FOREWORD INTRODUCTION

# Propylene Glycol Ethers

# SIDS Initial Assessment Report

# For

# SIAM 17

Arona, Italy, 11-14 November 2003

| | |
|---|---|
| **1. Chemical Name:** | Propylene Glycol Ethers |
| **Category Members:** | Propylene glycol n-butyl ether (PnB), CAS No. 29387-86-8 (5131-66-8)<br>Dipropylene glycol n-butyl ether (DPnB), CAS No. 29911-28-2 (35884-42-5)<br>Dipropylene glycol methyl ether acetate (DPMA), CAS No 88917-22-0<br>Tripropylene glycol methyl ether (TPM), CAS No. 25498-49-1 & 20324-33-8<br>Propylene glycol methyl ether (PM) CAS No. 107-98-2<br>Propylene glycol methyl ether acetate (PMA) CAS No. 108-65-6<br>Dipropylene glycol methyl ether (DPM) CAS No. 34590-94-8 |
| **2. CAS Number:** | |
| **3. Sponsor Country:** | United States<br><br>National SIDS Contact Point in Sponsor Country:<br>U.S. Environmental Protection Agency<br>Mr. Oscar Hernandez, Director<br>Risk Assessment Division (7403M)<br>1200 Pennsylvania Ave., NW<br>Washington, DC 20460 |
| **4. Shared Partnership with:** | |
| **5. Roles/Responsibilities of the Partners:** | |
| • Name of industry sponsor /consortium | Dr. Susan A. Lewis<br>American Chemistry Council<br>1300 Wilson Boulevard<br>Arlington VA 22209 |
| • Process used | |
| **6. Sponsorship History** | In the U.S., PnB, DPnB, DPMA, and TPM were subjected to extensive testing. Where data gaps existed for required endpoints, testing results from three closely related propylene glycol ethers, propylene glycol methyl ether (PM), dipropylene glycol methyl ether (DPM), and propylene glycol methyl ether acetate (PMA) were used. These three glycol ethers were evaluated at SIAM 11 and 12 and found to be of low priority for |

further testing. Analysis of this extensive database indicates that category members are of low priority for further testing.

Because the four new chemicals are the main focus of this analysis, the robust summaries/dossiers for these four chemicals also contain key studies for PM, DPM, and PMA. However, additional non-key studies for PM, DPM, and PMA are occasionally discussed in the SIAR where appropriate; these additional studies are contained in the robust summaries/dossiers that were presented at SIAMs 11 and 12.

- How was the chemical or category brought into the OECD HPV Chemicals Programme ?

**7. Literature Search and Dossier Preparation:**

Studies of the environmental and toxicological properties of the four new category members of propylene glycol ethers (PnB, DPnB, DPMA, and TPM) were identified from sources such as IUCLID (2000), ECETOC (1995) and Patty's Toxicology (2002). These sources were supplemented by a literature search of ToxLine and TSCATS. In addition, internal company resources were available by which to identify studies. Once critical studies were identified, they were obtained from the published scientific literature or, if unpublished, they were requested from the sponsoring companies. Once obtained, these reports were evaluated and robust summaries were generated from them. When available, the original IUCLID profile was used as a template to which robust summaries were added. These became the "dossiers" for the four new category members. Other sections of the original IUCLID profiles were supplemented. These included sections pertaining to chemical identity, physicochemical information, and chemical fate. Original IUCLID entries for which Robust Summaries were not generated usually were not edited but left intact. Where information was particularly sparse or incomplete for such original IUCLID entries, it was not deemed appropriate to delete them in the interest of presenting a complete database for a chemical. Occasionally, such entries were supplemented where the original report or a reliable summary was available.

**8. Quality check process:**

**9. Date of Submission:**

**10. Date of last Update:**

**11. Comments:**

No testing: (x)

Testing ( )

## SIDS INITIAL ASSESSMENT PROFILE

| | |
|---|---|
| **CAS No.** | 5131-66-8(29387-86-8)<br>29911-28-2 (35884-42-5)<br>88917-22-0<br>20324-33-8 and 25498-49-1 |
| **Chemical Name** | Propylene Glycol n-Butyl Ether (PnB)<br>Dipropylene Glycol n-Butyl Ether (DPnB)<br>Dipropylene Glycol Methyl Ether Acetate (DPMA)<br>Tripropylene Glycol Methyl Ether (TPM) |
| **Structural Formula** | $[CH_3\text{-}CH_2(OH)\text{-}CH_2\text{-}O]_n\text{-}(R)$<br><br>Where n = 1, 2, or 3; and R = alkyl (methyl or butyl)<br><br>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 13$^{th}$ 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 x 10$^{-9}$ atm-m$^3$/mole for TPM to 2.7 x 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.

# SIDS Initial Assessment Report

## 1 IDENTITY

### 1.1 Identification of the Category

The Propylene Glycol Ethers Category consists of four new members: propylene glycol n-butyl ether, or PnB (CAS No. 5131-66-8); dipropylene glycol n-butyl ether, or DPnB (CAS No. 29911-28-2); dipropylene glycol methyl ether acetate, or DPMA (CAS No. 88917-22-0); and tripropylene glycol methyl ether, or TPM (CAS No. 25498-49-1 and 20324-33-8). These chemicals form a category based on similar structural, physicochemical, and toxicological properties. Propylene glycol ethers may appear in two isomeric forms. The predominant form consists of a secondary alcohol (also sometimes referred to as the alpha isomer) and a minor form (the beta isomer), consisting of a primary alcohol. This distinction has toxicological significance as will be discussed later.

Three glycol ethers used to support the category and are also part of the category are: propylene glycol methyl ether, or PM (CAS No. 107-98-2); propylene glycol methyl ether acetate, or PMA (CAS No. 108-65-6); and dipropylene glycol methyl ether, or DPM (CAS No. 34590-94-8). Data from these are used to fill data gaps of category members. These glycol ethers are considered as category members due to their structural and toxicological similarities. These three chemicals were evaluated at SIAM 11 and 12 and found to be low priority for further testing. The details and references for each study selected are given in the robust summary/dossier sets for each category member.

There are some inconsistencies in how chemicals are reported throughout the world and what CAS numbers are used. It should be noted that in the original IUCLID dossiers, some studies that were conducted using the commercial mixtures had incorrectly used CAS numbers that are specific to the alpha isomer. However, testing was usually carried out on the commercially produced products that were nominated as HPV chemicals, all of which are mixtures containing at least a minimal amount of beta isomer (usually less than 5%); rarely, when noted in the IUCLID, the study may have been conducted on a more purified form of either the alpha or beta isomer. Unless specifically stated in the dossiers, the purified beta isomer was not tested. Please see Annex I for a more detailed discussion of these issues.

Members of the category are identified in Table 1 and the previously evaluated chemicals are identified in Table 2. In headings, the names of the new category members will be bolded while the names of the previously evaluated category members will be unbolded.

### 1.2 Physico-Chemical properties

Category members are closely related in physicochemical properties. As noted in Section 1.1, they are all liquids with similar boiling points, low to moderate volatility, and high water solubility. Increasing boiling point and vapor pressure are consistent with increasing molecular weight over the series. The physicochemical properties for the category members are shown in Table 3.

**Table 1. Members of the Propylene Glycol Ethers Category**

| 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) |
|---|---|---|---|---|
| IUPAC Name | 1-butoxypropan-2-ol | 1-(2-Butoxy-1-methylethoxy)propan-2-ol | 1(or 2)-(2-Methoxymethyl ethoxy)propanol, acetate | [2-(2-Methoxymethylethoxy) methylethoxy]propanol |
| OECD Name | 1-butoxypropan-2-ol | 1-(2-butoxy-1-methylethoxy)propan-2-ol | 1(or 2)-(2-Methoxymethyl ethoxy)propanol, acetate | [2-(2-Methoxymethylethoxy) methylethoxy]propanol |
| EINECS Number | 249-598-7 | 249-951-5 | Not on EINECS; nominated to ELINCS by unknown party (ELINCS # 406-880-6) | 247-045-4 |
| CAS Nos. | 29387-86-8 (mixture)<br>5131-66-8 (alpha isomer)<br>15821-83-8 (beta isomer) | 35884-42-5 (mixture)<br>29911-28-2 (alpha isomer)<br>24083-03-2 (alpha/beta conjugate with free secondary alcohol) | 88917-22-0 (mixture) | 25498-49-1 (mixture)<br>20324-33-8 (alpha isomer) |
| Molecular Formula | $C_7H_{16}O_2$ | $C_{10}H_{22}O_3$ | $C_9H_{18}O_4$ | $C_{10}H_{22}O_4$ |
| Molecular Weight | 132.20 | 190.28 | 190.24 | 206.32 |
| Structural Formula | $C_4H_9OCH_2CH(CH_3)OH$ | $C_4H_9O[CH_2CH(CH_3)O]_2H$ | $CH_3O[CH_2CH(CH_3)O]_2$ $\{C=OCH_3\}$ | $CH_3O[CH_2CH(CH_3)O]_3H$ |
| Synonyms | 1-Butoxy-2-propanol;<br>1-Butoxypropan-2-ol;<br>Propylene glycol normal-butyl ether; | 1-(2-butoxy-1-propoxy)-2-propanol; [rearranged<br>n-Butoxy-propoxy-propanol;<br>1-(2-Butoxy-1-propoxy)propan-2-ol | 1-methyl-(1-propoxy)-2-propanol, , acetate;<br>1-(2-Methoxy-1-propoxy)-1-propan-2-ol | Methyltripropylene glycol;<br>[2-(2-Methoxypropoxy) propoxy]propanol;<br>[1-[2-Methoxy-1-propoxy)-1-propoxy]-2-propanol, [rearranged] |
| Composition (Chemical Name, CAS No. and Percent Composition) | PnB (mixed isomers): 99.0% minimum<br><br>PnB is a mixture of two isomers. Commercial PnB is produced only as a two-isomer mixture and hence all testing was conducted on the commercial mixture. The two individual isomers are not separated nor produced as individual chemicals<br><br>Water: 0.15% maximum | DPnB (mixed isomers): 98.5% minimum<br><br>DPnB is a mixture of four isomers. Commercial DPnB is produced only as a four-isomer mixture and hence all testing was conducted on the commercial mixture. The four individual isomers are not separated nor produced as individual chemicals<br><br>Water: 0.30% maximum | DPMA (mixed isomers): 98.0% minimum<br><br>DPMA is a mixture of four isomers. Commercial DPMA is produced only as a four-isomer mixture and hence all testing was conducted on the commercial mixture. The four individual isomers are not separated nor produced as individual chemicals<br><br>DPM: 0.50% maximum<br><br>Water: 0.05% maximum | TPM (mixed isomers): 97.5% minimum<br><br>TPM is a mixture of eight isomers. Commercial TPM is produced only as an eight-isomer mixture and hence all testing was conducted on the commercial mixture. The eight individual isomers are not separated nor produced as individual chemicals<br><br>Water: 0.10% maximum |

**Table 2: Identity of Previously Evaluated Category Members**

| Chemical Name | Propylene Glycol Methyl Ether (PM)* | Propylene Glycol Methyl Ether Acetate (PMA)* | Dipropylene Glycol Methyl Ether (DPM)** |
|---|---|---|---|
| IUPAC Name | 1-methoxypropan-2-ol | 2-methoxy-1-methylethyl acetate | (2-methoxymethylethoxy) propanol |
| OECD Name | 1-methoxypropan-2-ol | 2-methoxy-1-methylethyl acetate | (2-methoxymethylethoxy) propanol |
| EINECS Number | 203-539-1 | 203-603-9 | 252-104-2 |
| CAS Nos. | 107-98-2 (alpha isomer)<br>1589-42-5 (beta isomer)<br>1320-67-8 (mixture) | 108-65-6 (alpha isomer)<br>70657-70-4 (beta isomer)<br>84540-57-8 (mixture) | 34590-94-8 (mixture)<br>13429-07-7<br>20324-32-7 (alpha isomer)<br>13588-28-8<br>55956-21-3 |
| Molecular Formula | $C_4H_{10}O_2$ | $C_6H_{12}O_3$ | $C_7H_{16}O_3$ |
| Molecular Weight | 90.12 | 132.16 | 148.20 |
| Structural Formula | $CH_3OCH_2CHOHCH_3$ | $CH_3OCH_2(CH_3)$-O-$COCH_3$ | $CH_3O[CH_2CH(CH_3)O]_2H$ |
| Synonyms | 1-Methoxypropan-2-ol;<br>1-Methoxy-2-propanol;<br>1-Methoxypropanol-2;<br>1-Methoxy-2-hydroxypropane | 2-Methoxy-1-methylethyl acetate;<br>1-Methoxy 2-acetoxy propane;<br>1-Methoxy-2-acetoxypropane;<br>1-Methoxy-2-propanol acetate;<br>1-Methoxy-2-propyl acetate;<br>2-Acetoxy-1-methoxypropane | 2-(2-methoxypropoxy)propanol;<br>5-methyl-4,7-dioxa-2-heptanol;<br>1(or 3)-(2-methoxymethylethoxy)-propanol,;<br>1(or 2)-(2-methoxy propoxy)-propanol, |
| Composition (Chemical name, CAS No., and Percent Composition) | PM (mixed isomers): 99.5% minimum<br><br>Alpha/beta isomer ratios<br>PM alpha isomer: >99.5%<br>PM beta isomer: <0.5%<br><br>Water: 0.10% maximum | PMA (mixed isomers): 99.5% minimum<br><br>Alpha/beta isomer ratios<br>PMA alpha isomer: >99.5%<br>PMA beta isomer: <0.5%<br><br>PM: 0.30% maximum<br><br>Water: 0.05% maximum<br><br>Acetic Acid: 0.02% maximum | DPM (mixed isomers): 99.0% minimum<br><br>DPGME is a mixture of four isomers. Commercial DPGME is produced only as a four-isomer mixture and hence all testing was conducted on the commercial mixture. The four individual isomers are not separated nor produced as individual chemicals.<br><br>Water: 0.15% maximum |

* Reviewed at SIAM 11

**Reviewed at SIAM 12

**Table 3. Physical and Chemical Properties**

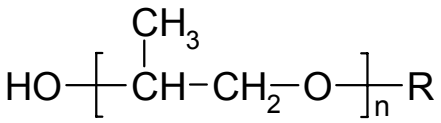
| Category Member | PnB | DPnB | DPMA | TPM | **PM** | **PMA** | **DPM** |
|---|---|---|---|---|---|---|---|
| **CAS No.** | 29387-86-8 or 5131-66-8 | 29911-28-2 25884-42-5 | 88917-22-0 | 20324-33-8 25498-49-1 | 107-98-2 | 108-65-6 | 34590-94-8 |
| Physical form of marketed product | **Liquid** | **Liquid** | **Liquid** | **Liquid** | **Liquid** | **Liquid** | **Liquid** |
| Melting point ($^{o}$C) | <-85[a] | **<-75[a]** | **-25.2[a]** | **-77.8[a]** | **-96.7[a]** | **-66.0[a]** | **-82.8[a]** |
| Boiling point ($^{o}$C) | 171[b] | **230[b]** | **209[b]** | **243[b]** | **120[c]** | **145.8[c]** | **184-197[c]** |
| Density (g/cm$^{3}$) | 0.88[b] | **0.910[b]** | **0.976[b]** | **0.962[b]** | **0.919[b]** | **0.966[b]** | **0.951[b]** |
| Vapor pressure (hPa) @ 25°C | **1.63[a]** | **0.091[a]** | **0.17[a]** | **0.028[a]** | **15.7[a]** | **5.17[a]** | **0.55[a]** |
| Partition coefficient (Log $K_{ow}$) | 1.15[a] | **1.523[a]** | **0.803[a]** | **0.309[a]** | **-0.437[a]** | **0.430[a]** | **-0.064[a]** |
| Water solubility (mg/l ) | **55,000[a]** | **45,000[a]** | 160,000[a] | Miscible[a] | Miscible[a] | 160,000[a] | Miscible[a] |
| Flash point ($^{o}$C) | **63[b]** | **100[b]** | **86[b]** | **121[b]** | **31.1[b]** | **46[b]** | **79.4[b]** |
| Autoignition temperature ($^{o}$C) | **260[b]** | **194[b]** | **321[d]** | **277[b]** | **287[b]** | **333[b]** | **ND** |

ND = not determined

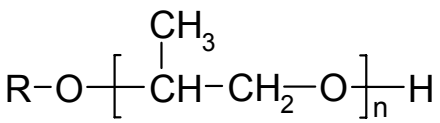
[a] Staples and Davis (2002); [b]Dow Chemical Company MSDS; [c] ECETOC Monograph (1995); [d] 3M MSDS (1999)

## 1.3 Category Justification

Category members are closely related in molecular structure and physicochemical properties and thus, the potential for toxicological effects. Most category members are glycol ethers that can be represented by the following generic molecular structure:



alpha isomer (secondary alcohol)



beta isomer (primary alcohol)

Where n = 1, 2, or 3 and R = alkyl (methyl or n-butyl). In addition, in the case of the acetates, DPMA and PMA, an acetate moiety is substituted for the hydrogen atom on the free hydroxyl group. Under physiological conditions, this acetate moiety is easily separated from the oxygen atom of the alcohol by the process of hydrolysis to yield the parent ether and acetic acid. Structures of the individual isomers are shown in Annex I along with their Chemical Abstract Service (CAS) numbers. Annex I also explains the nature of the mixtures of isomers more completely and shows the molecular structures of the predominant isomers, illustrating their close structural similarity. The reader is advised to read Annex I for questions regarding the chemical nature of propylene glycol ethers.

With regard to the category member, dipropylene glycol ether acetate (DPMA), research on the close structural analogue, monopropylene glycol ether acetate (PMA), by Domoradzki (2001) as cited in Corley *et al*. (2003), showed that this PGE acetate is hydrolyzed to its parent ether *in vivo* with a half-life of 1.6 to 3.4 minutes. These researchers showed that the pharmacokinetics of PMA were indistinguishable from PM when PMA was infused intravenously. Hydrolysis is attributed to naturally occurring esterases present in blood and other tissues. In an older study, Miller *et al*., (1984) showed that the metabolism and disposition of PMA in male Fischer 344 rats was practically indistinguishable from PM. Hoffmann and Jackh (1985) showed that the beta isomer of PMA hydrolyzed *in vitro* to the free ether in rat plasma with a half-life of 0.64 minutes. Thus, it is appropriate to include the acetate in this category of chemicals due to its rapid conversion to its parent ether and nearly identical toxicity.

Note that all of the monopropylene glycol ethers may exist in two isomeric forms, alpha or beta. The alpha form, which is thermodynamically favored during synthesis, consists of a secondary alcohol configuration. The beta form consists of a primary alcohol. The two isomeric forms are shown above. The di- and tripropylene glycol ethers may form up to 4 and 8 isomeric forms, respectively. Even so, all isomers exhibit either the “alpha” or “beta” configuration, existing as secondary or primary alcohols, respectively. The distribution of isomeric forms for the di- and tripropylene glycols, as with the mono-PGEs, also results in predominantly the alpha form (i.e., a secondary alcohol). It should be noted that only the alpha isomer and isomeric mixtures (consisting predominantly of the alpha isomer) are produced commercially; the purified beta isomer is not produced at this time.

Testing of a wide variety of propylene glycol ethers has shown that propylene glycol-based ethers are less toxic than some ethers of the ethylene series. The common toxicities associated with the lower molecular weight homologues of the ethylene series, such as adverse effects on reproductive organs, the developing embryo and fetus, blood (hemolytic effects), or thymus, are not seen with the commercial-grade propylene glycol ethers. In the ethylene series, metabolism of the terminal

hydroxyl group produces an alkoxyacetic acid (Patty's Toxicology, 5th Ed., 2001). The reproductive and developmental toxicities of the lower molecular weight homologues in the ethylene series are due specifically to the formation of methoxyacetic and ethoxyacetic acids. Longer chain length homologues in the ethylene series are not associated with the reproductive toxicity but can cause hemolysis in sensitive species, also through formation of an alkoxyacetic acid. The predominant alpha isomer of all the propylene glycol ethers (thermodynamically favored during manufacture of PGEs) is a secondary alcohol incapable of forming an alkoxy propionic acid. This alpha isomer comprises greater than 95% of the isomeric mixture in the commercial product. Because the alpha isomer cannot form an alkoxypropionic acid, this is the most likely reason for the lack of toxicity shown by the propylene glycol ethers as distinct from the lower molecular weight ethylene glycol ethers. More importantly, however, very extensive empirical test data show that this class of commercial-grade glycol ether presents a low toxicity hazard. Propylene glycol ethers, whether mono, di- or tripropylene glycol-based (and no matter what the alcohol group), show a very similar pattern of low to non-detectable toxicity of any type at doses or exposure levels greatly exceeding those showing pronounced effects from the ethylene series. One of the primary metabolites of the propylene glycol ethers is propylene glycol, which is of low toxicity and completely metabolized in the body.

# 2 GENERAL INFORMATION ON EXPOSURE

## 2.1 Production Volumes and Use Pattern

Manufacture

Members of the Propylene Glycol Ethers Category are manufactured in closed, continuous equipment by the reaction of propylene oxide with methyl alcohol or n-butyl alcohol (CEH, 2000). This reaction can produce glycol ethers of varying chain length depending on the molar ratio of reactants and the temperatures and pressures used in the reaction. Milder conditions and lower molar ratios of propylene oxide to alcohol will produce the monopropylene glycol ethers, while using more propylene oxide and higher temperatures and pressures produce the di- and tripropylene glycol mono-alkyl ethers. The products are purified by distillation. Three of the four propylene glycol ethers in the category are of 97.5% purity or greater. The three previously submitted glycol ethers are at least 99% purity.

In the United States, approximately 285 million pounds (129,275 metric tons) of all propylene glycol ethers were produced in 1999 (CEH, 2000). In this same year, European production was 472 million pounds (214,545 metric tonnes) and Japanese production was 53 million pounds (24,090 metric tonnes), accounting for total worldwide production of 810 million pounds (367,400 metric tonnes). Due to low toxicity and low volatility, consumption of PGEs has been growing. It is estimated that in 2004, total propylene glycol ether production in the U.S. will increase to 340 million pounds (154,545 metric tons). For PnB, DPnB, and TPM, 1999 production was 23, 10.5, and 6 million pounds (10454, 4772, and 2727 metric tonnes), respectively. 2004 production for these ethers is projected to be 29, 14, and 7 million pounds (13182, 6363, and 3182 metric tonnes). 1993 production volume for DPMA was 1-2 million pounds. The volumes are confirmed by the 1998 Inventory Update Rule (IUR).

Uses

The most significant current uses of the category members are as components of coatings, (e.g., paints and varnishes), cleaning fluids, inks, resins, cosmetics, and as inert carrier solvents in pesticide formulations (CEH, 2000). Uses for specific category members are provided below.

Propylene Glycol n-Butyl Ether (PnB): Because of high solvency, oil solubility, surfactant, and coupling properties, and due to good evaporation rate control, high formulating flexibility, low viscosity, as well as low toxicity, PnB may be used as a coupling agent and solvent in domestic and commercial cleaning solutions such as degreasers, paint removers, metal cleaners, and hard surface cleaners. These characteristics also allow PnB to be used as a coupling agent in water-based agricultural formulations, facilitating the homogenous blending of ingredients with diverse solubility characteristics. PnB is also used as a coalescent for lowering minimum film formulation temperature (MFFT) in water-borne latex coatings and as a chemical intermediate for the production of epoxides, acid ester derivatives, solvents, and plasticizers.

Dipropylene Glycol n-Butyl Ether (DPnB): DPnB has many performance characteristics that are similar to PnB but with lower volatility and higher viscosity. Uses for DPnB include: coupling agent (i.e., blending facilitator) for cleaners such as degreasers, paint removers, metal cleaners, and hard surface cleaners; coalescent for lowering MFFT in latex coatings; solvent for water-reducible coatings; chemical intermediate for production of epoxides, acid ester derivatives, solvents, and plasticizers.

Dipropylene Glycol Methyl Ether Acetate (DPMA): DPMA has uses similar to PMA for applications requiring lower evaporation and flammability. Because of it's high solvency and coalescing abilities, it's high dilution ratio, moderate evaporation rate and viscosity control, DPMA is used as an active solvent in solvent-based coatings, solvent-based silkscreen printing inks, and as a tailing solvent in coatings.

Tripropylene Glycol Methyl Ether (TPM): Because of its high polymer solvency and low evaporation rate, TPM is used in inks for ballpoint and felt-tipped pens and inkpads to prevent drying. Because it has a high boiling point and flash point, it is used in oven cleaners and as a tailing solvent in high-solids, solvent-based coatings. It is used also in rust, paint, and varnish removers, and in penetrating oils.

Manufacturers transport PGEs in tank cars and tank trucks to formulators of the above products. The processors blend the PGEs in enclosed equipment with other components to produce formulations that meet performance specifications for their products.

Table 4 shows the production volumes for the various ethers in the United States for the year 1993, along with the types of products for which they were used in that year, percent of production, the ratio of industrial versus commercial use and the approximate amount of the ether constituting the product (Patty's, 2001).

**Table 4. 1993 U.S. Production Volumes and Uses for PGEs***

| Chemical | 1993 Production Volume ($10^6$ lb) | Types of Commercial End Products | Percent of Production (%) | Industrial/ Commercial Use Ratio | Approx. Wt. Fraction in Product Types |
|---|---|---|---|---|---|
| PnB | 6-10 | Surface Coatings<br>Cleaners | 50<br>50 | N/D | 2-20%<br>2-10% |
| DPnB | 5-10 | Surface Coatings<br>Inks<br>Cleaners | 10<br>5<br>85 | N/D | 2-20%<br>2-20%<br>2-10% |
| DPMA | 1-2 | Surface Coatings<br>Cleaners<br>Miscellaneous | 30<br>60<br>10 | 100/0<br>100/0<br>90/10 | N/D |
| TPM | 3-5 | Inks<br>Cleaners<br>Functional Fluids | 7<br>80<br>13 | <br>100/0<br>100/0 | 2-20%<br>2-50%<br>N/D |
| PM | 110-130 | Surface Coatings<br>Cleaners<br>Inks<br>Miscellaneous<br>PMA Production | 30<br>23<br>6<br>7<br>34 | <br><br><br>100/0 | 2-20%<br>2-50%<br>2-30% |
| PMA | 72 | Surface Coatings<br>Inks<br>Cleaners<br>Miscellaneous | 89<br>5<br>5<br>3 | 100/0<br><br><br>100/0 | 5-30%<br>2-30%<br>5-50% |
| DPM | 20-30 | Surface Coatings<br>Cleaners<br>Inks<br>Dyes<br>Miscellaneous | 19<br>63<br>5<br>3<br>9 | N/D | 2-20%<br>2-50%<br>N/D<br>2-20%<br>2-10% |

* Patty's Toxicology, 5th Edition, Chapter 87 (2001)

## 2.2 Environmental Exposure and Fate

### 2.2.1 Sources of Environmental Exposure

The propylene glycol ethers typically enter the environment through slow escape and evaporation from the solvent or coating systems used. Spills of such products can also occur during application of coatings. Emissions to the atmosphere or surface water occurring via industrial wastes or effluents during manufacture or processing are limited by predominately enclosed processing and low volatility.

Data for Henry's Law Constants, photodegradation rate constants, and environmental transport for all category members were gathered directly from the manufacturers technical reports, IUCLID dossiers, or they were estimated (calculated) using EPIWIN modeling, including Mackay Level III fugacity modeling or similar approaches. As shown in Table 5, category members are closely related in environmental fate parameters. Their consistently low Henry's Law constants indicate that members will not partition preferentially from water to air. Their photodegradation rate constants suggest moderately rapid atmospheric degradation (i.e., half-lives less that a day). All members have similar predicted environmental distributions and are stable in the presence of neutral water at ambient temperatures.

**Table 5. Comparison of Environmental Fate Parameters**

| Chemical | Henry's Law Constant[a] (atm-$m^3$/mole) | Photodegradation OH radical rate constant[a] ($cm^3$/molecule-sec) | Soil-Water or Sediment-Water Partition Coefficient (Koc) [a] | Predicted Environmental Distribution (Mackay III fugacity model)[a] | | | |
|---|---|---|---|---|---|---|---|
| | | | | Air (%) | Water (%) | Soil (%) | Sed. (%) |
| **PnB 29387-86-8 or 5131-66-8** | 2.69 E-06 | 28.0 E-12 | 1.3 | 2.30 | 50.1 | 47.5 | 0.0829 |
| **DPnB 29911-28-2 or 35884-42-5** | 2.79 E-07 | 49.7 E-12 | 10 | 0.827 | 50.9 | 48.2 | 0.0947 |
| **DPMA 88917-22-0** | 1.99 E-07 | 33.6 E-12 | 10 | 1.07 | 52.0 | 46.8 | 0.0902 |
| **TPM 20324-33-8 or 25498-49-1** | 5.70 E-09 | 63.2 E-12 | 10 | 0.247 | 48.5 | 51.1 | 0.0813 |
| PM 107-98-2 | 1.40 E-06 | 16.5 E-12 | 1.0 | 2.19 | 54.7 | 43.0 | 0.0914 |
| PMA 108-65-6 | 4.24 E-06 | 11.9 E-12 | 1.8 | 3.11 | 53.1 | 43.7 | 0.0913 |
| DPM 34590-94-8 | 1.58 E-07 | 38.2 E-12 | 10 | 0.942 | 53.4 | 45.6 | 0.0893 |

[a] Calculated using EPIWIN (v3.10) Suite of Programs. Level III fugacity module used for environmental distributions. HENRYWIN module used for Henry's Law Constants (VP/Wsol estimate using EPI values).

### 2.2.2 Photodegradation

Estimated photodegradation hydroxyl radical rate constants (Table 5) for category members are in close agreement. Photodegradation rates for PnB, DPnB, DPMA, and TPM (estimated using the EPIWIN/AOP model) result in atmospheric photodegradation half-lives of 4.6, 2.6, 3.8, and 2.0 hours respectively, based on a 12-hour day (of sunlight) and an average hydroxy radical concentration of 1.5 x $10^6$ OH/$cm^3$.

### 2.2.3 Stability in Water

The ether linkages of the category members are not expected to hydrolyze readily. The EPIWIN/HYDROWIN program is not able to estimate stability in water (hydrolysis) because it cannot calculate the hydrolysis rate constant for the ether function (R-O-R, where R=organic alkyl group). However, ether groups generally are stable in water under neutral conditions at ambient temperatures. PGEs are intended to be mixed with water and remain chemically stable. Material safety data sheets (MSDSs) indicate the category members to be chemically stable under a variety of conditions, including in the presence of water. Halogen acids, particularly hydrogen iodide may be used as catalysts to hydrolyze the ether function (Fieser and Fieser, 1960). As has been shown for PMA, the acetate moiety of DPMA may be expected to hydrolyze under alkaline conditions but should be stable in water at acidic or neutral pH.

### 2.2.4 Volatilization

As can be seen from Table 3, the category members are highly soluble to miscible in water, possess relatively high boiling points (171-243°C) and relatively low vapor pressures (0.028-1.63 hPa). The estimated Henry's Law Constants, falling in the range of $2.7E^{-6}$ to $5.7E^{-9}$ atm-$m^3$/mol @ $25^o$ C (Table 5), indicate a limited potential to partition from water to air.

### 2.2.5 Transport and Distribution

The distributions of the category PGEs in the various environmental media have been estimated using the Mackay Level III fugacity modeling approach (EPIWIN). Such models estimate relative distribution within different environmental compartments, based on key physical and chemical property parameters. The Level III estimated mass balances for category members (at equilibrium), shown in Table 5, reflect the limited volatilization and high water solubility characteristics of the PGEs and indicate a preference for partitioning to water and soil. The glycol ethers in this category possess physical properties that suggest that once they enter the aqueous compartment, they tend to remain dissolved in water. Soil/water-sediment/water partition coefficients (Koc) in the range of 1 to 10 have been estimated for the category member using the EPIWIN/PCKOCWIN (Table 5). These results suggest that the category members have uniformly high soil mobility. Thus, these products can leach from soil deposits to groundwater, but can also be transported to environments where aerobic biodegradation can take place.

### 2.2.6 Biodegradation

Experimentally derived biodegradation data are available for all of the category members (Table 6). The data presented in Table 6 are derived from the IUCLID Dossiers containing Robust Summaries compiled for the individual category members and from the IUCLID dossiers for the previously evaluated category members. These data illustrate that all category members biodegrade reasonably rapidly when released to water. Except for DPMA, OECD guideline studies indicate "ready biodegradability" for all category members by at least one assay. For DPMA, two studies are found that address biodegradability. One study shows only hydrolysis of the acetate to form DPM with little further degradation (Matsue, 2000). A second assay reaches 60% degradation after 28 days and within a 10-day window but uses "acclimated" or pre-adapted inoculum, which does not meet the strict definition of "ready biodegradability" (Wu, 1996). None of the ethers demonstrate marked resistance to biodegradative processes.

**Table 6. Comparison of Biodegradation Rate Ranges**

| Category Member | Biodegradation Rate Ranges | References |
|---|---|---|
| PnB<br>29387-86-8 or<br>5131-66-8 | In one test, >60% after 28 days but not within a 10-day window, measured by $CO_2$ evolution. In a second test, >90% biodegradation after 28 days within a 10-day window measured by DOC removal, indicating ready biodegradability | Cardinaals & de Crom 1987a & b<br>JETOC, 1992<br>McLaughlin 1993 |
| DPnB<br>29911-28-2 or<br>35884-42-5 | In one test (Closed Bottle), 0% degradation after 28 days measured by $O_2$ consumption. In a second test (Modified Sturm) measuring $CO_2$ evolution, 50% degradation after 28 days. In a third test (Modified OECD Screening) measuring DOC, DPnB was 91% degraded after 28 days and achieved 60% degradation within a 10-day window, indicating ready biodegradability. | Cardinaals & de Crom 1987c & d<br>Handley & Mead 1993<br>Wuthrich 1992 |
| DPMA<br>88917-22-0 | In one assay, 16% "biodegradation" (consisting solely of conversion to DPM, i.e., hydrolysis of the acetate moiety, without further mineralization). In a second assay using pre-adapted or "acclimated" inoculum, >60% degradation after 28 days within a 10-day window, measured by $O_2$ consumption, indicating a potential for the substance to degrade in adapted conditions (e.g., an industrial treatment facility). | Matsue 2000<br>Wu et al. 1996 |
| TPM<br>20324-33-8 or<br>25498-49-1 | In one test using pre-adapted or "acclimated" inoculum, >60% degradation after 28 days within a 10-day window, measured by $O_2$ consumption. In a second test using typical inoculum (OECD 301F: Manometric Respirometry), TPM was 60% degraded after 28 days, measured by $O_2$ consumption, 51% by $CO_2$ evolution, and 66% when measured by removal of dissolved organic carbon (DOC). Thus, by two of the measurement criteria in this latter test, TPM was "readily biodegradable," having degraded to 60% after 28 days and within a 10-day window. | Goodwin & West 1998<br>Wu et al. 1996 |
| PM<br>107-98-2 | PM showed >90% degradation after 28 days and within a 10-day window when tested by 301E Modified OECD Screening Test. Thus, PM is "Readily Biodegradable" by OECD criteria. | BASF 1985 |
| PMA<br>108-65-6 | >60% after 28 days within a 10-day window, measured by $O_2$ consumption, $CO_2$ evolution, or removal of dissolved organic carbon (DOC), indicating ready biodegradability. | Dow 1998a |
| DPM<br>34590-94-8 | >60% after 28 days within a 10-day window, measured by $O_2$ consumption, $CO_2$ evolution, or removal of dissolved organic carbon (DOC), indicating ready biodegradability. | Dow 1998b |

### 2.2.7 Bioaccumulation

The category members have a very limited potential to bioaccumulate based on low log $K_{ow}$s and bioconcentration factors. Log $K_{ow}$s for the category members are 1.15, 1,523, 0.803, and 0.309 for PnB, DPnB, DPMA, TPM, respectively. Log $K_{ow}$s for the previously evaluated category members are even lower. Predicted bioconcentration factors (BCFs) for the category members are 1.53 (log BCF = 0.185), 1.47 (log BCF = 0.168), 3.16 (log BCF = 0.500), and 3.16 (log BCF = 0.500) for PnB, DPnB, DPMA, TPM, respectively (EPIWIN/BCF Program). BCFs for the other PGEs chemicals are comparable.

