SIDS INITIAL ASSESSMENT PROFILE

CAS No.	5131-66-8(29387-86-8) 29911-28-2 (35884-42-5) 88917-22-0 20324-33-8 and 25498-49-1
Chemical Name	Propylene Glycol n-Butyl Ether (PnB) Dipropylene Glycol n-Butyl Ether (DPnB) Dipropylene Glycol Methyl Ether Acetate (DPMA) Tripropylene Glycol Methyl Ether (TPM)
Structural Formula	$[CH_3\text{-}CH_2(OH)\text{-}CH_2\text{-}O]_n\text{-}(R)$ Where n = 1, 2, or 3; and R = alkyl (methyl or butyl) Note: In the case of n =1, the structures shown represent the predominant (alpha) isomers. For n=2 or 3, carbon atoms next to ether linkages may be either primary or secondary, leading to isomeric mixtures.

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The category contains four structurally related propylene glycol ethers:

Propylene Glycol n-Butyl Ether (PnB, 5131-66-8, major ("alpha") isomer, 29387-86-8 isomeric mixture)
Dipropylene Glycol n-Butyl Ether (DPnB, 29911-28-2 major isomer or 35884-42-5 isomeric mixture))
Dipropylene Glycol Methyl Ether Acetate (DPMA, 88917-22-0 isomeric mixture)
Tripropylene Glycol Methyl Ether (TPM, 20324-33-8 one of the isomers and 25498-49-1 isomeric mixture)

The alpha (secondary alcohol) form is kinetically favored during synthesis. PnB is available as the isomeric mixture in which the alpha isomer is the predominant isomer (ca. 95%. DPnB, DPMA and TPM are commercially produced as mixtures of isomeric components in which the internal ether linkages may be adjacent to either primary or secondary carbon atoms. Thus, for DPMA and DPnB the commercially produced products may contain up to 4 such isomers. In the case of TPM, the commercially produced product may contain up to 8 such isomers.

Data for these propylene glycol ethers are supplemented with data from three propylene glycol ethers that are closely related to the category members in molecular structure, physicochemical properties and toxicity and thus extend the category. These compounds are:

Propylene Glycol Methyl Ether (PM; CAS No. 107-98-2)
Propylene Glycol Methyl Ether Acetate (PMA; CAS No. 108-65-6)
Dipropylene Glycol Methyl Ether (DPM; CAS No. 34590-94-8 isomeric mixture and 20324-32-7 major isomer)

PM and PMA were reviewed at SIAM 11 and DPM was reviewed at SIAM 12. All were assigned as low priority for further work.

Human Health

As a class, the propylene glycol ethers are rapidly absorbed and distributed throughout the body when introduced by inhalation or oral exposure. Dermal absorption is somewhat slower but subsequent distribution is rapid. Most excretion for PGEs is via the urine and expired air. A small portion is excreted in the feces.

This category of propylene glycol ethers (PGEs) exhibits low acute toxicity by the oral, dermal, and inhalation routes. Rat oral LD50s range from >3,000 mg/kg (PnB) to >5,000 mg/kg (DPMA). Dermal LD50s are all > 2,000 mg/kg (PnB, & DPnB; where no deaths occurred), and ranging up to >15,000 mg/kg (TPM). Inhalation LC50 values were higher than 5,000 mg/m3 for DPMA (4-hour exposure), and TPM (1-hour exposure). For DPnB the 4-hour LC50 is >2,040 mg/m3. For PnB, the 4-hour LC50 was >651 ppm (>3,412 mg/m^3), representing the highest practically attainable vapor level. No deaths occurred at these concentrations for any of the four new category members. PnB and TPM are moderately irritating to eyes while the remaining category members are only slightly irritating to non-irritating. PnB is moderately irritating to skin while the remaining category members are slightly to non-irritating. None of the category members are skin sensitizers.

In repeated dose studies ranging in duration from 2 to 13 weeks, few adverse effects were found even at high exposure levels and effects that did occur were mild in nature. By the oral route of administration, NOAELs of 350 mg/kg-d (PnB – 13 wk) and 450 mg/kg-d (DPnB – 13 wk) were observed for liver and kidney weight increases (without accompanying histopathology). LOAELs for these two chemicals were 1000 mg/kg-d (highest dose tested). Dermal repeated-dose toxicity tests have been performed for all of the category members but DPMA. For PnB, no effects were seen in a 13-wk study at doses as high as 1,000 mg/kg-d. A dose of 273 mg/kg-d constituted a LOAEL (increased organ weights without histopathology) in a 13-week dermal study for DPnB. For TPM, increased kidney weights (no histopathology) and transiently decreased body weights were found at a dose of 2,895 mg/kg-d in a 90-day study in rabbits. By inhalation, no effects were observed in 2-week studies in rats at the highest tested concentrations of 3244 mg/m^3 (600 ppm) for PnB and 2,010 mg/m^3 (260 ppm) for DPnB. TPM caused increased liver weights without histopathology by inhalation in a 2-week study at a LOAEL of 360 mg/m^3 (43 ppm). In this study, the highest tested TPM concentration, 1010 mg/m^3 (120 ppm), also caused increased liver weights without accompanying histopathology. Although no repeated-dose studies are available for the oral route for TPM, or for any route for DPMA, it is anticipated that these chemicals would behave similarly to other category members.

