SIDS INITIAL ASSESSMENT PROFILE

CAS No.	124-41-4 865-33-8
Chemical Name	Category of Methanolates: Sodium methanolate, Potassium methanolate
Structural Formula	$H_3C\text{-}O^-\ Na^+$; $H_3C\text{-}O^-\ K^+$

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The production and use pattern of sodium and potassium methanolates are comparable. The two chemicals have very similar physical and chemical properties. In contact with water they react very fast, quantitative and exothermic to methanol and the corresponding alkali hydroxides.
One mol of sodium or potassium methanolate (54.02 g or 70.13 g) yields one mol of methanol (32.04 g) and sodium- or potassium hydroxide (40 g or 56.11 g) respectively.
Due to the very high pK_a-value of methanol of 15.5, the equilibrium is on the side of the reaction products. Toxicological and ecotoxicological studies of methanol and sodium and potassium hydroxide are therefore relevant for these products as well. The main toxicological characteristic is the corrosivity to skin and mucous membranes that limits the possibility of exposure to methanol and warrants strict exposure controls. In the environment, both effects through pH-changes by the hydroxides and effects of methanol need to be considered.
For potassium hydroxide SIAM 13, and for sodium hydroxide SIAM 14 concluded: "Environment and Human Health: no further work is recommended if sufficient control measures are in place to avoid significant human and environmental impact, including prevention of accidental exposure. Due to the corrosivity of the substance, no further studies are required under SIDS program."

For methanol, SIAM 19 decided that, in terms of human health, this chemical is a candidate for further work. In the US, further work is being performed regarding the use and refinement of pharmacokinetic models for extrapolating animal data to human. Methanol exhibits potential hazardous properties for human health (neurological effects, CNS depression, ocular effects, reproductive and developmental effects, and other organ toxicity). The effects of methanol on the CNS and retina in humans only occur at doses at which formate accumulates due to a rate-limiting conversion to carbon dioxide. In primates, formate accumulation was observed at methanol doses greater than 500 mg/kg bw (which would require a sodium methanolate dose of more than 840 mg/kg bw and a potassium methanolate dose of greater than 1000 mg/kg bw). Repeated exposure to such high dose levels of methanolates that are already in the acutely toxic range is highly unlikely due to their corrosive properties. The only exposure situation for sodium and potassium methanolate that could perhaps lead to methanol and formate blood levels resulting in acute neurophysiological and visual disturbances would be accidental dermal exposure to corrosive concentrations that could lead at the same time to an uptake of toxic amounts of methanol through the skin. For this exposure situation the post SIDS work for methanol is considered relevant as well and no specific work on sodium and potassium methanolate is considered necessary. In terms of the environment, methanol is currently of low priority for further work, due to its low hazard profile.

Human Health

The predominant effect of sodium and potassium methanolate on humans is their corrosivity to skin and mucous membranes, due to the rapid and exothermic reaction with tissue water yielding alkaline hydroxides. The abiotic hydrolysis of sodium and potassium methanolates with tissue water results in the hydroxides formation of sodium and potassium ions respectively, hydroxide ions and methanol. Exposure to non-irritant levels of methanolates via the dermal or inhalation route is not expected to lead to relevant uptake of the ionic degradation products sodium or potassium ions or hydroxide ions in amounts that would exceed the normal physiological levels.
The sodium ion is a normal constituent of the blood and an excess is excreted in the urine. Uptake of sodium

following exposure to sodium methanolate can be considered negligible compared to the uptake of sodium via food (3.1 to 6 g/day).
Potassium ions are normal constituents of body fluids. K+ plays an essential role in human physiology, but starts to be toxic at plasma concentrations of 250 mg/l. Its concentration in blood is regulated principally by renal excretion/re-absorption and controlled by an effective feed-back auto-regulation system. A systemic intoxication by potassium methanolate is not expected as the uptake will be limited by the corrosive properties of the substance.
Exposure to hydroxide ions from sodium or potassium methanolate exposure could potentially increase the pH of the blood and lead to alkalosis. However, the pH of the blood is regulated between narrow ranges pH 7.0 to 7.8 and an excessive pH of the blood is prevented by the bicarbonate buffer system, respiration and renal compensation mechanisms.

