SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	111-90-0, 112-15-2, 6881-94-3, 124-17-4, 112-59-4
Category Name	Diethylene glycol ethers category (Di EGEs)
Structural Formulas	$HO(CH_2\ CH_2O)_2CH_2CH_3$ Diethylene glycol ethyl ether (DGEE, CAS No. 111-90-0), $CH_3C(=O)O(CH_2CH_2O)_2CH_2CH_3$ Diethylene glycol ethyl ether acetate (DGEEA, CAS No. 112-15-2), $HO(CH_2CH_2O)_2\ CH_2CH_2CH_3$ Diethylene glycol propyl ether (DGPE, CAS No. 6881-94-3), $CH_3C(=O)O(CH2\ CH_2O)_2O\ CH_2CH_2CH_2CH_3$ Diethylene glycol butyl ether acetate (DGBEA, CAS No. 124-17-4), $HO(CH_2\ CH_2O)_2CH_2CH_2\ CH_2CH_2\ CH_2CH_3$ Diethylene glycol hexyl ether (DGHE, CAS No. 112-59-4)

SUMMARY CONCLUSIONS OF THE SIAR

Category and Use of Supporting Chemicals Justification

The category includes five diethylene glycol ethers or acetates (DGEE, DGEEA, DGPE, DGBEA and DGHE). The members of this category all have similar molecular structures, functionality and metabolic pathways and demonstrate similar physicochemical and environmental fate properties and mammalian toxicity. However, for aquatic toxicity, diethylene glycol ethers (DGEE, DGPE and DGHE) and diethylene glycol ether acetates (DGEEA and DGBEA) are considered separately because diethylene glycol ether acetates do not hydrolyze readily in water at environmental conditions.

Three additional structural analogs are included to support this category. Each of them has previously been endorsed at a SIAM. The chemicals are: diethylene glycol butyl ether (DGBE, CAS No. 112-34-5; SIAM4), ethylene glycol hexyl ether (EGHE, CAS No. 112-25-4; SIAM19), and ethylene glycol butyl ether acetate (EGBEA, CAS No. 112-07-2; SIAM19). EGHE and EGBEA are members from the monoetheylene glycol ethers category. DGBE is included to fill data gaps for mammalian and aquatic toxicity and provide supplemental data for the other category members. The molecular weight of DGBE is in between DGPE and DGHE, and DGBEA is rapidly hydrolyzed to DGBE in mammalian systems. The reader should refer to the existing SIDS dossier (SIAM 4) and EU Risk Assessment for additional information. Additionally, EGHE and EGBEA are included for the aquatic toxicity endpoints. These materials provide missing information for the corresponding diethylene glycol ethers/acetates DGHE and DGBEA. The reader should refer to the existing SIDS dossier (SIAM19) for any additional information.

Toxicokinetics

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The rate of dermal absorption of DGBE and DGBEA is similar. Once absorbed, DGBEA is rapidly hydrolyzed to DGBE by enzymes present in rat blood. Available metabolism studies in animals for members of the diethylene glycol ethers category indicate the principal route of elimination is via the urine. Only small or trace amounts of metabolites are found in expired air or feces. Limited human data indicate similar conclusions. The primary urinary metabolites of diethylene glycol ethers and acetates are alkoxyethoxy acetic acids. The metabolic fate of DGEE, DGPE and DGHE is expected to be similar to that of DGBE due to similarities in structure. Since DGBEA is rapidly hydrolyzed to DGBE by rat blood, DGEEA is expected to undergo rapid hydrolysis to DGEE in vivo. Therefore, the toxicological profiles of the acetates are expected to be similar to those of their corresponding glycol ethers.

Human Health

There are adequate oral, inhalation and/or dermal toxicity studies on the category members. Oral LD_{50} values in rats for all category members are all > 3000 mg/kg bw, with values generally decreasing with increasing molecular weight. Four to eight hour acute inhalation toxicity studies were conducted for all category members except DGPE in rats at the highest vapour concentrations achievable. No lethality was observed for any of these materials under these conditions. Dermal LD_{50} values in rabbits range from 2000 mg/kg bw (DGHE) to 15000 mg/kg bw (DGEEA). Signs of acute toxicity in rodents are consistent with non-specific CNS depression typical of organic solvents in general. All category members are slightly irritating to skin and slightly to moderately irritating to eyes (with the exception of DGHE, which is highly irritating to eyes). Sensitization tests with DGEE, DGEEA, DGPE, DGBE and DGBEA in animals and/or humans were negative.