One and two-generation reproductive toxicity testing has been conducted in mice, rats, and rabbits via the oral or inhalation routes of exposure on PM and PMA. In an inhalation rat study using PM, the NOAEL for parental toxicity is 300 ppm (1106 mg/m^3) with decreases in body and organ weights occurring at the LOAEL of 1000 ppm (3686 mg/m^3). For offspring toxicity the NOAEL is 1000 ppm (3686 mg/m^3), with decreased body weights occurring at 3000 ppm (11058 mg/m^3). For PMA, the NOAEL for parental and offspring toxicity is 1000 mg/kg/d. in a two-generation gavage study in rats. No adverse effects were found on reproductive organs, fertility rates, or other indices commonly monitored in such studies. In addition, there is no evidence from histopathological data from repeated-dose studies for the category members that would indicate that these chemicals would pose a reproductive hazard to human health.

Regarding developmental toxicity, all category members but DPMA have been tested by various routes of exposure and in various species at significant exposure levels and show no frank developmental effects. Due to the rapid hydrolysis of DPMA to DPM, DPMA would not be expected to show teratogenic effects. At high doses where maternal toxicity occurs (e.g., significant body weight loss), an increased incidence of some anomalies such as delayed skeletal ossification or increased 13th ribs, have been reported. Commercially available propylene glycol ethers showed no teratogenicity.

The weight of the evidence indicates that propylene glycol ethers are not likely to be genotoxic. *In vitro*, negative results have been seen in a number of assays for PnB, DPnB, DPMA and TPM. Positive results were only seen in 3 out of 5 chromosome aberration assays in mammalian cells with DPnB. However, negative results were seen in a mouse micronucleus assay with DPnB and PM. Thus, there is no evidence to suggest these propylene glycol ethers would be genotoxic *in vivo*. In a 2-year bioassay on PM, there were no statistically significant increases in tumors in

rats and mice.

Environment

Category members are all liquids at room temperature and all are water-soluble. Log octanol-water partition coefficients (Log Kow's) range from 0.309 for TPM to 1.523 for DPnB. Calculated BCF's range from 1.47 for DPnB to 3.16 for DPMA and TPM, indicating low bioaccumulation. Henry's Law Constants, which indicate propensity to partition from water to air, are low for all category members, ranging from 5.7×10^{-9} atm-m^3/mole for TPM to 2.7×10^{-9} atm-m^3/mole for PnB. Fugacity modeling indicates that category members are likely to partition roughly equally into the soil and water compartments in the environment with small to negligible amounts remaining in other environmental compartments (air, sediment, and aquatic biota). Propylene glycol ethers are unlikely to persist in the environment. Once in air, the half-life of the category members due to direct reactions with photochemically-generated hydroxyl radicals, range from 2.0 hours for TPM to 4.6 hours for PnB. In water, 3 of the 4 new category members and all 3 existing members are "readily biodegradable" under aerobic conditions. (DPMA degraded within 28 days (and within the specified 10-day window) but only using pre-adapted or "acclimated" inoculum.) In soil, biodegradation is rapid for PM and PMA. Acute aquatic toxicity testing indicates low toxicity for both ethers and acetates. For ethers, effect concentrations are > 500 mg/L. For acetates, effect concentrations are > 151 mg/L.

Exposure

According to the Chemical Economics Handbook (SRI International, 2000), in 1999, approximately 810 million pounds (368 thousand tonnes) of all propylene glycol ethers were produced worldwide. The US accounted for 285 million pounds (130 thousand tonnes), Europe 472 million pounds (215 thousand tonnes), and Japan 53 million pounds (24 thousand tonnes). In the USA, a production volume of 340 million pounds (155 thousand tonnes) of all propylene glycol ethers is estimated for 2004. In 1999, production of PnB, DPnB, and TPM was 23, 10.5 and 6 million pounds (10, 4.8 and 2.7 thousand tonnes), respectively. Modern production methods result in alpha isomer content in excess of 95% and beta isomer content less than 5% for the mono-propylene glycol ethers. Estimated 2004 production for these specific ethers is 29, 14 and 7 million pounds (13, 6.4 and 3.2 thousand tonnes) respectively. These production volumes agree fairly well with the Inventory Update Rule (IUR). 1993 production information for DPM acetate was 1-2 million pounds (0.5 – 0.9 thousand tonnes). The four propylene glycol ethers comprising this category are used in the manufacture of a wide variety of industrial and commercial products, including surface coatings (paints and varnishes), cleaners, inks, resins, cosmetics, and as inert carrier solvents in pesticide formulations. Exposures to these propylene glycol ethers are likely to occur by both the inhalation and dermal routes for workers and consumers.

RECOMMENDATION

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

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemicals in this category are currently of low priority for further work. Some of the chemicals in this category possess properties indicating hazards to human health (skin and eye irritation). Although this hazard does not warrant further work (as it is related to non-adverse, reversible, transient effects), it should nevertheless be noted by chemical safety professionals and users.