

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Memo to File for the Propylene Glycol n-butyl-ethers (PnB)

CAS Numbers:

5131-66-8 1-butoxy-2-propanol (alpha isomer)
15821-83-7 2-butoxy-1-propanol (beta isomer)
29387-86-8 propylene glycol n-butyl ether (mixed isomers)
63716-40-5 n-butoxy propanol (mixed isomers)
TRADE NAMES Propasol® Solvent B, ARCOSOLV® PNB,
DOWANOL® PNB

FROM: Margaret M Sadoff, Toxicologist

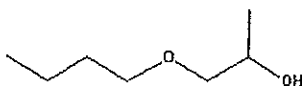
DATE: March 21, 2007

SUBJECT: Re-Evaluation of Screening Level

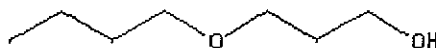
The ITSL for the propylene glycol n-butyl ethers is 77 ug/m³, annual average.

Propylene glycol n-butyl ether (PnB) exists as a mixture of the alpha and beta isomers. The alpha isomer [CAS# 5131-66-8] is thermodynamically favored and comprises > 95% of most commercial mixtures. The beta isomer is not produced commercially. The above-referenced CAS numbers were evaluated together to determine if any new toxicological data exist that could be used to update the screening level. Currently, AQD has an ITSL of 70 ug/m³ (annual) for CAS Nos. 5131-66-8 and 29387-86-8 based on acute and short-term inhalation studies.

A search of the literature and the following databases was performed for information regarding the propylene glycol n-butyl ethers: American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Integrated Risk Information System (IRIS), Registry of Toxic Effects of Chemical Substances (RTECS), Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, CAS Registry Online, Hazardous Substance Data Bank (HSDB), National Library of Medicine/Toxline, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Study Database, IPCS Intox Databank, Entrez PubMed literature search engine, Scirus literature search engine, Acute Toxicity Values (AEGLs, ERPGs, TEELs), ATSDR acute and chronic MRLs, and CalEPA's Toxicity Values Database.



5131-66-8 (alpha isomer)



29387-86-8 (generic, mixed isomers)

Physical/Chemical Properties and Uses

The propylene glycol ethers are a class of widely used chemical in solvent applications such as paints, lacquers, resins, other surface coatings and cleaners. PnB is a mixture of a primary and secondary alcohol and is used as a coupling agent and solvent in domestic and commercial cleaning solutions such as degreasers, paint removers, metal cleaners, and hard surface cleaners. With a boiling point of 171°C and a vapor pressure < 1 mmHg, this chemical has low volatility. Atmospheric half-life is approximately 4 hours. Occupational and consumer exposure is expected to be primarily through the inhalation and dermal routes.

Human Exposure and Occupational Limits

There are no occupational exposure limits for any of the PnB CAS numbers. A German OEL of 200 ppm was proposed but never adopted. There are no human case studies reported in the literature. ATSDR has an intermediate MRL for the parent compound, propylene glycol, of approximately 30 µg/m³ based on nasal hemorrhaging in rats.

The following acute and subchronic data is based on unpublished industry reports (DOW and Union Carbide) as reported in *OECD SIDS Initial Assessment Report for SIAM 17 for Propylene Glycols* as part of the High Production Volume Program Evaluation, 2002. Some of this data was also reported in summary by HG Verschuuren of DOW Europe (1996) *Toxicological Studies with Propylene Glycol n-Butyl Ether, Occupational Hygiene 2: 311-318*.

Acute Oral Toxicity

Three groups of Wistar rats (5/sex/dose) received single oral doses of 1800, 2400 or 3200 mg/kg PnB via cannula. Animals were observed for signs of toxicity for 14 days. All deaths occurred within 24 hours of dosing. The calculated oral LD₅₀'s were as follows:

males (1)	5500 mg/kg
females	2700 mg/kg (95CL 2400-3600 mg/kg)
combined	3300 mg/kg (95CL 2800-4500 mg/kg)

Adverse signs included weight loss, lethargy, coma, hypopnea, gasping and dacryorrhea. Surviving rats showed no adverse signs by day two and no gross lesions upon necropsy. Rats that died from treatment exhibited hemorrhage of the stomach and small intestine and hyperemia of the bladder.