## 2.3 Human Exposure

The most likely routes of human exposure to category members are via inhalation or dermal contact. While exposure may occur during manufacture or processing, greater exposure potential exists for commercial workers and other consumers when coatings are applied to surfaces or when liquid products containing PGEs are otherwise used.

### 2.3.1 Occupational Exposure

Exposure during manufacture is limited by the use of enclosed equipment, necessitated by the hazardous properties of the reactant propylene oxide. Bulk storage, handling and transport of product further limits exposure potential. Processors use enclosed equipment for the formulation of products containing category members. Worker exposure is more likely to occur while applying

coating products containing PGEs to various surfaces. Dermal contact and inhalation exposure are expected exposure routes. Exposure limits have not been established for PnB, DPnB, DPMA and TPM but they do exist for PM, PMA and DPM ranging from 50-100 ppm.

### 2.3.2 Consumer Exposure

Individuals applying paint or other PGE-containing coatings may be exposed to category ethers. Dermal contact through minor spills or usage contact is a source of exposure, as is inhalation from aerosol or vapor generated during application or usage.

### 2.3.3 Indirect Exposure via the Environment

General population exposure is also possible through inhalation of ambient air containing low concentrations of PGEs that may be released from industrial processes or through evaporation of coatings or other products containing them. Ingestion of drinking water containing category members as contaminants also is possible.

## 3 HUMAN HEALTH HAZARDS

### 3.1 Effects on Human Health

### 3.1.1 Pharmacokinetics and Metabolism

Disposition (i.e., absorption, distribution, and excretion) and metabolism studies have been conducted for DPnB and TPM. For the DPMA, hydrolysis studies indicate that the acetate rapidly hydrolyses in plasma to yield DPM (Hoffman *et al*., 1985). No metabolism studies were found for PnB. Disposition and metabolism studies have been conducted for PM, PMA, and DPM. The toxicokinetics of PM and PMA are almost identical. That for DPM also is very similar to the rest of the category.

Metabolism of PGEs takes place predominantly in the liver where mixed function oxidase cleaves the ether linkage, yielding propylene glycol and an alcohol. These two byproducts may be consumed in intermediary metabolism to $CO_2$ and water, with the latter ultimately being excreted in expired air. Alternatively, the parent PGE (or intermediate metabolite) may be conjugated in the liver with glucuronide, sulfate, or glutathione for ultimate excretion, predominantly in the urine.

Absorption, Distribution, and Excretion

As a class, the propylene glycol ethers are rapidly absorbed and distributed throughout the body when introduced by inhalation or oral exposure. Metabolism studies (by oral exposure) conducted with several PGEs support this conclusion (see below). While not tested directly, absorption by inhalation exposure also would be expected to be rapid for vapors of PGEs and for aerosols that are in the respirable range. Dermal absorption would be expected to be somewhat slower but, once absorbed, subsequent distribution also should be rapid. When a single dose of DPnB was administered orally to rats, most of the dose was eliminated within 48 hours indicating rapid excretion (Zemple et al., 1991). Similar rapid absorption, distribution, and elimination occurred within 48 hours for TPM (Calhoun et al., 1986). Most excretion for PGEs is via the urine and expired air. A small portion is excreted in the feces.

Metabolism

The metabolism of two of the category members, DPnB and TPM, has been characterized in rats by oral exposure (Calhoun et al., 1986; Zemple et al., 1991). In rats, metabolism is rapid for these PGEs. All three of the previously evaluated PGEs have been similarly studied (Miller et al, 1983; Miller et al., 1985a; Morgott and Nolan, 1987). A higher proportion of PM and PMA was eliminated via the lungs as opposed to the urine than the larger molecular weight PGEs: DPM, DPnB and TPM. The ether bond may be broken via O-dealkylation by mixed function oxidase to yield mono-, di-, or tripropylene glycol (depending on the parent compound) and the alkyl alcohol. The (mono-, di-, or tri-) propylene glycol released may then undergo further metabolism to yield $CO_2$. Alternatively, PGEs or their partially metabolized by-products may be conjugated with glucuronide or sulfate and excreted via the kidneys into the urine. Because of its molecular structure, the secondary (alpha) alcohol isomer is not oxidized to the carboxylic acid. As has been shown for monopropylene glycol methyl ether acetate (see discussion on page 3), the acetate, DPMA, is also expected to be rapidly hydrolyzed to yield DPM, which would then be metabolized similarly to the non-acetate DPM.

**Dipropylene Glycol n-Butyl Ether (DPnB):** Four male rats were administered oral doses via gavage of 0.4 or 4.4 mmole of $C^{14}$-radiolabelled DPnB/kg body weight (Zemple et al., 1991). These doses correspond to approximately 75 or 840 mg DPnB/kg body weight. Rats were housed in metabolism cages where urine, feces, and expired air were collected in varying time increments over a total period of 48 hours and monitored for radioactivity. Urine was collected in 12 hour increments, feces in 24 hour increments, and expired air was collected at 6, 12, 24, 36, and 48 hours. In addition, at the end of 48 hours, brain, muscle, peri-renal fat, skin, kidneys, liver and the remaining carcass were analyzed for total radioactivity. Urine samples were fractionated using liquid chromatography and fractions containing radioactivity were analyzed to identify the structures of the metabolites. In a separate study, the kinetics of DPnB in the blood over time was evaluated in 4 male rats, with indwelling jugular-vein catheters. Blood was collected at 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hours.

After 48 hrs, 42% of the dose was excreted in urine and 42% as $C^{14}$-$CO_2$ at 0.4 mmol/kg BW; while the high dose rats excreted 51% in urine and 35% as $C^{14}$-$CO_2$. Fecal excretion accounted for 4% of the dose at the low dose and 11% at the high dose. Less than 1% of the dose was eliminated as expired volatile organics at both dose levels. Tissues and carcass retained 11% of the dose 48 hrs after 0.4 mmol DPnB/kg bw and 7% after 4.4 mmol/kg bw. The distribution of $C^{14}$-activity in tissues was similar between dose groups with liver, bone marrow and kidneys retaining the highest percentage. Peak blood levels of $C^{14}$-activity occurred at 0.5 hrs after dosing with 0.4 mmol/kg bw and at 4.0 hrs after 4.4 mmol/kg bw. Profiles of urinary $C^{14}$-activity were qualitatively similar between dose levels. The following urinary metabolites were identified: 1) sulfate conjugate of DPnB; 2) propylene glycol n-butyl ether; 3) dipropylene glycol; 4) propylene glycol, and; 5) parent material.

**Tripropylene Glycol Methyl Ether (TPM)**: $C^{14}$-radiolabeled TPM was administered as a single gavage dose (1 or 4 mmol/kg at 41.3 and 11.1 μCi/mmole, respectively) to male rats (3/dose) (Calhoun et al., 1986). Rats were housed in metabolism cages where urine, feces, and expired air were collected in varying time increments over a total period of 48 hours and monitored for radioactivity. Urine was collected in 12-hour increments, feces in 24-hour increments, and expired air was collected at 4-hour intervals for the first 12 hours and at 12-hour intervals thereafter. In addition, at the end of 48 hours, brain, muscle, peri-renal fat, skin, kidneys, liver and the remaining carcass were analyzed for total radioactivity. Urine samples were fractionated using liquid chromatography and fractions containing radioactivity were analyzed using GC/MS to identify the structures of the metabolites.

After 48 hrs, 75% of the dose was excreted in urine and 16% as $C^{14}$-$CO_2$ at 1 mmol/kg BW; while the high dose rats excreted 69% in urine and 16% as $C^{14}$-$CO_2$. Fecal excretion accounted for approximately 5% of the dose at both dose levels. Less than 1% of the dose was eliminated as expired volatile organics at both dose levels. The carcass retained between 1 and 2% of either dose. The distribution of $C^{14}$-activity in tissues was similar between dose groups with liver, kidneys, and skin containing the highest percentage after 48 hours (all less than 0.5% of the total dose). Metabolite profiles of urinary $C^{14}$-activity were qualitatively and, to some extent, quantitatively similar between dose levels. The following urinary metabolites were tentatively identified within Liquid Chromatography (LC) peaks using GC/MS techniques:

LC Peak A (11-18%) - sulfate conjugate of TPM

LC Peak B (12-25%) – 4 isomers of dipropylene glycol methyl ether and 6 isomers of TPM

LC Peak C (1.3-3.8%) - propylene glycol

LC Peak D (54-56%) – 3 isomers (50%) of dipropylene glycol and 2 isomers (50%) of 2-(1-hydroxy-2-propoxy) propanoic acid, described as “isomers of a cyclic dehydration product”.

LC Peak E (6-12%) – Isomers of tripropylene glycol

### 3.1.2 Acute Toxicity

For acute toxicity, a complete database exists for all category members and surrogates for all three routes of exposure. Table 7 shows the comparative acute dose mammalian toxicity LD50s for the category. Data have been compiled from the Dossiers with Robust Summaries for the category members and IUCLID dossiers for the surrogates (see reference section). Results from the acute studies indicate low toxicity by the oral, inhalation and dermal routes of exposure.

**Table 7. Acute Mammalian Toxicity**

| Category member | Acute rat oral $LD_{50}$ | Acute rat inhalation $LC_{50}$ (4 hr)[2] | Acute dermal $LD_{50}$ (24 hr)[4] |
|---|---|---|---|
| PnB<br>29387-86-8 or<br>5131-66-8 | 3300 mg/kg<br>(95% CL: 2800-4500 mg/kg)<br>Reijnders & Zucker-Keizer 1987a<br>1900 mg/kg, Rowe, 1947[6] | >651 ppm (>3520 $mgm^3$)[1]<br>(no deaths)<br>Corley et al. 1987a | > 2,000 mg/kg[1] (rat)<br>(no deaths)<br>> 2,000 mg/kg (rabbits)[5]<br>Reijnders 1987a |
| DPnB<br>29911-28-2 or 35884-42-5 | 4000 mg/kg<br>(95% CL: 3200-4600 mg/kg)<br>Reijnders & Zucker-Keizer 1987b<br>1850 mg/kg, Rowe, 1947[6]<br>2160 mg/kg (mouse)<br>Algate et al. 1988[6] | > 42.1 ppm (vapor - measured)[3] (=328 $mg/m^3$)<br>(no deaths)<br>Gushow et al. 1987<br><br>> 2,040 $mg/m^{3-1}$ (aerosol – measured) (=262 ppm)<br>(no deaths)<br><br>Cieszlak et al. 1990 | > 2,000 mg/kg[1] (rat)<br>(no deaths)<br>Reijnders 1987b |
| DPMA<br>88917-22-0 | Females: 5,448 mg/kg<br>(95%CL: 4071-7635 mg/kg)<br>(2/6 female deaths at 5000 mg/kg)<br>Males: > 5,000 mg/kg (no male deaths at this dose)<br>Carreon et al. 1982 | > 5,700 $mg/m^{3-1}$(=733 ppm)<br>(no deaths)<br>Carreon et al. 1982 | > 5,000 mg/kg[1]<br>(no deaths)<br>Carreon et al. 1982 |
| TPM<br>20324-33-8 or<br>25498-49-1 | 3,500 mg/kg<br>(95% CL: 3100-3900 mg/kg)<br>Jones & Collier 1986 | > 200,000 $mg/m^{3-1}$<br>(aerosol - nominal)<br>(= 23700 ppm)<br>(1-hr exposure)<br>(no deaths)<br>Moreno 1975 | 15,400 mg/kg<br>(2/4 deaths)<br>(no deaths at next lower dose of 7,720 mg/kg)<br>Kuryla 1991 |
| PM<br>107-98-2 | > 5,000 mg/kg<br>(many tests; see PM dossier) | 18,200 $mg/m^3$ (18.2 mg/l)<br>(= 4938 ppm)<br>(7 hr)<br>Rowe et al. 1954 | ~13,000 mg/kg<br>Rowe et al. 1954 |
| PMA<br>108-65-6 | Males: >10,000 mg/kg<br>Females: 8,532 mg/kg<br>Dow 1980b | 4,345 ppm (6 hr)<br>(= 804 $mg/m^3$)<br>Dow 1980b | > 5,000 mg/kg (rat)<br>Dow 1980b |
| DPM<br>34590-94-8 | Males: 5,230 mg/kg<br>Females: 5180 mg/kg<br>Rowe 1954 | 500 ppm (supersat.)<br>(= 3031 $mg/m^3$)<br>(7 hr) – no deaths<br>Rowe 1954 | 10,000 mg/kg or greater<br>(many tests; see DPM dosser) |

$LD_{50}$ = Lethal dose in 50% of animals

[1] Highest dose used in study [2] Inhalation exposure was for 4 hours unless otherwise stated. [3] Highest practically attainable vapor concentration. [4] Rabbits unless otherwise noted. [5] One value from the dossier with robust summaries is less than 2,000 mg/kg but pertains to the 1,3 isomer, which is not in the commercial product. [6] Not critically evaluated.

All of the category members were subjected to acute toxicity bioassays by the three physiologically relevant routes of exposure (oral, inhalation, and dermal). Most followed modern protocols and conformed to GLPs for which a Robust Summary was generated. A few studies were older but still judged to be of reliable quality (e.g, Rowe 1954).

As a group, propylene glycol ethers show very low acute toxicity with LD50's above 1,000 mg/kg for oral studies, above 2000 mg/kg for dermal studies and, for inhalation studies, above 500 ppm unless the chemical's vapor pressure was insufficient to reach this concentration (in these cases, no

deaths occurred at concentrations lower than 500 ppm). When signs of toxicity were evident, they included a generalized central nervous system and respiratory system depression, characterized by narcosis, lethargy, prostration, ataxia, or unconsciousness, which, if doses were sufficiently high, might be followed by death within variable periods of time but not usually more than 2 to 3 days post dosing. At toxic doses, other signs might include salivation, piloerection, hunched posture, shallow and rapid breathing, tremors, ptosis, dacryorrhea, blood around the eyes and snout, rough coat, anorexia, or weight loss. Surviving animals usually showed no grossly observable lesions at necropsy 14 days post-treatment. Non-survivors at necropsy could show (usually at extreme dosages): 1) hemorrhage or bloating (with excess gas or fluid) of various parts of the gastrointestinal tract, 2) petechiae, congestion, or mottling of the liver, kidneys, lungs, or spleen, or 3) full urinary bladders or hyperemia of the bladder.

### 3.1.3 Irritation

Regarding skin and eye irritation, the dataset summarized in Table 8 is complete for the category. Some of the chemicals may be moderately irritating to eyes. All but PnB are slightly or non-irritating to skin. Undiluted PnB may be moderately irritating to skin. The acetates show either no or moderate potential for irritation to either eyes or skin.

**Table 8. Eye/Skin Irritation (Rabbits) and Sensitization (Guinea Pigs)**

| Category Member | Eye Irritation (Rabbits) | Skin Irritation (Rabbits) | Skin Sensitization (Guinea Pigs) [1] |
|---|---|---|---|
| PnB<br>29387-86-8 or<br>5131-66-8 | Moderately irritating according to OECD criteria<br>Weterings & Daamen 1987a | When tested undiluted, moderately irritating; Primary Irritation Index (PII) = 4/8<br>75% dilution PII = 2.5/8<br>50% dilution PII = 0.8/8<br>25% dilution PII = 0.0/8<br>Weterings & Daamen 1987b<br>Weterings & Daamen 1987c | Negative, Buehler Test<br>Vankerkom 1987 |
| DPnB<br>29911-28-2 or 35884-42-5 | Slightly irritating (PII = 12/110 at 1 hr)<br>Weterings & Daamen 1987d | Slightly irritating (PII = 2/8)<br>Weterings & Daamen 1987e | Negative, OECD Test 406<br>Also negative in Human patch test<br>Vanderkom 1987<br>Maclennon 1988 |
| DPMA<br>88917-22-0 | Non-irritating<br>24 hr: PII = 1.0/110<br>48 hr: PII = 0.3/110<br>Carreon et al. 1982 | Non-irritating (PII = 0.04/8)<br>Carreon et al. 1982 | No studies found<br>See PMA and DPM |
| TPM<br>20324-33-8 or<br>25498-49-1 | Moderately irritating (PII = 4/10)<br>Kuryla 1991 | Non-irritating (PII = 1.0/10)<br>Kuryla 1991 | No studies found. |
| PM<br>107-98-2 | Slightly irritating<br>(PII = 3/10)<br>BASF AG 1979<br>Rowe et al. 1954<br>Smyth et al. 1962 | Slightly irritating<br>BASF AG 1979<br>Smyth et al. 1962 | Negative, modified McGuire test<br>Carreon and Wall, 1984 |
| PMA<br>108-65-6 | Slightly to moderately irritating<br>Dow 1980b | Non-irritating<br>Dow 1980b | Negative, modified McGuire & Magnusson-Kligman maximization tests<br>Dow 1980b<br>Dow 1985<br>Zissu 1995 |
| DPM<br>34590-94-8 | Slightly irritating<br>Ballantyne, 1984a&b; Prehled Prumyslove Toxikol Org Latky, 1986; Union Carbide, 1971; Rowe *et al.*, 1954 | Non-irritating<br>Ballantyne, 1983; Rowe *et al.*, 1954; Smyth et al., 1962; Union Carbide, 1971 | Non-sensitizing in Human patch test<br>Row *et al*., 1954; Dow Chemical Company, 1951 |

[1] Unless another species is noted.

### 3.1.4 Sensitisation

Except for TPM, the dataset is also complete for skin sensitization (Table 8). None of the tested category caused skin sensitization. In view of the uniform lack of sensitization potential for the chemicals tested, it is unlikely that TPM would cause this effect.

### 3.1.5 Repeated Dose Toxicity

Except for DPMA, repeated dose toxicity data are available for all category members, although not by every route of exposure for every chemical. Where test results are lacking, data from other category members of similar structure may be used. Major test results are summarized below in Table 9, compiled from Dossiers with Robust Summaries for category members or IUCLID for previously evaluated category members. All category members, with the exception of DPMA, have been subjected to a repeated dose toxicity study by at least one route of exposure. In the case of DPMA, data from DPM may be used directly, given the rapid hydrolysis of the acetate moiety from

DPMA to yield DPM. The other close structural analogues, PM and PMA, also may both be used to extrapolate the toxicity of DPMA.

**Table 9. Repeated Dose Mammalian Toxicity**

| Category Member | Oral (NOAEL, LOAEL in mg/kg-day) | Inhalation (NOAEL, LOAEL in mg/kg-day) | Dermal (NOAEL, LOAEL in mg/kg-day) |
|---|---|---|---|
| PnB<br><br>29387-86-8 or 5131-66-8 | (13-wk drinking water, rat)<br>NOAEL = 350 mg/kg-d<br>LOAEL = 1000 mg/kg-d)<br>(liver & kidney weight increases – no histopathology)<br>Granjean & Szabo 1992 | 2-wk, rats – (2 studies)<br>NOAELs > 600 & 700 ppm[1]<br>(3244 & 3785 mg/m$^3$)<br>Klonne et al 1989; Corely et al. 1987<br><br>31-day, rats<br>NOAEL > 600 ppm<br>Pozzani & Carpenter 1965 | (13-wk dermal – rabbits & rats)<br>Rat NOAEL = 1.0 ml/kg-d<br>or 880 mg/kg-day[1]<br>Rabbit NOAEL = 1.14 ml/kg-d<br>or 1000 mg/kg-day[1]<br>Jonker & Lina 1998<br>Hazleton 1987 |
| DPnB<br>29911-28-2 or 35884-42-5 | (13-wk diet – rat)<br>NOAEL = 450 mg/kg-day<br>LOAEL=1000 mg/kg-d<br>(liver weight increases – no histopathology)<br>Thevenaz 1989 | (2-wk aerosol – rat)<br>NOAEL = 200 mg/m$^3$ (25.7 ppm)<br>LOAEL = 810 mg/m$^3$ (104 ppm)<br>(nasal irritation; liver toxicity)<br>Cieszlak et al. 1991<br><br>(2-wk vapor – rat)<br>NOAEL = 40 ppm (320 mg/m$^{3,1}$<br>Lomax et al. 1987 | (13-wk - rat)<br>NOAEL = 91 mg/kg-day<br>(0.1 ml/kg-day)<br>LOAEL= 273 mg/kg-day<br>(0.3 ml/kg-day)<br>(decreased body weight and increased neutrophil counts)<br>Lina et al. 1988 |
| DPMA<br>88917-22-0 | No studies<br>(see PM & DPM as surrogates) | No Studies<br>(see PM, PMA, & DPM as surrogates) | No studies<br>(see PM & DPM as surrogates) |
| TPM<br>20324-33-8 or<br>25498-49-1 | No Studies<br>(see PM & DPM as surrogates) | (2-wk – rats & mice)<br>For Rats:<br>NOAEL = 1010 mg/m$^{3,1}$ (120 ppm)<br>For Mice:<br>NOAEL = 360 mg/m$^3$ (42.7 ppm)<br>LOAEL = 1010 mg/m$^3$ (120 ppm)<br>Inc liver wts w/histopathology<br>Miller et al. 1985b | (90-day – rabbit)<br>NOAEL = 965 mg/kg-d<br>LOAEL = 2895 mg/kg-d<br>Inc kidn wt; dec body wt<br>Rowe et al. 1954 |
| PM<br>107-98-2 | (13-wk diet – rat & dog)<br>NOAEL < 460 mg/kg-d<br>LOAEL = 460 mg/kg-d<br>CNS depressn; inc liver wts.<br>Stenger et al. 1972 | (13-wk – rats & rabbits)<br>NOAEL = 1,000 ppm (3686 mg/m$^3$)<br>LOAEL = 3,000 ppm[1] (11058 mg/m$^3$)<br>Inc liver wt; dec body wt; transient CNS depression<br>Landry et al. 1982<br>Lifetime rat & mouse inhalation study<br>(see Chronic tox/Carc section)<br>Spencer et al. 2002 | (21-day – rabbits)<br>NOAEL > 1,000 (21 day rabbit)[1]<br>No systemic toxicity but limited dermal irritation<br>Calhoun & Johnson 1984 |
| PMA<br>108-65-6 | (45-day gavage – rat)<br>NOAEL = 1000 mg/kg-d[1]<br>MHW Japan, 1998 | (2-wk – rats and mice)<br>Male Rats:<br>NOAEL: 300 ppm (1622 mg/m$^3$)<br>$\alpha_2$-µ-globulin nephropathy & olfactory degeneration<br>Female Rats:<br>NOAEL: 1000 ppm (5405 mg/m$^3$)<br>$\alpha_2$-µ-globulin nephropathy & olfactory degeneration<br>Mice:<br>LOAEL = 300 ppm (1622 mg/m$^3$)<br>Degen. Olfactory epithelium<br>Miller et al. 1984 | No Studies |

| | | | |
|---|---|---|---|
| DPM<br>34590-94-8 | (28-day – rat)<br>NOAEL = 200 mg/kg-day<br>LOAEL = 1000 mg/kg-d<br>(based on inc liver wt w/centrilobular hypertrophy & salivation)<br>Dow Chemical Japan, 2000 | (90 day – rats & rabbits)<br>NOAEL = 200 ppm[1] (1212 mg/m$^3$)<br>LOAEL > 200 ppm (1212 mg/m$^3$)<br>(other studies)<br>NOAEL > 200 ppm (1212 mg/m$^3$)<br>LOAEL = 140 ppm (849 mg/m$^3$)<br>Many studies see narrative below and DPM dossier | (90 day – rabbit)<br>NOAEL = 4750 mg/kg-d (5 ml/kg-d)<br>LOAEL = 9500 mg/kg-d (10 ml/kg-d)<br>Increased narcosis & mortality and hydropic degeneration of the kidney at LOAEL<br>Rowe, 1950; Rowe et al, 1954 |

NOAEL = no observable adverse effect level; LOAEL = lowest observable adverse effect level; NP = not performed

[1] Highest dose or exposure level used in the study

*Inhalation*

Repeat exposure inhalation studies have been conducted with the category members PnB, DPnB, and TPM, as well PM, PMA, and DPM. The repeat exposure inhalation toxicity of individual PGEs is discussed below.

**Propylene Glycol n-Butyl Ether (PnB):** Two 2-week inhalation studies showed minimal effects in rats exposed to PnB concentrations up to 700 ppm, or 3,785 mg/m$^3$ (Klonne et al., 1989; Corley et al., 1989). Increased liver weights without accompanying histopathology and slight eye irritation were found in the Klonne study at 600 ppm (3,244 mg/m$^3$). Exposure concentrations in this study were 0, 10, 100, 300, or 600 ppm (6 hr/d; 5 d/wk - 9 exposures over 11 days). No hematological effects or other effects were seen in the Corley study. Concentrations in the Corley study were 0, 50, 200, or 700 ppm (6 hr/d; 5 d/wk – 9 exposures total). In a longer duration inhalation study, Pozzani and Carpenter (1965) exposed rats to PnB concentrations of 600 ppm for 7 hr/day, 5 d/wk for a total of 31 exposures. Females exhibited increased liver weights without accompanying histopathology. Collectively, these studies establish a NOAEL of > 600 ppm (3,244 mg/m$^3$) based on the fact that liver weight increase was considered an adaptive rather than a toxic response and that eye irritation was minimal (without frank lesions) and reversible.

**Dipropylene Glycol n-Butyl Ether (DPnB):** Groups of 5 male and 5 female young adult Fischer 344 rats were exposed to an aerosol atmosphere of DPnB, at concentrations of 0, 200, 810, or 2010 mg/m$^3$ (0, 25, 100, or 250 ppm) by nose-only exposure, 6 hr/day, 5 d/wk over a 2 week period for a total of 9 exposures (Cieszlak et al., 1991). Rats were monitored for mortality and clinical signs, body and organ weight changes, eye irritation, hematology and chemistry, urinalysis, and gross and microscopic lesions. All rats survived the nine exposures with minimal clinical effects (lethargy for the first few days). The primary effects from DPnB exposure were decreased body weights in rats of both sexes at 2010 mg/m$^3$ and histopathological lesions in the liver and nasal cavities in both sexes at 810 and 2010 mg/m$^3$. The authors of the study concluded that the stress of the 6-hour confinement in the polycarbonate exposure tube contributed to the body weight decreases. The liver changes, although accompanied by slight necrosis in some instances, were characterized primarily by increased hepatocyte size, suggesting an adaptive response (i.e., mixed function oxidase enzyme induction). The concurrent liver weight increases support this conclusion. Hyperplasia, metaplasia, degeneration, and/or inflammation of the anterior nasal mucosa were considered a direct response to the irritant properties of DPnB, typical in mucous membranes. Depletion of cells in the thymus and spleen were considered secondary to the stress of confinement in polycarbonate tubes for the nine 6-hour exposure periods. The NOAEL for DPnB in this study was 200 mg/m$^3$ and the LOAEL was 810 mg/m$^3$ based on effects on the liver and nasal mucosa.

In a 2-week inhalation toxicity study, groups of 5 male and 5 female young adult Fischer 344 rats were exposed to a vapor atmosphere of DPnB at concentrations of 0, 20, or 40 ppm (equivalent to 0, 160, or 320 mg/m$^3$), by nose-only exposure (Lomax et al., 1987). Rats were exposed on weekdays

6 hr/day, 5 day/wk, for total of 9 exposures over a 2-week period. Rats were observed after each exposure for mortality and clinical signs of toxicity. The subjects were weighed prior to exposure on days 1, 3, 5, and 9 of the study. Hematology, clinical chemistry, and urinalyses were conducted prior to sacrifice. All animals were subjected to gross necropsy and over 50 tissues were collected and processed into slides for histological examination. DPnB did not cause toxicity by the inhalation (nose-only) route of exposure in Fischer 344 rats at atmospheric concentrations up to and including 40 ppm (320 mg/$m^3$) when exposed 6 hr/day on 9 separate days (over a 2-week period). The NOAEL is 40 ppm (320mg/$m^3$) and the LOAEL could not be established.

**Tripropylene Glycol Methyl Ether (TPM):** Groups of rats and mice (5/species/sex/dose) were exposed to TPM aerosol 6 hr/day, 5 d/wk at concentrations of 0, 150, 360, or 1010 mg/$m^3$ (0, 18, 43, or 120 ppm) over a two-week period for a total of 9 exposures (Miller et al, 1985b). Subjects were observed for mortality and clinical signs, body weight changes, clinical chemistry and hematology effects, gross lesions and organ weights at necropsy, and histopathological changes. In rats, the only effect found was increased liver weights without accompanying histopathology in the mid and high exposure groups. Similarly, the only effect found in mice was increased liver weights at all exposure levels in males (at the high level only in females). Liver weight increases were not accompanied by histologically observable damage except in the high dose males (increase eosinophilia – necrosis not reported). If liver weight increases without cellular damage in mice at the lower dose levels are considered adaptive in nature (i.e., not "adverse"), this establishes a NOAEL 360 mg/$m^3$ and a LOAEL of 1010 mg/$m^3$ based on liver changes with histopathology in mice and a NOAEL in rats of 1010 mg/m.$^3$

**Propylene Glycol Methyl Ether (PM):** Laboratory animals exposed to PGME via inhalation have reportedly developed central nervous systems effects (sedation), adaptive hepatic changes, and decreases in body weight gain. NOAELs ranged from 300 to 5,000 ppm (1,106 to 18,430 mg/$m^3$) in experiments in rats lasting 11 days to 6 months and longer (Spencer et al., 2002; Goldberg et al., 1964; Landry et al., 1983; Miller et al., 1981; Rowe et al., 1954). For mice, NOAELs ranged from 300 ppm to 1,000 ppm (1,106 to 11,058 mg/$m^3$) in experiments lasting 11 days to 13 weeks (Cieszlak et al., 1996; Miller et al., 1981). In experiments in rabbits lasting 6 months and 13 weeks, NOAELs of > 800 ppm and 1,000 ppm were observed, respectively (Landry et al., 1983; Rowe et al., 1954). In 13-week inhalation studies, rats and rabbits exhibited slight transient CNS depression at 3000 ppm but not at 1000 ppm. Rats exhibited minimal changes in liver weights at 3000 ppm with no histopathology (Landry et al., 1983). In more recent studies with rats and mice (Spencer et al., 2002), 3000 ppm of PGME (6 h/d, 13 weeks) produced sedation during the first week of exposure, which subsided in subsequent weeks. Rats and mice exhibited decreased body weight gains. In rats, hepatic mixed function oxidase activity and hepatocellular proliferation were increased at 3000 ppm and, to some extent, at 1000 ppm in these studies. Mild degenerative changes in the kidneys of rats exposed to 3000 ppm were correlated with deposition of male rat-specific alpha-2-microglobulin. This was accompanied by minimal nephropathy in male rats. Male and female B6C3F1 mice displayed a similar hepatic cellular proliferation and hepatic enzyme induction at 3000 ppm. See section 3.7 Chronic Toxicity/Carcinogenicity for further details on the Spencer et al. study. In other inhalation studies lasting 6 months, NOAELs of 800 ppm and > 3,000 ppm were observed for monkeys and guinea pigs, respectively (Rowe et al., 1954).

**Propylene Glycol Methyl Ether Acetate (PMA):** F344 rats and B6C3F1 mice (5/ sex/exposure level/species) were exposed to PMA at concentrations of 0, 300, 1,000 or 3,000 ppm (0, 1.62, 5.39 or 16.18 mg/L or 0, 1,618, 5,390, or 16, 180 mg/$m^3$) for six hours per day on 5 consecutive days, followed by 4 additional consecutive days of exposure after a weekend interruption (Miller et al. 1984). Hematology and clinical chemistry analyses revealed no treatment-related changes in either species. In rats, kidneys of all males and two females from the 3,000 ppm group (and 1 male from the 1000 ppm group) showed a slight increase in the eosinophilic granularity of the proximal

convoluted tubules of the kidneys. These renal changes are consistent with the accumulation of the protein complex, alpha-2-μ-globulin that is unique to the male rat particularly of the Fischer 344 strain and, consequently, may be unrelated to potential human hazard. Three of five male rats and one of five females in the 3,000 ppm-exposure group also exhibited slight-to-moderate degeneration of olfactory epithelium in the nasal cavities. This nasal change is likely caused by acetic acid from PMA hydrolysis at the exposure site. A NOAEL was established at 300 ppm (1.62 mg/L) for male rats and at 1,000 ppm (5.39 mg/L) for female rats. In mice, degeneration of olfactory epithelium, similar to that in rats, was present to some degree in all male and female mice in the 300, 1,000, and 3,000 ppm exposure group. Although minimal at 300 ppm, this degenerative change occurred in a dose-related manner. A NOAEL was not established and LOAEL was 300 ppm (1.62 mg/L) for males and females.

**Dipropylene Glycol Methyl Ether (DPM):** Laboratory animals exposed to DPM via inhalation have reportedly developed mild symptoms of toxicity, including central nervous systems effects (sedation), adaptive hepatic changes, and decreases in body weight gain at concentrations of 140-400 ppm (849 – 2,425 mg/$m^3$). NOAELs ranged from 50 to 400 ppm in experiments in rats lasting 2 to 28 weeks (Landry et al., 1981; Landry and Yano, 1984; Rowe et al., 1954). For mice, a NOEL of 50 ppm (303 mg/$m^3$) and a LOEL of 140 ppm (849 mg/$m^3$) in an experiment lasting 2 weeks were reported (Landry and Yano, 1984). Since the NOEL and LOEL were based on increased liver weights without accompanying histopathology, the response may be considered adaptive rather than a toxic effect. In experiments in rabbits lasting 13 and 31 weeks, NOAELs of 200 ppm (highest dose tested) and 300-400 ppm were observed, respectively (Landry et al., 1983; Rowe et al., 1954). In the 31-week study, however, changes in liver histology were observed at doses of 300-400 ppm (Rowe et al., 1954).

*Dermal*

Repeated-dose dermal studies have been conducted with the category members PnB, DPnB, and TPM, as well PM and DPM. The repeated-dose dermal toxicity of individual PGEs is discussed below.

**Propylene Glycol n-Butyl Ether (PnB):** PnB was applied daily (5 d/wk; 24 hr/d; non-occluded with collars) to the clipped skin of Wistar rats (10/sex/dose) for 13 weeks at doses of 0, 1, 0.3, or 1.0 ml/kg-day (Jonker and Lina, 1988). The following endpoints were monitored: signs of toxicity, local skin reactions, body weights, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, gross lesions at necropsy, organ weights, and histopathology. Other than local skin reactions, no endpoint changes were considered treatment-related, yielding a NOAEL at the highest dose tested of 1.0 ml/kg-day (880 mg/kg-day). Rabbits (5/sex/dose) were treated topically with PnB at doses of 0, 10, 100, or 1000 mg/kg 7 hr/day, 5 d/wk, for 13 weeks (Hazleton Laboratories, 1987). Toxicological endpoints monitored were as above. Local skin reactions were observed at 100 and 1000 mg/kg-day. Females from the 2 highest dose groups exhibited slight but statistical increases (not decreases) in erythrocyte count, hematocrit, and mean corpuscular hemoglobin, which the authors of the report considered spurious due to an unusually low control value. Consequently, no systemic toxicity was observed even at the highest dose tested, establishing a NOAEL of 1000 mg/kg-day (1.14 ml/kg-day).

**Dipropylene Glycol n-Butyl Ether (DPnB):** Wistar rats (10/sex/dose) were treated topically for 13 weeks (5 d/wk; 24 hr/d; non-occluded with collars) with DPnB at doses of 0, 0.1, 0.3, or 1.0 ml/kg-day (0, 91, 273, or 910 mg/kg-day) (Lina et al., 1988). The following endpoints were monitored: signs of toxicity, local skin reactions, body weights, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, gross lesions at necropsy, organ weights, and histopathology. Local skin irritation occurred at all dose levels, increasing in severity with DPnB dose. Mid and high-dose animals showed increased white cell counts (neutrophils) in both sexes

and lower body weights in mid and high dose males only. Liver weights were increased in high dose rats of both sexes with increased ALT and AST in high-dose males and increased triglycerides and decreased glucose in high-dose females. Histopathology was unrevealing in tissues other than skin at the site of application. This study resulted in a NOAEL of 0.1 ml/kg-day (91 mg/kg-day) and a LOAEL of 0.3 ml/kg-day (273 mg/kg-day), based on body weight decreases in males and increased neutrophil counts (i.e., hematological findings) in both sexes.

