SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2807-30-9, 111-76-2(surrogate only), 112-07-2, 112-25-4
Chemical Name	Monoethylene glycol ethers category (Mono EGEs)
Structural Formula	$HOCH_2\ CH_2OCH_2CH_2CH_3$ Ethylene glycol propyl ether (EGPE, CAS No. 2807-30-9), $HOCH_2\ CH_2O\ CH_2\ CH_2CH_2\ CH_3$ Ethylene glycol butyl ether (EGBE, CAS No. 111-76-2), $CH_3C(=O)OCH_2\ CH_2O\ CH_2CH_2CH_2CH_3$ Ethylene glycol butyl ether acetate (EGBEA, CAS No. 112-07-2), $HOCH_2\ CH_2OCH_2CH_2\ CH_2CH_2\ CH_2CH_3$ Ethylene glycol hexyl ether (EGHE, CAS No. 112-25-4)

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The four substances of this category all have similar molecular structures, functionality and metabolic pathways. The category members demonstrate similar physicochemical properties and mammalian toxicity. EGBE is included in the category only to fill data gaps for mammalian toxicity. A separate dossier on EGBE is not included as this chemical's data set was previously agreed to at SIAM 6. The reader should refer to the existing SIDS dossier for additional information on EGBE. The acetylated glycol ether, EGBEA, although rapidly metabolized *in vivo* to its corresponding glycol ether, is not expected to hydrolyze rapidly to EGBE in the aqueous environment. Therefore, EGBEA aquatic toxicity data are not extrapolated to the other category members.

Toxicokinetics

EGPE, EGBE and EGHE are substrates for alcohol dehydrogenase isozyme ADH-3, which catalyzes the conversion of their terminal alcohols to aldehydes (which are transient metabolites). Further, rapid conversion of the aldehydes by aldehyde dehydrogenase produces alkoxyacetic acids, which are the predominant urinary metabolites of mono substituted glycol ethers; for example, 2-propoxy acetic acid (PAA) is a metabolite of EGPE and butoxy acetic acid (BAA) is a metabolite of EGBE. At equivalent concentrations, metabolism of EGPE is less rapid than EGBE and more rapid than EGHE.

Human Health

Oral LD_{50} values in rats for all category members range from 739 (EGHE) to 3089 mg/kg bw (EGPE), with values increasing with decreasing molecular weight. Four to six hour acute inhalation toxicity studies were conducted for these chemicals in rats at the highest vapour concentrations practically achievable. Values range from $LC_0 > 85$ ppm (508 mg/m^3) for EGHE, $LC_{50} > 400$ppm (2620 mg/m^3) for EGBEA to $LC_{50} > 2132$ ppm (9061 mg/m^3) for EGPE. No lethality was observed for any of these materials under these conditions.Dermal LD_{50} values in rabbits range from 435 mg/kg bw (EGBE) to 1500 mg/kg bw (EGBEA). Overall these category members can be considered to be of low to

moderate acute toxicity. All category members cause reversible irritation to skin and eyes, with EGBEA less irritating and EGHE more irritating than the other category members. EGPE and EGBE are not sensitizers in experimental animals or humans.

Signs of acute toxicity in rats, mice and rabbits are consistent with hemolysis (with the exception of EGHE) and non-specific CNS depression typical of organic solvents in general. Alkoxyacetic acid metabolites, PAA and BAA, are responsible for the red blood cell hemolysis. Signs of toxicity in humans deliberately ingesting cleaning fluids containing 9-22% EGBE are similar to those of rats, with the exception of hemolysis. Although decreased blood hemoglobin and/or hemoglobinuria were observed in some of the human cases, it is not clear if this was due to hemolysis or hemodilution as a result of administration of large volumes of fluid. Red blood cells of humans are many-fold more resistant to toxicity from EGPE and EGBE *in vitro* than those of rats. Accepted PBPK models are available for rats and humans which predict the distribution and metabolism of EGBE. These demonstrate that even at saturated vapor concentrations of EGBE, it is not possible to reach haemolytic blood concentrations of BAA in humans by the inhalation route of exposure.

Evaluation of hemolysis and its associated effects in the liver, spleen, and kidney of rodents and rabbits was done by repeatedly exposing rats via inhalation to 100, 200, or 400 ppm EGPE (425, 850, or 1700 mg/m^3) 6h/day, 5d/week for 14 weeks or to EGBE (rats and mice) at 31, 62.5, 125, 250, 500 ppm (150, 302, 603, 1207 or 2415 mg/m^3) and to EGHE (rats) at 20, 41 or 71 ppm (120, 245 or 425 mg/m^3). The NOAEL for EGPE in rats was 100 ppm and those for EGBE were less than 31 ppm (150 mg/m^3) in rats and 62.5 ppm (302 mg/m^3) in mice, respectively. For EGHE the NOAEL was 41 ppm (245 mg/m^3). Orally administered EGPE to rats at gavage doses of 195, 390, 780, or 1560 mg/kg bw/day for 6 weeks, generated a NOAEL of 195 mg/kg bw/day. Hemolysis and histopathological changes in the liver and kidney were not seen in rats exposed for 14 weeks with up to 71 ppm (425 mg/m^3) EGHE by inhalation, suggesting that this material is not as potent a hemolytic agent as EGBE. In the case of EGBE and EGPE, the hemolytically active agents have been shown to be the acid metabolites, BAA and PAA, respectively.