(From an unpublished study by Reijnders, JBJ & Zucker-Keizer AMM (1987). Evaluation of the acute oral toxicity of Dowanol-PNM in the rat. NOTOX Report No. 0482/699.)

Other rat LD50's reported in this HPV chemical summary (with no accompanying detail) were: 2490, 2500 and 5200 mg/kg.

Acute Inhalation Toxicity

A single group of Fischer 344 rats (5/sex) was exposed via whole body inhalation for 4 hours to a vapor concentration of 651ppm PnB (3,412 mg/m³). After 14 days of observation, no signs of toxicity were noted during or after exposure and there were no deaths. No lesions were observed at necropsy except for a unilateral distension of the ovarian bursa in one female which was considered unrelated to exposure. The reported LC50 from this study is > 651ppm (3,412 mg/m³).

(From an unpublished study by Corley et al. (1987). Propylene glycol n-butyl ether: an acute vapour inhalation study in Fischer 344 rats. Dow Report No. K-005473-004.)

One other rat LC50 was reported in this HPV chemical summary (with no accompanying detail) as 5,830 mg/m³ (8 hrs).

Additional information reported include: 1) animals exposed to saturated vapors for 8 hours survived with no significant adverse effects and 2) six female rats exposed to concentrated vapor (approx. 5.83 mg/L) for 8 hours survived with hypoactivity reported as the principle clinical sign.

PnB is mild to moderately irritating to skin and eyes but is not a skin sensitizer. Dermal LD50's in rats are > 2000 mg/kg and 2640 mg/kg, Dermal LD50's in rabbits are: 1400, 3100, and 3133 mg/kg.

Suchronic Toxicity Testing

Species/Study	Route	Exposure	Duration	LOAEL/NOAEL (effect)
Fischer 344 Rats M/F/ DOW	Inhalation	270, 1080, 3780 mg/m ³ 6h/d 5d/wk*	2 weeks	3780 mg/m ³ (slight but not statistically significant increased relative liver weight)
Fischer 344 & Sprague-Dawley Rats M/F/ Union Carbide	Inhalation	54, 540, 1622, 3244 mg/m ³ 6h/d 5d/wk	11 days	3244 mg/m ³ (ocular toxicity & increased liver weight)
Rats M/F/ DOW	Inhalation	3244 mg/m ³ 7h/d 5d/wk	31 days	3244 mg/m ³ (increased liver weight w/no

				accompanying histopathology)
Sprague-Dawley Rats M/F/ DOW	Oral - gavage	0, 100, 200, 400 mg/kg/d	2 weeks	400 mg/kg (none)**
Fischer 344 Rats M/F/ DOW	Oral – Drinking water	100, 350, 1000 mg/kg/d***	13 weeks w/4 weeks post obs	350 mg/kg (none) 1,000 mg/kg (increased liver weights in males and increased kidney weights in females w/no accompanying histopathology)
Wistar Rats M/F/ Hazleton Labs	Dermal	≈ 0, 88 264, 880 mg/kg/d****	13 weeks	880 mg/kg (no systemic toxicity)

* 98.5% alpha isomer, 1.1% beta isomer; 9.2ppm peroxides.

** In particular, hemolytic effects were examined due to the ability of ethylene glycol n-butyl ether to cause red cell hemolysis at relatively low doses. No hemolytic effects were noted with PnB..

*** Actual doses received may have been higher than target doses by a factor of 10-15%. 99.4% alpha isomer; 3.23% beta isomer.

**** 95% alpha isomer; 5% beta isomer.

In vitro Genetic Toxicity

PnB is not considered to be mutagenic. It has consistently produced negative results on Ames tests, mouse lymphoma assays, or tests for unscheduled DNA synthesis and chromosomal aberrations.