**Tripropylene Glycol Methyl Ether (TPM):** In an older study by Rowe et al. (1954), rabbits (5 to 8 adults/dose) were treated topically (5 d/wk; 24 hr/d) with TPM doses of 0, 1.0, 3.0, 5.0, or 10.0 ml/kg-day for a total of 65 applications over a 90-day period. Doses were occluded with an impervious dressing. Body weights were monitored weekly. Hematology was characterized just prior to treatment, at 30 days, and after 90 days. Organ weights were recorded at necropsy and major organs/tissues were processed for histopathological examination. Narcosis and death occurred in 7 of 8 subjects at the high dose of 10 ml/kg-day. No other deaths occurred during the study. Hematology was normal in all subjects evaluated. Weight loss occurred late in the study at doses of 3.0 ml/kg-day and higher and kidney weights were increased at necropsy. Organs from all subjects appeared normal at necropsy. Histopathology indicated local skin reactions and spurious changes in the kidney (tubular necrosis at 1.0 and 3.0 but not at 5.0 ml/kg-day) not considered treatment related. This study established a NOAEL for TPM of 1.0 ml/kg-day (965 mg/kg-day) and a LOAEL of 3.0 ml/kg-day (2895 mg/kg-day) based on increased kidney weights and decreased body weights.

**Propylene Glycol Methyl Ether (PM):** Rabbits were treated topically with 15 daily PM doses over the course of 21 days at a dose of 1000 mg/kg-d (Calhoun and Johnson, 1984). No systemic toxicity occurred but a slight scaling and minimal inflammation was observed at the site of application. In an older study, Rowe et al. (1954) applied 65 doses over the course of 90 days of PM to the skin of rabbits (occluded). Doses were 0, 2.0, 4.0, 7.0, or 10.0 ml/kg-day. Doses of 7.0 ml/kg-day and higher caused narcosis and death. Excluding local skin irritation, a dose of 2.0 ml/kg (1840 mg/kg-day) was without effect (NOAEL).

**Dipropylene Glycol Methyl Ether (DPM):** Rowe et al. (1954) evaluated the dermal toxicity of DPM in rabbits (5 to 7 adults/dose). Sixty-five daily doses of DPM were applied over the course of 90 days. DPM doses (occluded) were 0, 1.0, 3.0, 5.0, or 10 ml/kg-day (0, 950, 2850, 4750, or 9500 mg/kg-day). Six of 7 deaths occurred at the high dose level, accompanied by narcosis. An increase in hydropic degeneration of the kidney was reported in animals in the 9500 mg/kg-day (10 ml/kg-day) group (Rowe, 1950). No other signs of toxicity were noted, establishing a NOAEL of 5.0 ml/kg-day (4750 mg/kg-day). In a more recent dermal toxicity study conducted by Fairhurst et al. (1989), rats treated topically with 0, 100 or 1000 mg/kg-day, 5 day/wk, 4 hr/day over a 4 week period did not show any evidence of systemic toxicity.

*Oral*

Repeated-dose oral studies have been conducted with the category members PnB and DPnB, as well as the surrogates PM and DPM. The repeated-dose oral toxicity of individual PGEs is discussed below.

**Propylene Glycol n-Butyl Ether (PnB)**: Rats (10/sex/dose level) were administered PnB in their drinking water for 13 consecutive weeks at concentrations equivalent to doses of 0, 100, 350, or 1000 mg/kg-day (Granjean et al. 1992). A large number of toxicological endpoints were monitored including organ and body weights, food consumption, clinical signs, clinical chemistry, hematology, urinalysis, ophthalmic examinations, a functional observational battery, gross lesions at autopsy, and a comprehensive list of tissues examined histopathologically. Only the highest dose caused increased liver weights in males and increased kidney weights in females, both without

associated histopathology. Slight alterations in clinical chemistries, electrolytes, and hematology also were noted in both sexes at the high dose level. This study resulted in a NOAEL of 350 mg/kg-day and a LOAEL of 1000 mg/kg-day based on organ weight effects. When tested specifically for possible hematological toxicity in male and female rats (6/sex/dose level), PnB administered by gavage for 14 consecutive days at doses of 0, 100, 200, or 400 mg/kg-day showed no signs of hemolysis when assessed by measurement of erythrocyte fragility, hematocrit levels, mean corpuscular hemoglobin, or other parameters (Debets, 1987a). The negative results from this study are significant because lower molecular weight glycol ethers in the ethylene series have been shown to cause hemolysis.

**Dipropylene Glycol n-Butyl Ether (DPnB)**: DPnB was administered in the diet to rats (20/sex/dose) at concentrations equivalent to doses of 0, 200, 450, or 1000 mg/kg-day for 13 consecutive weeks (Thevenaz, 1989). Again, a very comprehensive set of toxicological endpoints was monitored in this study. Body weights were decreased slightly but statistically in high-dose males. Livers were enlarged but without associated histopathology in high-dose males. Liver findings were corroborated by clinical chemistry results in which some parameters reflective of liver injury were slightly elevated in the high dose groups of either or both sexes. Some urinary parameters in high dose rats were altered. Most of these findings occurred after 4 as well as after 13 weeks of exposure to DPnB. The NOAEL is 450 mg/kg-day and the LOAEL, based on decreased body weights, increased liver and kidney weights (without histopathology) and slight alterations in clinical chemistry parameters, is 1000 mg/kg-d. A hematotoxicity study similar to that conducted for PnB (see above), was conducted for DPnB, again showing no hematotoxicity (Debets, 1987b).

**Propylene Glycol Methyl Ether (PM):** When PM was administered in the diet to rats for 13 weeks at equivalent doses of 0, 0.5, 1.0, 2.0, or 4.0 mL/kg-day (0, 460, 1836, or 3672 mg/kg-day), mild to severe CNS depression (apparently at all dose levels) and liver enlargement with centrilobular necrosis occurred at 2.0 mL/kg-day and higher doses with significant mortality at the highest dose (Stenger et al., 1972). CNS depression and spermiophages in the epididymis also were observed in dogs treated with similar doses (ibid.). This study is well reviewed in Pattys (2001).

**Propylene Glycol Methyl Ether Acetate (PMA):** In a reproductive toxicity test, Crj:CD (SD) rats (# per group not specified) were administered PMA by gavage at doses of 0, 100, 300, or 1000 mg/kg-day for 40-45 days following a typical reproduction study protocol (MHW Japan, 1998). At the high dose level, males showed depressed of body weight gain and a lower food consumption. Females at this dose exhibited low body weight gain during the premating period, decreased glucose and inorganic phosphorus, and increased adrenal weights. In addition, female body weight gain was lower than in the control during the premating period. No histopathology was evident.

**Dipropylene Glycol Methyl Ether (DPM):** In rats dosed by stomach tube with 0, 40, 200, or 1000 mg/kg-day DPM for 4 weeks, salivation (immediately after dosing) and liver effects (increased relative liver weight with accompanying centrilobular hypertrophy, an adaptive response with no necrosis or other cell injury) were observed in animals exposed to the highest dose (Dow Chemical Japan, 2000). No effects were observed in rats exposed to 200 mg/kg-day.

Conclusion

Results indicate that by all three routes of exposure, repeated dosing of these chemicals at high levels is well tolerated for all the category members indicating low toxicity for this category of chemicals. Sometimes, the NOAELs were the highest doses or concentrations tested. This is the case for the inhalation and dermal studies with PnB. In all cases, the doses comprising either the NOAEL or LOAEL were substantial. When effects were observed, they were seen at relatively high doses and were mild in nature.

The studies described show that these propylene glycol ethers do not generally cause the toxicities commonly associated with low molecular weight ethylene glycol ethers at low doses. Even when tested at high dose levels, the PGEs 1) do not cause toxicity to the blood and blood forming organs (including bone marrow), commonly manifested as hemolysis, lymphocytopenias and even pancytopenias; 2) do not cause birth defects even at maternally toxic doses (see section 3.5), 3) do not cause damage to the testis; and 4) do not cause damage to the thymus. The beta isomers of propylene glycol ethers, which are primary rather than secondary alcohols, form the metabolite, alkoxypropionic acid, similar to the ethylene glycol ether metabolite, alkoxyacetic acid. The low molecular weight beta isomer of the PM has been shown capable of causing birth defects and the other toxicities characteristic of EGEs but to a much lesser extent. However, commercial PGEs contain only a small amount of the beta isomer, and as shown in these studies with commercial product, do not cause the toxicities associated with the low molecular weight ethylene glycol ethers, even at high dose levels. The toxicities that are produced by the propylene glycol ethers occur at high exposure/dose levels and, when they do occur, are mild in nature, typically consisting of transient sedation, reduced body weights, increased liver weights (usually without associated histopathology), and/or local irritation of the skin or mucous membranes.

### 3.1.6 Mutagenicity

Category members have been subjected to considerable genotoxicity testing. Table 10 illustrates the tests performed along with abbreviated results. Complete results are available in the Dossiers containing Robust Summaries for category members and IUCLID dossiers for previously evaluated chemicals.

**Table 10. *In vitro* and *in vivo* Genotoxicity Testing**

| Category Member | *In Vitro* Testing | *In Vivo* Testing |
|---|---|---|
| PnB<br><br>29387-86-8 or<br>5131-66-8 | 2 Ames Tests – Negative – Bruce et al. 1987; Lawlor et al. 1987<br>Mouse Lymphoma – Negative – Kirby et al. 1987<br>Unscheduled DNA Synthesis – Negative - Thilagar et al. 1986<br>CHO Cytogenetics – Negative – Bhaskar et al. 1988a<br>CHO Cytogenetics – Negative – Putman 1987 | Not Tested |
| DPnB<br>29911-28-2 or<br>35884-42-5 | Ames Test – Negative – Van de Waart & Enninga 1987<br>CHO Cytogenetics –<br>2 Negative: Bhaskar et al. 1988b; Linscombe & Verschuuren 1991<br>3 Positive: Waalkens & Enninga 1987; Enninga 1987; Enninga & van de Waart 1989<br>CHO/HGPRT Forward Mut. – Negative – Linscombe et al. 1995 | Mouse Micronucleus – Negative<br>McClintock et al. 1998 |
| DPMA<br>88917-22-0 | Ames Test – Negative – Sakata 2000<br>*E. coli* – Negative – Sakata 2000 | Not Tested |
| TPM<br>20324-33-8 or<br>25498-49-1 | Ames Test – Negative – Mendrala & Schumann 1982a<br>Unscheduled DNA Synthesis – Negative – Mendrala & Schumann 1982b | Not Tested |
| PM<br>107-98-2 | Ames Test – Negative - Dow Europe 1983<br>Unscheduled DNA Synthesis – Negative – Mendrala 1983<br>V79 Mutation – Negative – Elias 1996<br>Sister Chromatid Exchange – Negative – Elias 1996<br>CHO Cytogenetics –Negative – Dow Europe 1983<br>V79 Micronucleus – Negative – Elias 1996<br>SHE Cell Transformation – Negative – Elias 1996 | Mouse Micronucleus – Negative |
| PMA 108-65-6 | Ames Test – Negative – MHW Japan, 1998<br>*E. coli* – Negative – MHW Japan 1998<br>Unscheduled DNA Synthesis – Negative – Mendrala 1983<br>CHO Cytogenetics –Negative – MHW Japan 1998 | Not Tested |
| DPM<br>34590-94-8 | Ames Test – Negative –Dow Japan 2000<br>*E. coli* – Negative – Dow Japan 2000<br>Unscheduled DNA Synthesis – Negative – Mendrala 1983<br>CHO Cytogenetics –Negative – Dow Japan 2000 | Not Tested |

*In vitro* genotoxicity assays have been conducted for all the category members. In most instances several different types of *in vitro* tests were conducted, ranging from bacterial (Ames and *E. Coli*) and mammalian cell (HGPRT) mutation tests, to unscheduled DNA repair or cytogenetics (chromosome aberration) assays. DPnB and PM have been tested in *in vivo* genotoxicity tests.

Ames tests were conducted with a minimum of four tester strains, including TA 98, 100, 1535, 1537, and/or 1538, with and without Aroclor-induced rat S-9 microsomal activation systems, with appropriate positive and negative controls, and evaluated PGEs at concentrations up to 5,000 µg/plate and higher. Other in vitro tests listed in Table 11 also included metabolic activation systems, appropriate positive and negative controls, and tested concentrations usually ranging up to or exceeding 5,000 mg/ml of incubation medium. Detailed descriptions (Robust Summaries) of all the assays are contained in the dossiers.

All of the more than 25 *in vitro* tests were negative for each category member except for DPnB. For DPnB, an Ames and CHO/HGPRT Forward Mutation assay were negative. Three of five cytogenetics (chromosome aberration) tests were positive (from a single laboratory) for DPnB and two were negative (from a second single laboratory). Attempts to account for the differences between the two laboratories were not successful. In order to resolve the equivocal *in vitro*

cytogenetics results, a follow-up *in vivo* mouse micronucleus test was conducted with DPnB. In this *in vivo* assay DPnB was administered at doses up to 2500 mg/kg and 1000 polychromatic erythrocytes from each animal (5/sex/dose) were examined for the presence of micronuclei. Results from this *in vivo* test were negative. Using the tiered approach set forth in the EPA genotoxicity risk assessment guidelines, the *in vivo* results take precedence and leads to the conclusion that DPnB is not genotoxic. No other positive results were found, either *in vivo* or *in vitro*, for any of the category members. Thus, the "weight of the evidence" of the overwhelming number of negative in vitro genetic toxicity studies (including CHO Cytogenetics) for the other category members lends support to the conclusion that propylene glycol ethers are not reactive toward DNA. Overall, results indicate that these structurally-related propylene glycol ethers, consistent with the ethylene series of glycol ethers, are unlikely to pose a genotoxicity hazard.

### 3.1.7 Chronic toxicity/carcinogenicity

The sole propylene glycol ether that has been subjected to chronic toxicity/carcinogenicity testing is propylene glycol methyl ether (PM). Thus, the PM study is used as a surrogate for the category members for this non-required toxicity endpoint. PM, tested by inhalation in rats at concentrations up to 3,000 ppm, caused very little chronic toxicity and caused no cancer.

**Propylene Glycol Methyl Ether (PM):** In a chronic toxicity/carcinogenicity study, Fischer rats and B6C3F1 mice (50/sex/exposure level) were exposed to vapor concentrations of propylene glycol methyl ether (PM) at concentrations of 0, 300, 1000, or 3000 ppm (0, 1106, 3686, or 11058 $mg/m^3$) 6 hr/day, 5 days/wk for 2 years (Spencer et al., 2002). Over the course of the study, these subjects were evaluated for clinical signs and body weights. At the end of two years, survivors were subjected to clinical chemistry and hematological examinations, urinalyses, determination of body organ weights, and histopathological examination of a large number of tissues. In order to evaluate potential toxicity at interim time intervals during the exposure period, additional subjects were exposed to PGME vapors and subjected to routine and specialized toxicological tests. Interim time points (3, 6, 12, and 18 months) were evaluated in 5 to 10 rats and mice/sex/exposure level that included clinical chemistry and hematology evaluations, urinalyses, and determination of histopathological changes. Specialized tests conducted in both mice and rats at the interim time intervals included evaluation of 1) cell proliferation in liver and kidneys, 2) hepatic mixed function oxidase (MFO) activity, and 3) $\alpha_2\mu$-globulin nephropathy.

The major changes seen in this study were 1) decreased body weights in both species, 2) liver effects including increased weight, increased MFO activity and increased cell proliferation primarily in males of both species, 3) $\alpha_2\mu$-globulin nephropathy typical of the Fischer 344 strain, and 4) slightly increased mortality occurring after 18 months of exposure in males of both species. Clinical chemistry parameters reflected and corroborated these effects.

Rats exhibited a NOAEL of 300 ppm (1106 $mg/m^3$) based on altered hepatocellular foci in males. Mice showed a NOAEL of 1000 ppm (3686 $mg/m^3$) based on slight body weight decreases in both sexes. The LOAELS were correspondingly higher. No carcinogenic effect as evidenced by any increase in tumor incidence, even in kidneys of the male rats, occurred from exposure to PM at any concentration in either species.

### 3.1.8 Toxicity for Reproduction

Reproductive toxicity studies are not available for PnB, DPnB, DPMA and TPM. However, PM and PMA have undergone this type of testing. PM and PMA at doses up to 1000 mg/kg-day orally and 3000 ppm via inhalation, did not cause direct reproductive toxicity in either case. For PM, ovarian weights were decreased (with accompanying atrophy) at 3000 ppm but not 1000 ppm,

considered secondary to severe maternal weight loss of 21% at 3000 ppm. PM did not cause any reduction in sperm counts or mobility. For the category member, DPMA, PMA is directly applicable. For the remaining category members, the results from PM are more directly applicable. Results from the category do not indicate a potential for reproductive toxicity.

Since all of the category members except DPMA have undergone repeated dose toxicity testing at substantial doses with extensive histopathology, definitive conclusions can be drawn regarding damage to reproductive organs. Results from these repeated dose tests indicate that none of the category members caused toxicity to the testes as has been seen with the lower molecular weight ethylene glycol ethers. Specifically, no reduction in testicular weight, no damage to the sperm or sperm-producing cells, and no damage to the epididymis or seminiferous tubules were reported. Likewise, no damage to female reproductive organs was found. Further inferences may be drawn from developmental toxicity studies (see next section). Specifically, all of the category members have been tested for developmental toxicity and none show a reduction in female fecundity. Table 11 shows results from reproductive toxicity and relevant repeated-dose toxicity tests that have been performed on the category.

**Table 11. Reproductive Toxicity**

| Category Member | Route of Exposure Species, Doses/Exposure Levels | Results: Parental Effects (NOAEL, LOAEL) | Results: Offspring (NOAEL, LOAEL) | Reference |
|---|---|---|---|---|
| PnB<br>29387-86-8<br>or<br>5131-66-8<br><br>Repeated-dose toxicity studies only | 90-day drinking water, rat<br>0, 100, 350, 1000 mg/kg-d | No effects on reproductive organs<br>NOAEL > 1000 mg/kg-d[1] | Not evaluated | Granjean & Szabo 1992 |
| | 90-day dermal, rat<br>0.1, 0.3, 1.0 ml/kg-d<br>(88, 264, 880 mg/kg-d) | No effects on reproductive organs<br>NOAEL > 1.0 ml/kg-d (880 mg/kg-d) [1] | Not evaluated | Jonker & Lina 1988 |
| | 90-day dermal, rabbit<br>0, 10, 100, 1000 mg/kg-d | No effects on reproductive organs<br>NOAEL > 1000 mg/kg-d[1] | Not evaluated | Hazleton Labs 1987 |
| | 14-day gavage, rats<br>0, 100, 200, 400 mg/kg-d | No effects on reproductive organs<br>NOAEL > 1000 mg/kg-d[1] | Not evaluated | Debets 1987 |
| | 2-week inhalation, rats<br>0, 10, 100, 300, 600 ppm<br>(0, 54, 540, 1622, 3244 mg/m3) | No effects on reproductive organs<br>NOAEL > 600 ppm[1] | Not evaluated | Klonne et al. 1987 |
| | 2-week inhalation, rats<br>0, 50, 200, 700 ppm<br>(0, 270, 1081, 3785 mg/m3) | No effects on reproductive organs<br>NOAEL > 700 ppm[1] | Not evaluated | Corley et al. 1987 |
| DPnB<br>29911-28-2<br>or<br>35884-42-5<br><br>Repeated-dose toxicity studies only | 90-day dietary, rat<br>0, 100, 350, 1000 mg/kg-d | No effects on reproductive organs<br>NOAEL > 1000 mg/kg-d[1] | Not evaluated | Thevenaz 1989 |
| | 90-day dermal, rat<br>0.1, 0.3, 1.0 ml/kg-d<br>(88, 264, 880 mg/kg-d) | No effects on reproductive organs<br>NOAEL > 1.0 ml/kg-d (880 mg/kg-d)[1] | Not evaluated | Lina et al. 1988 |
| | 2-week aerosol inhalation, rats<br>0, 200, 810, 2010 mg/m$^3$<br>(0, 26, 105, 258 ppm) | No effects on reproductive organs<br>NOAEL > 2010 mg/m$^3$ (258 ppm)[1] | Not evaluated | Cieszlak et al. 1987 |
| | 2-week nose-only vapor inhalation, rats<br>0, 20, 40 ppm | No effects on reproductive organs<br>NOAEL > 40 ppm[1] | Not evaluated | Lomax et al. 1987 |

| | | | | |
|---|---|---|---|---|
| DPMA<br>88917-22-0 | No studies<br>(see DPM & PMA as surrogates) | No Studies<br>(see PM & DPM as surrogates) | No studies<br>(see PM & DPM as surrogates) | |
| TPM<br>20324-33-8<br>or<br>25498-49-1<br><br>Repeated-dose toxicity studies only | Inhalation, rats & mice<br>0, 150, 360 or 1010 mg/m$^3$<br>(0, 18, 43, 120 ppm)<br><br>90-day dermal, rabbit<br>0, 1.0, 3.0, 5,0, 10 ml/kg-d<br>(0, 265, 2895, 4825, 9650 mg/kg-d) | No effects on parental reproductive organs at any exposure level<br>NOAEL > 1010 mg/m$^3$ (120 ppm)<br><br>No testicular effects when evaluated histopathologically<br>NOAEL for testicular effects > 10 ml/kg-d (9650 mg/kg-d) [1] | Not evaluated<br><br>Not evaluated | Miller et al.<br>1985b<br><br>Rowe et al.<br>1954 |
| PM<br>107-98-2<br><br>2-Gen. Repro. Studies | Rats (inhalation)<br>0, 100, 300, 1000, 3000 ppm<br>(0, 368, 1106, 3686, 11058 mg/m3)<br><br>Mice (drinking water) – 0, 0.5, 1.0, 2.0% | Sedation/body weight loss @ 3000 ppm, both generations<br>LOAEL 3000 ppm<br>NOAEL 1000 ppm<br>NOAEL for parental repro effects 3000 ppm[1]<br><br>Body weight loss, decreased prostate, epidymis & testis weights (high exposure - second generation)<br>No change in reproductive performance<br>LOAEL 2.0%<br>NOAEL 1.0% | Reduced viability, survival, & body weights at 3000 ppm<br>LOAEL 3000 ppm<br>NOAEL 1000 ppm<br><br>Decreased body weights at high exposure level in both generations<br>LOAEL 2.0%<br>NOAEL 1.0% | Carney et al.<br>1999<br><br>Chapin & Sloane<br>1997 |
| PMA<br>108-65-6<br><br>2-Gen Repro | Gavage – Rat<br>0, 100, 300, 1000 mg/kg-d | Non-Repro Parental Toxicity NOAEL = 300 mg/kg-d<br>Non-Repro Parental Toxicity LOAEL = 1000 mg/kg-d<br>No parental reproductive effects found<br>NOAEL > 1000 mg/kg-d[1] | No effects found<br>NOAEL > 1000 mg/kg-d[1] | MHW Japan<br>1998 |
| DPM<br>34590-94-8 | No studies | No studies | No studies | |

[1] Highest dose/exposure concentration tested.
NOAEL = no observable adverse effect level; LOAEL = lowest observable adverse effect level.

**Propylene Glycol n-Butyl Ether (PnB):** Repeated dose studies for this category member have been discussed previously under Section 3.3 "Repeated Dose Toxicity." Potential effects on reproductive tissues have been evaluated in six such studies with PnB. Specifically, these include the 14-day gavage rat toxicity study of Debets (1987a), the 90-day rat drinking water study of Granjean & Szabo (1992), the 90-day rat dermal study by Jonker & Lina (1988), the 90-day rabbit dermal toxicity study (Hazleton Laboratories, 1987), and the two 2-week rat inhalation studies (Klonne et al., 1989 & Corley et al, 1989). In all of these studies at a minimum, testes and ovaries were examined histopathologically for potential chemically induced injury. In the 90-day studies, in addition, prostate, epididymides, seminal vesicles in males, and uterus and vagina in females were examined histopathologically. No chemically related damage to any of these reproductive tissues was reported in these six studies.

**Dipropylene Glycol n-Butyl Ether (DPnB):** Potential effects on reproductive tissues have been evaluated in four repeated dose studies with DPnB. Specifically, these include the 90-day rat dietary study by Thevenaz (1989), the 90-day rat dermal study by Lina et al. (1988), the 2-week rat aerosol inhalation study by Cieszlak et al. (1991), and the 2-week nose-only vapor inhalation study by Lomax et al. (1987). In all four studies at a minimum, testes, prostate, epididymides, seminal

vesicles in males and ovaries, uterus, and vagina in females were examined histopathologically. No chemically related damage to these reproductive organs was reported in these four studies.

**Dipropylene Glycol Methyl Ether Acetate (DPMA)**: No repeated-dose toxicity studies are available for this chemical.

**Tripropylene Glycol Methyl Ether (TPM):** Potential effects on reproductive tissues have been evaluated in two repeated dose studies with TPM. Specifically, these include 2-week aerosol rat and mouse inhalation study by Miller et al. (1985b) and the 90-day male rabbit dermal study by Rowe et al. (1954). In these two studies, testes were evaluated (the older Rowe study only evaluated males). In the Miller 2-week inhalation study with mice and rats, prostate, epididymides, seminal vesicles also were evaluated in addition to testes in males. In females from the Miller study, ovaries, cervix, uterus, and vagina in females were examined histopathologically. No chemically related damage to these reproductive organs was reported in these two studies.

**Propylene Glycol Methyl Ether (PM):** Chapin and Sloane (1997) summarized the results of 90 NIEHS and NTP-sponsored studies, which included a 2-generation reproductive toxicity test with PM. PM was administered to Swiss CD-1 mice at 0, 0.5, 1.0, or 2.0% in the drinking water. There were no changes in body weight or food consumption in any of the first generation exposure groups except for a 4% reduction in pup weight at the highest dose tested. In the second-generation exposure groups, reductions in high dose male and female body weight were noted (14% reduction during nursing; 8% reduction in body weight in males during and after mating, and epididymis and prostate weights were 9 and 8% below controls, respectively). There was no evidence of reproductive toxicity. Specifically, mating or fertility indices in parental generations did not decrease. In F1 and F2 offspring, the number of live pups and their viability was not decreased. Among F1 offspring, mean pup weight was decreased in the 2% group. F2 offspring from the 2% group displayed reduced pup weight at birth, which continued postnatally during nursing. At sacrifice, female body weights in the 2% group were lower than controls; in males, absolute testis, and relative epididymis and prostate weights were also reduced. F1 female body-weight-adjusted liver weights were increased.

In a 2-generation inhalation reproductive toxicity study by Carney et al. (1999), Sprague-Dawley rats (30/sex/exposure level) were exposed to PM-containing atmospheres of 0, 100, 300, 1000, or 3000 ppm (0, 368, 1106, 3686, or 11058 mg/m$^3$) PM 6 hr/day, 5 days/wk prior to mating and 7 days/week during mating, gestation and lactation, for two generations. At 3000 ppm, toxicity in the P1 and P2 adults was marked, as evidenced by sedation during and after exposure for several weeks, and mean body weights which were as much as 21% lower than controls. Toxicity at this exposure level was accompanied by lengthened oestrous cycles, decreased fertility, decreased ovary weights, reduced pup survival and litter size, slight delays in puberty onset, and histologic changes in the liver and thymus of the F1 and F2 offspring. At 3000 ppm, there was an increase in histologic ovarian atrophy in P1 and P2 females, and at 1000 ppm, there was a decrease in pre-mating body weight in the P1 and P2 females. No treatment-related differences in sperm counts or motility were observed among the P1 or P2 males. The NOAEL for parental toxicity (non-reproductive) is 300 ppm (1106 mg/m$^3$) and for offspring toxicity is 1000 ppm (3686 mg/m$^3$). Effects appear secondary to parental weight loss. The NOAEL for parental reproductive toxicity is 1000 ppm (3686 mg/m$^3$) and the LOAEL is 3000 ppm (11058 mg/m$^3$).

**Propylene Glycol Methyl Ether Acetate (PMA):** Using the OECD combined repeat dose and reproductive/developmental toxicity screening test [OECD TG 422], SD (Crj: CD) rats received gavage doses of 0 (vehicle; distilled water), 100, 300 or 1,000 mg/kg-day (MHW, Japan, 1998). Males were treated 44 days from 2 weeks prior to mating and females were treated 41-45 days from 14 days before mating to day 3 postpartum. Females were sacrificed on day 4 of lactation. Effects were seen in the parental generation only at the highest dose tested. Males at the high dose showed decreased weight gain and a tendency toward lower food consumption. Males at this level also

showed changes in blood chemistries including decreased glucose and inorganic phosphorus levels and increases in relative adrenal weights. Females at the high dose level showed a lower body weight gain than controls during the premating period. Reproductive toxicity of PMA in rats by oral administration was not observed at the highest dose or any other level in this study. No effects related to the chemical exposure were observed in fetal data at any dose level. For toxicity to the parental generation, a LOAEL of 1000 mg/kg-day (based on body weight changes and other effects listed above) and an NOAEL of 300 mg/mg-day was established in this study. For reproductive toxicity in parents and for fetal effects, a NOAEL was established at 1000 mg/kg-day.

*Developmental Toxicity*

Developmental toxicity data are available for three of the four category members and all three of previously evaluated PGEs by at least one route of exposure. For the single member lacking a developmental toxicity study, DPMA, the studies for PMA and DPM may be substituted. Results, summarized below in Table 12, were compiled from Dossiers with Robust Summaries for category members and IUCLID dossiers for previously evaluated glycol ethers. All protocols followed OECD guidance, exposing dams during the appropriate period of organogenesis.

**Table 12. Developmental Toxicity**

| Category Member | Route of Exposure<br>Species, Doses/Exposure Levels | Results: Maternal Tox.<br>(NOAEL, LOAEL) | Results: Offspring<br>(NOAEL, LOAEL) | References |
|---|---|---|---|---|
| PnB<br>29387-86-8 or<br>5131-66-8 | Dermal – Rat<br>0, 264, or 880 mg/kg-d<br><br>Dermal –Rabbit<br>0, 10, 40, or 100 mg/kg-d | No effects at any dose level<br>NOAEL > 880 mg/kg-d<br>LOAEL > 880 mg/kg-d<br><br>No effects at any dose level<br>NOAEL > 100 mg/kg-d<br>LOAEL > 100 mg/kg-d | No effects at any dose level<br>NOAEL > 880 mg/kg-d<br>LOAEL > 880 mg/kg-d<br><br>No effects at any dose level<br>NOAEL > 100 mg/kg-d<br>LOAEL > 100 mg/kg-d | Waalkens-Berendsen et al. 1988<br><br>Gibson 1989 |
| DPnB<br>29911-28-2 or<br>35884-42-5 | Dermal – Rat<br>0, 273, or 910 mg/kg-d | No effects at any dose level<br>NOAEL > 910 mg/kg-d<br>LOAEL > 910 mg/kg-d | No effects at any dose level<br>NOAEL > 910 mg/kg-d<br>LOAEL > 910 mg/kg-d | Wilmer and van Marwijk, 1988 |
| DPMA<br>88917-22-0 | No studies<br>(see DPM & PMA as surrogates) | No Studies<br>(see PM & DPM as surrogates) | No studies<br>(see PM & DPM as surrogates) | |
| TPM<br>20324-33-8 or<br>25498-49-1 | Inhalation (aerosol) – Rat<br>0, 100, 300 or 1000 mg/m$^3$<br>(0, 11.8, 35.5, or 118 ppm) | No effects: 0, 100, or 300 mg/m$^3$<br>Muzzle staining at 1000<br>NOAEL = 300 mg/m$^3$<br>LOAEL = 1000 mg/m$^3$ | No effects at any dose level<br>NOAEL > 1000 ppm<br>LOAEL > 1000 ppm | Breckenridge 1985 |
| PM<br>107-98-2 | Multiple species, multiple routes – high doses/exposure levels<br>Inhalation<br>500 - 3000 ppm (1843-11058 mg/m3) – rats<br>500 - 3000 ppm - rabbits<br><br>Gavage<br>0.05 to 0.8 ml/kg – rats<br>0.5 to 2 ml/kg - mice<br>0.25 to 1 ml/kg – rabbits | In inhalation studies, CNS depression and decreased food consumption in rats and rabbits and decreased weight gain in rats only at 3000 ppm. No effect on dams reported in oral studies. | No birth defects in any species at highest doses tested; slight delayed ossification at high dose in rats only | Inhalation study: Hanley et al., 1984<br><br>Oral studies:<br>Stenger et al. 1972 |
| PMA<br>108-65-6 | Inhalation (vapor) – Rat<br>500, 2,000, 4,000 ppm<br>(2703, 10810, 21621 mg/m3)<br><br>Gavage – Rat (2-Gen Repro with teratology)<br>0, 100, 300, 1000 mg/kg-d | Porphyria, reduced body wts at 2000 & 4000 ppm,<br>NOAEL = 500 ppm<br>LOAEL = 2,000 ppm<br><br>Non-Repro Parental Toxicity<br>NOAEL = 300 mg/kg-d<br>Non-Repro Parental Toxicity<br>LOAEL = 1000 mg/kg-d<br>No parental reproductive effects found<br>NOAEL > 1000 mg/kg-d[1] | No effects at any dose level<br>NOAEL > 4000 ppm<br>LOAEL > 4000 ppm<br><br>No teratogenic effects found<br>NOAEL > 1000 mg/kg-d[1] | Asaki and Houpt, 1990<br><br>MHW Japan 1998 |
| DPM<br>34590-94-8 | Inhal (vapor) – Rat & Rabbit<br>0, 50, 150, or 300 ppm (highest attainable vapor concentration) | No effects found<br>NOAEL > 300 ppm<br>LOAEL > 300 ppm | No effects found<br>NOAEL > 300 ppm<br>LOAEL > 300 ppm | Breslin et al. 1990 |

NOAEL = no observable adverse effect level; LOAEL = lowest observable adverse effect level. [1] Highest dose tested.

None of the four category members tested produced developmental toxicity by oral, inhalation, or dermal routes of exposure even when tested at high doses or exposure levels. Some embryo-and/or fetotoxicity was found where maternal toxicity existed. Similarly, increased incidences of anomalies (e.g., delayed skeletal ossification, increased incidence of 13$^{th}$ ribs) were sometime noted at high dose levels in conjunction with maternal toxicity. Most important, none of the category members produced frank developmental toxicity (i.e., no birth defects). This also is true for all three of the previously submitted propylene glycol ethers. For the one category member not tested,

DPMA, the close structural analogs, PMA and DPM, both were negative for developmental toxicity. Together, these studies show that category members are not selectively toxic to the developing rat, rabbit, or mouse conceptus, even at the high doses used in these studies and even if those high doses produced toxicity in the dam. The developmental toxicity of individual propylene glycol ethers is discussed below.

**Propylene Glycol n-Butyl Ether (PnB):** Propylene glycol n-butyl ether (PnB) (or the negative control, propylene glycol) was applied daily on gestation days 6 through 15 to the shaved skin of three groups of pregnant Wistar rats (≥20/sex/dose level) at various dilutions in propylene glycol (PG) equivalent to doses of 0 (PG-only; 1.5 ml/kg-day), 0.3 or 1.0 ml PnB/kg-day (Waalkens-Berendsen et al., 1988). These doses equate to 0, 264, or 880 mg PnB/kg-day. Rats were observed for clinical signs of toxicity and skin reactions on a daily basis (week days). Maternal body weights and food consumption were monitored. At sacrifice, all animals were subjected to necropsy and examined for gross abnormalities. The ovaries, uterus, kidneys, and livers were removed and weighed. The number of corpora lutea was counted. Fetuses were removed from the uterus, weighed, lengths recorded, and examined for gross abnormalities. Early and late resorptions and live and dead fetuses were counted. Implantation sites in both uterine horns were counted and the empty uterus weighed. Half the fetuses from each litter were eviscerated, skinned and stripped of most subcutaneous tissue, then fixed in 96% ethanol. These fetuses were then stained with Alizarin Red S and examined for skeletal anomalies. The remaining fetuses were fixed in Bouin's fluid, transferred to 70% ethanol and sectioned into slices (after Wilson) for soft tissue analysis. Percentages of pre- and post-implantation loss were calculated, as was the degree of ossification for each fetus. Soft tissue and skeletal anomalies or abnormalities were recorded.