SIAM 19 concluded for methanol: "Methanol is readily absorbed by inhalation, ingestion and dermal contact and partitions rapidly and equally throughout the organism in relation to the water content of organs and tissues. A small amount is excreted unchanged by the lungs and kidneys. Half-lives of methanol in the body are roughly 2.5 to 3 hours at doses less than 100 mg/kg bw. At high doses disproportionate increases of the parent compound in blood are obtained in rodents, but not in humans. On the other hand, in humans the metabolite formate accumulates at high doses. This important difference mirrors the different enzymes and enzyme capacities involved in the oxidative pathway from methanol to carbon dioxide. Specifically, two different rate limiting processes have been identified: in rodents, high doses (after inhalation of 2.5 – 3.3 mg/l) lead to the saturation of catalase, resulting in the accumulation of methanol whereas formate levels remain low, whereas in primates (especially humans), the parent compound is well oxidized and does not accumulate, but formate increases disproportionately. From studies in humans and monkeys exposed to concentrations of 0.26 – 2.6 mg/l (administered for 6 to 8 hours), it can be concluded that methanol remains close to 50 mg/l in blood. At inhalation exposures of 2.6 mg/l, rats also exhibit methanol blood levels that are not much higher (at about 80 mg/l), whereas the level in mice was 400 mg/l. At a higher inhalation exposure (6.5 mg/l), humans show the lowest blood methanol level (at 140 mg/l), followed by monkeys, rats, and mice, with the level in mice being more than 10 times higher than humans. Formate accumulation in primates has been observed at methanol doses greater than 500 mg/kg."
The corresponding dose levels for sodium and potassium methanolate that would lead to accumulation of formate in primates would be 840 and 1000 mg/kg bw. Such dose levels are already in the acutely toxic dose range. Due to the corrosive nature of the methanolates it is unlikely that repeated exposure to methanolates could result in an uptake of toxic doses of methanol. The only exposure situation for sodium and potassium methanolate that could perhaps lead to methanol and formate blood levels resulting in acute neurophysiological and visual disturbances would be accidental dermal exposure to corrosive concentrations that could lead at the same time to an uptake of toxic amounts of methanol through the skin. It has been assumed that an inhalation exposure to methanol of 260 mg/m^3 for 8 hours does not lead to any adverse effects. This exposure level corresponds to a systemic dose of 2600 mg methanol/d (assuming an inhalation volume of 10 m^3 during an 8-hour working day) or 37 mg/kg bw day (for a 70 kg human). It would require doses of 44.4 and 65 mg/kg bw of sodium or potassium methanolate, respectively, to achieve a systemic dose of 2600 mg methanol/d. The rate of dermal uptake for methanol was reported to be 0.192 mg/cm^2/min. Accidental exposure of both hands (850 cm^2) to sodium or potassium methanolate for one minute resulting in corrosive effects could then theoretically additionally lead to an uptake of methanol exceeding the dose level of 37 mg/kg bw. Such an exposure situation does however not reflect any human exposure situation under normal handling conditions as precautions are taken because of the corrosivity of the substances.

No signs of toxicity were observed in rats exposed to a dust enriched atmosphere of sodium methanolate for 8 hours, the dermal LD_{50} of a 50 % aqueous solution was > 2000 mg/kg bw in rats. Skin necrosis was observed in this study. After oral administration the acute toxicity is dependent on the local tissue concentration and the dose rate of the substance and its degradation product sodium hydroxide. The LD_{50} in water or water soluble solvents was between 800 and 1687 mg/kg bw, when administered in corn oil the LD_{50} was 2037 mg/kg bw. The acute toxicity is consistent with that of sodium hydroxide and it can be assumed that the primary mode of action is local irritation/corrosion at the site of first contact.
For potassium methanolate no data are available, but due to the reaction with water and the liberation of hydroxide ions and the alkaline reaction the mode of action will be the same and the acute toxicity will be comparable to that of sodium methanolate and potassium hydroxide. The acute toxicity of both substances is mediated by their alkalinity and the hydroxide ion.
Sodium methanolate was highly corrosive to rabbit skin and eyes. For potassium methanolate no studies are available. Due to its alkaline reaction and exothermic reaction with water it will be similarly corrosive. Based on the skin and eye irritation data it can be assumed that both methanolates will also cause irritation/corrosion to the

mucous membranes of the upper respiratory tract in case of an exposure via the inhalation route.

