SIDS INITIAL ASSESSMENT PROFILE

CAS No. (Nos.)	107-21-1, 111-46-6, 112-27-6, 112-60-7, 4792-15-8
Chemical Name(s)	Ethylene glycol, Diethylene glycol, Triethylene glycol, Tetraethylene glycol, Pentaethylene glycol (Ethylene Glycols Category)
Structural Formula	$HOCH_2CH_2OH$, $HO(CH_2CH_2O)_2H$, $HO(CH_2CH_2O)_3H$, $HO(CH_2CH_2O)_4H$, $HO(CH_2CH_2O)_5H$

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

Category members are represented by the generic molecular structure, $HO(CH_2\ CH_2\ O)_n\ H$, where n = 1-5. All category members therefore possess two terminal hydroxy groups and the members differ from each other only in the number of oxyethylene units. Because of this it is appropriate to classify EG and the higher glycols (up to and including n=5) as a single group. At n = 6-8, absorption from ingestion decreases and certain physicochemical attributes change significantly. Adequate studies are available for most of the required SIDS endpoints for the category members. A category approach is used where experimental data are not available.

Category members ethylene glycol and the higher glycols (di-, tri-, tetra-, and penta-) are closely related in structure and have physicochemical properties which differ in a regular and expected way as a result of increasing molecular weight and consistent functionality of a relatively less stable hydroxy moiety on each end of the molecule. Thus, the hazard profile and dose response are also expected to change consistently, with decreasing potential for adverse effect with increasing molecular weight. Available data and quantitative structure activity modeling for the category for several toxicological endpoints confirm this expectation, indicating that it is reasonable to assume consistent changes in toxicological effects for the relatively few instances where experimental data for the category are lacking.

Available data and modeling confirm that as the molecular weight increases, the potential for systemic, reproductive, and developmental toxicity decreases. Available data for several ecotoxicological endpoints demonstrate that the potential for these effects is consistently low throughout the category in that the LOELs are greater than the limit dose (1000 mg/kg). Polyethylene glycol 200 (PEG 200, CAS No. 25322-68-3), which is not a category member, is a mixture of EGs (n=2 to 8, thereby containing category members and other higher molecular weight ethylene glycols) with an average molecular weight of approximately 200 and an average of 4 oxyethylene units. It has some properties similar to the category members and data from this mixture are used to support the trend that as molecular weight increases, toxicity decreases within the five-member category.

Human Health

EG, DEG and TEG are almost completely absorbed by laboratory animals via oral routes as would be expected from their total miscibility with water. As tetraEG and pentaEG are likewise completely miscible with water and are of relatively low molecular weight, it is reasonable to assume that they are likewise extensively absorbed via the oral route. The absorption estimate for inhaled EG is approximately 100 percent. No direct measures of inhalation absorption are available for DEG, TEG, tetraEG and pentaEG. In *in vivo* rodent dermal absorption studies, 1-51% of EG was absorbed. Dermal bioavailability of DEG was estimated as 9%. No direct measures of dermal absorption are available for TEG, tetraEG, and pentaEG. Since the EGs are completely soluble in water, they are expected to be well distributed throughout the aqueous tissues of the body with lower concentrations in adipose tissue; Uniform distribution has been demonstrated to a limited extent for EG. The main metabolic pathway for metabolism of the EGs is oxidation via alcohol dehydrogenases and aldehyde dehydrogenases. The main metabolites of EG are carbon dioxide, oxalic acid and glycolic acid. Identified DEG and TEG metabolites include carbon dioxide, oxalic acid and other acid metabolites. EG, DEG, and TEG may be directly eliminated by urinary excretion. Acid metabolites of EG, DEG and TEG are also eliminated in urine and may also be metabolized to carbon dioxide and eliminated in exhaled breath.

Results of acute mortality studies in rodents indicate that the EGs are generally of low acute toxicity by the oral, inhalation and dermal routes of exposure with the values for reported endpoints being greater than a limit dose. Acute lethality by the oral route is greater than that for the other category members. The acute toxic effects of EG in laboratory animals and humans can include narcotic effects, metabolic acidosis and renal toxicity. Acute oral toxicity in rats (measured as LD50 in mg/kg) ranged from 5890 in EG to over 16000 in pentaEG. Tested members of the EG category have LOAELs greater than a limit dose (1000mg/kg) for repeated dose toxicity studies by the dermal, inhalation and oral routes. No adverse effects were seen in dermal studies performed with EG and tetra EG. Oral repeated dose toxicity (NOAEL in mg/kg/day) ranged from approximately 150 for EG and DEG to greater than 2000 for tetraEG and pentaEG. Studies by the oral route demonstrate that repeated oral exposure to the lower molecular weight category members (EG and DEG) induces renal toxicity. However, TEG had only minor effects on the kidney and as the number of oxyethylene units increases to four and five oxyethylene units, no renal toxicity is observed even at high doses. Due to the structural and physical similarities of pentaEG with the other category members and data for the EG mixture PEG 200, it can be reasonably assumed that pentaEG also will have low potential for repeated dose mammalian toxicity.