Slight skin reactions were found in the dams from all treatment groups and thus, were not considered to be treatment related. No maternal toxicity was found: clinical signs and organ or body weights did not differ between treatment and controls groups. No deaths occurred in any groups over the course of the study. No embryo- or fetotoxicity was evident since pre- and post-implantation losses were comparable among treatment and control groups. PnB did not cause frank developmental toxicity in skeletal or soft tissue. The high dose group did exhibit a slight increase in the incidence of supernumerary rudimentary thoracic ribs when compared to controls. However, this finding was not considered significant by the authors of the study since the incidence was within normal limits for these species. In this study, PnB was not maternally toxic, embryo- or fetotoxic, or teratogenic in Wistar rats receiving dermal doses up to 1.0 ml/kg-d during organogenesis (days 6 – 15). The NOAEL for maternal toxicity, embryo- or fetal toxicity, or developmental toxicity is > 1.0 ml/kg-d (880 mg/kg-d) and a LOAEL also was > 1.0 ml/kg-day.

A similar dermal developmental toxicity study was conducted with pregnant rabbits at doses of 0, 10, 40, or 100 mg PnB/kg-day during organogenesis (Gibson et al., 1989). PnB did not cause maternal toxicity, embryo- or fetal toxicity, or developmental abnormalities in fetuses at any dose level. The NOAEL for these effects is 100 mg/kg (highest dose tested) and the LOAEL is > 100 mg/kg. Because this study did not reach a limit dose of 1000 mg/kg/day and showed no effects, it is limited in its ability to demonstrate effects of the chemical. However, because the previous study (above) was conducted at a limit dose, the endpoint is considered to be adequately covered.

**Dipropylene Glycol n-Butyl Ether (DPnB):** Dipropylene glycol n-butyl ether (DPnB) was applied daily to the skin of pregnant rats on gestation days 6 through 15 (Wilmer and van Marwijk, 1988). DPnB was applied to the clipped skin of two groups of Wistar rats (≥20/sex/dose level) at various dilutions in propylene glycol (PG) equivalent to doses of 0 (PG-only; 1.5 ml/kg-day), 0.3 or 1.0 ml DPnB/kg-day. These doses equate to 0, 273, or 910 mg DPnB/kg-day. Rats were observed for clinical signs of toxicity and skin reactions. Individual body weights were recorded and food consumption was monitored. At sacrifice, all animals were subjected to necropsy and examined for gross abnormalities. The ovaries, uterus, kidneys, and livers were removed and weighed. The

number of corpora lutea was counted. Fetuses were removed from the uterus, weighed, lengths recorded, and examined for gross abnormalities. Early and late resorptions and live and dead fetuses were counted. Implantation sites in both uterine horns were counted and the empty uterus weighed. Half the fetuses from each litter were eviscerated, skinned and stripped of most subcutaneous tissue, then fixed in 96% ethanol. These fetuses were then stained with Alizarin Red S for examination for skeletal anomalies. The remaining fetuses were fixed in Bouin's fluid, transferred to 70% ethanol and sectioned into slices (after Wilson) for soft tissue examination. Percentages of pre- and post-implantation loss were calculated, as was the degree of ossification for each fetus. Soft tissue and skeletal anomalies or abnormalities were recorded.

Slight skin reactions were found in the dams from all treatment groups and thus were not considered treatment related. No maternal toxicity was found: clinical signs and organ or body weights did not differ between treatment and controls groups. No deaths occurred in any groups over the course of the study. Fecundity was comparable among groups. No embryo- or fetotoxicity was evident since pre- and post-implantation loss, number of viable fetuses, and fetal weights and lengths were comparable between treatment and control groups. DPnB did not cause frank developmental toxicity in skeletal or soft tissue. The high dose group did exhibit a slight increase in the incidence of supernumerary rudimentary thoracic ribs when compared to controls. However, this finding was not considered significant by the authors of the study since the incidence was within normal limits for these species.

DPnB is not maternally toxic, embryo- or fetotoxic, or teratogenic in Wistar rats receiving dermal doses up to 1.0 ml/kg-d during organogenesis (days 6 – 15). The NOAEL for maternal toxicity, embryo- or fetal toxicity, or developmental toxicity is 1.0 ml/kg-d (910 mg/kg-d) and a LOAEL was not established.

**Tripropylene Glycol Methyl Ether (TPM):** Mated female Sprague-Dawley rats (25/group) were exposed to aerosol atmospheres of tripropylene glycol methyl ether (TPM) at concentrations of 0, 0.1, 0.3, or 1.0 mg TPM per liter of air (0, 100, 300, or 1000 mg/$m^3$ or 0, 11.8, 35.6, or 118 ppm), 6 hours per day on gestation days 6 through 15 (Breckenridge et al., 1985). Rats were observed for clinical signs of toxicity, abortion, and delivery over the exposure and post-exposure periods. Individual body weights were recorded and at sacrifice (day 20 of pregnancy), all animals were necropsied and examined for gross abnormalities. The ovaries, uterus, kidneys, and livers were removed and weighed. The number of corpora lutea was counted in each ovary. Early and late resorptions and live and dead fetuses were counted. Implantation sites in both uterine horns were counted and the empty uterus weighed. Fetuses were removed from the uterus, weighed, lengths recorded, and examined for gender and external and internal gross abnormalities. Heads were removed from 2/3 of the fetuses and examined after the method of Wilson. The bodies of these fetuses, as well as the remaining 1/3, were stained with Alizarin Red S and skeletons were examined. Percentages of pre- and post-implantation loss were calculated, as was the degree of ossification for each fetus. Soft tissue and skeletal anomalies or abnormalities were recorded. Findings were categorized into major malformation, minor anomalies, and common variants.

No maternal deaths occurred in any of the groups. Fifteen of 25 dams in the high exposure group exhibited red staining around the muzzle, compared to 0/25, 1/25, and 0/25 in the control, low, and mid-exposure groups, respectively. No other clinical signs of toxicity were noted. No effect upon body or organ weights was noted in the dams. Pregnancy and abortion rates were comparable among all groups. The pregnancy rate was comparable among groups. No effects were noted from TPM exposure on the number of live fetuses, fetal weights, sex ratio, or early or late resorptions. No fetal variations or abnormalities were found to occur at a greater incidence in TPM-treated subjects than in air-only controls. TPM did not cause embryo-, fetal, or developmental toxicity in fetuses at any exposure level. Maternal toxicity was evident in the high exposure level only, based on an increased incidence of red staining of the muzzle compared to controls. The NOAEL for

maternal toxicity is 0.29 mg/liter and the LOAEL is 1.02 mg/liter, based on stained muzzles. The NOAEL for developmental effects is > 1.02 mg/liter and a LOAEL was not established.

**Propylene Glycol Methyl Ether (PM):** In a study of rats and rabbits exposed to PGME via inhalation at concentrations of 0, 500, 1500, or 3000 ppm (0, 1842, 5529, or 11058 mg/m$^3$), NOAELs of 1,500 ppm (for maternal toxicity), 1,500 ppm (for fetotoxicity), and 3,000 ppm (for developmental toxicity) were established for both species (Hanley et al., 1984). Effects observed in maternal animals at 3,000 ppm included mild transient central nervous system depression and decreased food consumption and body weight gains. PGME was slightly fetotoxic (delayed sternebral ossification) at concentrations of 3,000 ppm. No frank teratogenic effects were observed at concentrations up to and including 3,000 ppm, the highest exposure level tested. For maternal toxicity and fetotoxicity, LOAELs of 3000 ppm were established in this study while no LOAEL was established for teratogenicity, as the highest dose tested (established as a no observed adverse effect level), did not cause this effect.

Via gavage, no maternal toxicity, fetotoxicity, or teratogenicity was observed in rats, mice, and rabbits administered PM at multiple dose levels. NOAELs of 0.8, 2, and 1 ml/kg-day were observed for rats, mice, and rabbits, respectively, in each case, the highest dose tested (Stenger et al., 1972). Only the rat fetus showed a developmental variation consisting of delayed ossification of the skull at the highest dose given (0.8 ml/kg-day). Similarly, these doses did not produce maternal or frank birth defects in mice when administered by injection.

**Propylene Glycol Methyl Ether Acetate (PMA):** Pregnant rats were exposed to PMA vapor on days 6 through 15 of gestation, once daily for 6 hours/day at nominal concentrations of 0, 500, 2,000, or 4,000 ppm (0, 2,700, 10,800, 21,600 mg/m$^3$). The animals were sacrificed on day 20 of gestation and evaluated for potential maternal, embryonic/fetal and teratogenic toxicity (Asaki and Houpt, 1990). Most of the effects observed in dams were transient in nature. Reductions in muscle tone (2,000 and 4,000 ppm), food consumption (500, 2,000 and 4,000 ppm) and body weight (2,000 and 4,000) were seen during the exposure period. At 2,000 and 4,000 ppm, dyspnea, ruffled pelt and red discharges from the eyes or mouth were observed. No toxic signs were observed in the 500 ppm exposure group. There was no difference in the percent of fetuses per litter that were malformed. In addition, there were no differences in the percent of litters, which contained a malformation, a variation or contained all normal fetuses. No teratological or other developmental effects were seen in fetuses at concentrations as high as 4,000 ppm (the highest concentration tested). A NOAEL was established at 500 ppm (2,700 mg/m$^3$, measured) for maternal toxicity and, for offspring, a NOAEL exceeded 4,000 ppm (22,464 mg/m$^3$, measured) for fetal toxicity and developmental effects. No developmental toxicity was observed in this experiment.

Similarly, no developmental toxicity was seen in an oral (gavage) 2-generation reproductive toxicity with developmental toxicity study (MHW Japan, 1998). This study is reviewed above in Section 3.4 Reproductive Toxicity. No developmental effects were seen at the highest dose tested of 1000 mg/kg-day.

**Dipropylene Glycol Methyl Ether (DPM):** Breslin et al. (1990) evaluated the developmental toxicity of DPM in rats and rabbits via the inhalation route of exposure at concentrations of 0, 50, 150, or 300 ppm (0, 303, 909, or 2728 mg/m$^3$). 300 ppm is the highest concentration attainable at room temperature and normal pressure. No maternal toxicity, embryo/fetal toxicity, or developmental toxicity was found in either species, even at the highest concentrations tested.

### 3.2 Initial Assessment for 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 $13^{th}$ 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.

# 4 HAZARDS TO THE ENVIRONMENT

## 4.1 Aquatic Effects

Acute toxicity studies in fish and daphnia have been performed on all category members. Phytotoxicity testing is less comprehensive. Data are presented separately for the ethers and the acetates because the acetates do not hydrolyze into alcohols readily at environmental conditions (pH = 7). Table 13 presents data for ethers and Table 14 presents data for the acetates.

**Table 13. Comparative Aquatic Toxicity of the Ethers**

| Chemical | Fish Acute Toxicity $LC_{50}$ (mg/l)[a] | Daphnia Acute Toxicity $LC_{50}$ (mg/l)[b] | Phytotoxicity $EC_{50}$ (mg/l)[c] |
|---|---|---|---|
| PnB<br>29387-86-8 or 5131-66-8 | 560-1000 (guppy)<br>Van der Hoeven & Welboren, 1987a | > 1000<br>Borgers & Welboren, 1987a | Algae<br>Hughes, 1987<br>42% growth inhib. at 1000 mg/l<br>EPIWIN Modeling (ECOSAR module) predicts Green Algae 96-hr EC50 of 524.7 mg/L and ChV of 29.10 mg/L |
| DPnB<br>29911-28-2 or 35884-42-5 | 841 (guppy)<br>Van der Hoeven & Welboren, 1987b | > 1000<br>Borgers & Welboren, 1987b | EPIWIN Modeling (ECOSAR module) predicts Green Algae 96-hr EC50 of 556.4 mg/L and ChV of 33.65 mg/L |
| TPM<br>20324-33-8 or<br>25498-49-1 | 11,619 (fathead minnow)<br>Dill, 1978 | >10,000<br>Dill, 1978 | Duckweed<br>Caux et al. 1986<br>NOEC = 483, LOEC = 965<br>EPIWIN Modeling (ECOSAR module) predicts Green Algae 96-hr EC50 of 9067 mg/L and ChV of 254.2 mg/L |
| PM<br>107-98-2 | 20,800 (fathead minnow)<br>BASF AG, 1994<br>4,600 (golden orfe)<br>Bartlett et al., 1981 | EC50 = 23,300<br>Bartlett et al., 1981 | Algae<br>Dill & Milazzo, 1988<br>EC50 > 1000 |
| DPM<br>34590-94-8 | >10,000 (fathead minnow)<br>Bartlett 1979 | 1,919<br>Bartlett 1979 | Algae<br>Kirk et al., 2000<br>$EC_{50}$ (72 hr) > 969 mg/L |

[a] Lethal concentration in 50% (96 hr unless otherwise stated); [b] Lethal concentration in 50% 48 hr (EC50 for immobilization, if so stated)

[c] Inhibition of fluorescence in 50%, 72 hr (for algae) unless otherwise noted for other plant species.

**Table 14. Comparative Aquatic Toxicity of the Acetates**

| Chemical | Fish Acute Toxicity $LC_{50}$ (mg/l)[a] | Daphnia Acute Toxicity $LC_{50}$ (mg/l)[b] | Phytotoxicity $EC_{50}$ (mg/l)[c] |
|---|---|---|---|
| DPMA<br>88917-22-0 | 151 (fathead minnow)<br>Dill & Applegath, 1983 | 1090<br>Dill & Applegath, 1983 | Not Tested (see PMA results)<br>EPIWIN Modeling (ECOSAR module) predicts Green Algae 96-hr EC50 of 11.37 mg/L and ChV of 8.565 mg/L |
| PMA<br>108-65-6 | 161 (fathead minnow)<br>Dow, 1980a<br>100-180(rainbow trout)<br>BASF AG, 1987 | EC50 > 500<br>BASF AG, 1987 | Algae<br>MHW Japan, 1998<br>$EC_{50}$ (72 hr) > 1,000mg/L<br>NOEC(72 hr) > 1,000mg/L<br>(Growth inhibition)<br>EPIWIN Modeling (ECOSAR module) predicts Green Algae 96-hr EC50 of 11.37 mg/L and ChV of 8.565 mg/L |

[a] Lethal concentration in 50% (96 hr unless otherwise stated); [b] Lethal concentration in 50% 48 hr (EC50 for immobilization, if so stated). [c] Inhibition of fluorescence in 50%, 72 hr (for algae) unless otherwise noted for other plant species.

*Acute Toxicity to Fish*

The ethers show LC50s in fish that exceed 500 mg/liter.

The acetates, PMA and DPMA have LC50s in the 100 to 200 mg/liter range.

*Acute Toxicity to Daphnia*

Acute toxicity studies in daphnia have been performed on all category members. Data for all of the ethers show LD50s or EC50s of 1000 mg/liter or higher.

The acetates show $EC_{50}$ or $LC_{50}$ values of 500 mg/liter or higher.

*Acute Toxicity to Algae and other Aquatic Plant Species*

Of the ethers, algal toxicity studies were conducted for PnB DPM, and PM. TPM was tested with another aquatic plant species, duckweed.

Although the acetate DPMA was not evaluated in the algae toxicity assay, the results from PMA are useful for comparison since both are acetates.

Toxicity of ethers to algae also was predicted using the ECOSAR module (ver. 0.99) of the EPA EPIWIN family of models, designed to predict fate and effects in the environment. Results from Table 13 predict EC50 values of 500 mg/liter or greater for PnB, DPnB, and TPM. All three values reflect low toxicity to algae.

Predicted values for DPMA (Table 14) are in the moderate toxicity range, perhaps due to the acetate moiety. ECOSAR predicted chronic LC50 values (ChV), as expected, are considerably lower than predicted EC50 values. These modeled results with DPMA are in sharp contrast to measured data for the structural analogue, PMA, which showed study results of >1000mg/L obtained for a 72-hour study. ECOSAR modeling of PMA for green algae (96hr) also shows a predicted EC50, of 9.3 mg/L, which is much lower than the measured data for PMA. ECOSAR results may be overly conservative for green algae for the acetates (but not the parent ethers) in this category.

## 4.2 Terrestrial Effects

None of the propylene glycol ethers have been shown to bioaccumulate in terrestrial species and they appear to present little exposure hazard to either flora or fauna. For fauna, the conclusion of low bioaccumulation potential is supported by the very rapid elimination of the propylene glycol ethers shown in rodent species where greater than 95% elimination occurred within 48 hours (see metabolism section). This may be due to their high water solubility and rapid metabolism.

Toxicity to terrestrial flora: For three of the propylene glycol ethers, tests on mono- and dicotyledonous terrestrial plants show relatively low toxicity to several terrestrial species (Table 15).

Toxicity to terrestrial fauna: The extensive acute and repeated dose toxicity database conducted with rats, mice, rabbits, guinea pigs, and other species, support the conclusion that propylene glycol ethers pose a low risk of toxicity to mammalian terrestrial wildlife (see Tables 7 and 8).

**Table 15. Terrestrial Phytotoxicity of Three PGEs**

| Chemical | Terrestrial Phytotoxicity |
|---|---|
| PnB<br>29387-86-8 or 5131-66-8 | Monocotyledon growth (corn, wheat)<br>NOEC = 25% (solutions applied at 200 liters/hectare)<br>Dicotyledon growth<br>(oilseed rape, soybean, cotton, vines, tomato)<br>NOEC = 25%<br>Hart & Verschuuren, 1990 |
| DPnB<br>29911-28-2 or 35884-42-5 | Monocotyledon growth (corn, wheat)<br>NOEC = 25% (solutions applied at 200 liters/hectare)<br>Dicotyledon growth<br>(oilseed rape, soybean, cotton, vines, tomato)<br>LOEC = 6.25%<br>Hart & Verschuuren, 1990 |
| DPM<br>34590-94-8 | Dicotyledon growth (rape, wine grape, soybean, tomato, cotton)<br>EC50 > 500 g/liter (50% solution)<br>NOEC = 250 g/liter (25% solution)<br>Dicotyledon growth (wheat, maize)<br>EC50 > 500 g/liter (50% solution)<br>NOEC = 500 g/liter (50% solution)<br>Monocotyledon growth (*Tritium aestivum*)<br>NOEC > 1000 g/liter (100% solution)<br>Hart, 1991 |

## 4.3 Initial Assessment for the 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 x $10^{-9}$ atm-$m^3$/mole for TPM to 2.7 x $10^{-9}$ 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.

## 5 RECOMMENDATIONS

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.

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## ANNEX: DETAILED DESCRIPTION OF CATEGORY MEMBERS AND PREVIOUSLY EVALUATED PROPYLENE GLYCOL ETHERS

The category consists of four new members and three previously evaluated PGEs.

Note that all of the monopropylene glycol ethers may exist in two isomeric forms, alpha and beta. The alpha form is thermodynamically favored during synthesis and consists of a secondary alcohol configuration. The beta form consists of a primary alcohol. These two isomeric forms are shown below for PnB. The di- and tripropylene glycol ethers may exist as up to 4 and 8 isomers, respectively. The various isomers for the di- and tripropylene glycol ethers still may be divided into two groups consisting of secondary alcohols (alpha isomers) and primary alcohols (beta isomers). The distribution of isomeric forms for the di- and tripropylene glycols, as with the mono-PGEs, also should result in predominantly the alpha form (i.e., a secondary alcohol) for the terminal propylene group.

CAS numbers can be assigned to the alpha isomers, the beta isomers and the isomeric mixtures. Presently, the beta isomers are not produced commercially. CAS numbers assigned to the isomeric mixtures are not associated with a definitive chemical structure but because of thermodynamically favored synthesis, they are predominately in the form of the alpha isomer. The CAS numbers assigned to the mixtures are usually the most appropriate numbers to be associated with the commercial products that are the subject of this SIAR.

However, there are some inconsistencies in how chemicals are reported throughout the world and what CAS numbers are used. This can lead to confusion. It should be noted that in the original IUCLID dossiers, some studies that were conducted using commercial mixtures incorrectly used CAS numbers specific to the alpha isomer. Unless specifically stated in the dossiers, the purified beta isomer was not tested. Testing was usually carried out on the commercially-produced products that were nominated as HPV chemicals, all of which are mixtures containing at least a minimal amount of the beta isomer (usually less than 5%); rarely, when noted in the IUCLID, the study may have been conducted on a more purified form of either the alpha or beta isomer.

**PnB** 5131-66-8 = alpha isomer
29387-86-8 = isomeric mixture (nominated HPV chemical)
15821-83-7 = beta isomer (not produced commercially)

**DPnB** 29911-28-2 = alpha, alpha isomer (nominated HPV chemical; contains small amount of the beta isomer)
24083-03-2 = alpha, beta isomer (not produced commercially)
35884-42-5 = isomeric mixture

**DPMA** 88917-22-0 = isomeric mixture (nominated HPV chemical)

**TPM** 20324-33-8 = alpha isomer, and
25498-49-1 = isomeric mixture (both nominated HPV chemicals)

**PM** 107-98-2 = alpha isomer (nominated HPV chemical)
1320-67-8 = isomeric mixture
1589-47-5 = beta isomer (not produced commercially)

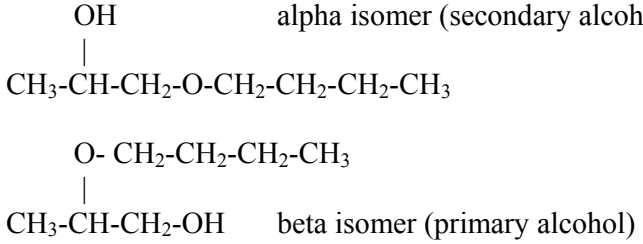
**PMA** 108-65-6 = alpha isomer (nominated HPV chemical)
84540-57-8 – isomeric mixture
70657-70= beta isomer (not produced commercially)

**DPM** 20324-32-7 = alpha isomer, and
34590-94-8 = isomeric mixture (both nominated HPV chemicals)

The molecular structures shown below demonstrate the close similarity among category members.

(1) Propylene glycol n-butyl ether (PnB)

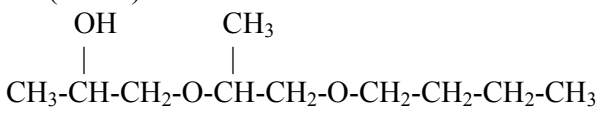
Molecular structure:




Only a **generic alpha form** is shown for the following category members:

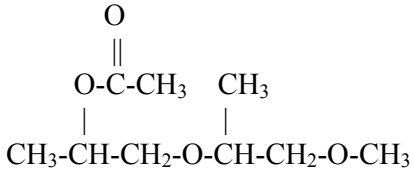
(2) Dipropylene glycol n-butyl ether (DPnB)

Molecular structure:



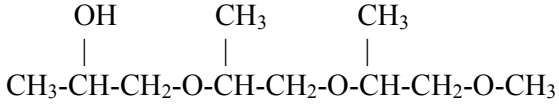

(3) Dipropylene glycol methyl ether acetate (DPMA)

Molecular structure:



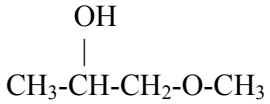

(4) Tripropylene glycol methyl ether (TPM)

Molecular structure:




(5) Propylene glycol methyl ether (PM) *

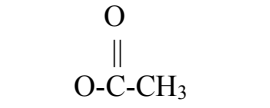
Molecular structure:




*Reviewed at SIAM 11

(6) Propylene glycol methyl ether acetate (PMA) *

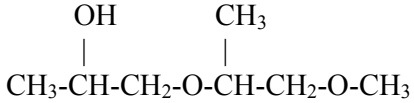
Molecular structure:




*Reviewed at SIAM 11

(7) Dipropylene glycol methyl ether (DPM)**

Molecular structure:




**Reviewed at SIAM 12

# Propylene Glycol n-Butyl Ether
# CAS Nos. 29387-86-8

# IUCLID with Robust Summaries (Dossier)

| | | |
|---|---|---|
| **Existing Chemical** | : | ID: 29387-86-8 |
| **CAS No.** | : | 29387-86-8(mixed isomers)<br>5131-66-8 (alpha isomer; secondary alcohol) |
| **EINECS Name** | : | 1-butoxypropan-2-ol |
| **EINECS No.** | : | 249-598-7 |
| **Molecular Weight** | : | 132.2 |
| **Structural Formula** | : | C4 H9 OCH2 CH (CH3) OH |
| **Molecular Formula** | : | C7H16O2 |

**Producer Related Part**

| | | |
|---|---|---|
| **Company** | : | American Chemistry Council |
| **Creation date** | : | 09.01.2002 |

**Substance Related Part**

| | | |
|---|---|---|
| **Company** | : | American Chemistry Council |
| **Creation date** | : | 09.01.2002 |
| **Memo** | : | |
| **Printing date** | : | 09.01.2002 |
| **Revision date** | : | 09.01.2002 |
| **Date of last Update** | : | 09.01.2002 |
| **Number of Pages** | : | 8340 |
| **Chapter (profile)** | : | Chapter: 1, 2, 3, 4, 5, 7 |
| **Reliability (profile)** | : | Reliability: without reliability, 1, 2, 3, 4 |
| **Flags (profile)** | : | Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS |

### 1.0.1 OECD AND COMPANY INFORMATION

| | | |
|---|---|---|
| **Type** | : | |
| **Name** | : | CHEMOXY INTERNATIONAL PLC |
| **Partner** | : | |
| **Date** | : | |
| **Street** | : | ALL SAINTS REFINERY, CARGO FLEET ROAD |
| **Town** | : | TS3 6AF MIDDLESBROUGH, CLEVELAND |
| **Country** | : | United Kingdom |
| **Phone** | : | 44 0642 248555 |
| **Telefax** | : | 44 0642 244340 |
| **Telex** | : | 587185 CEMINT G |
| **Cedex** | : | |

| | | |
|---|---|---|
| **Type** | : | |
| **Name** | : | Dow Deutschland Inc |
| **Partner** | : | |
| **Date** | : | |
| **Street** | : | Werkstade PO Box 1120 |
| **Town** | : | 21677 Stade 5 |
| **Country** | : | Germany |
| **Phone** | : | +49.414.6910 |
| **Telefax** | : | +49.414.6912600 |
| **Telex** | : | |
| **Cedex** | : | |

### 1.0.2 LOCATION OF PRODUCTION SITE

### 1.0.3 IDENTITY OF RECIPIENTS

### 1.1 GENERAL SUBSTANCE INFORMATION

| | | |
|---|---|---|
| **Substance type** | : | Organic chemical. Commercial product is a mixture consisting of predominantly (>95%) secondary alcohol (alpha isomer) with less than 5% primary alcohol (beta isomer). Unless otherwise stated, results in this dossier pertain to commercial mixture. |
| **Physical status** | : | Liquid |
| **Purity** | : | % w/w |

### 1.1.0 DETAILS ON TEMPLATE

### 1.1.1 SPECTRA

### 1.2 SYNONYMS

2-propanol, 1-butoxy

| | | |
|---|---|---|
| **Source** | : | CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND<br>Dow Deutschland Inc Stade 5 |

2PG 1BE

**Source** : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND
Dow Deutschland Inc Stade 5

Dowanol PnB
**Source** : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND
Dow Deutschland Inc Stade 5

PnB
**Source** : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND
Dow Deutschland Inc Stade 5

Propylene glycol monobutyl ether
**Source** : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND
Dow Deutschland Inc Stade 5

## 1.3 IMPURITIES

Currently, PnB (mixed alpha & beta isomers) consists of greater than 99% purity. Water may be present at a maximum of 0.15%.

## 1.4 ADDITIVES

## 1.5 QUANTITY

Worldwide production (1999): 10,000 tonnes (23 million pounds)

## 1.6.1 LABELLING

## 1.6.2 CLASSIFICATION

## 1.7 USE PATTERN

Because of high solvency, oil solubility, surfactant, and coupling properties, and due to good evaporation rate control, high formulating flexibility, low viscosity, as well as low toxicity, PnB may be used as a coupling agent and solvent in domestic and commercial cleaning solutions such as degreasers, paint removers, metal cleaners, and hard surface cleaners. These characteristics also allow PnB to be used as a coupling agent in water-based agricultural formulations, facilitating the homogenous blending of ingredients with diverse solubility characteristics. PnB also is used as a coalescent for lowering minimum film formulation temperature (MFFT) in water-borne latex coatings and as a chemical intermediate for the production of epoxides, acid ester derivatives, solvents, and plasticizers.

## 1.7.1 TECHNOLOGY PRODUCTION/USE

## 1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

**Remark** : None established.
**Source** : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND

**Remark** : A proposal of 200 ppm has been submitted to MAK in Germany.
DFG (94) MAK und BAT-Werte Liste, TEIL Neuaufnahme p. XII

**Source** : Dow Deutschland Inc Stade 5

**1.9 SOURCE OF EXPOSURE**

**Remark** : Occupational exposure to PnB is limited due to the enclosed systems in which this chemical is manufactured. End use consumers may be exposed during the application of coatings in which PnB is used. For such use, exposure would be by inhalation or dermal exposure. After application of coatings, PnB would evaporate slowly from the coating and escape at low concentrations into the atmosphere. Spills of small quantities (e.g., 1 gallon or less) into the environment could occasionally be expected during coating applications.

**Source** : Dow Deutschland Inc Stade 5

**1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES**

**1.10.2 EMERGENCY MEASURES**

**1.11 PACKAGING**

**1.12 POSSIB. OF RENDERING SUBST. HARMLESS**

**1.13 STATEMENTS CONCERNING WASTE**

**1.14.1 WATER POLLUTION**

**1.14.2 MAJOR ACCIDENT HAZARDS**

**1.14.3 AIR POLLUTION**

**1.15 ADDITIONAL REMARKS**

**Remark** : Disposal:
- incineration
- industrial effluent treatment.

**Source** : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND (19)

**Remark** : Disposal:
- incineration
- industrial effluent treatment

**Source** : Dow Deutschland Inc Stade 5

### 1.16 LAST LITERATURE SEARCH

### 1.17 REVIEWS

### 1.18 LISTINGS E.G. CHEMICAL INVENTORIES

## 2.1 MELTING POINT

**Value** : <85°C (Critical Value)
**Decomposition** :
**Sublimation** :
**Method** :
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : PnB
**Source** : Staples & Davis (2002)

(50)

**Value** : < -75 ° C
**Decomposition** : No at ° C
**Sublimation** : No
**Method** : Other
**Year** :
**GLP** : No
**Test substance** :
**Source** : Dow Deutschland Inc Stade 5

(30)

## 2.2 BOILING POINT

**Value** : = 171 ° C at 1013 hPa (Critical Value)
**Decomposition** : No
**Method** : Other
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** :
**Source** : Dow Deutschland Inc Stade 5

(31)

## 2.3 DENSITY

**Value** : = .88 g/cm3 at 20° C (Critical Value)
**Method** : other: DIN51747 (Pat0)
**Year** : 1989
**GLP** : No
**Reliability** : Assigned Klimisch score of 2 since methodology available.
**Test substance** :
**Source** : Dow Deutschland Inc Stade 5

(31)

### 2.3.1 GRANULOMETRY

## 2.4 VAPOUR PRESSURE

**Value** : 1.63 hPa at 25°C (Critical Value)
**Decomposition** :

**Method** : Not reported
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : PnB
**Source** : Staples & Davis (2002)

(50)

**Value** : = 1.13 hPa at 20° C
**Decomposition** :
**Method** other (calculated)
**Year** :
**GLP** : No
**Test substance** :
**Source** : Dow Deutschland Inc Stade 5

(30)

**Value** : = 1.304 hPa at 20° C
**Decomposition** :
**Method** other (calculated)
**Year** : 1992
**GLP** : no data
**Test substance** :
**Source** : Dow Deutschland Inc Stade 5

(29)

## 2.5 PARTITION COEFFICIENT

**Log Pow** : = 1.15 at 20° C (Critical Value)
**Method** other (calculated)
**Year** :
**GLP** : no data
**Reliability** : Assigned Klimisch score of 2 since estimation methodology was reported.
**Test substance** :
**Remark** : Method: Pomona-Medchem structural fragment method
**Source** : Dow Deutschland Inc Stade 5 & Staples and Davis (2002)

(30,50)

## 2.6.1 WATER SOLUBILITY

**Value** : 55,000 mg/liter @ 25C (Critical Value)
**Qualitative** :
**Pka** :
**PH** :
**Method** : Not specified
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Year** :
**GLP** : No
**Test substance** : PnB
**Source** : Staples and Davis (2002)

(50)

**Value** : = 6 vol% at 20 ° C
**Qualitative** :
**Pka** : at 25 ° C
**PH** : at and ° C

**Method** : other
**Year** :
**GLP** : No
**Test substance** :
**Source** : Dow Deutschland Inc Stade 5

(30)

**Value** : = 64 g/l at 20 ° C
**Qualitative** :
**Pka** : at 25 ° C
**PH** : at and ° C
**Method** : other
**Year** : 1992
**GLP** : no data
**Test substance** :
**Source** : Dow Deutschland Inc Stade 5

(29)

**Value** : > 10 g/l at ° C
**Qualitative** :
**Pka** : at 25 ° C
**PH** : at and ° C
**Method** : other
**Year** : 1992
**GLP** : no data
**Test substance** :
**Source** : Dow Deutschland Inc Stade 5

(21)

### 2.6.2 SURFACE TENSION

## 2.7 FLASH POINT

**Value** : = 63 ° C (Critical Value)
**Type** : closed cup
**Method** : other: DIN51758
**Year** : 1989
**GLP** : No
**Reliability** : Assigned Klimisch score of 2 since methodology was reported.
**Test substance** :
**Remark** : Method: Pensky Martens Closed Cup
**Source** : Dow Deutschland Inc Stade 5

(30)

## 2.8 AUTO FLAMMABILITY

**Value** : = 260 ° C at 1013 hPa (Critical Value)
**Method** : other: DIN51794
**Year** : 1989
**GLP** : No
**Reliability** : Assigned Klimisch score of 2 since methodology was reported.
**Test substance** :
**Source** : Dow Deutschland Inc Stade 5

(30)

## 2.9 FLAMMABILITY

**Remark** : Lower and upper flammability limit of Dowanol PnB is 1.1 %vol/vol at 80 deg. C and 8.4 %vol/vol at 145 deg. C.
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Source** : Dow Deutschland Inc Stade 5

(30)

## 2.10 EXPLOSIVE PROPERTIES

**Result** : not explosive
**Method** : other
**Year** :
**GLP** : No
**Test substance** :
**Remark** : Dowanol PnB is stable under normal storage conditions.
**Source** : Dow Deutschland Inc Stade 5

(30)

## 2.11 OXIDIZING PROPERTIES

**Result** : no oxidizing properties
**Method** : other
**Year** :
**GLP** : No
**Test substance** :
**Source** : Dow Deutschland Inc Stade 5

## 2.12 ADDITIONAL REMARKS

**Remark** : Disposal considerations
---
Incinerate under controlled conditions according to local and national regulations.
**Source** : Dow Deutschland Inc Stade 5

(30)

### 3.1.1 PHOTODEGRADATION

| | | |
|---|---|---|
| **Photodegradation OH radical rate constant** | : | 28.20x 10-12 cm3/molecule-sec |
| **Half-life** | : | 0.382 days or 4.58 hours (assumes 12 hrs of light per dayand an hydroxy radical concentration of 1.5 x $10^6$ OH/$cm^3$) |
| **Remark** | : | These modeled values represent an estimation based on the molecular structure of the alpha isomer. (AOP version 1.90) |
| **Source** | : | EPIWIN/AOP (v3.10) Program |

(51)

### 3.1.2 STABILITY IN WATER

| | | |
|---|---|---|
| **Remark** | : | Ether functions are generally stable in water under neutral conditions at ambient temperatures. PnB is chemically stable under a variety of conditions. |
| **Source** | : | Fieser and Fieser, 1960; Dow MSDS |

(25, 30)

### 3.1.3 STABILITY IN SOIL

| | | |
|---|---|---|
| **Remark** | : | no studies |
| **Source** | : | Dow Deutschland Inc Stade 5 |