Valid repeated-dose studies have been performed using most category members. One inhalation study with DGEE in rats (nose only, for 28 days) showed mild respiratory effects at 270 or 1100 mg/m^3 but no systemic toxicity. Repeated inhalation exposure of up to 94 mg/m^3 DGBE for 90 days had no effect on Wistar rats. Dermal studies were conducted in rabbits with DGEE, DGBEA, and DGHE as well as the supporting chemical DGBE. Effects from two dermal DGEE studies (30 days and 12 weeks) included unspecified percent mortality (unspecified doses in the 30 day study), and some kidney and liver effects, although results could not be verified. A 90-day dermal study with 489 to 3912 mg/kg/day DGBEA in rabbits resulted in hemoglobinuria and hemolysis at unspecified doses; a subchronic LD50 of 1956 mg/kg bw/day was determined. DGBE via the dermal route (13 weeks) had slight effects in rats (e.g., skin irritation at ≥ 200 mg/kg/day, slight blood in urine at ≥ 600 mg/kg/day). In a 9-day dermal study in rabbits, 100 to1000 mg/kg DGHE resulted in skin irritation and/or dermatitis. Valid oral studies conducted using DGEE, DGPE, DGBEA, DGHE and the supporting chemical DGBE ranged in duration from 30 days to 2 years. Effects predominantly included kidney and liver toxicity, absolute and/or relative changes in organ weights, and some changes in hematological parameters. All effects were seen at doses greater than 800-1000 mg/kg bw/day from oral or dermal studies; no systemic effects were observed in inhalation studies with less than continuous exposure regimens.

DGEE, DGEEA, DGBE, DGBEA and DGHE generally tested negative for mutagenicity in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and DGBEA tested negative in E. coli WP2uvrA, with and without metabolic activation. *In vitro* cytogenicity and sister chromatid exchange assays with DGBE and DGHE in Chinese Hamster Ovary Cells with and without metabolic activation and *in vivo* micronucleus or cytogenicity tests with DGEE, DGBE and DGHE in rats and mice were negative, indicating that these diethylene glycol ethers are not likely to be genotoxic.

Reliable reproductive toxicity studies on DGEE, DGBE and DGHE show no effect on fertility at the highest oral doses tested (4,400 mg/kg/day for DGEE in the mouse and 1,000 mg/kg/day for DGBE and DGHE in the rat). The dermal NOAEL for reproductive toxicity in rats administered DGBE also was the highest dose tested (2,000 mg/kg/day). Although decreased sperm motility was noted in F_1 mice treated with 4,400 mg/kg/day DGEE in drinking water for 14 weeks, sperm concentrations and morphology, histopathology of the testes and fertility were not affected. Results of the majority of adequate repeated dose toxicity studies in which reproductive organs were examined indicate that DGPE and DGBEA do not cause toxicity to reproductive organs (including the testes). Test material-related testicular toxicity was not noted in the majority of the studies with DGEE or DGEEA. However < in one study, DGEE of unknown purity reported testicular edema at a very high dose (approximately 4000 mg/kg bw/day). It is possible that the testicular effect was due to an impurity although a direct effect of DGEE cannot be

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ruled out.

Results of the developmental toxicity studies conducted with DGEE, DGBE and DGHE are almost exclusively negative. In these studies, effects on the fetus are generally not observed (even at concentrations that produced maternal toxicity). Exposure to 102 ppm (560 mg/m3) DGEE by inhalation (maximal achievable vapor concentration) or 1385 mg/kg/day DGEE by the dermal route during gestation did not cause maternal or developmental toxicity in the rat. Maternal toxicity and teratogenesis were not observed in rabbits receiving up to 1000 mg/kg/day DGBE by the dermal route during gestation; however a transient decrease in body weight was observed, which reversed by Day 21 In the mouse, the only concentration of DGEE tested (3500 mg/kg/day by gavage) caused maternal, but no fetal toxicity. Also, whereas oral administration of 2050 mg/kg/day DGBE (gavage) to the mouse and 1000 mg/kg/day DGHE (dietary) caused maternal toxicity, these doses had no effect on the developing fetus.