As the corrosivity is mediated by the exothermic liberation of sodium or potassium hydroxide the data for the two hydroxides may be important for the evaluation of this endpoint as well. For sodium hydroxide it was concluded that based on the animal data a NaOH solution of 8 % can be considered corrosive. Based on human data concentrations of 0.5 to 4 % were irritating to the skin and concentrations slightly lower than 0.5 % were considered non-irritating. Potassium hydroxide is corrosive at concentrations of about 2 % and higher. Between 0.5 % and 2 % it is irritating.
From the data of the hydrolysis products it can be concluded that sodium and potassium methanolate are not expected to have a notable skin sensitization potential.

No data on repeated dose toxicity of sodium and potassium methanolate are available. The tolerable dose levels will be determined by the corrosive nature of the substances. At non-irritant concentrations, the K+ or Na+ ions, and the OH^- ions are unlikely to have any adverse effects. The specific ocular and CNS toxicity of methanol in primates is based on the accumulation of formate in blood. Formate accumulation in primates has been observed at methanol doses greater than 500 mg/kg. The corresponding dose levels for sodium and potassium methanolate that would lead to accumulation of formate in primates would be 840 and 1000 mg/kg bw. Such dose levels are already in the acutely toxic dose range. Due to the corrosive nature of the methanolates it is very unlikely that exposure to methanolates could result in an uptake of toxic doses of methanol.

No data on mutagenicity of sodium or potassium methanolate are available with the exception of one negative Ames assay with a limited number of strains conducted with sodium methanolate. Due to the rapid hydrolysis of methanolates in *in vitro* test systems and tissue water *in vivo*, data for the hydrolysis products are relevant for methanolates as well. For sodium and potassium hydroxide there is no evidence for a mutagenic potential. For methanol the weight of evidence suggests that the substance is unlikely to have any relevant mutagenic activity. Therefore it can be concluded that there is no concern with regard to a mutagenic activity of sodium or potassium methanolate.

No data are available on the carcinogenicity of sodium and potassium methanolate. For potassium hydroxide it was concluded at SIAM 13 that there is no evidence of carcinogenicity in exposure situations that are relevant for humans. There was no evidence for a carcinogenic potential of methanol in two long-term inhalation studies on rats and mice. Based on the available data, there is therefore no concern for carcinogenicity of sodium and potassium methanolates.

No data are available on reproductive or developmental toxicity of sodium and potassium methanolate. For hydroxide, sodium and potassium ions, no relevant reproductive toxicity potential has been identified. For methanol reproductive and developmental toxicity effects have been described in rats, mice and monkeys. Blood methanol concentrations associated with serious developmental effects and reproductive toxicity in rodent studies are in the range associated with formate accumulation. It is unlikely that concentrations associated with serious developmental effects in rodents could be reached by administration of sodium or potassium methanolate to experimental animals, as those dose levels would be in the acutely toxic dose range and associated with massive local irritation at the site of first contact. The maximum tolerated dose in such studies is therefore likely to be below the dose that would result in methanol mediated developmental effects. In addition, for animal welfare reasons, it is not recommended to perform further animal studies with sodium and potassium methanolate.

Environment

Both sodium and potassium methanolate are white to yellowish organic solid salts that decompose above 300 °C (sodium methanolate) or at 300 °C (potassium methanolate). Sodium and potassium methanolate have a calculated vapor pressure of 6.39×10^{-6} hPa. On contact with water both substances decompose rapidly and exothermically under formation of methanol and the corresponding alkali hydroxides, sodium- or potassium hydroxide, respectively.
Photodegradation of methanol by hydroxyl radicals takes place with a half-life of 17 - 18 days. For the partitioning in the environmental compartments the hydrolysis products are of relevance. Sodium and potassium hydroxide are inorganic salts that partition predominantly into the water phase and will not adsorb to particulate matter or surfaces. For methanol it was concluded that based on the Henry's law constant of 0.461 Pa m^3/mol it is not expected to significantly volatilize from the aquatic compartment and adsorption is not expected to be significant due to its high water solubility and low octanol-water partition coefficient. A distribution calculation performed with the Mackay level III model predicts that the air is the target environmental compartment for methanol. After

rapid hydrolysis in water the relevant organic reaction product, methanol is readily biodegradable (76 – 82 % BOD removal after 5 days). As sodium and potassium methanolate react with water under formation of sodium or potassium hydroxide and methanol, an octanol-water partition coefficient cannot be experimentally established and bioaccumulation of the substances themselves is unlikely. Methanol will be the species that distributes into the octanol phase or could be taken up by organisms. For methanol the log K_{ow} was –0,74 indicating a low bioaccumulation potential. This was confirmed by experimental BCF-values below 10 that have been determined in different fish species.