### 3.2 MONITORING DATA

| | | |
|---|---|---|
| **Remark** | : | no studies |
| **Source** | : | Dow Deutschland Inc Stade 5 |

### 3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

| | | |
|---|---|---|
| **Type** | : | Fugacity Model Level III |
| **Method** | : | Mackay Level III (Equal releases to all media assumed) |
| **Year** | : | 2002 |
| **Input Parameters and Results** | : | CHEMICAL PROPERTIES AND OTHER INPUT PARAMETERS<br>Where input parameters were estimated, alpha isomer was used, Where input parameters were measured, commercial mixture was used (>95% alpha isomer)<br><br>INPUT PARAMETERS<br><br>Chemical Type: 1<br>Molecular Mass (g/mol): 132.2<br>Data Temperature (Degrees Celsius): 25<br>LogKow: 1.15<br>Water Solubility (g/m3): 55000<br>Water Solubility (mol/m3): 416.0363<br>Henry's Law Constant (Pa.m3/mol): 0.3917927<br>Vapour Pressure (Pa): 163<br>Melting Point (Degrees Celsius): -85 |

RESULTS (HALF-LIVES)

Half-Life in Air (h): 9.2
Half-Life in Water (h): 552
Half-Life in Soil (h): 672
Half-Life in Sediment (h): 2688
Half-Life in Suspended Sediment (h): 2688
Half-Life in Fish (h): 24
Half-Life in Aerosol (h): 24

PARTITION COEFFICIENTS (RESULTS)
(All amounts are dimensionless, except where noted)

Log Octanol-Water Partition Coefficient: 1.15
Octanol-Water Partition Coefficient: 14.12537
Organic Carbon-Water Partition Coefficient (L/kg): 5.791404
Air-Water Partition Coefficient: 1.58056200062368E-04
Soil-Water Partition Coefficient: 0.277987375735796
Soil-Water Partition Coefficient (L/kg): 0.115828073223248
Sediment-Water Partition Coefficient: 0.555974751471592
Sediment-Water Partition Coefficient (L/kg): 0.231656146446496
Suspended Sediment-Water Partition Coefficient: 2.77987385076862
Suspended Sediment-Water Partition Coefficient (L/kg): 1.15828077115359
Fish-Water Partition Coefficient: 0.678018
Fish-Water Partition Coefficient (L/kg): 0.678017973899841
Aerosol-Water Partition Coefficient: 0
Aerosol-Air Partition Coefficient: 36809.8156670924

**Reliability** : (1) Valid without restriction
**Source** : Mackay Level III Modeling

### 3.3.2 DISTRIBUTION

| | | |
|---|---|---|
| **Distribution at Equilibrium** | : | See EPIWIN modeling results below |
| **Air** | : | 2.30% |
| **Water** | : | 50.1% |
| **Soil** | : | 47.5% |
| **Sediment** | : | 0.0829% |
| **Remark** | : | Results are estimates based on the Mackay Level III fugacity model (part of EPIWIN Suite) |
| **Source** | : | EPIWIN/AOP (v3.10) Program (51) |
| **Remark** | : | Henry's Law Constant = 2.69E-06 atm-m3/mol (or 2.72E-01 Pa-m3/mol). (VP/Wsol estimate using EPI values)<br><br>HLC = 1.30E-7 atm-m3/mol ("Bond Method")<br>HLC = 4.88E-8 atm-m3/mol ("Group Method")<br><br>Results are estimates based on the HENRYWIN V3.10 module of the EPIWIN Suite |
| **Source** | : | EPIWIN (v3.10) Program (51) |
| **Remark** | : | Henry's Law Constant = 3.86E-06 atm-m3/mol (or 3.91E-01 Pa-m3/mol). |
| **Source** | : | Dow Chemical Company |

(49, 50)

## 3.4 MODE OF DEGRADATION IN ACTUAL USE

**Remark** : Biodegradation in water.
**Source** : Dow Deutschland Inc Stade 5

## 3.5 BIODEGRADATION

**Type** : Aerobic (C02 Evolution or Modified Sturm Test)
**Inoculum** : Sediment and activated sludge from a domestic sewage treatment plant.
**Concentration** : 0, 9.89, or 19.78 mg PnB/liter
**Contact time** : 28 days
**Degradation** : High concentration = 67.0.% after 28 days
Low concentration = 66.1% after 28 days
Sodium Acetate (reference control – 21.53 mg/l) = 63.5% after 28 days
**Result** : PnB is biodegradable to 60% after 28 days but not within a 10-day window
**Kinetics of test substance (high dose)** : Day 4 = 26.3.%
Day 8 = 57.5.%
Day 18 = 64.8.%
Day 22 = 65.8%
Day 28 = 67.0%
**Deg. Product** : N/A
**Protocol Guideline** : OECD Guideline 301 B "Ready Biodegradability: Modified Sturm Test" (since designated “CO2 Evolution Test“).
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | XZ 95410.00 |
| Purity: | “More than 98%” |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Aqueous solution. |
| Specific Gravity: | 0.88 g/ml. |
| Solubility: | 6% in water. |
| Storage: | At ambient temperature in the dark. |
| Stability: | Stable up to 200°C. |

**Method** : To test for its biodegradability potential, PnB was incubated for 28 days in continuously agitated closed bottles in the dark at two concentrations with inoculum freshly collected from a local municipal sewage treatment facility. The incubation temperature was 20±1°C and pH ranged from 5.7 to 6.3. Water hardness was not reported. Water used in the test was purified by reverse osmosis, passage over an ion exchange cartridge, and aeration to O2 saturation. This water had a resistance of 18 M cm and was kept at 20°C before use. The concentration of inoculum was approximately 1.6 x 105 microorganisms per milliliter of test solution. The concentrations of PnB were: 9.89, or 19.78 mg/liter. Controls were: sodium acetate at 21.53 mg/liter with inoculum (positive or reference control) and inoculum alone (to determine CO2 production without an exogenous organic substrate and correct the samples with organic substrate by this amount). Degradation of PnB was monitored by assessing the evolution of CO2 gas from mineralization of the exogenous organic substrate by the inoculum. CO2 was trapped with barium hydroxide (as a barium carbonate precipitate) and the remaining Ba(OH)2 was titrated with HCl, using phenolphthalein as an indicator, to determine the amount of CO2 evolved. CO2 was measured as it evolved, approximately every other day for the first 8 days and, thereafter, every 5th day until the 28th day. Degradation was calculated by dividing the amount of CO2 evolved by the theoretical CO2 (ThCO2).

**Results** : The low concentration of PnB (9.89 mg/l) showed 66.1% degradation after 28 days and the high concentration (19.78 mg/l) showed 67.0% degradation (see above for intermediate time periods). The sodium acetate reference compound showed 63.5% degradation after 28 days. However, the 60% level was not reached within a 10-day window, thus PnB, while biodegradable, did not meet the strict criteria for “ready biodegradability” in this test. The negative control blanks showed appropriate levels of CO2 production.

**Conclusions** : Both concentrations of PnB degraded over 60% within 28 days, indicating biodegradability but not the strict definition of “ready biodegradability,” as the degradation of PnB did not occur within the specified 10-day window.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 301 B "Ready Biodegradability: Modified Sturm Test" (since designated “CO2 Evolution Test“) was followed. Specifically, the incubation conditions and the inoculum used were mostly as prescribed in the aforementioned guidance. An exception was that the inoculum was “pre-adapted“ or “acclimated,“ which consists of exposing the test material to the microorganisms for a period of time prior to the test. Acclimation is intended, through adaptation of the microorganisms, to facilitate or enhance the microorganisms’ ability to metabolize, and thereby, degrade the test material. This is not permitted under today’s guidelines in order for a chemical to qualify as “readily biodegradable“ although it is widely recognized that this commonly used procedure may show that a compound does have an inherent ability to biodegrade. Test material characterization was adequate. The concentrations tested, the length of the monitoring period (28 days), and methods for measuring test compound degradation were typical for this type assay and adequately recorded.

**References** : Cardinaals, J.M., de Crom, P.J.W., (1987). Assessment of the ultimate biodegradability of Dowanol PnB in the modified Sturm test. Dow Chemical Company Study No. DET 1024. July 1987. Unpublished study.

**Other** : It should be noted that the OECD guidelines do not recommend preadaptation or acclimatization of the inoculum to the test substance, as was done in this study.

**Source** : Dow Deutschland Inc Stade 5

(9)

**Type** : Aerobic (Closed Bottle Test)
**Inoculum** : Domestic sewage
**Concentration** : 0, 1.86, or 9.29 mg PnB/liter.
**Contact time** : 28 days
**Degradation** : = 60.5% after 28 day
**Degradation Kinetics of test substance (low concentration)** : 5 day = 1.1.%
15 days = 33.3.%
28 day = 60.5.%
**Result** : Under test condition biodegradable but not readily biodegradable.
**Deg. Product** : N/A
**Protocol Guideline** : OECD Guideline 301 D "Ready Biodegradability: Closed Bottle Test"
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | XZ 95410.00 |
| Purity: | “More than 98%” |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Aqueous solution. |
| Specific Gravity: | 0.88 g/ml. |
| Solubility: | 6% in water. |
| Storage: | At ambient temperature in the dark. |
| Stability: | Stable up to 200°C. |

**Method** : To test for its ready biodegradability potential, PnB was incubated for 28 days in continuously agitated closed bottles in the dark at two concentrations with inoculum (secondary effluent) collected from a local municipal sewage treatment facility. The incubation temperature was 19.7-20.0°C, pH ranged from 7.2 to 7.3, and the concentration of inoculum was one droplet per liter of test solution. Water hardness was not reported. Water used in the test was purified by reverse osmosis, passage over an ion exchange cartridge, and aeration to O2 saturation. This water had a resistance of 18 M cm and was kept at 20°C before use. O2 content was the measured variable. The concentrations of PnB were: 0 (oxygen control with inoculum), 1.96, or 9.78 mg/liter. Other controls were: sodium acetate at 4.14 mg/liter with inoculum (positive or reference control), PnB and sodium acetate with inoculum (to determine if PnB inhibited NaAc degradation), an oxygen blank (no PnB or inoculum), and an inoculum blank (same as oxygen blank but with inoculum). Dissipation of oxygen in the test solution over time was used to monitor PnB degradation (i.e., measuring dissolved oxygen content with an oxygen electrode at various time points). Oxygen content was measured (in duplicate bottles) on days 0, 5, 15, and 28. Degradation was calculated by dividing the biochemical oxygen demand (BOD) expressed as mg O2 per mg PnB, by the theoretical oxygen demand (ThOD).

| | | |
|---|---|---|
| **Results** | : | Over the 28-day course of the study, PnB at the low concentration (1.96 mg/liter) biodegraded by 60.5% of its ThOD. However, the time to reach this level of biodegradation took longer than the allowable 10-day window (starting at 10% biodegradation). At the higher concentration of 9.78 mg/liter, the 60% degradation level was not reached. The sodium acetate referenced reached 64.7%, indicating active inoculum. Oxygen depletion in the oxygen and inoculum blanks slightly exceeded validation limits by 0.1 mg O2/liter. PnB appeared to inhibit slightly the biodegradation of sodium acetate. |
| **Conclusions** | : | PnB, although reaching the biodegradation limit of 60% within 28 days, did not do so within a 10-day window. Thus, PnB is not readily biodegradable according to the criteria of this test. The slight exceedance of oxygen depletion in the oxygen and inoculum blanks is not considered to have adversely affected the outcome of this study. |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 301 D "Ready Biodegradability: Closed Bottle Test" was followed. Specifically, the incubation conditions and the inoculum used were as prescribed in the aforementioned guidance. Test material characterization was adequate. The concentrations tested, the length of the monitoring period (28 days), and methods for measuring test compound degradation were typical for this type assay and adequately recorded. |
| **References** | : | Cardinaals, J.M., de Crom, P.J.W., (1987). Assessment of the biodegradability of Dowanol PnB in the closed bottle test. Dow Study No. DET 1021. February 1987. Unpublished study. |
| **Other** | : | With the high concentration of PnB, the test substance was biodegraded by 6.6% by day 15 and all oxygen was consumed by day 28. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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| | | |
|---|---|---|
| **Type** | : | Aerobic (Ready Biodegradability: Modified OECD Screening Test) |
| **Inoculum** | : | Other: Fresh activated sludge filtrate |
| **Concentration** | : | 17.21mg/l related to DOC (Dissolved Organic Carbon) |
| **Contact time** | : | |
| **Degradation** | : | = 90 . % after 28 day |
| **Result** | : | Readily biodegradable |
| **Deg. Product** | : | |
| **Protocol Guideline** | : | OECD Guideline 301 E "Ready biodegradability: Modified OECD Screening Test" |
| **Year of Study** | : | 1993 |
| **GLP** | : | Yes |

**Test substance** : Identity: Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8)
Product Code No.: 05790
Purity: Not reported.
Supplied as: 60 gram aliquot.
Appearance: Clear colorless liquid.
% carbon: 61.2%.
Administered as: Dilution in inoculum medium.
Specific Gravity: Not reported.
Solubility: Not reported.
Storage: At ambient temperature in the dark.
Stability: Not reported.

**Method** : To test for its biodegradability potential, PnB was incubated for 28 days in continuously agitated 2 liter open beakers (in duplicate) in the dark with an inoculum originally collected from a local municipal sewage treatment facility. In this assay, biodegradation, or the catabolism of the organic test compound, is measured by the disappearance of dissolved organic carbon (DOC) over time. DOC was measured at 0, 7, 14, 21, 27, and 28 days. The incubation temperature was 18.7-23.0°C, pH at study initiation was 7.4, O2 concentration, measured with an YSI Oxygen Meter (model 508), ranged from 7.50 to 8.05 mg/L over the study, and the concentration of inoculum was 1.0 ml inoculum per liter of test solution. The concentration of PnB corresponded to 17.2 mg DOC/liter (or 28 mg PnB/liter). Controls included: 1) sodium benzoate at ~31 mg/liter (~18 mg DOC/liter) with inoculum (constituting the positive or reference control) and 2) inoculum alone (to determine disappearance of DOC without an exogenous organic substrate and correct the samples with organic substrate by this amount). Degradation of PnB was monitored by assessing the removal of DOC (as supplied either by PnB or sodium benzoate – the exogenous substrate) by the inoculum. DOC was analyzed in duplicate at each time point using a Dorhmann DC-80 Carbon Analyzer. Degradation was calculated by subtracting the amount of DOC in the negative (inoculum only) control from that in the test material or positive control sample at any given time point and dividing by the initial DOC concentration at time 0.

**Results** : The 28-day mean percent biodegradation was 90.0% for Dowanol PnB. This level of biodegradation was reached within the prescribed 10-day window. The 10-day window for Dowanol PnB started on day 7 and ended on day 14 where biodegradation exceeded 70%. For the positive control agent, sodium benzoate, the mean percent biodegradation was 92.1%.

**Conclusion** : PnB is readily biodegradable under the conditions of this study.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

| | | |
|---|---|---|
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 301 E "Ready biodegradability: Modified OECD Screening Test" was followed. Specifically, the incubation conditions and the inoculum used were as prescribed in the aforementioned guidance. Test material characterization was adequate. The concentrations tested, the length of the monitoring period (28 days), and methods for measuring test compound degradation were typical for this type assay and adequately recorded. |
| **References** | : | McLaughlin, S.P., (1993). Dowanol PnB – Ready biodegradability: modified OECD Screening Test: OECD Method 301E (Modified OECD Screening Test). Springborn Study No. 1003.0593.18106.1764. Dow Report No. 2127. September 21, 1993. Unpublished report. |
| **Other** | : | These results are consistent with other, similar assays. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(24)

| | | |
|---|---|---|
| **Type** | : | Aerobic |
| **Inoculum** | : | activated sludge |
| **Concentration** | : | 100mg/l related to Test substance<br>Related to |
| **Contact time** | : | |
| **Degradation** | : | = 82 .- 95 % after 28 day |
| **Result** | : | |
| **Deg. Product** | : | |
| **Protocol Guideline** | : | other: MITI I/II, equivalent to OECD Guideline 301C/302C |
| **Year of Study** | : | 1992 |
| **GLP** | : | no data |
| **Test substance** | : | other TS: 1-n-butoxy-2-propanol |
| **Remark** | : | Aerobic degradation was 82-95% (BOD as % of ThOD) in 4 weeks. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(21)

| | | |
|---|---|---|
| **Type** | : | Aerobic |
| **Inoculum** | : | activated sludge, industrial, adapted |
| **Concentration** | : | 3.75mg/l related to DOC (Dissolved Organic Carbon)<br>Related to |
| **Contact time** | : | |
| **Degradation** | : | = 92 . % after 28 day |
| **Result** | : | readily biodegradable |
| **Deg. Product** | : | |
| **Protocol Guideline** | : | other: OECD Guideline 301 D (closed bottle test) |
| **Year of Study** | : | 1994 |
| **GLP** | : | no data |
| **Test substance** | : | as prescribed by 1.1 - 1.4 |
| **Remark** | : | Biodegradation was determined over 28 days using sewage sludge (250 mg/l solids) previously acclimated for 15 days. Sodium benzoate was included as positive control. Results demonstrated ready biodegradability. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(4)

## 3.6 BOD5, COD OR BOD5/COD RATIO

**Remark** : no data
**Source** : Dow Deutschland Inc Stade 5

## 3.7 BIOACCUMULATION

**Modeling results** : EPIWIN
**Estimated log BCF** : 0.185
**Estimated BCF** : 1.533
**Source** : EPIWIN Program (v3.10) BCFWIN module (v2.14) (51)

**Remark** : Low potential for bioaccumulation based on high water solubility (Log Kow = 1.15).
**Source** : Dow Chemical Company
: (49)

## 3.8 ADDITIONAL REMARKS

**Remark** : no remarks
**Source** : Dow Deutschland Inc Stade 5

## 4.1 ACUTE/PROLONGED TOXICITY TO FISH

**Type** : Static (fresh water)
**Species** : Poecilia reticulata (guppy)
**Exposure period** : 96 hour(s)
**Unit** : mg PnB/liter
**Analytical monitoring** : Nominal concentrations were used.
**NOEC** : = 180 .
**LC50** : = 560 .- 1000
**EC50** : = 180 .- 320
**Protocol Guideline** : OECD Guideline 203 "Fish, Acute Toxicity Test"
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | XZ 95410.00 |
| Purity: | More than 98% |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Solution in water. |
| Specific Gravity: | 0.88 g/ml. |
| Solubility: | ~6% in water. |
| Storage: | At ambient temperature in the dark. |
| Stability: | Stable up to 200°C. |

**Method** : Young Poecilia reticulata (guppies) were exposed for 96 hours to nominal concentrations of 0, 100, 180, 320, 560, or 1000 mg PnB/liter. These concentrations were selected from a previously conducted range-finding study. Ten guppies were exposed at each concentration in duplicate batches under static conditions.

Exposures were conducted in 1-liter glass vessels maintained at a temperature of 20-22°C. Two vessels were employed at each concentration (i.e., exposures were conducted in duplicate). Ten guppies of 1-3 cm length were exposed in each test vessel. Fish were not fed one day prior to exposure or throughout the 96-hour exposure period. Oxygen concentration (pO2) and pH were recorded at the initiation of exposure and every 24 hours thereafter. Oxygen concentration ranged from 8.0 to 8.3 mg/L and pH from 7.0 to 9.5 (average pH = 8.2 ± 0.2). Water hardness was 11.7°DH. The content of each vessel was renewed midway through the exposure period.

Fish were observed for mortality and clinical signs at 3, 24, 48, 72, and 96 hours. Clinical signs included: loss of equilibrium, changes in swimming behavior, respiratory behavior, or pigmentation. At the end of the 96-hour test period, the LC50 (with confidence limits and concentration-response slope), the EC50 (concentration at which 50% of the subjects showed clinical signs of toxicity), and NOEC (no observed effect concentration) were determined for each time point.

**Results** : No mortality was observed at concentrations up to and including 560 mg PnB/liter. Mortality occurred only at the highest concentration tested. At 1000 mg/liter, 7 of 10 (vessel 1) and 6 of 10 (vessel 2) guppies died after 2 hours. By 48 hours 2 more had died in the first vessel and the remaining 4 in vessel 2. The remaining single subject from this high concentration group succumbed after 72 hours of exposure. No subjects from the 1000 mg/liter group survived the entire 96-hour exposure period.

No clinical signs were observed at concentrations of 180 mg/liter or less. At 320 mg/liter, all guppies showed an inhibition of swimming ability and a portion (6 of 20 total at this concentration) showed increased pigmentation. At 560 mg/liter, all subjects showed increased pigmentation and reduced swimming ability at all time points. Swimming ability was progressively inhibited with time to the point of immobilization and in a progressively increasing proportion of the subjects over the exposure period; touching the caudal peduncle stimulated reaction. In survivors at any concentration, no loss of equilibrium was observed.

In the negative control, mortality was zero and no clinical signs were observed.

**Conclusions** : The LD50s and EC50's at the observed time points (calculated after Finney, 1971, Probit Analysis, Cambridge U Press, 3rd Ed.), are listed in the table below.

| | 24 hr | 48 hr | 72 hr | 96 hr |
|---|---|---|---|---|
| LC50 | 910 | 768 | 768 | 560-1000 |
| LC50 95%CL | 828-1059 | 721-856 | 721-856 | * |
| LC50 Slope | 9.4 | 14.4 | 14.4 | * |
| EC50 | 320-560 | 365 | 180-320 | 180-320 |
| EC50 95% CL | * | 320-461 | * | * |
| EC50 Slope | * | 7.9 | * | * |

* Could not be calculated.

The NOEC level is 180 mg PnB/liter.

These results indicate that PnB is not highly toxic to freshwater aquatic species.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 203 "Fish, Acute Toxicity Test" was followed. Specifically, the fish breeding and maintenance conditions were as prescribed in the aforementioned guidance. Test material characterization was adequately described in the report. The concentrations tested, the length of the exposure and observation period (96 hours), and methods for calculating results were typical for this type assay and adequately recorded.

**References** : Van der Hoeven, J.C.M, Welboren, G.T.G., (1987). Assessment of the acute toxicity of Dowanol-PnB in Poecilia reticulata. Dow Report No. DET 1016. July 1987. Unpublished report.

**Other** : The authors speculated that the immobilization observed might have been due to a paralysis since some apparently dead fish revived when placed into fresh tap water.

No actual concentrations were measured. Completeness of dissolution of test substance in the water environment of the fish was made only on a visual basis. Since the water solubility of PnB is ~55,000 mg/liter, the test material is easily theoretically soluble at the highest concentration tested. Moreover, because of its low Henry's Law Constant of 0.39 Pa-m3/mol (reflecting its low vapor pressure and relatively high hydrophilicity), PnB will not have a propensity to evaporate from the water. Finally, the chemical stability of PnB suggests that this chemical will not break down spontaneously over the 4 day exposure period. The mortality observed in the highest exposure group indicates that the test material had not degraded chemically and was soluble and stable enough to exert toxic effects.

**Source** : Dow Deutschland Inc Stade 5

(33)

**Type** : Other
**Species** : Petromyzon marinus
**Exposure period** : 24 hour(s)
**Unit** : mg/l
**Analytical monitoring** : no data
**LC50** : > 5
**Method** : other
**Year of Study** : 1987
**GLP** : no data
**Test substance** : no data
**Remark** : The study was conducted at about 13 deg. C in six lampreys. No effects were observed at 5 mg/l and higher concentrations were not tested.
**Source** : Dow Deutschland Inc Stade 5

(2)

**Type** : Other
**Species** : other: Oncorhynchus mykiss, Lepomis macrochirus, Carassius auratus
**Exposure period** : 24 hour(s)
**Unit** : mg/l
**Analytical monitoring** : no data
**LC50** : > 5
**Method** : other
**Year** : 1987
**GLP** : no data
**Test substance** : no data
**Remark** : The study was conducted at about 13 deg. C with the standard range of water quality tests. Higher concentrations were not studied and it is unlikely that tests were duplicated. [Total hardness (300 ppm, soap method) exceeded that recommended by the OECD guidelines]. The substance may also have been tested in the Yellow Perch (Perca flavescens), but this is unclear from the study description.
**Source** : Dow Deutschland Inc Stade 5

(14)

## 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

**Type** : Static
**Species** : Daphnia magna (Crustacea)

**Exposure period** : 48 hour(s)
**Unit** : mg/liter
**Analytical monitoring** : Nominal concentrations used.
**NOEC** : = 560 mg/liter.
**Protocol Guideline** : OECD Guideline 202, part 1 "Daphnia sp., Acute Immobilisation Test"
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | XZ 95410.00 |
| Purity: | More than 98% |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Solution in water. |
| Specific Gravity: | 0.88 g/ml. |
| Solubility: | ~6% in water. |
| Storage: | At ambient temperature in the dark. |
| Stability: | Stable up to 200°C. |

**Method** : In a dose-range finding study, ten Daphnia magna less than 24 hours old were exposed for 48 hours to concentrations of 0, 0.01, 0.1, 1, 10, 100, or 1000 mg PnB/liter water. Immobilization was observed only at a PnB concentration of 1000 mg/liter. In the subsequent defining test, 10 daphnia per glass vessel (in duplicate for a total of 20 daphnia per concentration) were exposed to 0, 100, 180, 320, 560, or 1000 mg PnB/liter.

Exposures were conducted in 100 milliliter glass vessels maintained at a temperature of 19±1°C. Two vessels were employed at each concentration (i.e., exposures were conducted in duplicate). Daphnia were not fed during the 48-hour exposure period. Oxygen concentration (pO2) and pH were recorded at the initiation of exposure and at 48 hours. Water was not changed or aerated during the 48-hour exposure period.

Daphnia were observed for immobilization at 24 and 48 hours. The criterion for determining immobilization consisted of a lack of movement by the daphnia within 15 seconds after gentle agitation of the test water. At 24 and 48 hours, the EC50 were determined (with, where possible, confidence limits and concentration-response slope).

**Results** : No immobilization occurred at PnB concentrations of 560 mg/liter or less. Two of twenty daphnia exhibited immobilization when exposed to the highest concentration of 1000 mg PnB/liter in this limit test (0 of 10 in one vessel and 2 of 10 in the second vessel). Immobilization occurred in one daphnia after 24 hours and in two after 48 hours. Consequently, the 48-hour EC50 is greater than 1000 mg/liter. Results did not permit calculation of an actual EC50 with 95% confidence limits and a slope. The K2Cr2O7 positive control reference material showed an EC50 of 1.41 mg/liter at 24 hours (with 95% confidence limits from 1.21 – 1.76 mg/l and a slope of 8.2) and 0.91 mg/l at 48 hours (with 95% confidence limits from 0.83 – 1.06 mg/l and a slope of 13.6).

**Conclusions** : These results indicate that PnB is of low toxicity to daphnia under the conditions of this test.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 202 "Daphnia sp., Acute Immobilization Test and Reproduction Test" was followed. Specifically, the breeding and maintenance conditions were as prescribed in the aforementioned guidance. Test material characterization was adequately described in the report. The concentrations tested, the length of the exposure and observation period (48 hours), and methods for calculating results were typical for this type assay and adequately recorded.

**References** : Bogers, M., Welboren, G.T.G., (1987). Assessment of the acute effects of Dowanol-PnB on the mobility of Daphnia magna. Dow Report No. DET 1014. July 1987. Unpublished report.

**Other** : In the range-finding study, 9 of 10 daphnia were immobilized after 48 hours at 1000 mg PnB/liter. In the definitive test, only 2 of 20 were immobilized at this final time point. Oxygen and pH ranges were determined to be within predefined safe limits. The pH ranged from 8.2 to 8.5 and pO2 ranged from 8.2 to 8.7 mg/L over the 48-hour exposure period. Water hardness was 11.7 DH. A K2Cr2O7 positive control group showed immobilization at the expected concentrations.

Nominal rather than actual concentrations were used. No actual concentrations were measured. Completeness of dissolution of test substance in the water environment of the daphnia was made only on a visual basis. Since the water solubility of PnB is ~55,000 mg/liter, the test material is easily theoretically soluble at the highest concentration tested. Moreover, because of its low Henry's Law Constant of 0.39 Pa-m3/mol (reflecting its low vapor pressure and relatively high hydrophilicity), PnB will not have a propensity to evaporate from the water. Finally, the chemical stability of PnB suggests that this chemical will not break down spontaneously over the 4 day exposure period. The immobilization observed in the highest exposure group indicates that the test material had not degraded chemically and was soluble and stable enough to exert toxic effects.

**Source** : Dow Deutschland Inc Stade 5

(6)

## 4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

**Type** : Static
**Species** : Selenastrum capricornutum
**Exposure period** : 96 hours
**Unit** : mg/liter
**Concentrations Tested** : 0, 100, 180, 320, 560, or 1000 mg PnB/liter
**Analytical monitoring** : Nominal concentrations used.
**Toxicity Endpoint** : Growth inhibition (50% inhibition level or EC50).
**NOAEL** : 560 mg/liter
**Protocol Guideline** : No specific guidance cited. General guidance cited: EPA TSCA Requirements, Final Rules and Proposed Rules, Fed. Reg. Vol. 52, No. 97, May 20, 1987. Generally follows OECD Guideline 201 "Alga, Growth Inhibition Test"
**Year of Study** : 1987
**GLP** : Yes
**Test substance** : Identity: Dowanol-PnB (1-butoxy-2-hydroxypropane or

propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8)

| | |
|---|---|
| Batch No.: | Not specified. |
| Purity: | “100% active ingredient” |
| Supplied as: | Not specified. |
| Appearance: | Clear liquid. |
| Administered as: | Solution in water. |
| Specific Gravity: | Not specified. |
| Solubility: | “soluble in water” |
| Storage: | Room temperature. |
| Stability: | Not specified. |

**Method** : PnB was mixed with 20,000 cells/ml Selenastrum capricornutum in exponential growth phase in nutrient media (AAP) at PnB concentrations of 0, 100, 180, 320, 560, or 1000 mg/liter and incubated at 24 ± 2°C for 96 hours (three replicates/concentration). At 48 and 96 hours, cells were counted with a Model ZBI Coulter Counter equipped with a C-1000 Channelyzer and MHR computer (three counts per replicate). PH was adjusted to 7.5 ± 1 and illumination was continuous at 4306 ± 646 lumens/m2, provided by overhead white fluorescent light. Water hardness and dissolved oxygen content were not reported. Test flasks were mixed continuously during incubation. Results were expressed as cell counts as a percentageof controls.

**Results** : After 96 hours exposure to PnB, algae showed no growth inhibition at concentrations up to and including 320 mg PnB/liter. Below these concentrations, stimulation of growth was observed. At 560 mg/liter, a 5.8% inhibition was observed. At 1000 mg/liter, a 42% inhibition of growth was found. A NOAEC of 560 mg PnB/liter was determined after statistical analysis using ANOVA and multiple range statistical tests. The 5.8% inhibition at this concentration level was not statistically different from controls. Because inhibition at the highest concentration tested did not reach 50%, no EC50 could be calculated and it is concluded that the EC50 is greater than 1000 mg/liter.

**Conclusions** : PnB is relatively non-toxic to this algal species.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 2.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included a study review statement, signed by the Study Director and laboratory supervisory personnel indicating that a quality assurance inspection had been performed. The study report provided documentation that OECD Protocol 201 "Alga, Growth Inhibition Test" was followed. Specifically, the microorganism growth and maintenance conditions were as prescribed in the aforementioned guidance. Test material characterization was described in the report. The concentrations tested, the length of the exposure and observation period (48 hours), and methods for calculating results were typical for this type assay and adequately recorded.

**References** : Hughes, J.S., (1987). The toxicity of B0964.01 to Selenastrum capricornutum. Malcolm Pirnie Project no. MPI 0165-20-1100. July 10, 1987. Unpublished report.

**Other** : Low toxicity of PnB in this test is consistent with the low toxicity observed with other divergent organisms.

Nominal rather than actual concentrations were used. No actual concentrations were measured. Completeness of dissolution of test substance in the water environment of the organism was made only on a visual basis. Since the water solubility of PnB is ~55,000 mg/liter, the test material is easily theoretically soluble at the highest concentration tested. Moreover, because of its low Henry's Law Constant of 0.39 Pa-m3/mol (reflecting its low vapor pressure and relatively high hydrophilicity), PnB will not have a propensity to evaporate from the water. Finally, the chemical stability of PnB suggests that this chemical will not break down spontaneously over the 4 day exposure period. The immobilization observed in the highest exposure group indicates that the test material had not degraded chemically and was soluble and stable enough to exert toxic effects.

**Source** : Dow Deutschland Inc Stade 5 (44)

**Remark** : The EPIWIN suite of models is able to predict toxicity values for chemicals based on their physicochemical characteristics of Kow, molecular weight, molecular structure, etc. The ECOSAR program module (v0.99) of EPIWIN (v3.10) predicted a Green Algae 96-hour EC50 of 525 mg/L and a ChV of 29.10 mg/L.

**Source** : ECOSAR Module of EPIWIN Modeling Suite (51)

### 4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

**Remark** : No information available.

### 4.5.1 CHRONIC TOXICITY TO FISH

**Remark** : no studies
**Source** : Dow Deutschland Inc Stade 5

### 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

**Remark** : no studies
**Source** : Dow Deutschland Inc Stade 5

### 4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

**Remark** : no studies
**Source** : Dow Deutschland Inc Stade 5

### 4.6.2 TOXICITY TO TERRESTRIAL PLANTS

**Species** : Terrestrial plants: dicotyledonous species (oilseed rape, soybeans, cotton, vines, tomatoes).
**Endpoint** : Visible damage, growth rates (height), & fresh weights.

| | | |
|---|---|---|
| **Exposure period** | : | Single spraying at early growth stage (2 to 5 leaf sprouts). |
| **Unit** | : | Liter per hectare equivalents. |
| **NOEC** | : | . 25% or 50 liters/hetare |
| **Protocol Guideline** | : | None specified (or found in OECD or EPA Guidance) |
| **Year of Study** | : | 1990 |
| **GLP** | : | No |
| **Test substance** | : | Dowanol-PnB |
| **Method** | : | To assess PnB's ability to act as a solvent for pesticide formulations, various concentrations of PnB were sprayed on sprouts of the dicotyledons, cotton (Gossypium hirsutum), oilseed rape (Brassica napus), soybean (Glycine max), cotton (Gossypium hirsutum), vines (Vitis vinifera), and tomatoes (Lycopersicon esculentum). Plants were in the 2 to 5 leaf sprout stage at the time of application and the concentrations sprayed onto them (in pentuplicate) were 0% (Polyglycol P26-2 or water), 6.25%, 12.5%, 25%, 50%, or 100%. These solutions were sprayed once only (overhead) at a rate equivalent to 200 liters/hectare<br><br>Toxicity was assessed for 21 days by monitoring 1) visible damage (e.g., lack of leaf unfolding, leaf scorching, necrotic spotting, inter-venal necrosis, plant death), expressed as percent of plants affected, 2) growth rate, in millimeters, measured weekly for three weeks following application as height of the plant from the soil to the meristem or tallest leaf, and 3) fresh weights (i.e., vegetable mass) measured on day 21 post-treatment. |
| **Results** | : | At concentrations of 25% or less no damage from PnB to dicotyledonous species was evident. |
| **Conclusions** | : | At concentrations to be applied in the field, no damage would be expected from PnB. |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). Although this was not GLP and did not follow prescribed guidelines (there are none for this assay), methods were thoroughly described and results comprehensively reported. |
| **References** | : | Hart, D., Verschuuren, H.G., (1990). Report on the phytotoxicity of Dowanol PnB following foliar spray application. Dow Report No. DET 1428, K-005473-026. October 1990. Unpublished report. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(18)

| | | |
|---|---|---|
| **Species** | : | Terrestrial plants, Monocotyledonous species: Corn (Zea mays), wheat (Tritium aestivum) |
| **Endpoint** | : | Visible damage, growth rates (height), & fresh weights |
| **Exposure period** | : | Single spraying at early growth stage (2 to 3 leaf sprout) |
| **Unit** | : | Liter per hectare equivalents |
| **NOEC** | : | 50 liters/hectare. |
| **Protocol Guidline** | : | None specified (or found in OECD or EPA Guidance) |
| **Year of Study** | : | 1990 |
| **GLP** | : | No |
| **Test substance** | : | Dowanol-PnB |

**Method** : To assess PnB's ability to act as a solvent for pesticide formulations, various concentrations of PnB were sprayed on sprouts of the monocotyledons, corn (Zea mays) and wheat (Triticum aestivum). The corn and wheat were in the 2 to 3 leaf sprout stage at the time of application and the concentrations sprayed onto them (in pentuplicate) were 0% (Polyglycol P26-2 or water), 6.25%, 12.5%, 25%, 50%, or 100%. These solutions were sprayed once only (overhead) at a rate equivalent to 200 liters/hectare. As comparative controls, Solvesso 150 and Solvesso 200 (two currently used pesticide solvents) were applied at the same concentrations and rates of application.