Environment

Members of the category are high boiling liquids (boiling points in the 196-259ºC range), with low melting points (-90 to -25°C). Vapor pressures are in the range of <0.01-0.168 hPa at room temperature. The diethylene glycol ethers are soluble in water. Octanol-water partition coefficients (log Kow values) range from -0.69 to +1.3. Henry's Law Constants range from 8.63 E-10 to 9.91 E-8 atm-m^3/mole. Estimated hydroxyl radical-induced atmospheric photodegradation half-lives range from 3.18 to 4.41 hours.

DGEE, DGPE, and DGHE possess no functional groups in their molecular structures that are readily subject to hydrolysis in the presence of water. The acetate ester groups of DGEEA and DGBEA will hydrolyze, with the hydrolysis rate dependent on temperature, pH and possible presence of impurities that can act as catalysts for hydrolysis. Level III fugacity modeling indicates that category members, when released to air and water, will partition to water (48.7-66.6%), soil (30.4-50.7%), air (0.52-2.88%), and sediment (0.08-0.15%). Estimates of soil and sediment partition coefficient (Kocs ranging from 1 – 10) suggest that category members would exhibit high soil mobility. Estimated bioconcentration factors (log BCF) range from 0.299 to 0.609. Category members for which adequate data are available (DGEE, DGHE and DGBEA) are readily biodegradable. These physicochemical and environmental fate properties indicate that category members will not persist in the environment or bioaccumulate.

The aquatic toxicity data for the diethylene glycol ethers (DGEE, DGPE and DGHE) and diethylene glycol ether acetates (DGEEA and DGBEA) are considered separately because diethylene glycol ether acetates do not hydrolyze readily in water at environmental conditions. The EC/LC_{50} values for the diethylene glycol ethers in fish range from 200 (for DGHE) to > 5000 mg/l (for DGPE and DGEE). In invertebrates, values range from 433 for DGHE to > 10,000 mg/l for DGEE and DGPE. No algae data are available for the category members; based on data from supporting chemicals, toxicity is expected to be > 100 mg/l for DGHE and > 500 mg/l for other category members.

The LC_{50} values for fish are 110 mg/l for DGEEA and 77 mg/l for DGBEA. Measured or estimated values for invertebrates are higher (665 mg/l measured for DGBEA, with higher estimated values for both chemicals). No algae data are available for the acetates; based on experimental data for EGBEA, EC_{50} values are expected to be > 500 mg/l.

Exposure

Annual U.S. production volumes for DGEEA, DGPE, and DGHE are each in the range of 450-2,270 metric tons. Annual U.S. production volumes of DGEE and DGBEA are each in the range of 4,500 – 22,700 metric tons. The use patterns for these materials are similar, with qualitative differences. All are used predominately as solvents or coalescing aids in formulations, such as for surface coatings, automotive coatings, metal cleaners, printing and silk screen inks, brake fluids. These are applications mostly in industrial settings. Some use is as chemical intermediates.

Numerous uses in consumer product formulations include in latex paints, lacquers, thinners, varnishes, window cleaners, kitchen, bathroom and other household cleaners, air fresheners, floor polishes and finishes, and paint and

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varnish removers. DGEEA is used in cosmetic formulations and DGEE is used in hair colorants. Consumer products are reported to contain 1-25% of diethylene glycol ethers.

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 processing and use, solvent application conditions may vary widely, and atmospheric releases are expected through solvent evaporation.

Consumers may be exposed through use of consumer products containing category members and also from environmental concentrations. Because category members photodegrade and biodegrade readily in the environment, environmental exposure will be decreased. Exposure monitoring information is not readily available.

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

Human Health: The chemicals are currently of low priority for further work. The substances in the category possess properties indicating a hazard for human health (skin and eye irritation and potential testicular toxicity of DGEE at high doses). Although these hazards do not warrant further work (as they are related to reversible effects or toxicity which may become evident only at high exposure levels), they should nevertheless be noted by chemical safety professionals and users. Although hemolysis is noted in rats, mice and rabbits repeatedly exposed to high oral or dermal concentrations of DGEE, DGPE, DGBE and DGBEA humans are many-fold less sensitive to red blood cell hemolysis by the major metabolites of similar chemicals (the monoethylene glycol ethers) than rats.

Environment: DGEE, DGPE, DGHE and DGEEA are of low priority for further work due to their low hazard profile. DGBEA has properties indicating a hazard for the environment (acute aquatic EC/LC50 values between 1 and 100 mg/l). However the chemical is currently of low priority for further work for the environment because of its rapid biodegradation and its limited potential for bioaccumulation.

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