The toxicity of sodium and potassium methanolate to aquatic organisms is mediated by their degradation products due to the rapid reaction with water yielding sodium or potassium hydroxide and methanol. The aquatic toxicity of methanol is low with acute EC_{50} or LC_{50} values > 10 000 mg/l and therefore its contribution to the methanolate toxicity is considered negligible. The limited data available for sodium methanolate are consistent with the aquatic toxicity of the alkali hydroxides. For sodium methanolate the acute toxicity to fish (48-h LC_{50}) for *Leuciscus idus melanotus* was 346 mg/l (equivalent to 256 mg/l of sodium hydroxide). The corresponding 48-h LC_{50} value for sodium hydroxide was 189 mg/l the 96-h LC_{50} for *Gambussia officinalis* was 125 mg/l for sodium hydroxide and 80 mg/l for potassium hydroxide. For invertebrates a 48-h LC_{50} value of 40 mg/l (*Ceriodaphnia dubia*) and toxicity threshold concentrations (TTC) between 40 and 240 mg/l (*Daphnia magna*) were reported for sodium hydroxide. Lethal concentrations to molluscs of sodium hydroxide ranged between 150 mg/l (*Bulinus truncatus, Lymnea caillaudi*) and 450 mg/l (*Biomphalaria a. alexandria*), the 48-h LC_{50} values for *Ophryotrocha* (marine polychaete) were between 33 and 100 mg/l. The 24-h EC_{50} for algae (assimilation inhibition) was 302 mg/l for sodium methanolate. However, as concluded for sodium and potassium hydroxide already, acute toxicity data cannot be used to derive a PNEC or a $PNEC_{added}$ for the compounds releasing hydroxide. Aquatic ecosystems are characterized by an alkalinity/pH and the organisms of the ecosystems are adapted to these specific natural conditions. Based on the natural alkalinity of waters, organisms will have different optimum pH conditions, ranging from poorly buffered waters with a pH of 6 or less to very hard waters with pH values up to 9. A lot of information is available about the relationship between pH and ecosystem structure and also natural variations in the pH of aquatic ecosystems have been quantified and reported extensively in ecological publications and handbooks.
Normally a PNEC or a $PNEC_{added}$ has to be derived from available ecotoxicity data. A $PNEC_{added}$ is a PNEC which is based on the added concentrations of a chemical (added risk approach). Based on the available data it is not considered useful to derive a PNEC or $PNEC_{added}$ for the sodium and potassium methanolate as their effect is based on hydroxide ions or a pH change. The natural pH of aquatic ecosystems can vary significantly and the sensitivity of aquatic ecosystems to a change of the pH can vary significantly between aquatic ecosystems. The change in pH due to anthropogenic OH- addition through methanolate releases is influenced significantly by the buffer capacity of the exposed ecosystem.
Although a PNEC or $PNEC_{added}$ was not calculated, there is a need to assess the environmental effect of an OH^- release through sodium or potassium methanolate release into the environment. Based on the pH and the buffer capacity of the effluent and receiving water and the dilution factor of the effluent, the pH of the receiving water after discharge can be calculated or its pH can be measured. The change in pH should be compared with the natural variation in pH of the receiving water. Based on this comparison it should be assessed if the pH change is acceptable.
To illustrate the procedure and to get an idea about the order of magnitude for a maximum anthropogenic addition, the maximum methanolate concentration will be calculated for 2 representative cases. According to Dir. 78/659/EEC, the pH of surface water for the protection of fish should be between 6 and 9. The 10th percentile and the 90th percentile of the bicarbonate concentration of 77 rivers of the world were 20 and 195 mg/l respectively. If it is assumed that only bicarbonate is responsible for the buffer capacity of the ecosystem and that an increase of pH to a value of 9 would be the maximum accepted value, then the maximum anthropogenic addition of sodium methanolate would be 1.4 mg/l and 8.2 mg/l (corresponding to 1.0 and 6.1 mg NaOH/l) and for potassium methanolate 1.1 mg/l and 10.4 mg/l (corresponding to 0.86 and 8.3 mg KOH/l) for bicarbonate concentrations of 20 and 195 mg/l respectively.
Sodium methanolate was moderately toxic to bacteria with a 24-hour EC50 of 97 mg/l. The toxicity is likely mediated through a pH effect by the release of hydroxide ions.
There is only one study with potassium hydroxide available indicating a low level of terrestrial toxicity (90-day EC_{50} in *Enchytraeus sp.* (> 95 % *Cogentia sphagnetorium*) of 850 mg/l (artificial soil)). The terrestrial toxicity will depend on the buffer capacity of the soil.