Toxicity was assessed for 21 days by monitoring 1) visible damage (e.g., lack of leaf unfolding, leaf scorching, necrotic spotting, inter-venal necrosis, plant death), expressed as percent of plants affected, 2) growth rate, in millimeters, measured weekly for three weeks following application as height of the plant from the soil to the meristem or tallest leaf, and 3) fresh weights (i.e., vegetable mass) measured on day 21 post-treatment.

**Results** : At concentrations of 25% or less no damage from PnB to wheat or corn was evident.

**Conclusions** : On a comparative basis, PnB was as safe as or safer than Solvesso 150 or Solvesso 200 and could be used as a vehicle for pesticide application to monocotyledonous crops.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). Although this was not GLP and did not follow prescribed guidelines (there are none for this assay), methods were thoroughly described and results comprehensively reported.

**References** : Hart, D., Verschuuren, H.G., (1990). Report on the phytotoxicity of Dowanol PnB following foliar spray application. Dow Report No. DET 1428, K-005473-026. October 1990. Unpublished report.

**Other** : A concentration of 6.25%, the lowest concentration tested in this assay, represents a high concentration for a pesticide solvent under real-world field conditions. More usually, a solvent concentration of 2% would be applied to a corn or wheat crop. Thus, this bioassay evaluated high concentrations of both the test and comparative solvents. Phytotoxicity would be expected to be lower under actual usage conditions.

**Source** : Dow Deutschland Inc Stade 5

(17)

### 4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

**Remark** : no studies
**Source** : Dow Deutschland Inc Stade 5

### 4.7 BIOLOGICAL EFFECTS MONITORING

**Source** : Dow Deutschland Inc Stade 5

(25)

## 4.8 BIOTRANSFORMATION AND KINETICS

**Source** : Dow Deutschland Inc Stade 5

(25)

## 4.9 ADDITIONAL REMARKS

**Remark** : no remarks
**Source** : Dow Deutschland Inc Stade 5

### 5.1.1 ACUTE ORAL TOXICITY

| | | |
|---|---|---|
| **Type** | : | LD50 |
| **Species** | : | Rat |
| **Strain** | : | Wistar |
| **Sex** | : | males and females |
| **Number of animals** | : | 5 per sex |
| **Vehicle** | : | No vehicle; test material was tested undiluted. |
| **Value** | : | ca. 3300 . mg/kg bw |
| **Protocol Guideline** | : | OECD Guideline 401 "Acute Oral Toxicity" |
| **Year of Study** | : | 1987 |
| **GLP** | : | Yes |
| **Test substance** | : | |

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | XZ 95410.00 |
| Purity: | "More than 98%" |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Undiluted liquid. |
| Specific Gravity: | 0.88 g/ml. |
| Solubility: | 6% in water. |
| Stability: | Stable up to 200°C. |

**Method** : Three groups of Wistar rats (5/sex/dose level) received single oral doses of 1800, 2400, or 3200 mg/kg propylene glycol n-butyl ether (PnB), administered undiluted using a stainless steel stomach cannula attached to a syringe. Animals were fasted overnight prior to dosing and were not allowed food until 5.5 hr after dosing. Subjects were observed for mortality and signs of toxicity several times on the day of dosing (Day 0) and on weekdays thereafter for up to 14 additional days. Body weights were recorded immediately prior to dosing, weekly thereafter, and at death. Non-survivors were necropsied as soon as possible and surviving animals were subjected to necropsy on day 14.

**Results** : No rats died from a dose of 1800 mg/kg PnB. One female died after a dose of 2400 mg/kg. Four females and one male died at 3200 mg/kg. The calculated oral LD50 for males alone was 5500 mg/kg (no 95% confidence limits), for females alone was 2700 mg/kg (95% CL: 2400 – 3600 mg/kg), and for both sexes combined was 3300 (95% CL: 2800 – 4500 mg/kg).

All deaths occurred within one day of dosing. Adverse signs included weight loss, lethargy, coma, hypopnea, gasping, and dacryorrhea. Surviving rats showed no adverse signs by day 2. At necropsy, surviving rats showed no grossly observable lesions. Rats dying from treatment exhibited hemorrhage of the stomach and small intestine, bloody content of the small intestine and bladder, yellow liquid within the small intestine, and hyperemia of the bladder.

**Conclusions** : With an oral LD50 of 3300 mg/kg, propylene glycol n-butyl ether has a low degree of acute toxicity.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

| | | |
|---|---|---|
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 401: "Acute Oral Toxicity" was followed. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the aforementioned guidance. Test material characterization was adequate. The dose level tested satisfied the appropriate OECD upper limit (i.e., 2 gm/kg), the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded. |
| **References** | : | Reijnders, J.B.J., Zucker-Keizer, A.M.M., (1987). Evaluation of the acute oral toxicity of Dowanol-PnB in the rat. NOTOX Report No. 0482/699. July 1987. Unpublished study. |
| **Other** | : | The oral LD50 found in this study is consistent with other published values for CAS#'s 5131-66-8 and 29387-86-6. |
| **Source** | : | Dow Deutschland Inc Stade 5 (28) |

| | | |
|---|---|---|
| **Type** | : | LD50 |
| **Species** | : | Rat |
| **Strain** | : | |
| **Sex** | : | |
| **Number of animals** | : | |
| **Vehicle** | : | |
| **Value** | : | ca. 2500 . mg/kg bw |
| **Method** | : | other: see remark |
| **Year** | : | 1974 |
| **GLP** | : | no data |
| **Test substance** | : | other TS: 3-Butoxypropanol, mixed isomer |
| **Remark** | : | Experimental methods described in:<br>Smyth H. et al. (1962) Amer. Ind. Hyg. Ass. J., 23:95-107<br>Study classification: 4b (Secondary literature) |
| **Source** | : | Dow Deutschland Inc Stade 5 (10) |

| | | |
|---|---|---|
| **Type** | : | LD50 |
| **Species** | : | Rat |
| **Strain** | : | |
| **Sex** | : | |
| **Number of animals** | : | |
| **Vehicle** | : | |
| **Value** | : | ca. 5200 . mg/kg bw |
| **Method** | : | other: see remark |
| **Year** | : | 1969 |
| **GLP** | : | no data |
| **Test substance** | : | other TS: 3-Butoxy-1-propanol |
| **Remark** | : | Experimental methods described in:<br>Smyth H. et al. (1962) Amer. Ind. Hyg. Ass. J., 23:95-107<br>Study classification: 4b (Secondary literature) |
| **Source** | : | Dow Deutschland Inc Stade 5 (32) |

| | | |
|---|---|---|
| **Type** | : | LD50 |
| **Species** | : | Rat |

| | | |
|---|---|---|
| **Strain** | : | |
| **Sex** | : | |
| **Number of animals** | : | |
| **Vehicle** | : | |
| **Value** | : | = 2490 . mg/kg bw |
| **Method** | : | other |
| **Year** | : | 1964 |
| **GLP** | : | No data |
| **Test substance** | : | other TS: described as mixed isomers |
| **Remark** | : | Test substance was administered to non-fasted rats (90-120 gram). The animals were observed over 14 days. Clinical signs after dosing included ataxia and sluggish gait. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(3)

### 5.1.2 ACUTE INHALATION TOXICITY

| | | |
|---|---|---|
| **Type** | : | LC50 |
| **Species** | : | Rat |
| **Strain** | : | Fischer 344 |
| **Sex** | : | Males and females |
| **Number of animals** | : | 5 per sex |
| **Vehicle** | : | None |
| **Exposure time** | : | 4 hours |
| **Value** | : | > 651 .ppm (> 3,412 mg/m3) |
| **Protocol Guideline** | : | Protocol guideline not specified in report. However, protocol meets criteria specified in OECD 403 “Acute Inhalation Toxicity.“ |
| **Year of Study** | : | 1989 |
| **GLP** | : | Yes |
| **Test substance** | : | 1-butoxy-2-propanol: 97.68% propylene glycol butyl ether isomers:0.10%<br>2-butoxy-1-propanol: 1.12% propylene glycol: 0.09%<br>butanol: 0.48% propylene glycol allyl ether: 0.05%<br>propylene glycol isobutyl ether: 0.33% |
| **Method** | : | A single group of Fischer 344 rats (5/sex) was exposed in whole-body inhalation chambers for 4 hours to vapors of propylene glycol n-butyl ether at a measured concentration of 651 ppm (3,412 mg/m3). Chambers were 112 liters in volume and airflow was 30 liters/min. Animals were observed for overt signs of toxicity during the exposure period (day 1) and after for 14 additional days. Rats were weighed prior to exposure and on days 2, 4, 8, 11 and 15. |
| **Results** | : | No rats died when exposed to 651 ppm (3,412 mg/m3) propylene glycol n-butyl ether for 4 hours. No signs of toxicity during or after exposure were noted and no lesions were observed at necropsy except for a unilateral distension of the ovarian bursa in one female. This lesion was considered unrelated to exposure since it occasionally occurs in unexposed females. |
| **Conclusions** | : | No deaths occurred and no signs of toxicity were reported for rats exposed to 651 ppm propylene glycol n-butyl ether for 4 hours. Thus, the LC50 is greater than 651 ppm (3,412 mg/m3). This low acute inhalation toxicity is consistent with other propylene glycol ethers. |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1. |

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although the study report did not specify that OECD Protocol 403: "Acute Inhalation Toxicity" was followed, the study satisfied the methods stipulated in Protocol 403. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the aforementioned guidance. Test material characterization was adequate. The dose level tested (in this limit test) satisfied the appropriate OECD upper limit (i.e., the maximum practically attainable), the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded.

**Reference** : Corley, R.A., Johnson, K.A., Battjes, J.E., Verschuuren, H.G. (1987). Propylene glycol n-butyl ether: an acute vapour inhalation study in Fischer 344 rats. Dow Report No. K-005473-004. January 4, 1989. Unpublished report.

**Other** : The nominal test concentration was 688 ppm (3,720 mg/m3), computed using the amount of test material consumed divided by the airflow. The measured or actual concentration of 651ppm (3,412 mg/m3) was within 6% of nominal and within 25% of the theoretical maximum attainable concentration of 790 ppm (4,271 mg/m3). The authors of the report indicated that concentrations higher than 650 ppm lead to condensation within the chamber. Thus, 651 ppm represented a practical upper limit concentration.

**Source** : Dow Deutschland Inc Stade 5

(11)

**Type** : LC0
**Species** : Rat
**Strain** :
**Sex** :
**Number of animals** :
**Vehicle** :
**Exposure time** : 8 hour(s)
**Method** : other: see remark
**Year** : 1974
**GLP** : No data
**Test substance** : other TS: 3-Butoxypropanol, mixed isomers
**Remark** : Animals exposed to saturated vapors for 8 hours survived with no significant adverse effects.
Experimental methods described in:
Smyth H. et al. (1962) Amer. Ind. Hyg. Ass. J., 23:95-107
Study classification: 4b (Secondary literature)
**Source** : Dow Deutschland Inc Stade 5

(10)

**Type** : LC50
**Species** : Rat
**Strain** :
**Sex** :
**Number of animals** :
**Vehicle** :
**Exposure time** : 8 hour(s)
**Value** : = 5.83 . mg/l (5,830 mg/m3 or 1,078 ppm)

| | | |
|---|---|---|
| **Method** | : | Other |
| **Year** | : | 1964 |
| **GLP** | : | No data |
| **Test substance** | : | Other TS: described as mixed isomers |
| **Remark** | : | Six female rats were exposed to "concentrated vapour" (approx. 5.83 mg/l) for 8 hours. Hypoactivity was the principle clinical sign. There were no deaths. May have been some aerosol; particle size not reported. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(3)

### 5.1.3 ACUTE DERMAL TOXICITY

| | | |
|---|---|---|
| **Type** | : | LD50 (Limit Test) |
| **Species** | : | Rat |
| **Strain** | : | Wistar |
| **Sex** | : | Males and females |
| **Number of animals** | : | 5 per sex |
| **Vehicle** | : | Test material was tested undiluted. |
| **Value** | : | > 2000 mg/kg bw |
| **Protocol Guideline** | : | OECD Guideline 402 "Acute dermal Toxicity" |
| **Year of Study** | : | 1987 |
| **GLP** | : | Yes. A quality assurance statement was provided in the study report, signed by the laboratory QA officer. This statement indicates that OECD Good Laboratory Practices were followed. |
| **Test substance** | : | |

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | XZ 95410.00 |
| Purity: | “More than 98%” |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Undiluted liquid. |
| Specific Gravity: | 0.88 g/ml. |
| Solubility: | 6% in water. |
| Stability: | Stable up to 200°C. |

**Method** : A group of 5 male and 5 female Wistar rats was treated with a single application of 2,000 mg/kg propylene glycol n-butyl ether applied topically to the clipped, intact skin under occlusion for a period of 24 hours. Subjects were observed for clinical signs of toxicity and mortality during the application period and for a period of 14 days after removal of the test material. The skin of the rats at the site of application was also evaluated for signs of irritation over the course of the study. The undiluted test material was applied at a single dose of 2,000 mg/kg to approximately 10% of the total body surface area of skin (clipped, non-abraded) of the rats. The test material was applied to gauze patches, which were then affixed to the clipped area of the skin and covered with foil and wrapped with a bandage around the torso. The test material was held in contact with the skin for a period of 24 hours whereupon it was removed and the treated area was washed with water to remove remaining test material. On the day of treatment (day 0), animals were observed for toxicity and morbidity approximately every two hours. Subjects were checked once daily thereafter except for weekends and holidays. Individual body weights were recorded on test days 0, 7, and 14. The treated areas of skin were examined on test days 4, 7, and 14 for signs of irritation. Animals were sacrificed on day 14 and subjected to gross necropsy.

| | | |
|---|---|---|
| **Results** | : | No deaths, clinical signs of toxicity, or skin irritation occurred over the course of the study. The dermal LD50 for propylene glycol n-butyl ether is greater than 2,000 mg/kg for male and female Wistar rats. See comment below (under "Other"), regarding skin irritation potential, |
| **Conclusions** | : | These results indicate that propylene glycol n-butyl ether exhibits a relatively low degree of acute dermal toxicity, or EPA Category III. (achieving Category IV requires testing 5 g/kg). |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 402: "Acute Dermal Toxicity" was followed. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the aforementioned guidance. Test material characterization was adequate. The dose level tested (in this limit test) satisfied the appropriate OECD upper limit (i.e., 2 gm/kg), the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded. |
| **References** | : | Reijnders, J.B.J., (1987). Evaluation of the acute dermal toxicity of Dowanol-PnB in the rat. NOTOX C.V. Study No. NOTOX 0482/700, July 1987. Sponsored by Dow Chemical Europe. Unpublished. |
| **Other** | : | The dermal LD50 found in this study is consistent with other published values for CAS#'s 5131-66-8 and 29387-86-6. Note that in a skin irritation study with albino rabbits, PnB showed moderate irritation potential after a 4 hour exposure. |
| **Source** | : | Dow Deutschland Inc Stade 5 (27) |
| **Type** | : | LD50 |
| **Species** | : | Rat |
| **Strain** | : | |
| **Sex** | : | |
| **Number of animals** | : | |
| **Vehicle** | : | |
| **Value** | : | ca. 2640 . mg/kg bw |
| **Method** | : | Other: according to Draize et al. (1944) J Pharmacol Exp Therap, 82:377 |
| **Year** | : | 1947 |
| **GLP** | : | No |
| **Test substance** | : | other TS: Propylene glycol, n-butyl ether |
| **Remark** | : | Dermal toxicity studies showed that all five animals receiving 1800 mg/kg survived, two of five receiving 2600 mg/kg survived, and none of five receiving 4400 mg/kg survived. When the material was confined under a cuff for 24hr, severe injury to the skin occurred and the animals became deeply narcotized. Deaths from the larger doses occurred within a few hours after application of the material, with all deaths occurring within 24 hr after treatment or not at all.<br>Study classification: 4b (secondary literature) |
| **Source** | : | Dow Deutschland Inc Stade 5 (35) |

| | | |
|---|---|---|
| **Type** | : | LD50 |
| **Species** | : | Rabbit |
| **Strain** | : | |
| **Sex** | : | |
| **Number of animals** | : | |
| **Vehicle** | : | |
| **Value** | : | ca. 3100 . mg/kg bw |
| **Method** | : | Other: see remark |
| **Year** | : | 1974 |
| **GLP** | : | no data |
| **Test substance** | : | other TS: 3-Butoxypropanol, mixed isomers |
| **Remark** | : | Experimental methods described in:<br>Smyth H. et al. (1962) Amer. Ind. Hyg. Ass. J., 23:95-107<br>Study classification: 4b (Secondary literature) |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(10)

| | | |
|---|---|---|
| **Type** | : | LD50 |
| **Species** | : | Rabbit |
| **Strain** | : | |
| **Sex** | : | |
| **Number of animals** | : | |
| **Vehicle** | : | |
| **Value** | : | ca. 1400 . mg/kg bw |
| **Method** | : | other: see remark |
| **Year** | : | 1969 |
| **GLP** | : | no data |
| **Test substance** | : | other TS: 3-Butoxy-1-propanol |
| **Remark** | : | Experimental methods described in:<br>Smyth H. et al. (1962) Amer. Ind. Hyg. Ass. J., 23:95-107<br>Study classification: 4b (Secondary literature) |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(32)

| | | |
|---|---|---|
| **Type** | : | LD50 |
| **Species** | : | Rabbit |
| **Strain** | : | |
| **Sex** | : | |
| **Number of animals** | : | |
| **Vehicle** | : | |
| **Value** | : | = 3133 mg/kg bw |
| **Method** | : | other |
| **Year** | : | 1964 |
| **GLP** | : | no data |
| **Test substance** | : | other TS: described as mixed isomers |
| **Remark** | : | The test substance was applied to rabbit skin for 24 hours, under occlusion. Marked erythema was reported; this was most probably due to the occlusive conditions used. The test substance was not harmful by skin contact. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(3)

### 5.1.4 ACUTE TOXICITY, OTHER ROUTES

| | | |
|---|---|---|
| **Remark** | : | no studies |
| **Source** | : | Dow Deutschland Inc Stade 5 |

### 5.2.1 SKIN IRRITATION

| | | |
|---|---|---|
| **Species** | : | Rabbit |
| **Strain** | : | New Zealand White |
| **Concentration** | : | Undiluted |
| **Exposure** | : | Topical on clipped dorsal back under semi-occlusive dressing |
| **Exposure time** | : | 4 hours |
| **Number of animals** | : | 3 (females) |
| **PDII** | : | 4.0 |
| **Result** | : | moderately irritating |
| **EC classification** | : | Irritating |
| **Protocol Guideline** | : | OECD Guideline 404 "Acute Dermal Irritation/Corrosion" |
| **Year of Study** | : | 1987 |
| **GLP** | : | Yes |
| **Test substance** | : | as prescribed by 1.1 - 1.4 |

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | XZ 95410.00 |
| Purity: | “More than 98%” |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Undiluted liquid. |
| Specific Gravity: | 0.88 g/ml. |
| Solubility: | 6% in water. |
| Stability: | Stable up to 200°C. |

**Method** : In a primary dermal irritation/corrosivity test, 0.5 milliliters of undiluted propylene glycol n-butyl ether was applied to a 6 x 6 cm square area of clipped, unabraded skin on the left flank of three young adult female New Zealand white rabbits. The test material was held in contact with the skin for a period of 4 hours under a semi-occlusive dressing. After this period, the dressing and test material were removed by washing with tissues and water. The site of application was evaluated for irritation by scoring 1) erythema/eschar and 2) edema. Both criteria were scored on a scale of 0 – 4 at approximately 30 minutes after removal of the test material, and at 24, 48, and 72 hours, and on days 7 and 14. The primary irritation index was calculated by averaging the group mean scores for both criteria at 24 and 72 hours.

**Results** : Undiluted propylene glycol n-butyl ether was found to have a primary irritation index of 4 (2.66 for erythema/eschar plus 1.33 for edema) averaged for the three animals at 24 and 72 hours. One subject had eschar over a large portion of the treated site, which did not completely disappear by day 14. This subject also exhibited chronic dermal irritation on day 14. The remaining two subjects showed well-defined erythema and slight edema with scaliness (days 2 and 3) that disappeared over the 14 day observation period.

**Conclusions** : The authors considered undiluted propylene glycol n-butyl ether to be moderately irritating. Classification: According to the criteria laid down in Annex VI of the EEC Council Directive 67/548/EEC (amended by Directive 83/467/EEC), the undiluted test substance should be labeled as a skin irritant.

**Data Quality** : The quality of the data from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 404: "Acute Dermal Irritation/Corrosion" was followed. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the aforementioned guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the observation period (14 days) was sufficient, and scoring criteria and averaging methods were typical for this type assay and adequately recorded.

**References** : Weterings, P.J.J.M., Daamen, P.A.M., (1987). Assessment of Primary Skin Irritation/Corrosion by Dowanol™-PnB in the Rabbit. NOTOX C.V. Study No. NOTOX 0482/701, May 1987. Unpublished.

**Source** : Dow Deutschland Inc Stade 5

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**Species** : Rabbit
**Strain** : New Zealand White
**Concentration** : 75%, 50%, and 25% in water.
**Exposure** : Topical on clipped dorsal back under semi-occlusive dressing
**Exposure time** : 4 hours
**Number of animals** : 3 females
**PDII** : 75%: 2.5
50%: 0.8
25%: 0.0
**Result** : Moderately irritating for pure PnB, less to non-irritating for dilutions
**EC classification** : Irritating
**Protocol Guideline** : OECD Guideline 404 "Acute Dermal Irritation/Corrosion"
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | XZ 95410.00 |
| Purity: | "More than 98%" |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Diluted in water (emulsions). |
| Specific Gravity: | 0.88 g/ml. |
| Solubility: | 6% in water. |
| Stability: | Stable up to 200°C. |

**Method** : In a primary dermal irritation/corrosivity test, separate solutions of 0.5 milliliters of propylene glycol n-butyl ether (PnB) diluted 75%, 50%, and 25% in water (as an emulsion) were applied to 6 x 6 cm square areas of clipped, unabraded skin on the flanks of three young adult female New Zealand white rabbits. The various dilutions were tested at different sites on each subject and compared to a water-only site. The test material was held in contact with the skin for a period of 4 hours under a semi-occlusive dressing. After this period, the dressing and test material were removed by washing with tissues and water. The sites of application were evaluated for irritation by scoring 1) erythema/eschar and 2) edema. Both criteria were scored on a scale of 0 – 4 at approximately 30 minutes after removal of the test material, and at 24, 48, and 72 hours, and on day 7. The primary irritation index was calculated by averaging the mean group scores for both criteria at 24 and 72 hours.

**Results** : At 75% concentration, PnB was found to have a primary irritation index of 2.5 (1.83 for erythema/ eschar plus 0.66 for edema) averaged for the three animals at 24 and 72 hours, indicating moderate irritation potential. Scores were zero by day 7 when the study was terminated. At 50%, the PII for PnB was 0.8, indicating slight irritation. At 25% concentration in water, the PII for PnB was 0. Skin irritation disappeared by day 7 in all groups.

**Conclusions** : Results indicate that propylene glycol n-butyl ether is a moderate dermal irritant at 75% dilution in water, a slight irritant at 50% and non-irritating at 25%.

**Data Quality** : The quality of the data from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study report) In addition, this study evaluated the effect of dilution of the test substance with water on skin irritation potential. The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 404: “Acute Dermal Irritation/Corrosion” was followed. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the aforementioned guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the observation period (7 days until disappearance of irritation) was sufficient, and scoring criteria and averaging methods were typical for this type assay and adequately recorded.

**References** : Weterings, P.J.J.M., Daamen, P.A.M., (1987). Assessment of Primary Skin Irritation/Corrosion by Dowanol™-PnB diluted to 75%, 50% and 25% in the Rabbit. NOTOX C.V. Study No. NOTOX 0482/748, June 1987. Unpublished.

**Other** : Classification: Based on these results and the clinical judgment of the report authors, the test substance should be considered as a moderate skin irritant at 75 per cent (according to the EEC classification/Ref 3), as a slight skin irritant at 50 per cent and as non-irritating to the skin at 25 per cent in water.

**Source** : Dow Deutschland Inc Stade 5

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**Species** : Rabbit

| | | |
|---|---|---|
| **Concentration** | : | |
| **Exposure** | : | |
| **Exposure time** | : | |
| **Number of animals** | : | |
| **PDII** | : | |
| **Result** | : | |
| **EC classification** | : | |
| **Method** | : | other: see remark |
| **Year** | : | 1974 |
| **GLP** | : | no data |
| **Test substance** | : | other TS: 3-Butoxypropanol, mixed isomers |
| **Remark** | : | Irritation on uncovered rabbit belly was scored with 3 out of 10<br>Experimental methods described in:<br>Smyth H. et al., Amer. Ind. Hyg. Ass. J., 23: 95-107, 1962).<br>Study classification: 4b (Secondary literature) |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(10)

| | | |
|---|---|---|
| **Species** | : | Rabbit |
| **Concentration** | : | |
| **Exposure** | : | |
| **Exposure time** | : | |
| **Number of animals** | : | |
| **PDII** | : | |
| **Result** | : | slightly irritating |
| **EC classification** | : | |
| **Method** | : | other: see reference |
| **Year** | : | 1947 |
| **GLP** | : | No |
| **Test substance** | : | other TS: Propylene glycol, n-butyl ether |
| **Remark** | : | Study classification: 4b (secondary literature)<br>Undiluted material was applied repeatedly to the rabbit ear and belly (10 times in 2 weeks). Boiling point of tests substance was 169.8 deg. Celsius at 1013 hPa. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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| | | |
|---|---|---|
| **Species** | : | Rabbit |
| **Concentration** | : | |
| **Exposure** | : | |
| **Exposure time** | : | |
| **Number of animals** | : | |
| **PDII** | : | |
| **Result** | : | |
| **EC classification** | : | |
| **Method** | : | Other: see remark |
| **Year** | : | 1969 |
| **GLP** | : | no data |
| **Test substance** | : | other TS: 3-Butoxy-1-propanol |
| **Remark** | : | Irritation on uncovered rabbit belly was scored with 2 out of 10<br>Experimental methods described in:<br>Smyth H. et al., Amer. Ind. Hyg. Ass. J., 23: 95-107, 1962).<br>Study classification: 4b (Secondary literature) |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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### 5.2.2 EYE IRRITATION

| | | | |
|---|---|---|---|
| **Species** | : | Rabbit | |
| **Strain** | : | New Zealand White | |
| **Concentration** | : | 100% | |
| **Dose** | : | 0.1 ml. | |
| **Exposure Time** | : | Unwashed | |
| **Number of animals** | : | 3 young adult females | |
| **Result** | : | moderately irritating | |
| **EC classification** | : | Irritating | |
| **Protocol Guideline** | : | OECD Guideline 405 "Acute Eye Irritation/Corrosion" | |
| **YEAR OF STUDY** | : | 1987 | |
| **GLP** | : | Yes | |
| **Test substance** | : | Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| | | Batch No.: | redacted |
| | | Purity: | "More than 98%" |
| | | Supplied as: | Not reported. |
| | | Appearance: | Clear liquid. |
| | | Administered as: | Diluted in water (emulsions). |
| | | Specific Gravity: | 0.88 g/ml. |
| | | Solubility: | 6% in water. |
| | | Storage: | At ambient temperature in the dark. |
| | | Stability: | Stable up to 200°C. |

**Method** : Undiluted PnB (0.1 ml) was instilled into the conjunctival sac of the left eye of three female white rabbits. Lids were held together for a few seconds after instillation and the treatment solution was not washed out after 30 seconds. Eyes were read for irritation (compared to the negative control right eye) at various time intervals over a period of 23 days. Readings were taken at 1 hour, 24 hours, 48 hours, 72 hours, 7 days, and 14 days after treatment. In addition at 24 hours, eyes were treated with fluorescene dye to determine the severity and areal extent of any corneal involvement that might be present. If necessary, evaluation with fluorescene was repeated on days 3, 7, and 14. Eyes were evaluated for irritation based on 1) damage to the cornea (corneal opacity and area involved, both scored on a scale of 0 to 4) 2) damage to the iris (obvious physical damage and reaction to light, scored on a scale of 0 to 2), and 3) damage to conjunctivae (erythema [scale of 0 – 3] and chemosis [scale of 0 – 4]). Overall scores were based on observations averaged from the 24, 48, and 72-hour observation intervals. In this assay, the score after one hour was used to categorize the test material.

**Results** : Instillation of 0.1 ml PnB caused slight corneal opacity in all three subjects that cleared in one rabbit after one day, the second rabbit in 2 days, and the third rabbit in 7 days (confirmed by evaluation with fluorescene dye). Iridial veins were swollen in two subjects, which cleared in one rabbit by 48 hours and in the second by 72 hours. Chemosis and erythema, sometimes severe, cleared by day 7 in all three rabbits. Lacrimation and discharge were observed 1 hour after instillation, which continued in one subject until 4 days after treatment.

Scores averaged over three time intervals (24, 48, and 72 hours) were 0 for corneal opacity, 0.2 for iridial damage, and 2.2 for conjunctival redness (erythema) and 1.0 for conjunctival swelling (chemosis). At one hour, a Draize score of 34 (out of 110) was calculated.

| | | |
|---|---|---|
| **Conclusions** | : | Based on the 1 hour Draize score of 34, PnB was classified as moderately irritating (according to the scheme of Kay and Calanddra). According to the EEC criteria for classification, PnB should be labeled as "eye irritant." |
| **Data Quality** | : | The quality of the data from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 405: "Acute Eye Irritation/Corrosion" was followed. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the aforementioned guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the observation period (14 days) was sufficient, and scoring criteria and averaging methods were typical for this type assay and adequately recorded. |
| **References** | : | Weterings, P.J.J.M., Daamen, P.A.M., (1987). Assessment of acute eye irritation/corrosion by Dowanol-PnB in the rabbit. Unpublished Dow report. |
| **Other** | : | According to EPA criteria, corneal involvement clearing within 7 days renders the test material a Category III irritant. |
| **Source** | : | Dow Deutschland Inc Stade 5 (40) |
| **Species** | : | Rabbit |
| **Concentration** | : | |
| **Dose** | : | |
| **Exposure Time** | : | |
| **Comment** | : | |
| **Number of animals** | : | |
| **Result** | : | |
| **EC classification** | : | |
| **Method** | : | other: see remark |
| **Year** | : | 1974 |
| **GLP** | : | no data |
| **Test substance** | : | other TS: 3-Butoxypropanol, mixed isomers |
| **Remark** | : | Corneal injury in rabbits was scored with 7 out of 10 (experimental methods described in:<br>Smyth H. et al., Amer. Ind. Hyg. Ass. J., 23: 95-107, 1962).<br>Study classification: 4b (Secondary literature) |
| **Source** | : | Dow Deutschland Inc Stade 5 (10) |
| **Species** | : | Rabbit |
| **Concentration** | : | |
| **Dose** | : | |
| **Exposure Time** | : | |
| **Comment** | : | |
| **Number of animals** | : | |
| **Result** | : | Irritating |
| **EC classification** | : | |
| **Method** | : | other: see reference |
| **Year** | : | 1947 |
| **GLP** | : | No |
| **Test substance** | : | other TS: Propylene glycol, n-butyl ether |

| | | |
|---|---|---|
| **Remark** | : | Boiling point of the test material was 169.8 deg. Celsius at1013 hPa<br>PnB was found to be appreciably irritating to the rabbit eye; one drop in an eye on five consecutive days caused marked conjunctival irritation and corneal cloudiness, which healed within a week.<br>Study classification: 4b (Secondary literature) |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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| | | |
|---|---|---|
| **Species** | : | Rabbit |
| **Concentration** | : | |
| **Dose** | : | |
| **Exposure Time** | : | |
| **Comment** | : | |
| **Number of animals** | : | |
| **Result** | : | |
| **EC classification** | : | |
| **Method** | : | other: see remark |
| **Year** | : | 1969 |
| **GLP** | : | no data |
| **Test substance** | : | other TS: 3-Butoxy-1-propanol |
| **Remark** | : | Corneal injury in rabbits was scored with 7 out of 10 (experimental methods described in:<br>Smyth H. et al., Amer. Ind. Hyg. Ass. J., 23: 95-107, 1962).<br>Study classification: 4b (Secondary literature) |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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## 5.3 SENSITIZATION

| | | |
|---|---|---|
| **Type** | : | Buehler Test |
| **Species** | : | Guinea pig |
| **Strain** | : | Hartley outbred (crl: (HA)BR) |
| **Number of animals** | : | 10/sex for treatment group; 5/sex for negative control |
| **Vehicle** | : | Propylene glycol |
| **Result** | : | not sensitizing |
| **Classification** | : | not sensitizing |
| **Protocol Guideline** | : | OECD Guideline 406 “Skin Sensitization” |
| **Year of Study** | : | 1987 |
| **GLP** | : | Yes |
| **Test substance** | : | |

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | XZ 95410.00 |
| Purity: | “More than 98%”* |
| Supplied as: | Not reported. |
| Appearance: | Transparent fluid. |
| Administered as: | Various dilutions (see below). |
| Specific Gravity: | 0.88 g/ml.* |
| Solubility: | 6% in water.* |
| Stability: | Stable up to 200°C.* |

* from acute oral toxicity report for PnB that used same sample lot.

**Method** : Initially, a preliminary dose range-finding study was conducted to determine the irritation potential of the test material in order to select the appropriate treatment solution concentration for the main sensitization study. Four concentrations of propylene glycol n-butyl ether (PnB) were tested (using propylene glycol as a diluent). Concentrations of 100%, 50%, 10%, and 5% were evaluated. Minimal irritation occurred at 100% and no irritation occurred at lower concentrations. Consequently, 80% PnB was selected as an appropriate concentration to use in the induction phase. For the challenge phase, 40% PnB was chosen as a non-irritating dose.

In the sensitization test, the backs of 20 Hartley guinea pigs (10/sex) were clipped free of hair and 0.3 ml of the 80% PnB test solution was topically applied to an application site on the flank using a Hill Top Chamber® secured with a bandage. The test material was held in contact with the skin for 6 hours whereupon it was removed with lukewarm water. This procedure was repeated for the second and third inductions, which followed at one-week intervals. The sites were read for irritation but results were not reported. For the challenge phase, conducted 10 days after the third induction, 0.3 ml of 40% PnB was applied to a naive site on the flanks of the guinea pigs and held in place for 6 hours using a Hill Top Chamber® and then removed, as described above. A control group of five males and five females was treated similarly except that propylene glycol was applied as the test material.

After the challenge dose, the site of skin application was depilitated using Veet cream and scored at 24 and 48 hours following removal of the test material. Responses were graded by evaluating erythema or edema on a scale that included: 0 (no reaction), "±" (slight, patchy reaction), 1 (slight but confluent, or moderate but patchy reaction), 2 (moderate erythema), or 3 (severe erythema with or without edema). These responses were compared with untreated sites on the same animal and with propylene glycol-treated negative controls. Other skin reactions were recorded if present (e.g., edema, eschar, necrosis). The experimental study design is shown below.

Study Design

| Group | Test/Control Material | No. Animals | Topical Induction Dose | Challenge Dose* (Topical) |
|---|---|---|---|---|
| 1. Test Group | Propylene Glycol n-Butyl Ether (PnB) | 20 (10/sex) | 0.3 ml of 80% PnB w/v in PG, applied for 6 hr. | 0.3 ml of 40% PnB w/v in PG, applied for 6 hr. |
| 2. Negative Control | Propylene Glycol (PG) | 10 (5/sex) | 0.3 ml of 100% pure PG, applied for 6 hr. | 0.3 ml of 100% PG, applied for 6 hr. |

Histopathology:None conducted.