Chronic Toxicity/Carcinogenicity

There is no data with regard to chronic or cancer effects from PnB. Dow did however conduct a 2-year inhalation study in rats and mice using propylene glycol methyl ether (PGME) at exposure concentrations of 0, 300, 1000 and 3000 ppm (1100, 3680 and 11,040 mg/m³) for 6 hrs/d, 5 d/wk. Similar to the subchronic study with PnB, liver and kidney weight changes were noted at the highest exposure level of PGME, but there were no accompanying histopathology changes and no increases in tumor incidence.

Reproductive Toxicity

There is one reproductive study of PnB by the dermal route in Wistar rats. PnB or negative control (PG) was applied daily on gestation days 6 through 15 to the shaved dorsal trunk skin of three groups of pregnant Wistar rats at doses equivalent to 0, 264, or 880 mg/kg/day. Slight skin reactions were observed in the dams from all treatment groups but no maternal toxicity or deaths were reported. No embryo or fetotoxicity was evident, although there was a slight statistical increase in the incidence of unilateral supernumary rudimentary thoracic ribs in the

highest dose group as compared to controls. The bilateral incidence was not elevated and the findings were not considered to be biologically relevant. Therefore, the developmental NOAEL from this study was 880 mg/kg/day.

(From Waalkens-Berendsen et al. (1988). Dermal embryotoxicity/teratogenicity study with propylene glycol n-butyl ether in rats. CIVO/TNO Study No. 991. DOW Deutschland, unpublished.)

A similar dermal study was also conducted in New Zealand white rabbits and reported a NOAEL/LOAEL of > 100 mg/kg.

(From Gibson WB, Nolen GA & Christian MS. (1989). Determination of the developmental toxicity potential of butoxypropanol in rabbits after topical administration. Fund Appl Toxicol 13: 359-365.)

Summary: PnB is mild to moderately irritating to eyes and skin. It has low systemic toxicity by the oral, inhalation and dermal routes in rats. Significant changes reported include increases in absolute and relative liver (by inhalation) and kidney weights (oral) but without accompanying histopathology, these changes could be considered adaptive. Since environmental exposures would primarily be through inhalation or dermal contact, data for these routes should be given higher consideration. **Collectively, the available short-term inhalation studies support a NOAEL/LOAEL of 600 ppm (3244 mg/m³) based on increased liver weights and minimal eye irritation.**

Recommendation

PnB is widely used in industrial and consumer products yet there remains a dearth of chronic toxicity data available. The systemic toxicity of PnB seems to be relatively low based primarily on unpublished acute, short-term and subchronic toxicity testing conducted by DOW (summarized in the OECD SIDS Initial Assessment Report). Its low reported short-term toxicity may help to explain why there is very little interest in further study of this chemical. Several classes of structurally related propylene glycol ethers, including PnB, were evaluated under the high production volume chemicals program and were deemed low priority for further research.

Based on the collective results of available inhalation studies, a LOAEL of 600 ppm (3244 mg/m³) is appropriate for ITSL derivation pursuant to R232(1)(d). Using the LOAEL algorithm with a UF of 3 (for the minimal effect of increased liver weight and eye irritation) gives an ITSL of 77 ug/m³ (annual average):

$$\begin{aligned} \text{ITSL} &= \frac{\text{LOAEL}}{35 \times 100 \times \text{UF}} \times \frac{\text{hrs exposed/day}}{24 \text{ hrs/day}} \\ &= \frac{3244 \text{ mg/m}^3}{35 \times 100 \times 3} \times \frac{6}{24} = 77 \text{ ug/m}^3 \end{aligned}$$

The ITSL derived above will be used for all four CAS numbers for propylene glycol n-butyl ether. The available toxicological testing utilized commercially available grades of PnB, consisting primarily of the alpha isomer (> 95%) with small amounts of the beta isomer (< 5%). The CAS

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numbers for the mixed isomers [29387-86-8 and 63716-40-5] are applicable to such commercial grades. It is also appropriate to use the above ITSL for the alpha isomer [CAS# 5131-66-8] since the commercial grade of PnB is largely composed of this isomer. The rationale for using the above ITSL for the beta isomer [CAS# 15821-83-7] is that it should always be emitted along with the alpha isomer. In addition, these ITSLs shall contain a footnote which restricts their combined impact to not exceed 77 ug/m^3 , annually.

MS:lh