The fact that the NOAEL for repeated dose toxicity of EGBE is less than that of EGPE is consistent with red blood cells being more sensitive to EGBE than EGPE. Blood from mice, rats, hamsters, rabbits and baboons were sensitive to the effects of BAA *in vitro* and displayed similar responses, which included erythrocyte swelling (increased hematocrit and mean corpuscular hemoglobin), followed by hemolysis. Blood from humans, pigs, dogs, cats, and guinea pigs was less sensitive to hemolysis by BAA *in vitro*.

In the absence and presence of metabolic activation, EGBE tested negative for mutagenicity in Ames tests conducted in *S. typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 and EGHE tested negative in strains TA98, TA100, TA1535, TA1537 and TA1538. *In vitro* cytogenicity and sister chromatid exchange assays with EGBE and EGHE in Chinese Hamster Ovary Cells with and without metabolic activation and in vivo micronucleus tests with EGBE in rats and mice were negative, indicating that these glycol ethers are not genotoxic.

The US National Toxicology Program (NTP) conducted a 2-year inhalation chronic toxicity and carcinogenicity study with EGBE in rats and mice. A significant increase in the incidence of liver hemangiosarcomas was seen in male mice and forestomach tumours in female mice. The data were evaluated by IARC in June 2004 and EGBE was classified as IARC Group 3 (inadequate evidence of carcinogenicity in humans and limited evidence of carcinogenicity in animals). In 2000, the EU classification of EGBE was reviewed under the European Commission process for the classification and labeling of dangerous substances. It was decided that based on the mode of action data available, there was no significant hazard for human carcinogenicity and there was no support for a category 3 (carcinogen) classification. This decision was reconfirmed in 2004.

The results of reproductive and developmental toxicity studies indicate that the glycol ethers in this category are not selectively toxic to the reproductive system or developing fetus, developmental toxicity is secondary to maternal toxicity. Results of the 2-generation, continuous breeding study in CD1-mice exposed by drinking water to 700, 1,300, or 2,100 mg/kg bw/day EGBE show that parental toxicity was observed at all doses tested (significantly reduced liver and kidney weights at the lowest dose, severe toxicity, including death at the mid and higher doses) and fertility was affected at the two highest doses. Although there was no effect of 700 mg/kg bw/day on fertility, live pup weights from animals in this group were slightly but statistically significantly reduced. The parental and offspring

LOAELs were 700 mg/kg bw/day but the NOAEL can be considered close to this value. The repeated dose toxicity studies in which reproductive organs were examined indicate that the members of this category are not associated with toxicity to reproductive organs (including the testes).

Results of the developmental toxicity studies conducted via inhalation exposures during gestation periods on category members EGPE (rabbits -125, 250, 500 ppm or 531, 1062, or 2125 mg/m^3 and rats - 100, 200, 300, 400 ppm or 425, 850, 1275, or 1700 mg/m^3), EGBE (rat and rabbit - 25, 50, 100, 200 ppm or 121, 241, 483, or 966 mg/m^3), and EGHE (rat and rabbit - 20.8, 41.4, 79.2 ppm or 124, 248, or 474 mg/m^3) indicate that the members of the category are not teratogenic.

Inhalation of a maternally toxic concentration of EGBE [100 ppm (or 483 mg/m^3) in the rat and 200 ppm (or 966 mg/m^3) in the rabbit] throughout gestation was associated with embryotoxicity, as evidenced by an increased number of resorptions, and a decreased number of implantations. An increase in the number of fetuses with skeletal variations was noted in offspring of rats exposed to maternally toxic concentrations of EGPE by inhalation (≥ 200 ppm or 966 mg/m^3). In rats exposed to EGHE and rabbits exposed to EGHE or EGPE by inhalation, no effects on the fetus were noted (even at concentrations that produced maternal toxicity).

The NOAELs for developmental toxicity are greater than 500 ppm or 2125 mg/m^3 (rabbit-EGPE), 100 ppm or 425 mg/m^3 (rat-EGPE), 50 ppm or 241 mg/m^3 (rat EGBE) and 100 ppm or 483 mg/m^3 (rabbit EGBE) and greater than 79.2 ppm or 474 mg/m^3 (rat and rabbit-EGHE). Based on the structural similarities between the members, developmental toxicity data for the tested glycol ethers are expected to be predictive of data for EGBEA.