**Methods continued** : Toxicity Endpoints Monitored

| | |
|---|---|
| Morbidity/mortality: | Every 2 hours on day 0 (day of test material administration) and once daily on workdays for 14 days thereafter. |
| Clinical signs: | Every 2 hours on day 0 (day of test material administration) and once daily on workdays for 14 days thereafter. |
| Body weights: | Taken on dose days –1 and post challenge day 3. |
| Food consumption: | Not recorded. |
| Necropsy: | None conducted. |

**Results** : Morbidity/Mortality: All subjects survived treatment with the test compound.

Clinical signs: None reported. No dermal effects reported at site of application.

Body weights: No effect on body weights reported.

Macroscopic Examinations: No gross lesions recorded.

Induction reactions and duration: No effects reported.

Challenge reactions and duration: At the 24-hour reading, all scores in treated animals were 0 for erythema or edema. Scores remained 0 at the 48-hour reading.

**Conclusions** : PnB did not cause contact hypersensitivity under the conditions of this test.

**Data Quality** : The number of animals tested (20) meets the guidance level for the procedure. Test material application, scoring intervals, and other study parameters followed guidance. All scoring criteria recommended in the guidance were evaluated. The data quality from this study is considered acceptable. The report included documentation for methods and results although too much reliance for documentation was placed on inclusion of the study protocol appended to the report. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. While the study report did not specifically cite OECD Protocol 406: “Skin Sensitization,” the numbers and type of test animals used and their husbandry conditions were as prescribed in the aforementioned guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, as did other procedures reflecting a modified Buehler assay, and findings were adequately recorded.

**References** : Vankerkom, J., (1987). Guinea pig sensitization study – modified Buehler method. S.C.K.-C.E.N. Study No. SS87B01, July 1987. Dow Chemical Company. Unpublished report.

**Other** : This finding is consistent with propylene glycol ethers in general.
**Source** : Dow Deutschland Inc Stade 5

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## 5.4 REPEATED DOSE TOXICITY

| | | |
|---|---|---|
| **Species** | : | Rat |
| **Sex** | : | Male/female |
| **Strain** | : | Fischer 344 |
| **Route of admin.** | : | Inhalation |
| **Exposure period** | : | 2 weeks (9 exposure) |
| **Frequency of treatment** | : | 6 h daily, 5 days/week |
| **Post Obs. period** | : | |
| **Doses** | : | 50, 200, 700 ppm (270, 1,081, 3,785 mg/$m^3$) |
| **Control group** | : | Yes |
| **NOAEL** | : | > 700 ppm (3,785 mg/$m^3$) |
| **LOAEL** | : | > 700 ppm (3,785 mg/$m^3$) |
| **Protocol Guideline** | : | OECD Guideline 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study" |
| **Year of Study** | : | 1989 |
| **GLP** | : | Yes |
| **Test substance** | : | As prescribed by 1.1 - 1.4 |
| **Remark** | : | Study classification: 1a (Guideline study)<br>Whole-body exposures of 5 male and 5 female Fischer 344 per group. Each animal was evaluated for changes in body weight, clinical chemistry, haematology, urinalysis, clinical observations, selected organ weights, and gross and histopathological lesions. The highest concentration of PnB that could be practically attained was 700 ppm (3,785 mg/$m^3$). No hematological or other signs or toxicity were observed. This study has been reviewed in Patty's Toxicology 5$^{th}$ Edition and ECETOC monograph in preparation for glycol ethers. Presence of aerosol or particle size not reported in reviews. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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| | | |
|---|---|---|
| **Species** | : | Rat |
| **Sex** | : | male/female |
| **Strain** | : | other: Fischer 344, Sprague-Dawley |
| **Route of admin.** | : | Inhalation |
| **Exposure period** | : | 11 days |
| **Frequency of treatment** | : | 6 hours/day, 9 exposures/11 days |
| **Post Obs. period** | : | |
| **Doses** | : | 10, 100, 300, 600 ppm (54, 540, 1622, 3,244 mg/$m^3$) |
| **Control group** | : | Yes |
| **NOAEL** | : | = 600 ppm (3,244 mg/$m^3$) |
| **Method** | : | other: see reference |
| **Year** | : | 1988 |
| **GLP** | : | No data |
| **Test substance** | : | No data |
| **Remark** | : | Klonne et al. (1989) cited in: ECETOC, Technical Report on Glycol ethers, in preparation.<br>Study classification: 4b (Secondary literature) |
| **Result** | : | The only exposure-related effects reported were increased liver weights in the 600 ppm group of F344 rats and a low incidence of mild eye lesions in the 300 and 600 ppm group of F344. This study has been reviewed in Patty's Toxicology 5$^{th}$ Edition and ECETOC monograph in preparation for glycol ethers. Presence of aerosol or particle size not reported in reviews. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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| | | |
|---|---|---|
| **Species** | : | Rat |

| | | |
|---|---|---|
| **Sex** | : | male/female |
| **Strain** | : | no data |
| **Route of admin.** | : | Inhalation |
| **Exposure period** | : | 31 days |
| **Frequency of treatment** | : | 7 hours/day, 5 days/week |
| **Post Obs. period** | : | no data |
| **Doses** | : | 600 ppm (3,244 mg/$m^3$) |
| **Control group** | : | Yes |
| **NOAEL** | : | = 600 ppm (3,244 mg/$m^3$) |
| **Method** | : | Other: see reference |
| **Year** | : | 1965 |
| **GLP** | : | No |
| **Test substance** | : | No data |
| **Remark** | : | Pozzani UC and Carpenter CP (1965) cited in: ECETOC, Technical Report on Glycol ethers, in preparation.<br>Six male and 6 female rats were used.<br>Study classification: 4b (Secondary literature)<br>This study has been reviewed in Patty's Toxicology 5th Edition and ECETOC monograph in preparation for glycol ethers. Presence of aerosol or particle size not reported in reviews. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(26)

| | | |
|---|---|---|
| **Type** | : | Hemolytic effects & subchronic toxicity (2-week oral) |
| **Species** | : | Rat |
| **Sex** | : | Male/female |
| **Strain** | : | Sprague-Dawley |

Age at dosing: Approximately 8 weeks of age.
Source: Charles River Wiga, Sulzfeld, F.R.G.
Acclimation period: At least one week.
Average weight (start of study): Males: 246-295 grams; Females: 169-200 grams.
Assignment to groups: Computerized, random number-based procedure.
Diet: RMH-B, pellet diameter 10 mm, Hope Farms, Woerden, The Netherlands.
Access to food: Available ad libitum.
Access to water: Available ad libitum (municipal water supply).
Method of Identification: Ear tags.
Housing: Individual polycarbonate cages with wire lids and purified saw dust (Woody Clean).

Environmental Conditions
Temperature: 20-21°C. Recording frequency not reported.
Humidity: 60-70%. Recording frequency not reported.
Air changes: Not specified.
Photoperiod: 12 hr light/12 hr dark.

| | | |
|---|---|---|
| **Route of admin.** | : | Oral (gavage) |
| **Exposure period** | : | 2 weeks (14 consecutive daily doses) |
| **Frequency of treatment** | : | Daily, 7 days/week |
| **Post Obs. period** | : | No |
| **Doses** | : | 0, 100, 200, or 400 mg/kg bw d |
| **Control group** | : | Yes, concurrent vehicle (propylene glycol) |
| **NOAEL** | : | = 400 . mg/kg bw |
| **LOAEL** | : | > 400 . mg/kg bw |
| **Protocol Guideline** | : | OECD Guideline 407 "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-d Study" |

**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | XZ 95410.00 |
| Purity: | >98% |
| Supplied as: | Not reported. |
| Appearance: | Transparent fluid. |
| Administered as: | Various dilutions (see below). |
| Specific Gravity: | 0.88 g/ml. |
| Solubility: | 6% in water. |
| Storage: | At ambient temperature in the dark. |
| Stability: | Stable up to 200°C. |

**Method** : Four groups of Sprague-Dawley rats (6/sex/dose level) received propylene glycol n-butyl ether (PnB) by gavage at doses of 0, 100, 200, or 400 mg/kg-day for 14 consecutive days. PnB was diluted in pharmacological grade propylene glycol to achieve the desired dosing volume. The negative controls (0 dose group 1) received propylene glycol only.

Study Design

| Group | Dose mg/kg-d | No./ Sex/ Dose | Treat-ment Period (Days) |
|---|---|---|---|
| 1 | 0 | 6 | 14 |
| 2 | 100 | 6 | 14 |
| 3 | 200 | 6 | 14 |
| 4 | 400 | 6 | 14 |

Rats were observed for mortality and clinical signs of toxicity once per day. Once weekly, animals were given a more detailed clinical examination. Body weights and food consumption were monitored weekly. Hematological evaluations were conducted on day 7 (blood collected from orbital sinus) and day 14 (from aorta). On day 14, additional blood was collected at sacrifice for clinical chemistries. At sacrifice, all rats were subjected to complete necropsy and the following organs/tissues were collected, weighed, and preserved: liver, spleen, kidneys, adrenals, heart, testes, ovaries, and abnormal tissues. These tissues were processed into slides for the control and high dose animals and examined microscopically.

Blood parameters measuring erythrocyte fragility were monitored due to the ability of ethylene glycol n-butyl ether to cause red cell hemolysis in rats at relatively low doses (e.g. 30 mg/kg). Thus, osmotic fragility, hematocrit, mean corpuscular hemoglobin, and other erythrocyte parameters were recorded.

**Results** : No mortality or clinically observable signs of toxicity were observed in any of the subjects. Body weights, organ weights/ratios, food consumption, and clinical chemistries were unaffected by PnB treatment. No effects on hematology, particularly for erythrocytes (including osmotic fragility), were detected. Gross or microscopic pathology revealed no test substance related changes.

**Conclusions** : The no observed adverse effect level (NOAEL) for this study is 400 mg/kg-day. No LOAEL was established. In contrast to ethylene glycol n-butyl ether, this normal-butyl ether of propylene glycol showed no hemolytic effects in rats at dosages more than 10 times higher than those causing hemolytic effects in ethylene glycol n-butyl ether-treated rats.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report specified that OECD Guideline“407 "Repeated Dose Oral Toxi–ity - Rodent: 28-day or 14-day ”tudy" was followed. The study satisfied the methods stipulated in this protocol. Specifically, the numbers and type of test animals used and their husbandry conditions, were as prescribed in the guidance. Test material characterization was adequate. The dose level tested was adequate and the toxicity endpoints monitored were typical for this type assay and adequately recorded.

**References** : Debets, F.M.H., (1987). Assessment of the oral toxicity, including the haemolytic activity, of Dowanol-PnB in the rat: 14-day study. Dow Report No. DET 1020. June 1987. Unpublished report.

**Other** : A pilot study was conducted prior to this main study in order to select dose levels. Two rats/sex/dose level were administered 0, 200, 500, or 1000 mg PnB/kg-day orally (gavage) for eight consecutive days. One male from the 500 mg/kg-day group died on day 6 and one female from the 1000 mg/kg-day group died on day 2. Signs of toxicity included lethargy, bloody eye encrustation, and gasping or rattled respiration. Surviving subjects recovered from these signs by day 4. Hematology and clinical chemistry parameters were unaffected. In the non-surviving male, necropsy revealed hemorrhages of the lungs and intestines while the female showed gas accumulation, yellow-reddish contents, and hemorrhage.

**Source** : Dow Deutschland Inc Stade 5

(13)

**Species** : Rat
**Sex** : male/female

**Strain** : Fischer 344

| | |
|---|---|
| Age at dosing: | At least 5 weeks of age. |
| Source: | Charles River Breeding Laboratory, Kingston, N.Y. |
| Acclimation period: | At least one week. |
| Average weight at start of study: | Males: 105 to 110 grams; Females: 87 to 89 grams. |
| Assignment to groups: | Computerized, weight-stratification and random number-based procedure. |
| Diet: | Purina Certified Rodent Chow #5002 (Purina Mills, Inc., Richmond, ID). |
| Access to food: | Available ad libitum in glass jars. |
| Access to water: | Available ad libitum in glass bottles with test material. |
| Method of Identification: | Ear tags. |
| Housing: | Individually in stainless steel cages with wire-mesh bottoms. |
| Environmental Conditions: | |
| Temperature: | Approximately 72°F. Recording frequency not reported. |
| Humidity: | Not reported. |
| Air changes: | 13 air changes per hour. |
| Photoperiod: | 12 hr light/12 hr dark. |

**Route of admin.** : Drinking water
**Exposure period** : 13 weeks
**Frequency of treatment** : Daily
**Post Obs. period** : 4 weeks
**Doses** : 100, 350, 1000 mg/kg bw d
**Control group** : Yes
**NOAEL** : = 350 . mg/kg bw
**LOAEL** : = 1000 . mg/kg bw
**Protocol Guideline** : Specific OECD Guideline not noted. EPA & OECD guidance is referenced. Follows #408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
**Year of Study** : 1992
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | EB 891121 |
| Purity: | 99.4% (96.17% 1-butoxy-2-propanol; 3.23% 2-butoxy-1-propanol) |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Dilution in water. |

**Method** : Four groups of Fischer 344 rats (10/sex/dose level) received propylene glycol n-butyl ether (PnB) in their drinking water at concentrations equivalent to target doses of 0, 100, 350, or 1000 mg/kg-day for 13 weeks. Two additional groups of 10/sex/dose receiving 0 or 1000 mg/kg-d for 13 weeks, were administered untreated water for four weeks following the 13-week exposure period in order to evaluate recovery. Rats were observed for clinical signs of toxicity on a daily basis (week days). Body weights, water, and food consumption were monitored weekly. Functional observational battery evaluations were conducted prior to treatment and at monthly intervals during treatment. Ophthalmological examinations were conducted prior to treatment and at sacrifice. Hematology, electrolytes, and clinical chemistries were evaluated at sacrifice and urinalyses were conducted one week prior to sacrifice. At sacrifice, all control and high dose animals were subjected to complete necropsy and histopathological evaluations. Selected organs evaluated histologically in lower dose subjects included liver, kidneys, adrenal glands, lungs, testes, and, potentially, other target organs identified in high dose animals.

Study Design

| Group | PnB Dose (mg/kg-d) | No./Sex/Dose | Treatment Period (Wks) | Recovery Period (Wks) |
|---|---|---|---|---|
| Group 1 | 0 | 10 | 13 | 0 |
| Group 2 | 100 | 10 | 13 | 0 |
| Group 3 | 350 | 10 | 13 | 0 |
| Group 4 | 1000 | 10 | 13 | 0 |
| Group 5 | 0 | 10 | 13 | 4 |
| Group 6 | 1000 | 10 | 14 | |

* Doses calculated from water consumption.

**Results** : Absolute and relative liver weights were increased in high dose males with no accompanying histopathology. In females at the high dose level, absolute and relative kidney weights were increased with no accompanying histopathology. Slight alterations in clinical chemistries, electrolytes, and hematology also were noted in both sexes at the high dose level. No changes in any other monitored parameters were noted at any dose level. The NOAEL for PnB is 350 mg/kg-day and the LOAEL is 1000 mg/kg-day (for organ weight changes)

Morbidity/Mortality: All rats survived treatment with the test compound.

Clinical signs: None reported.

Food Consumption: Slight decrease in high dose males and females (not statistically evaluated).

Water Consumption: Slight decrease in high dose males and females (not statistically evaluated).

Functional Observational Battery: No behavioral effects noted.

Body weights: Slight decrease (less than 5% but statistically significant) in high dose males on days 21 through day 42. Correlated to reduced water and food intake.

Organ Weights: High-dose males showed increased absolute and relative liver weights. Females showed increased absolute and relative kidney weights. No corresponding histopathology was found in these organs.

Clinical Chemistries/Electrolytes: In high dose males (1000 mg/kg-day), several parameters were statistically different from controls: Sodium (decrease), potassium (increase), chloride (decrease), creatine phosphokinase (increase), urea (increase), and cholesterol (increase). In the mid-dose group (350 mg/kg-day), slight statistically significant changes in sodium (decrease) and potassium (increase) were noted. High dose females showed slightly increased urea and creatine phosphokinase.

Hematology: Statistically decreased red blood cell count and hemoglobin in high-dose (1000 mg/kg-day) males at 13-week sacrifice. Statistically decreased platelet count in high dose females after 13 weeks. Statistically decreased platelet count in high dose recovery males. No corresponding hypertrophy or lesions in bone marrow or spleen for any group.

Urinalysis: No abnormalities noted.

Ophthalmological Examinations: No lesions noted.

Macroscopic Examinations: No lesions noted.

Histological Examinations: No lesions noted.

**Conclusions** : PnB at doses of 1000 mg/kg-d for 13 weeks caused increased absolute and relative liver weights in males and increased absolute and relative kidney weights in females. The authors of the study concluded that the slight decreases in red blood cell count and hemoglobin in high-dose males may be related to decreased water and food consumption. This may also explain the slight decrease in male body weights mid-way through exposures. Clinical chemistry changes, which may be similarly related to food and water consumption, were considered by the authors to be slight and not toxicologically significant. No effects from PnB were found at the lower dose levels of 100 or 350 mg/kg-day. The NOAEL for PnB is 350 mg/kg-day and the LOAEL is 1000 mg/kg-day.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although only referenced generally (i.e., the specific protocol number was not reported, the study and report followed OECD Protocol 408: "Repeated Dose 90-day Oral Toxicity Study in Rodents." The numbers and type of test animals used and their husbandry conditions were as prescribed in the aforementioned guidance. Test material characterization was adequate. The dose of test material complied with guidance, the length of the treatment period (90 days) was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

**References** : Granjean, M., Szabo, J.R. (1992) Propylene Glycol n-Butyl Ether: 13-Week Drinking Water Study in Fischer 344 Rats. Dow Study No. K-005473-007. April 14, 1992. Unpublished.

**Other** : Concentrations of PnB in drinking water were targeted to correspond to nominal doses of 0, 100, 350, or 1000 mg/kg-day. These concentrations were based on anticipated drinking water consumption volumes by the test animals. When the measured concentration of PnB in the treatment water was multiplied by the amount of water actually consumed, the actual dose of PnB was higher than the target doses (by a factor of 10-15%). However, wastage may have occurred that would reduce the dose and offset the 10-15% increased dose factor.

**Source** : Dow Deutschland Inc Stade 5

(16)

**Species** : Rat
**Sex** : male/female

**Strain/Husbandry** : Wistar
**Conditions**

| | |
|---|---|
| Age at dosing: | Approximately 10 weeks of age. |
| Source: | F. Winkelmann, Institute for the Breeding of Laboratory Animals GmbH & Co. KG, Borchen, West Germany. |
| Acclimation period: | Six days. |
| Average weight at start of study: | Males: 249 ± 2.9 grams; Females: 173 ± 1.5 grams. |
| Assignment to groups: | Computerized, random number-based procedure. |
| Diet: | Purina Certified Rodent Chow #5002 (Purina Mills, Inc., Richmond, ID). |
| Access to food: | Available ad libitum in glass jars. |
| Access to water: | Available ad libitum in glass bottles. |
| Method of Identification: | Ear tags. |
| Housing: | Individually in stainless steel cages with wire-mesh bottoms. |
| Environmental Conditions: | |
| Temperature: | 22 ± 2°C. Recording frequency not reported. |
| Humidity: | 40-85%. Recording frequency not reported. |
| Air changes: | 10 air changes per hour. |
| Photoperiod: | 12 hr light/12 hr dark. |

**Route of admin.** : Dermal
**Exposure period** : 13 weeks
**Frequency of treatment** : Once daily, 5 days/week
**Post Obs. period** : None
**Doses** : 0.1, 0.3, 1.0 ml/kg bw d
**Control group** : yes, concurrent vehicle
**NOAEL** : = 880 . mg/kg bw
**Protocol Guideline** : OECD Guideline“411 "Subchronic Dermal Toxicity: 90-day ”tudy"
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | “EH; dated 22-4-’87 (use within one year)” |
| Purity: | “more than 98%” |
| Specific Gravity: | 0.88 kg/l |
| Solubility: | 6% in water; soluble in propylene glycol |
| Storage: | Ambient temperature in the dark. |
| Appearance: | Clear liquid. |
| Administered as: | Dilution in propylene glycol. |

**Method** : Propylene glycol n-butyl ether (PnB) was applied daily (5 days/week) for 13 weeks to the skin of four groups of Wistar rats (10/sex/dose level) at various dilutions in propylene glycol (PG) equivalent to doses of 0 (PG-only; 1.5 ml/kg-day), 0.1, 0.3, or 1.0 ml PnB/kg-day. These doses equate to 0, 88, 264, or 880 mg PnB/kg-day. Treatment solutions were applied to the clipped dorsal trunk of each rat (. Dilutions of PnB in PG resulted in applied volumes of 1.5 to 2.5 ml test solution per kg body weight. Rats wore collars to prevent grooming and ingestion of test material. Solutions were applied unoccluded since the low vapor pressure of PnB and PG precluded evaporative loss. Contact time was 24 hr/day (skin was cleaned shortly before daily treatment).

Rats were observed for clinical signs of toxicity and skin reactions on a daily basis (week days). Body weights and food consumption were monitored weekly. Ophthalmological examinations were conducted in control and high dose subjects prior to treatment and on day 87 of the study. Hematology, clinical chemistries, and urinalyses were conducted at the end of the treatment period. At sacrifice, all animals were subjected to complete necropsy. An extensive list of tissues was preserved from all animals and histopathological evaluations of these tissues were conducted on control and high dose animals.

| Group | PnB Dose (ml/kg-d) | PnB Dose (mg/kg-d) | No./Sex/Dose Group | Treatment Period (wks) |
|---|---|---|---|---|
| Group 1 | 0 | 0 | 10 | 13 |
| Group 2 | 0.1 | 88 | 10 | 13 |
| Group 3 | 0.3 | 264 | 10 | 13 |
| Group 4 | 1.0 | 880 | 10 | 13 |

**Results** : Skin at the site of application showed irritation in all treatment groups including PG-controls. Skin lesions were characterized by focal necrosis of the epidermis, crust formation, mild inflammatory changes and acanthosis. While the severity of these lesions was higher in PnB-treatment groups than in the PG-control, the differences were not statistically significant and did not show a dose-response effect. Untreated skin was unaffected (one mid-dose male and one high-dose male showed “very slight” acanthosis). The authors considered skin lesions to be a direct, local effect from the solvents and the clipping procedure.

No changes were observed in clinical observations, food consumption, body weights, ophthalmology, hematology, clinical chemistries, urinalyses, or gross lesions/histopathology (other than skin). In females at the high dose level, relative but not absolute heart weights were slightly but statistically increased. Because no clinical chemistry or histopathology indicated damage to the heart, the authors considered increased relative weights to be a spurious finding without toxicological significance. This study established a systemic toxicity NOAEL for PnB of 1.0 ml/kg-day (880 mg/kg-day). A LOAEL for systemic toxicity was not established.

**Conclusions** : PnB in a propylene glycol vehicle, applied topically for 13 weeks, caused local skin reactions at the site of application but no systemic toxicity at doses of 0, 0.1, 0.3, and 1.0 ml/kg-day for 13 weeks. These doses correspond to 0, 88, 264, or 880 mg/kg-day. Skin reactions did not exhibit a dose-response and occurred also in the propylene glycol-only, vehicle control group with somewhat less incidence (females only) but equal severity. The systemic toxicity NOAEL for PnB is 1.0 ml/kg-day, or 880 mg/kg-day, and the LOAEL was not established in this study.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report followed OECD Protocol 411: "Subchronic Dermal Toxicity: 90-day Study." The numbers and type of test animals used and husbandry conditions were as prescribed in the aforementioned guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the treatment period (90 days) was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

**References** : Jonker, D., Lina, B.A.R. (1988) Subchronic (13-Week) Dermal Toxicity Study with Propylene Glycol n-Butyl Ether in Rats. TNO Study No. V 87.464/270613. April, 1988. Unpublished.

**Other** : PnB was relatively non-toxic and gave no evidence for hemolytic activity.

**Source** : Dow Deutschland Inc Stade 5

(22)

**Species** : Rabbit
**Sex** : Male/female
**Strain** : New Zealand White

| | |
|---|---|
| Age at dosing: | Not specified. |
| Source: | Not specified. |
| Acclimation period: | Minimum of 7 days. |
| Weight at start of study: | 2381 – 2884 grams. |
| Assignment to groups: | Randomized by weight. |
| Diet: | Not specified. |
| Access to food: | Not specified. |
| Access to water: | Not specified. |
| Method of Identification: | Not specified. |
| Housing: | Not specified. |

Environmental Conditions (for non-exposure periods):

| | |
|---|---|
| Temperature: | Not specified. |
| Humidity: | Not specified. |
| Air changes: | Not specified. |
| Photoperiod: | Not specified. |

**Route of admin.** : Dermal
**Exposure period** : 13 weeks
**Frequency of treatment** : 7 h/d 5 d/w
**Post Obs. period** : None
**Doses** : 0, 11.4, 114, or 1140 µl/kg bw-d; 0, 10, 100, or 1000 mg/kg bw-d
**Control group** : Yes, concurrent vehicle
**NOAEL** : For local skin irritation: 11.4µl/kg bw; 10 mg/kg bw-d
For systemic toxicity: 1140 .µl/kg bw; 1000 mg/kg bw-d
**LOAEL** : For local skin irritation: 114µl/kg bw; 100 mg/kg bw-d
For systemic toxicity: none established.
**Protocol Guideline** : OECD Guideline 411 "Subchronic Dermal Toxicity: 90-day Study"
**Year of Study** : 1987
**GLP** : Yes

**Test substance** : Identity: 1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether. CAS # 29387-86-8 (also 5131-66-8)
Code No.: B0964-01
Lot No.: TM-5-26 (from Olin Chemical).
Purity: 95% 1-butoxy-2-propanol: 5% 2-butoxy-1-propanol.
Specific Gravity: 0.88 kg/l
Solubility: 6% in water; soluble in propylene glycol
Storage: Room temperature & humidity.
Appearance: Clear liquid.
Administered as: Dilution in 50/50 v/v ethanol and water.

**Method** : Propylene glycol n-butyl ether (PnB) was applied daily (5 days/week) for 13 weeks to the skin of four groups of New Zealand White rabbits (5/sex/dose level) at various dilutions in a 50/50 v/v mixture of ethanol and water (vehicle), equivalent to volumetric PnB doses of 0 (vehicle-only), 11.4, 114, or 1140 µl/kg-day (total dose volume of 2 ml/kg-day). These doses corresponded to dilutions of 0, 0.569%, 5.69, or 56.9% (w/v) of PnB in the treatment solution. When adjusted for the density of PnB, the volumetric doses equate to mass doses of 0, 1, 100, or 1000 mg PnB/kg-day. Treatment solutions were applied to the clipped dorsal trunk of each rabbit. Rabbits wore collars to prevent grooming and ingestion of test material. Solutions were applied unoccluded since the low vapor pressure of PnB was assumed to precluded evaporative loss.

Rabbits were observed for clinical signs of toxicity and skin reactions on a daily basis (week days). Body weights were monitored weekly. Hematological evaluations were conducted at the beginning and end of the treatment period. Clinical chemistries, urinalyses, and ophthalmic examinations were not conducted. At sacrifice, all animals were subjected to complete necropsy and organs were weighed. An extensive list of tissues was preserved from all animals and slides were prepared, stained, and examined histopatholgically from the control and high dose animals.

| Group | PnB Dose (µl/kg-d) | PnB Dose (mg/kg-d) | No./Sex/Dose Group | Treatment Period (wks) |
|---|---|---|---|---|
| Group 1 | 0 | 0 | 5 | 13 |
| Group 2 | 11.4 | 10 | 5 | 13 |
| Group 3 | 114 | 100 | 5 | 13 |
| Group 4 | 1138 | 1000 | 5 | 13 |

**Results** : One female from the high dose group and one female from the mid dose group died during the treatment period. These deaths were attributed to enteritis and not related to treatment. Rabbits from various groups showed sporadic anorexia (2 from group and 1 from group 4), hyperactivity (one from group 2), and eye discharge (1 from group 2, 2 from group 3, and 2 from group 4) that did not appear to correlate to treatment.

Skin at the site of application showed irritation only in the two highest dose groups. Skin lesions were characterized by slight erythema in the mid-dose group. In the high dose group, treatment with 114 µl/kg-d PnB produced severe erythema, slight to moderate edema, slight to moderate atonia, moderate desquamation, and slight to moderate fissuring. The authors considered skin lesions to be a direct, local effect from the solvents and the clipping procedure.

No changes were observed in body weights or in absolute or relative organ weights when PnB-treated groups were compared to controls. Females in the mid- and high-dose groups exhibited slight, but generally statistically significant increases, in the related hematological parameters of erythrocyte count, hemoglobin and hematocrit values, as well as mean corpuscular hemoglobin (MCH). Males did not exhibit similar increases. In part the increases in females may be due to the slight decrease in these parameters in the control group when baselines were compared to values at sacrifice. The authors did not ascribe toxicological significance to these changes, nor did they consider the changes related to treatment with the test material.

Micropathological evaluation (EPL Laboratories) indicated test related changes only in the skin treated directly with the test substance (see above).

**Conclusions** : PnB in an ethanol/water (50:50 v/v) vehicle, applied topically for 13 weeks, caused local skin reactions at the site of application (2 highest dose groups only) but no systemic toxicity at doses of 0, 11.4, 114, and 1138 µl/kg-day for 13 weeks. These doses correspond to 0, 10, 100, or 1000 mg/kg-day.

This study established a NOAEL for PnB of 11.4 µl/kg-day (10.0 mg/kg-day) based on skin changes and a LOAEL for this effect of 114 µl/kg-day (100 mg/kg-day). The NOAEL for systemic toxicity is 1138 µl/kg-day (1000 mg/kg-day), if the hematological effects in the females are spurious as concluded by the authors. See comment below under “Other.”

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 2.

| | | |
|---|---|---|
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study report). Because the version of this report evaluated was “sanitized” (as part of a TSCA 8(d) submission to the US EPA), some contents were redacted The report did not included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although not explicitly cited, the study did follow OECD Protocol 411: “Subchronic Dermal Toxicity: 90-day Study.” The numbers and type of test animals used and their husbandry conditions were as prescribed in the aforementioned guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the treatment period (90 days) was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded. |
| **Reference** | : | Anonymous. (1987). 91-Day subchronic percutaneous toxicity. July 13, 1987. Part of a TSCA Section 8(d) submission. Subchronic test conducted at Hazleton Laboratories. NTIS Microfiche No. OTS0520507. EPA ID No. 86-980000466S. |
| **Other** | : | It is noteworthy that a lysing effect on the erythrocyte, as seen with some of the ethylene glycol ethers (particularly the n-butyl ether) decreases some of the hematological parameters (e.g., RBCs, hematocrit, hemoglobin) that were slightly increased in the female subjects from this study. Grossly observable hemoglobinuria, a hallmark of ethylene glycol ether RBC lysis, was not reported in this study (urinalysis not performed). Similarly, no compensatory hyperplastic effects on the marrow, spleen or other blood forming organs were reported at any dose level. Circulating reticulocytes were not increased. |
| **Source** | : | Anonymous TSCA 8(d) Submission. |

(20)

## 5.5 GENETIC TOXICITY ‘IN VITRO‘

| | | |
|---|---|---|
| **Type** | : | Ames test |
| **System of testing** | : | Salmonella/ mammalian-microsome bacterial mutagenicity assay. Strains TA98, TA100, TA1535, TA1537. |
| **Concentration** | : | 5.0, 15.8, 50, 158, 500, 1580, 5000 µg/plate |
| **Cycotoxic conc.** | : | PnB was not toxic to the test organism at concentrations up to and including 5000 µg/plate. |
| **Metabolic activation** | : | With and without |
| **Result** | : | Negative |
| **Protocol Guideline** | : | OECD Guideline 471 "Genetic Toxicology: Salmonella typhimurium Reverse Mutation Assay" |
| **Year of Study** | : | 1987 |
| **GLP** | : | Yes |

| | | | |
|---|---|---|---|
| **Test substance** | : | Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| | | Batch No.: | XZ 95410.00 |
| | | Purity: | >98% |
| | | Supplied as: | Not reported. |
| | | Appearance: | Transparent fluid. |
| | | Administered as: | Various dilutions (see below). |
| | | Specific Gravity: | 0.88 g/ml. |
| | | Solubility: | 6% in water. |
| | | Storage: | At ambient temperature in the dark. |
| | | Stability: | Stable up to 200°C. |

**Method** : Frozen stock cultures of Salmonella typhimurium (from Bruce Ames, U California, Berkeley) were transferred to nutrient rich broth and incubated at 37°C until reaching a pre-specified optical density at 650 nm (108 to 109 cells/ml). This was done for each of the four tester strains (TA98, TA100, TA1535, & TA1537). To optimize contact between the bacteria and PnB, the pre-incubation modification was employed. This entailed 1) mixing PnB, the S-9 activation system (when appropriate), and the bacteria in a tightly capped culture tube, 2) incubating the mixture for 30 minutes at 30°C, 3) adding supplemental top agar, then 4) pouring this mixture onto plates. The plates were then incubated at 37°C for two days during which time histidine independent revertant colonies developed. For strain TA100, PnB concentrations of 0, 5.0, 15.8, 50, 158, 500, 1580, or 5000 µg/plate were tested. Because no toxicity was elicited at any concentration (evidenced by normal background "lawns"), the remaining three strains were tested at the top five concentrations.

Colonies were counted with an Arteck Model 880 colony counter (or manually). Results were considered positive if the number of colonies exceeded twice background for any of the strains at any dose and if a dose-response relationship was observed in any strain, with or without S-9 activation. In addition the positive response had to be reproducible in a second experiment. Results were considered negative if the revertant counts did not exceed background for any tester strain and the negative response is reproducible in a second experiment.

The validity of the assay was assessed by determining that 1) negative and positive control revertant counts fell within historical control counts and 2) toxicity did not interfere with interpretation of results.

**Results** : PnB was not toxic to any strain of the test organism at concentrations up to and including 5000 µg/plate. PnB did not cause mutations in the Ames plate assay with or without S-9 metabolic activation. A repeat experiment with the four tester strains confirmed these results.

**Conclusions** : PnB did not cause mutations in the Ames plate assay with or without S-9 metabolic activation.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed, which were documented in the report. The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell lines used, test substance concentrations and dose spacing (several dose levels including negative control and a high upper dose), time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of plates scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 471 "Bacterial Reverse Mutation Test". The positive control agents gave the expected results showing that the cell line was responsive to reverse mutation.

**References** : Bruce, R.J., Bhaskar Gollapudi, B., Verschuuren, H.G., (1987). Evaluation of propylene glycol n-butyl ether in the Ames Salmonella/Mammalian-microsome bacterial mutagenicity assay. Dow Laboratory Report No. TXT:K-005473-003. November 1987. Unpublished report.

**Other** : Positive control substances were:
Sodium azide, 25 µg/plate, non-activated, strains TA100, TA1535
2-Nitrofluorene, 100 µg/plate, non-activated, TA98,)
ICR-191, 10 µg/plate, non-activated, strain TA1537
2-anthramine, 3 µg/plate, activated, strains TA98, TA100, TA 535, TA1537
Study classification: 1a (Guideline study)

**Source** : Dow Chemical Company

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**Type** : Ames test
**System of testing** : Salmonella/ mammalian-microsome bacterial mutagenicity assay. Strains TA98, TA100, TA1535, TA1537, TA1538.
**Concentrations** : 0, 1.0, 3.3, 6.7, 10, 20 µl/plate. Assuming a specific gravity for PnB of 0.88, these doses are equivalent to: 0, 0.88, 2.9, 5.9, 8.8, or 17.6 mg/plate or 0, 880, 2900, 5900, 8800, or 17600 µg/plate.
**Cycotoxic conc.** : PnB was not toxic to the test organism at concentrations up to and including 20 µl/plate. 20 µl/plate was the highest dose tested both in a dose range-finding study and in the main studies.
**Metabolic activation** : With and without Aroclor-induced rat liver S-9 homogenate
**Result** : Negative
**Protocol Guideline** : OECD Guideline 471 "Genetic Toxicology: Salmonella typhimurium Reverse Mutation Assay"
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | B0964-01 |
| Purity: | Not specified. |
| Supplied as: | Not specified. |
| Appearance: | Clear liquid. |
| Administered as: | Various dilutions (see below). |
| Specific Gravity: | Not specified. |
| Solubility: | Not specified. |
| Storage: | Room temperature. |
| Stability: | Not specified. |

**Method** : Frozen stock cultures of Salmonella typhimurium (from Bruce Ames, U California, Berkeley) were transferred to nutrient rich broth and incubated at 37°C until reaching a pre-specified optical density at 650 nm (108 to 109 cells/ml). This was done for each of the five tester strains (TA98, TA100,

TA1535, TA1537, & TA1538). DMSO was used as a vehicle solvent.