EG can produce skin irritation, but the other EGs tested on humans (DEG, TEG, and tetraEG) produce minimal irritation, and the human skin primary irritation index decreases with an increasing number of oxyethylene units. All category members produce only minor eye irritation. While DEG caused respiratory depression, the characteristics were not typical of a "pure" airway irritant (WIL, 2001). In a human clinical study of EG, all participants found exposure to 0.14mg/L to be irritating to the throat and exposures above 0.20mg/L could not be tolerated due to severe irritation. EG, DEG, TEG and tetraEG have not induced skin sensitization.

Mutagenicity studies in bacteria and *in vitro* mutagenicity studies in mammalian cells have been conducted for all category members. The results of the bacterial studies have been uniformly negative (± S9 activation). The results of *in vitro assays* for chromosomal aberrations and in sister chromatid exchange assays have also been uniformly negative for all category members. PentaEG was tested *in vitro* for chromosomal aberrations after the SIAM review, and the results were negative. PentaEG produced no biologically significant chromosomal damage in the mouse bone marrow micronucleus test. Evidence indicates that tetraEG causes chromosomal aberrations *in vitro*. However, results of *in vivo* genotoxicity studies have been negative (dominant lethal test) or equivocal (bone marrow chromosome aberrations in rats, peripheral blood micronucleus test in mice). In several studies conducted for EG, DEG and TEG some of which were limited, there was no evidence of carcinogenicity in animals. QSAR results from multiple models for mutagenicity *in vitro* (Salmonella, mouse lymphoma) and cancer were negative. No structural alerts were identified. Information on the genotoxicity of PEG 200 is not considered to contribute to interpretation of results for compounds in the category, due to the lack of assessment of some its components for mutagenicity.

EG, DEG, and TEG have been assessed using the Reproductive Assessment by Continuous Breeding protocol. EG and DEG produced decreased numbers of litters per fertile pair and live pups per litter. No reproductive effects were seen for TEG-exposed mice. TetraEG was negative in the rodent dominant lethal assay and repeat dosing with tetraEG for 4 weeks in rats produced no notable changes in the histopathology of the testes and epididymides. Extensive developmental toxicity data are available for EG, DEG, and TEG.. Observed effects include reduced fetal body weights and skeletal variations for EG, DEG and TEG and malformations at higher dose levels and dose rates for EG and DEG. By the oral route, DEG and TEG do not cause any developmental effects below a limit dose. There is a clear trend of NOAELs increasing with the number of oxyethylene units in the rat studies. Benchmark dose analysis indicated that the trend also held for the mouse. NOAELs for repeated oral exposure ranged from approximately 150mg/kg/day for EG (16-week study) to an estimate of over 2000 mg/kg/day for pentaEG. While studies of repeated dermal exposure to the EGs are limited, the two relevant studies indicate that these compounds are of low toxicity by the dermal route. No effect was observed in maternal animals dermally exposed to EG at 3549 mg/kg/d for 10 days and no toxicity was found in animals dermally exposed to 3360 mg/kg/d tetraEG for 13 weeks. These findings are consistent with the low dermal bioavailability determined for DEG and assumed for higher molecular weight EGs. Based on studies by different routes (oral vs. dermal), EG exposure below the limit dose results in developmental toxicity in animals only by the oral route and only when rapidly ingested (bolus).

Environment

The ethylene glycol category consists of liquids of low volatility and high water solubility. Partition coefficients (Log Kow) range from –1.20 for EG to –2.3 for pentaEG. Fish acute toxicity (measured as LC50 in mg/L) has been tested for all category members and ranges from 22800 for EG to greater than 50000 for pentaEG. The acute toxicity of the