Exposure

European production volumes for sodium and potassium methanolate are above 1000 metric tonnes per year. The US-volume of sodium methanolate reported to US-EPA in 2002 by all US manufacturers and importers was

between 4500 and 23 000 metric tonnes on a dry weight basis. Sodium and potassium methanolate are widely used in the chemical industry as intermediates, for example for the production of formic acid or the transesterification of fatty acid esters. One other major use is in biodiesel production as transesterification catalysts. Because of the predominant production and use in chemical industry under controlled conditions, environmental exposure from production and use is considered low. Furthermore due to the sensitivity of the substances to moisture it is unlikely that the products themselves enter the environment during production and use as they are immediately hydrolyzed to methanol and sodium or potassium hydroxide. Theoretically, the environment could be exposed to residues of the catalysts in consumer products. However, given the sensitivity of methanolates to moisture it is likely that any residual levels would rapidly hydrolyze under formation of methanol and sodium and potassium hydroxide.

In production and uses in chemical industry for which descriptions are available, from the process description very low occupational exposure is anticipated. As the majority of the products are used as intermediates in the chemical industry a controlled exposure situation is anticipated.

There is no information on possible consumer exposure for potassium methanolate. The only information available on sodium methanolate is from the Nordic Product Register of 2003, where consumer products are listed for Norway and Sweden (no details available on use or use concentrations). Theoretically, consumers could be exposed to residues of the catalysts in consumer products. However, given the sensitivity of methanolates to moisture it is likely that any residual levels would rapidly hydrolyze under formation of methanol and sodium and potassium hydroxide. Both products are listed in the Inventory of Processing Aids for food as catalysts for interesterified food oils of the Codex Alimentarius with residual levels below 1 mg/kg.

Sodium methanolate is contained in Nordic Product Registers for 2003: In Finland, 7 preparations for manufacture of chemicals and chemical products with a tonnage of 228 tonnes but no consumer products are listed. In Norway, 152 products with a total tonnage of 33.0 tonnes are listed, 6 of which are consumer products with a tonnage of 0.1 tonnes. Industrial uses listed in Norway are manufacture of chemicals and chemical products with a tonnage of 32.9 tonnes,. In Sweden, 6 preparations with a tonnage of 51.0 tonnes are listed with information on industrial use from 2001 (4 preparation with a tonnage of 51.0 tonnes for process regulators), and 2 preparations are consumer preparations in which sodium methanolate is not added intentionally. Potassium methanolate is listed in Nordic Product Registers for Norway and Finland in 2003, but all data are confidential. However, given the sensitivity of methanolates to moisture it is likely that any residual levels would rapidly hydrolyze under formation of methanol and sodium and potassium hydroxide.

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

Human Health: The chemicals in this category are currently of low priority for further work. The human health hazard is characterized by the rapid and exothermic degradation of the chemicals to methanol and the corresponding alkali hydroxides with known corrosivity. Based on data presented by the Sponsor country, exposure is well controlled in occupational settings, and exposure of consumers is negligible. Countries may wish to investigate exposure scenarios with potential human exposure.

Environment: The chemicals in this category are currently of low priority for further work due to their rapid degradation in the environment via hydrolysis. The reaction products (methanol, potassium hydroxide and sodium hydroxide) have been evaluated within the OECD SIDS program for their hazardous properties and have been considered of low priority for further work for the environment.