Environment

Members of the category are high boiling liquids (boiling points in the 150-208ºC range), with low melting points (-70 to -50°C). Vapor pressures are in the range of 0.067-1.3 hPa at room temperature. Water solubility values range from soluble (EGHE 9.9 g/L, EGBEA 15 g/L) to miscible (EGPE and EGBE). Octanol-water partition coefficients range from 0.79 to 1.97. Henry's Law Constants range from 7.38×10^{-8} to 6.38×10^{-6} atm-m^3/mole. Hydroxyl radical induced photodegradation half-lives range from 4.9 – 6.0 hours.

EGPE and EGHE, like other simple glycol ethers, possess no functional groups in their molecular structures that are readily subject to hydrolysis in the presence of water. EGBEA, however, possesses an ester group that is estimated to have a half-life of about 30 days in neutral ambient water under abiotic conditions. Level III fugacity modeling indicates that category members, when released to air and water, will partition predominately to water and, to a lesser extent, to air and soil. Estimates of soil and sediment partition coefficients (Kocs ranging from 1 – 10) suggest that category members would exhibit high soil mobility. Estimated bioconcentration factors (log BCF) range from 0.463 to 0.732. Biodegradation studies indicate that all category members are readily biodegradable. The physical chemistry and environmental fate properties indicate that category members will not persist or bioconcentrate in the environment.

The aquatic toxicity data for ethylene glycol ether acetate (EGBEA) and the glycol ethers (EGPE, EGBE and EGHE) are considered separately because glycol ether acetates do not hydrolyze rapidly into their corresponding glycol ethers in water under environmental conditions. The LC_{50} or EC_{50} values for EGHE (which has the longest chain length and highest log Kow value) are lower than those for EGPE and EGBE (which have shorter chain lengths and lower log Kow values). Overall, the LC_{50} values for the glycol ethers in aquatic species range from 94 to > 5000 mg/L. For EGHE, the 96-hour LC_{50} for *Brachydanio rerio* (zebra fish) is between 94 and215 mg/L, the 48-hour EC_{50} for *Daphnia magna* was 145 mg/L and the 72-hour EC_{50} values for biomass and growth rate of algae (*Scenedesmus subspicatus*) were 98 and 198 mg/L, respectively. LC_{50}/EC_{50} values for EGPE and EGBE in aquatic species are 835 mg/l or greater.

Aquatic toxicity data for EGBEA show a 96-hour LC_{50} of 28.3 mg/L for rainbow trout (*Oncorhynchus mykiss),* a 48-hour LC_{50} of 37-143 mg/L for *Daphnia magna,* a 72-hour EC_{50} of greater than 500 mg/L for biomass or growth rate of algae (*Scenedesmus subspicatus* and *Pseudokirchneriella subcapitata,* respectively), and a 7-day EC_{10} of 30.4

mg/L and a NOEC of 16.4 mg/L for reproduction in *Ceriodaphnia dubia* .

Exposure

Annual U.S. production volumes for EGPE and EGBEA are each in the range of 4,540 – 22,700 metric tons. The production volume for EGHE is 450 – 4,500 metric tons. The use patterns for these materials are similar, with qualitative differences. All are used predominately as solvents or coalescing aids for surface coatings, printing inks, metal cleaners, detergents, fire foams, oil field chemicals, pharmaceutical manufacture, agricultural chemicals, leather manufacture and finishing cleaners and adhesives. They are also used as chemical intermediates and in hair dyes. Most applications are industrial, but these materials may also be present at the 1-10% range in some consumer products.

Human exposures to category members occur primarily via inhalation and dermal contact. Exposures occur to some extent during manufacture and formulation into products, but are more likely to be associated with the widespread uses given above. Exposure during manufacture is limited by the predominately closed, continuous nature of the process and equipment. Some releases to the atmosphere and water may occur during manufacture through venting and aqueous streams. Aqueous waste streams are routinely biologically treated. Although engineering controls and work practices may limit exposures during industrial use, solvent application conditions may vary widely, and atmospheric releases are expected through solvent evaporation.

Consumers may be exposed through use of products containing category members and also from environmental concentrations. Because category members degrade readily in the environment, environmental exposure should not be a major concern. Exposure monitoring information is not readily available.

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

These chemicals are currently of low priority for further work.

Human Health: The substances in the category possess properties indicating a hazard for human health (reversible eye and skin irritation, reversible CNS depression). These hazards do not warrant further work. However, they should nevertheless be noted by chemical safety professionals and users. Hemolysis and associated organ toxicity are noted in rats, mice and rabbits exposed to EGPE and EGBE. Humans are many-fold less sensitive to these effects and associated organ toxicity. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: EGPE, EGBE, and EGHE are of low priority for further work because of their low hazard profile. EGBEA possesses properties indicating a hazard for the environment. These hazards do not warrant further work as they are related to acute toxicity which may become evident only at high exposure level and the substance is readily biodegradable. However, they should be noted by chemical safety professionals and users.