category members to invertebrates has also been tested. Toxicity to *Daphnia* (measured as LC50 in mg/L) is greater than 20,000 for all category members except tetraEG (LC50=7800 mg/L) indicating low toxicity, but the toxicity was not as uniform as in fish. Toxicity evaluations in another invertebrate, brine shrimp (A*rtemia salina)* were imprecise, but appear to be more consistent than the measured *Daphnia* toxicity values (no toxicity observed at the highest tested dose, 20g/l for EG, 10 g/l for DEG, TEG and tetraEG). Algal toxicity has been tested for EG, DEG, TEG, and PentaEG, and no toxicity was found at concentrations less than or equal to 100 mg/L. Based on the low toxicity of tested category members, it can reasonably be assumed that tetraEG likewise poses no appreciable hazard to algae. The QSAR predictions indicate that the category members should exhibit low toxicity, with trends of decreasing toxicity with increasing chain length and are supportive of the available experimental data. All evidence indicates that EG is readily biodegradable. The rate of degradation, however, decreases for other members of this category. Biodegradation of EGs may deplete levels of dissolved oxygen in receiving water-bodies near airports where these chemicals are used in high volume for deicing activities. Depletion of dissolved oxygen can result in adverse effects on aquatic organisms that may be present near points of effluent discharge. There is a limited potential for category members to bioaccumulate.

Exposure

Total global production capacity estimated for each category member in 2001 was as follows: EG- 15,841,000 metric tons; DEG- 1,584,000 metric tons; TEG- 150,000 metric tons; Tetra EG- 10,000 metric tons; and PentaEG- 3,000 metric tons.

Approximately 78% of EG is consumed in the manufacture of polyethylene terephthalate (PET) with an additional 13% used as an ingredient in automotive coolants. The largest use of DEG is in the production of unsaturated polyester resins, polyols and polyurethanes. The majority of TEG consumption is for natural gas dehydration. Commercial mixtures of tetra- and pentaEGs left over from distilling out lower boiling EG, DEG, and TEG are often processed into brake fluids, and can also be used as an aid in cement grinding.

Occupational exposure to members of the EG category is limited during manufacture by the enclosed, continuous nature of the manufacturing process. The most likely routes of occupational exposure to EG are dermal and inhalation of vapors and mists. The use with the highest potential for exposure is in deicing aircraft and runways. There is some potential for consumer exposure to lower molecular weight EGs. Consumers may come into dermal contact with EG and DEG infrequently and for short periods, when topping off radiator antifreeze in personal vehicles. Consumers may also come into dermal contact with low concentrations of EG present in a variety of commercial products and DEG in limited consumer products. Human exposure to EG in commercial products can occur through dermal contact and inhalation of air and ingestion of soil near point sources. Workplace exposure to DEG may occur during manufacture or use as an industrial intermediate. Exposure may also occur during its use as a solvent. Almost all DEG is used industrially. The most likely human exposure to TEG is in the industrial setting. The most likely route of exposure is through dermal contact (e.g., during quality control sampling). The primary uses of tetraEG, pentaEG, or mixtures containing these substances, are industrial. Therefore human exposure is most likely to occur in the work place, during such uses as a solvent, industrial extractant, plasticizer or humectant. The most likely route of industrial exposure is dermal, since tetraethylene and pentaethylene glycols possess extremely low vapor pressure(6×10^{-5} hPa or less).

RECOMMENDATIONS

Environment: The chemicals in this category are currently of low priority for further work.

Human Health: Ethylene glycol and diethylene glycol are candidates for further work. Depending upon use and exposure, member countries should assess possible risk associated with renal (EG and DEG) and/or developmental toxicity (EG) for the lower molecular weight EGs.. The remaining chemicals in this category are currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Environment

Available data for several ecotoxicological endpoints demonstrate that ecotoxicological effects due to direct exposure to ethylene glycols are unlikely to result. However, biodegradation of ethylene glycols may deplete levels of dissolved oxygen in receiving water-bodies near airports where these chemicals are used in high volumes for deicing activities. Depletion of dissolved oxygen can result in adverse effects on aquatic organisms that may be present near points of effluent discharge. Member countries (particularly Nordic countries) that use EG for deicing at airports should verify their exposure profile and risk management measures for this chemical to determine if there is a need for additional measures to be applied.

Human Health

Based on studies by different routes (oral vs. dermal) and different regimes (gavage vs. diet), EG exposure below the limit dose (1000 mg/kg/day) results in developmental toxicity in animals only by the oral route and only when rapidly ingested (bolus). Depending upon use and exposure, member countries should assess possible risk associated with renal (EG and DEG) and developmental toxicity (EG) for the lower molecular weight EGs. In this context, an additional study on dose-response for renal effects following long-term exposure to EG was completed, and the results, confirming previous chronic animal studies for renal effects, are included in the EG SIDS Dossier. An additional *in vitro* gene mutation assay for pentaEG in mammalian cells, the CHO/HPRT test, was completed to expand the genotoxicity profile of this substance, confirming the negative results for gene mutation assays for all members of the category.