to be about 17-18 days with a rate constant of 0.93 x 10^{-2} cm^3/molecule-sec. Methanol is readily biodegradable. Bioaccumulation in fish is expected to be low.

In several 96-hour studies in fish in which methanol concentrations were measured during the tests, LC50s ranged from 15,400 to 29,400 mg/L. In *Daphnia magna*, 24-hour and 48-hour EC50s were > 10,000 mg/L (highest dose tested). In one 24-hour study, the actual EC50 value reported in Daphnia magna was 21,400 mg/L. In aquatic plants, an EC50 for growth inhibition of *Chlorella pyrenoidosa* was calculated to be 28,440 mg/L over 10-14 days. No information on analytical monitoring was available for the invertebrate and plant studies.
The low toxicity of methanol for aquatic organisms is confirmed by QSAR calculations, resulting in acute toxicity values for fish, daphnids and algae well above 1000 mg/L.

Exposure

The world-production volume of methanol is approximately 30 million tonnes annually in 2000, about 11 million tonnes used in countries participating in NAFTA (North American Free Trade Agreement) and about 3.3 million tonnes in Western Europe, of which 70% is being used for the manufacture of formaldehyde, MTBE and acetic acid. Several additional compounds are synthesized from methanol.

Methanol occurs naturally in humans, animals and plants. The general population is exposed to methanol mainly through consumption of food and beverages and through use of consumer products such as paints, sealers and adhesives that contain methanol as a solvent. Worldwide, air concentrations of methanol have been measured at ranges from 1.05 to 13.1 x 10^{-5} mg/L.

Releases into the environment may occur from both natural and man-made sources. It is however released predominantly from production and use in industrial processes. According to the U.S. Toxics Release Inventory, about 89,225 tonnes of methanol were released on- and offsite for facilities in all industries in the U.S. in 2000. The largest emitter was the pulp and paper industry. About 90 percent of the emissions were to the air and about 1.7 percent was released to surface water.

The most important routes of potential exposure are inhalation and dermal exposure at the workplace.
A mean background body burden of 0.5 mg methanol/kg bw has been estimated based on baseline blood levels and elimination kinetics of methanol.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: This chemical is a candidate for further work. Methanol exhibits potential hazardous properties for human health (neurological effects, CNS depression, ocular effects, reproductive and developmental effects, and other organ toxicity). Rapid metabolism and excretion is noted depending on the dose. In the US (the Integrated Risk Information System), further work is being performed regarding the use and refinement of pharmacokinetic models for extrapolating animal data to humans.

Environment: The chemical is currently of low priority for further work, due to its low hazard profile.