Results were considered positive if the number of colonies exceeded twice background for any of the strains at any dose and if a dose-response relationship was observed in any strain, with or without S-9 activation. In addition the positive response had to be reproducible in a second experiment. Results were considered negative if the revertant counts did not exceed background for any tester strain and the negative response is reproducible in a second experiment.

The validity of the assay was assessed by determining that 1) negative and positive control revertant counts fell within historical control counts and 2) toxicity did not interfere with interpretation of results.

**Results** : Results for all but strain TA1535 were negative with or without activation. With activation, results were negative for strain TA1535. In the first assay without activation, the highest concentration of 20 µl/plate did not quite reach twice background. Because it was close, however, the assay was repeated a second time with TA1535 (without activation). In this second assay, the highest concentration produced 2.2 times the background concentration. In a third assay in TA1535 without activation, the highest concentration did not produce twice background (31 colonies vs. 20 for the control) but the second highest concentration produced 2.2 time the control revertant rate (44 colonies vs. 20 for controls). Because these rates were so low and not reproducible and because a clear dose-response was not evident, these results were considered negative.

**Conclusions** : PnB did not produce a positive response in this Ames test.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed, which were documented in the report. The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell lines used, test substance concentrations and dose spacing (several dose levels including negative control), time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of plates scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 471 "Bacterial Reverse Mutation Test". The positive control agents gave the expected results showing that the cell line was responsive to reverse mutation.

**References** : Lawlor, T., Kirby, P.K., Innis, J.D., (1987). Salmonella/mammalian-microsome mutagenesis assay (Ames test): B0964-01, Propylene glycol monobutyl ether (29387-86-8). NTIS Microfiche No. OTS0572348, US EPA No. 86-940000245. Microbiological Associates Lab. Study No. T5294.501. Unpublished report.

**Other** : The response was also negative in the Dow-sponsored Ames assay.
**Source** : Protor and Gamble Company

(45)

**Type** : In vitro L5178Y TK+/- Mouse Lymphoma Cell Assay
**System of testing** : Mouse lymphoma cells deficient in thymidine kinase (-/-) may grow in the presence of the cell inhibitor, trifluorothymidine (TFT). A mutation from L5178Y TK+/- to -/- permits cell growth in the presence of TFT and detection of agents that cause this mutation.

| | | |
|---|---|---|
| **Concentration** | : | Up to 6000 microG/ml |
| **Cycotoxic conc.** | : | 5000 ug/ml and above. |
| **Metabolic activation** | : | With and without Aroclor-induce rat S-9 supernatant. |
| **Result** | : | Negative |
| **Protocol Guideline** | : | No specific protocol guidelines were mentioned in the report. However, EPA and OECD guidelines were cited as having been followed. OECD Guideline 476 “In Vitro Mammalian Cell Gene Mutation Test“ was followed (see “Quality Check“). |
| **Year of Study** | : | 1987 |
| **GLP** | : | Yes |
| **Test substance** | : | Identity: 1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether. CAS # 29387-86-8 (also 5131-66-8)<br>Batch No.: B0964-01<br>Purity: Not specified.<br>Solubility in water: 6%.<br>Appearance: Clear liquid.<br>Source: Proctor and Gamble Co.<br>Administered as: Dilution in culture medium. |
| **Method** | : | T5178Y TK+/- lymphoma cells in logarithmic growth phase, grown to a density of 1 x 106 cells/ml, were used in the assay. To determine the doses to be used in the mutation assay, a range-finding cytotoxicity assay was first performed with PnB concentrations of 100, 50, 10, 5.0, 1.0, 0.5, 0.1, 0.05, 0.01, or 0.005 µl PnB/ml. From results of the cytotoxicity assay, concentrations of 5.0, 4.0, 3.5, 2.5, 2.0, 1.5, 1.0, or 0.5 µl/ml were employed for both the activation and non-activation phases of the main mutation assay. Appropriate solvent controls were used as were positive control agents. In the activation phase, dimethylbenzanthracene (DMBA), diluted in acetone, was the positive control agent and ethylmethanesulfonate (EMS) in DMSO was the positive control in the non-activation phase.<br><br>In the mutation assay, cells were exposed in duplicate test tubes to PnB at the concentrations described above for 4 hours in a roller drum at 37°C in an atmosphere of 5% CO2 and 95% air. A second identical set of test tubes was prepared containing S-9 metabolic activation system (from Aroclor 1254-induced rat liver). After incubation, cells were pelleted by centrifugation, rinsed twice, resuspended in medium, and incubated for 20 and 44 hours to allow for expression of potential mutations. After adjusting cell density, cells were incubated in cloning medium to select for -/- revertants not inhibited by the presence of the cell growth inhibitor, trifluorothymidine (TFT). Cells were then plated on medium containing TFT and incubated at 37°C for 10 to 12 days to allow for expression of -/- colonies. At the end of this period, colonies were enumerated for each plate using an automatic colony counter. |
| **Results** | : | In the range finding toxicity test, no growth occurred at PnB concentrations of 5 µl/ml and above, with or without S-9.<br><br>In the first mutation assay, no increase in revertant frequencies were observed in cells treated with PnB, with or without metabolic activation. Cells at all PnB concentrations exhibited acceptable relative growth. For the EMS positive control (without activation), revertants were within historical ranges for the laboratory. However, for the DMBA control, revertants were below normal. Therefore, a repeat, second assay, only with S-9 activation, was undertaken. Results from this second assay showed DMBA revertant rates that were ~8-fold higher than solvent controls. Again, revertant rates for PnB samples were no higher than concurrent negative controls. |

**Conclusions** : PnB is not mutagenic in the in vitro L5178Y +/- mouse lymphoma assay under the conditions of this test.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed, which were documented in the report. The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell line used, test substance concentrations and dose spacing, time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of cells scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 476 “In Vitro Mammalian Cell Gene Mutation Test.“

**References** : Kirby, P.E., Pant, K.J., Brauminger, R.M., Melhorn, J.M., Law, L.C., (1987). Test for chemical induction of mutation in mammalian cells in culture: The L5178Y TK+/- mouse lymphoma assay, B0964-01. Propylene glycol monobutyl ether (29387-86-8). Sitek Study Number 0048-2400. March 5, 1987. Unpublished report.

**Other** : These results are consistent with other propylene glycol ethers.

**Source** : Proctor and Gamble Company

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**Type** : In Vitro Unscheduled DNA Synthesis
**System of testing** : Autoradiography method of evaluating unscheduled DNA synthesis (via increased 3H-thymidine uptake) in primary rat hepatocytes.
**Concentration** : Up to 6000 microG/ml
**Cycotoxic conc.** : 5000 ug/ml and above.
**Result** : Negative
**Protocol Guideline** : No specific protocol guidelines were mentioned in the report. However, EPA and OECD guidelines were cited as having been followed. OECD Guideline 482 “Genetic Toxicology: DNA Damage and Repair/Unscheduled DNA Synthesis in Mammalian Cells in vitro“ was followed (see “Quality Check“).
**Year of Study** : 1986
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | 1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether. CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | B0964-01 |
| Purity: | not specified. |
| Solubility in water: | 6%. |
| Appearance: | Clear liquid. |
| Source: | Proctor and Gamble Co. |
| Administered as: | Dilution in culture medium. |

**Method** : 2.5 x 105 cells of freshly collected rat (Sprague-Dawley) hepatocytes were seeded onto 35 mm tissue culture plates. Six replicate plates were seeded per concentration level. Three replicates were used to evaluate cytotoxicity and three replicates were used to evaluate unscheduled DNA synthesis. Dimethylbenzanthracene (DMBA) was used as the positive control agent and appropriate negative solvent controls were also employed. Prior to this a cytotoxicity assay was conducted to determine doses for the main assay. In the main assay, eight concentrations of PnB were evaluated: 0.0, 0.01

(0.01 apparently not a misprint), 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, or 0.80 µl PnB per ml medium. Cells were exposed to PnB and 3H-thymidine for 18 hours at 37°C. Cells were then washed, fixed, affixed to slides, and a photosensitive emulsion was applied to detect 3H-thymidine incorporated into nuclear material. The three highest concentrations produced relative toxicities in excess of 75% and, therefore, were not scored. Fifty nuclei from healthy appearing cells were scored "blind" for UDS per test concentration. The average net number of nuclear grain counts (minus background) per dose level (2 slides per dose level) were recorded. Also recorded for each dose level were the number of nuclei with 5 or more grain counts.

**Results** : Nuclear grain counts were not increased in PnB treated cells at any dose level, indicating that PnB does not induce unscheduled DNA synthesis. The positive control agent, DMBA, showed the expected increase in nuclear grain counts.

**Conclusions** : PnB does not induce unscheduled DNA synthesis under the conditions of this test.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed, which were documented in the report. The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cells used, their derivation, test substance concentrations and dose spacing, time exposed to the test and control agents, positive control agents used, number of replicates, the number of cells scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 482 "Genetic Toxicology: DNA Damage and Repair/Unscheduled DNA Synthesis in Mammalian Cells in vitro."

**References** : Thilagar, A., Pant, K.J., Brauninger, R.M., Melhorn, J.M., Law, L.C., (1986). Test for chemical induction of unscheduled DNA synthesis in primary cultures of rat hepatocytes (by Autoradiography) B0964-02, propylene glycol monobutyl ether (29387-86-8). Sitek Study number 0048-5100. December 23, 1986. Unpublished report.

**Other** : These results are similar to other propylene glycol ethers.
**Source** : Proctor and Gamble Company

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**Type** : Cytogenetics assay
**System of testing** : In vitro chromosomal aberration assay with Chinese Hamster Ovary (CHO) cells
**Concentration** : 500, 1667, 5000 ug PnB/ml culture medium
**Cycotoxic conc.** : None established at 5000 ug/ml
**Metabolic activation** : with and without Aroclor-induced rat liver S-9 supernatant
**Result** : Negative
**Protocol Guideline** : No specific protocol guidelines were mentioned in the report. However, OECD Guideline 473 "Genetic Toxicology: In Vitro Mammalian Cytogenetic Test" was followed (see "Quality Check").
**Year of Study** : 1988
**GLP** : Yes

**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-PnB (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | EH Sample No. 25611 |
| Purity: | 99.5% |
| Solubility in water: | 6%. |
| Appearance: | Clear liquid. |
| Source: | Dow Chemical G.m.b.H Stade, Federated Republic of Germany. |
| Administered as: | Dilution in culture medium. |

**Method** : Chinese Hamster Ovary (CHO-K1) cells in logarithmic growth phase were tyrpsinized and plated in medium containing 10% serum at a density 2 x 105 cells/60 mm petri dish (2 x 102 for toxicity assay). After 26 hours, the medium was changed to new medium (2.5% serum) containing the test or control agents, with or without the S-9 supernatant metabolic activation system (from Aroclor 1254-induced rats). Cells were exposed to test material (4 concentrations; 0, 500, 1667, or 5000 ug PnB/ml culture medium) and control agents for 4 hours at 37°C. Positive control agents were: ethylmethanesulfonate (EMS) without the activation system and cyclophosphamide (CP) with the activation system. At the end of 4 hours, cells were removed from the test and control agents by washing with phosphate-buffered saline and then maintained in culture medium (10% serum) until harvest. Duplicate cultures of each of the four dose levels of the test material-exposed cells and of the positive control agent-exposed cells were harvested 18 hours after exposure. Two hours prior to harvest, cells were arrested in metaphase by addition of Colcemid. At harvest, cells were trypsinized, swollen by hypotonic treatment, fixed on slides and stained with Giemsa. Mitotic indices were computed by dividing the number of cells in metaphase by 500 cells examined (per replicate) and expressing this number as a percentage. 50 cells in metaphase per duplicate (total of 100) at each dose level (including positive controls) were examined for chromosomal aberrations. Structural chromosomal abnormalities that were scored included chromatid and chromosome gaps, chromatid breaks and exchanges, chromosome breaks and exchanges, and chromosomal disintegration. Chromatid and chromosome gaps were not included in the number of total aberrations.

**Results** : Results are shown in the table below:

| Dose Level (ug/ml) | With/without S-9 | Cytotoxicity | Aberrations |
|---|---|---|---|
| 0 PnB | ± | Negative | Negative |
| 500 PnB | ± | Negative | Negative |
| 1667 PnB | ± | Negative | Negative |
| 5000 PnB | ± | Negative | Negative |
| 1242 EMS | - | N/A | Positive |
| 14 CP | + | N/A | Positive |

**Conclusions** : Propylene glycol n-butyl ether did not cause cytotoxicity or chromosomal aberrations under the conditions of this test. The NOAEL is 5000 ug/ml and no LOAEL was established.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were documented in the study report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell line used, test substance concentrations and dose spacing (4 dose levels including negative control, with highest being 5000 ug/ml), time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of cells scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test". The positive control agents gave the expected results showing that the cell line was appropriately responsive to chromosomal aberration insult.

**References** : Bhaskar Gollapudi, B., Linscombe, V.A., Verschuuren, H.G., (1988). Evaluation of propylene glycol n-butyl ether in an in vitro chromosomal aberration assay utilizing Chinese Hamster Ovary (CHO) Cells. Dow Chemical Company Report Number TXT:K-005473-002. January 1988. Unpublished report.

**Other** : Cultures treated with 1242 ug/ml ethylmethanesulfonate and 14 ug/ml cyclophosphamide served as positive controls for the non-activation and activation assays, respectively. Negative control cultures were treated with culture medium (the solvent used to dissolve the test material). No cytotoxicity was detected at the highest concentration tested (5000 ug). The medium was tested for pH and osmolality and was found to be within normal limits at the highest concentration of test material.

**Source** : Dow Deutschland Inc Stade 5

(5)

**Type** : Cytogenetics assay
**System of testing** : In vitro chromosomal aberration assay with Chinese Hamster Ovary (CHO) cells
**Concentration** : With S-9: 0, 2600, 3400, or 4500 ug PnB/ml culture medium
Without S-9: 0, 3400, 4500, or 6000 ug PnB/ml culture medium
**Cycotoxic conc.** : 6000 ug/ml
**Metabolic activation** : With and without Aroclor-induced rat liver microsomal S-9 supernatant
**Result** : Negative
**Protocol Guideline** : No specific protocol guidelines were mentioned in the report. However, EPA and OECD guidelines were cited as having been followed. OECD Guideline 473 "Genetic Toxicology: In Vitro Mammalian Cytogenetic Test" was followed (see “Quality Check“).
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | 1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether. CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | B0964-01 |
| Purity: | 99.5% |
| Solubility in water: | 6%. |
| Appearance: | Clear liquid. |
| Source: | Proctor and Gamble Co. |
| Administered as: | Dilution in culture medium. |

**Method** : Chinese Hamster Ovary cells in logarithmic growth phase were tyrpsinized and plated in (Ham’s F-12 nutrient) medium supplemented with 10% serum. After 16-24 hours, the medium was changed to new medium (2.5% serum) containing the test or control agents, with or without the S-9 supernatant metabolic activation system (from Aroclor 1254-induced rats). Cells were exposed to test material, with or without S-9 rat liver

homogenate, at nine logarithmically spaced concentrations ranging from 0.6 to 6000 ug PnB/ml culture medium and control agents for 4 hours at 37°C. Based upon cytotoxicity, the dose levels selected for scoring (i.e., with scorable metaphases) were: 0, 3400, 4500, and 6000 ug/ml without S-9 activation and 0, 2600, 3400, and 4500 ug/ml with S-9 metabolic activation. A negative control sample with distilled water was included. Positive control agents were: triethylenemelamine (TEM) without the activation system and cyclophosphamide (CP) with the activation system. At the end of 4 hours, cells were removed from the test and control agents by washing with phosphate-buffered saline and then maintained in culture medium (10% serum) until harvest. Based upon average cell generation times, duplicate cultures of each of the selected dose levels of the test material-exposed cells and of the positive control agent-exposed cells were harvested after exposure (8 and 12 hours for the nonactivated samples and 12 and 20 hours for the activated samples). Two hours prior to harvest, cells were arrested in metaphase by addition of Colcemid. At harvest, cells were trypsinized, swollen by hypotonic treatment, fixed on slides and stained with Giemsa. Mitotic indices were computed by dividing the number of cells in metaphase by 500 cells examined (per replicate) and expressing this number as a percentage. 50 cells in metaphase per duplicate (total of 100) at each dose level (including positive controls) were examined for chromosomal aberrations. Structural chromosomal abnormalities that were scored included chromatid and chromosome gaps, chromatid breaks and exchanges, chromosome breaks and exchanges, and chromosomal disintegration. Chromatid and chromosome gaps were not included in the number of total aberrations.

**Results** : Propylene glycol n-butyl ether did not cause claustogenic damage to nuclear material in rat hepatocytes at any dose level, with or without metabolic activation.

**Conclusions** : PnB does not induce chromosomal aberrations under the conditions of this test. The NOAEL is 6000 ug/ml without activation and 4500 ug/ml with activation. The latter doses was the highest scored since higher doses caused toxicity.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed, which were documented in the study report. The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell line used, test substance concentrations and dose spacing (4 dose levels including negative control, with highest being 6000 ug/ml), time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of cells scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test". The positive control agents gave the expected results showing that the cell line was appropriately responsive to chromosomal aberration insult.

**References** : Putman, D.L., (1987). Cytogenicity study – Chinese hamster ovary (CHO) cells in vitro (modified). Test Article B0964-01. Propylene glycol monobutyl ether (29387-86-8). Microbiological Associates Laboratory Study No. T5294.33B. March 25, 1987. Unpublished report.

**Other** : These results are consistent with other propylene glycol ethers.

**Source** : Proctor & Gamble Company

(43)

## 5.6 GENETIC TOXICITY 'IN VIVO'

**Remark** : No studies
**Source** : Dow Deutschland Inc Stade 5

## 5.7 CARCINOGENITY/CHRONIC TOXICITY

Propylene glycol methyl ether (surrogate chemical)

**Type** : Chronic Toxicity/Carcinogenicity (inhalation in rats and mice)
**Species** : Rats and mice

Fischer 344 Rats
Age at dosing: 6-8 weeks.
Source: Charles River (Portage, MI).
Acclimation period: 7 days.
Weight at start of study: 143 g (males); 117 g (females).
Assignment to groups: Randomized by weight.
Diet: Certified Rodent Chow #5002 (Purina Mills, Inc., St Louis, MO).
Access to food: Ad libitum except during inhalation exposures.
Access to water: Ad libitum.
Method of Identification: Implanted microchip.
Housing: 2 per stainless steel wire-mesh cage.
Environmental Conditions (for non-exposure periods):
Temperature: 22 ± 2°C.
Humidity: 40-60%.
Air changes: 12/hr.
Photoperiod: 12 hr light/12 hr dark.

B6C3F1 Mice
Age at dosing: 6-8 weeks.
Source: Charles River (Portage, MI).
Acclimation period: 14 days.
Weight at start of study: 24 g (males); 17 g (females).
Assignment to groups: Randomized by weight.
Diet: Certified Rodent Chow #5002 (Purina Mills, Inc., St Louis, MO).
Access to food: Ad libitum except during inhalation exposures.
Access to water: Ad libitum.
Method of Identification: Implanted microchip.
Housing: 2 per stainless steel wire-mesh cage.
Environmental Conditions (for non-exposure periods):
Temperature: 22 ± 2°C.
Humidity: 40-60%.
Air changes: 12/hr.
Photoperiod: 12 hr light/12 hr dark.

**Sex** : Males and females
**Strain** : Rats: Fischer 344
Mice: B6C3F1
**Route of admin.** : Vapor Inhalation (whole-body)
**Exposure period** : Lifetime with interim sacrifices
**Frequency of treatment** : 6 hr/day, 5 days/week

**Post Obs. period** : None
**Exposure levels** : 0, 300, 1000, or 3000 ppm
**Control group** : Air-only
**NOAEL** : Rats: 300 ppm based on altered hepatocellular foci in males.
Mice: 1000 ppm based on slight body weight decreases in both sexes.

**LOAEL** : Rats: 1000 ppm based on altered hepatocellular foci in males.
Mice: 3000 ppm based on slight body weight decreases in both sexes.

**Protocol Guideline** : Meets requirements of US EPA Health Effects Test Guidelines OPPTS 870.4300: "Combined Chronic Toxicity/Carcinogenicity" and OECD Guideline for Testing of Chemicals 453 "Combined Chronic Toxicity/Carcinogenicity Studies"

**Year of Study** : 1999 (in-life completion)
**GLP** : Yes
**Test substance** : Propylene glycol methyl ether (PGME) as surrogate for propylene glycol n-butyl ether

| | |
|---|---|
| Identity: | 1-methoxy-2-hydroxypropane or propylene glycol methyl ether. CAS # 107-98-2 |
| Source: | Dow Chemical Company (Midland, MI) |
| Lot No.: | Not specified. |
| Purity: | >97% 1-methoxy-2-propanol: <3% 2-methoxy-1-propanol (> 99.96% both isomers combined). |

**Method:** : In a chronic toxicity/carcinogenicity study, Fischer rats and B6C3F1 mice (50/sex/exposure level) were exposed to vapor concentrations of propylene glycol methyl ether (PGME) at concentrations of 0, 300, 1000, or 3000 ppm 6 hr/day, 5 days/wk for 2 years. Over the course of the study, these subjects were evaluated for clinical signs and body weights. At the end of two years, survivors were subjected to clinical chemistry and hematological examinations, urinalyses, determination of body organ weights, and histopathological examination of a large number of tissues.

In order to evaluate potential toxicity at interim time intervals during the exposure period, additional subjects were exposed to PGME vapors and subjected to routine and specialized toxicological tests at the times shown in the experimental design table below. Subchronic toxicity (at 13 weeks) was evaluated in 5 to 10 mice/sex/exposure level that included clinical chemistry and hematology evaluations, urinalyses, and determination of histopathological changes.

Specialized tests conducted in both mice and rats at the time intervals shown in the table included evaluation of 1) cell proliferation in liver and kidneys, 2) hepatic mixed function oxidase (MFO) activity, and 3) $\alpha_2\mu$-globulin nephropathy.

Study Design:

Summary Chronic Study (with mechanistic substudies), Number of Rats (R) and Mice (M) per exposure level (males/ females)

| | | 6 mos | | 12 mos | | 18 mos | | 24 mos | |
|---|---|---|---|---|---|---|---|---|---|
| ppm | Group * | R | M | R | M | R | M | R | M |
| 0 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | D | 5/0 | -- | 5/0 | -- | -- | -- | | |
| 300 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | -- | -- | -- | -- | -- | -- | -- | -- |
| | D | 5/0 | -- | 5/0 | -- | -- | -- | -- | -- |
| 1000 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | -- | -- | -- | -- | -- | -- | -- | -- |
| | D | 5/0 | 5/0 | 5/0 | -- | -- | -- | -- | -- |
| 3000 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | D | 5/0 | -- | 5/0 | -- | -- | -- | -- | -- |

* Group A: routine study, Group B: cell proliferation in liver and kidneys, Group C: Hepatic MFO induction, Group D: α2µ-g nephropathy evaluation.

Table reproduced from chronic portion of Spencer et al. (46)

**Methods (continued)** : Atmospheres of PGME were generated by metering the test material into a glass J-tube assembly through which compressed, heated air was channeled. Evaporated PGME in the heated air was diluted with room temperature air to the desired concentration at a flow rate of 2900 liters per minute into whole-body inhalation chambers. Airflow in the chambers was maintained at a level that provided approximately 12 changes/hour and normal oxygen concentration. PGME concentrations were measured from the breathing zone of the animals inside the chambers two times per hour using a Miran 1A infrared spectrophotometer. Analytical concentrations were within 0.5% of nominal concentrations throughout the study.

**Results** : Some results from additional, shorter-term studies are discussed in Spencer et al. (46), and not in this chronic toxicity/carcinogenicity section.

At 3000 ppm, both mice and rats exhibited decreased activity, incoordination, and transient sedation during the first week of exposure. Subjects recovered 1-2 hours after removal from the chambers. These signs disappeared in both species after the second week but returned in rats 12-18 months into the study. Mortality was unaffected until 18 months when males but not females of both species showed higher mortality rates that were not ascribable to any particular cause. During the course of the study, body weights in both species were decreased at the 3000 ppm exposure level. These decreases were not large but were statistically significant in all but male rats. Decreased body weights also occurred in mice at the 1000 ppm level. Despite changes during the study, body weights were not statistically different from controls at terminal sacrifice.

No clinical chemistry changes were evident in the subchronic mouse

evaluation. In the chronic study, no hematology or urinalysis changes were evident in either species. However, several clinical chemistry parameters in male rats exposed to 3000 ppm PGME were altered at the 24 month sacrifice: creatinine increased 78% and urea nitrogen increased 100%. Serum alkaline phosphatase was increases as well and earlier, at 6 through 24 months at the 3000 ppm level, and at 1000 ppm, at 24 months in male rats. Changes in SGOT (AST) and SGPT (ALT), which could be associated with liver injury, were mildly and inconsistently increased in male rats during the first year of exposure at 3000 ppm but not after. No histological changes accompanied these effects. Liver weights were increased at 3000 ppm in both sexes of both species. Kidney weights were increased at this exposure level only in rats.

**Results (continued)** : Dark foci in the liver were grossly observable in male rats exposed to 1000 and 3000 ppm PGME after 24 months. These subjects also exhibited eosinophilic hepatocellular foci and cystic degeneration microscopically that was not reported in female rats or mice of either sex. Male rats and, to a lesser extent, male mice showed increased S-phase DNA synthesis when exposed to 3000 ppm PGME. This effect was not pronounced (reported in a separate, 2-week study), and was evident to a lesser extent in female rats. MFO activity was increased in the livers of rats and mice exposed to 3000 ppm PGME.

In the kidney, histopathology revealed that male rats had $\alpha_2\mu$-globulin nephropathy as is typical for this strain. The incidence and severity of this condition was increased in males exposed to 1000 and 3000 ppm PGME compared to controls. No increase in renal epithelial tumors was observed in rats or mice.

**Conclusions** : The major changes seen in this study were 1) decreased body weights in both species, 2) liver effects including increased weight, increased MFO activity and increased cell proliferation primarily in males of both species, 3) kidney effects (in rats) of $\alpha_2\mu$-globulin nephropathy typical of the Fischer 344 strain, and 4) slightly increased mortality occurring only after 18 months of exposure in males of both species. Clinical chemistry parameters reflected and corroborated these effects.

Rats exhibited a NOAEL of 300 ppm based on altered hepatocellular foci in males. Mice showed a NOAEL of 1000 ppm based on slight body weight decreases in both sexes. The LOAELS were correspondingly higher.

No carcinogenic effect as evidenced by any increase in tumor incidence, even in kidneys of the male rats, occurred from exposure to PGME at any concentration in either species.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed, which were documented in the study report. The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The test system used, test substance concentrations and dose spacing (3 dose levels including negative control), time exposed to the test agent, the number of subjects used, the toxicity endpoints monitored, and scoring criteria all followed or exceeded guidance as specified in US EPA Health Effects Test Guidelines OPPTS 870.4300: “Combined Chronic Toxicity/Carcinogenicity” and OECD Guideline for Testing of Chemicals 453 “Combined Chronic Toxicity/Carcinogenicity Studies”.

| | | |
|---|---|---|
| **References** | : | Spencer, P.J., Crissman, J.W., Stott, W.T., Corley, R.A., Cieszlak, F.S., Schumann, A.M., Hardisty, J.F. (2002). Propylene glycol monomethyl ether (PGME): Inhalation toxicity and carcinogenicity in Fischer 344 rats and B6C3F1 mice. Accepted for publication in *Toxicologic Pathology*, January 2002. |
| **Other** | : | Since no chronic or carcinogenicity studies have been conducted with PnB, PGME is used in this report as a representative surrogate chemical. |
| **Source** | : | Dow Chemical Company |

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## 5.8 TOXICITY TO REPRODUCTION

| | | |
|---|---|---|
| | | Propylene glycol methyl ether (surrogate chemical) |
| **Study Type** | : | 2-Generation Reproduction |
| **Species/strain** | : | Mouse/CD-1 |
| **Sex** | : | Male and Female |
| **Route of Admin.** | : | Oral (drinking water) |
| **Exposure Period** | : | Before mating, through gestation, and post-birth. |
| **Treatment Frequency** | : | Daily |
| **Post-exposure observ.** | : | Not reported. |
| **Premating exposure** | : | 7 days for males and females. |
| **Exposure Levels** | : | 0, 0.5, 1.0, or 2.0 percent in drinking water |
| **Control Group** | : | Yes, water |
| **NOAEL Patenal** | : | 1% |
| **NOAEL F1 Offspring** | : | 1% |
| **NOAEL F2 Offspring** | : | 1% |
| **Protocol Guideline** | : | Not specified. |
| **Year of Study** | : | 1997 |
| **GLP** | : | Not specified. |
| **Test Substance** | : | Details not provided. |
| **Method** | : | Details not provided. The publication describing results was a summary of 90 studies on a variety of chemical substances conducted by the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP). Only a two-page summary of results was provided for PM. The methodology cited was the “RACB protocol” after Morrissey et al., Fundam Appl Toxicol. 13:747-777. |
| **Results** | : | The referenced study is an abstract. There were no changes in body weight or food consumption in any of the first generation exposure groups except for a 4% reduction in pup weight at the highest dose tested. In the second generation exposure groups, reductions in male and female body weight were noted (14% reduction during nursing; 8% reduction in body weight in males during and after mating, and epididymus and prostate weights were 9 and 8% below controls in males, respectively). There was no evidence of reproductive toxicity; mating and fertility indices, and the number and viability of F1 and F2 offspring were not affected. Among F1 offspring, mean pup weight was decreased in the 2% group. F2 offspring from the 2% group displayed reduced pup weight at birth, which continued postnatally during nursing. At sacrifice, female body weights in the 2% group were lower than controls; absolute testis, and relative epididymis and prostate weights were also reduced. F1 female body-weight-adjusted liver weights were increased. |
| **Conclusions** | : | NOAELs occurred at the 1% level. Effects seen did not include reproductive toxicity related to mating, fertility indices, or offspring viability. The effects on parental organ weights (epididymis and prostate) may have |

been secondary to body weight decreases which paralleled these decreases in magnitude.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study appeared to follow modern guidance.

**Reference** : Chapin RE and Sloane RA (1997) Environ Health Perspect , 105 (Suppl 1), 233-234.

**Other** : N/A
**Source** : Dow Chemical Co.

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Propylene glycol methyl ether (surrogate chemical)

| | | |
|---|---|---|
| **Study Type** | : | 2-Generation Reproduction |
| **Species/strain** | : | Rat/Sprague-Dawley |
| **Sex** | : | Male and Female |
| **Route of Admin.** | : | Inhalation (whole-body) |
| **Exposure Period** | : | Before mating, through gestation, and post-birth. |
| **Treatment Frequency** | : | 6 hr/day |
| **Post-exposure observ.** | : | Not reported. |
| **Premating exposure** | : | 5 days/week prior to mating; 7 days/week post mating |
| **Exposure Levels** | : | 0, 300, 1000, or 3000 ppm (0, 1,622, 5,407, 16,220 mg/m3) |
| **Control Group** | : | Yes, air-only. |
| **NOAEL Patenal** | : | 300 ppm (1,622 mg/m3) |
| **NOAEL F1 Offspring** | : | 1000 ppm (5,407 mg/m3) |
| **NOAEL F2 Offspring** | : | 1000 ppm (5,407 mg/m3) |
| **Protocol Guideline** | : | OECD 416. |
| **Year of Study** | : | 1997. |
| **GLP** | : | Yes. |
| **Test Substance** | : | Identity: 97.99% - 98.07% 1-methoxy-2-hydroxypropane or propylene glycol methyl ether (alpha isomer). CAS # 107-98-2<br>1.86% –1.90% 2-methoxy-1-hydroxypropane or propylene glycol methyl ether (beta isomer). |
| | | Source: Dow Chemical Company (Midland, MI) |
| | | Lot No.: MM950417. |
| | | Purity: See above. Impurities: none detected at >0.1% |

**Method** : In a 2-generation reproductive toxicity study by Carney et al. (1999) exposed Sprague-Dawley rats (30/sex/exposure level) to 0, 300, 1000, or 3000 ppm (0, 1,622, 5,407, 16,220 mg/m3) PM 6 hr/day, 5 days/wk prior to mating and 7 days/week during mating, gestation and lactation, for two generations.

**Results** : At 3000 ppm (16,220 mg/m3), toxicity in the P1 and P2 adults was marked, as evidenced by sedation during and after exposure for several weeks, and mean body weights which were as much as 21% lower than controls. This marked parental toxicity was accompanied by lengthened estrous cycles, decreased fertility, decreased ovary weights, reduced pup survival and litter size, slight delays in puberty onset, and histologic changes in the liver and thymus of the F1 and F2 offspring. At 3000 ppm (16,220 mg/m3), there was an increase in histologic ovarian atrophy in P1 and P2 females, and at 1000 ppm (5,407 mg/m3), there was a decrease in pre-mating body weight in the P1 and P2 females. No treatment-related differences in sperm counts or motility were observed among the P1 or P2 males.

**Conclusions** : The NOAEL for paternal toxicity is 300 ppm (1,622 mg/m3) and for offspring toxicity is 1000 ppm (5,407 mg/m3). Effects appear secondary to parental weight loss.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : The protocol followed OECD 416.

**Reference** : Liberacki AB et al. (1997) Propylene glycol monomethyl ether: Two-generation inhalation reproduction study in Sprague-Dawley rats. Dow Chemical Company. Unpublished report

Carney, E.W., Crissman, J.W., Liberacki, A.B., Clements, C.M., Breslin, W.J., (1999). Assessment of adult and neonatal reproductive parameters in Sprague-Dawley rats exposed to propylene glycol monomethyl ether vapors for two generations. Toxicol. Sci. 50:249-258.

**Other** : The nature of the reproductive/neonatal effects and their close individual correlation with decreased paternal body weights suggest that these effects were secondary to general toxicity and/or nutritional stress. No such effects were observed at 1000 ppm (5,407 mg/m3), a concentration which caused less marked, but significant body weights effects without sedation. Assume complete vapor atmosphere (no aerosol) up to 3000 ppm for PM.

**Source** : Dow Chemical Company.

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## 5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

**Species** : Rat
**Sex** : Female

**Strain/Husbandry** : Wistar derived SPF-bred albino rats (Bor;WISW, SPF TNO)

**Conditions**

| | |
|---|---|
| Age at dosing: | Approximately 13 weeks (females) and 14 weeks (males) of age. |
| Source: | F. Winkelmann Versuchstierzucht GmbH & Co. KG, Borchen, West Germany. |
| Acclimation period: | Seven days. |
| Average weight at start of study: | Males: not specified; Females: 182.3 to 217.5 grams. |
| Assignment to groups: | Computerized, random number-based procedure. |
| Diet: | "Basal Diet" (analysis provided in report. |
| Access to food: | Available ad libitum. |
| Access to water: | Available ad libitum. |
| Method of Identification: | Ear marks. |
| Housing: | Individually in stainless steel cages with wire-mesh bottoms. |
| Environmental Conditions (for non-exposure periods): | |
| Temperature: | 21 ± 1°C. Recording frequency not reported. |
| Humidity: | at least 40%. Recording frequency not reported. |
| Air changes: | 8-10 air changes per hour. |
| Photoperiod: | 12 hr light/12 hr dark. |

**Route of admin.** : Dermal
**Exposure period** : days 6-15 of gestation
**Frequency of treatment** : Daily
**Duration of test** : 21 d
**Doses** : 0, 264, 880 mg/kg bw d
**Control group** : Yes, concurrent vehicle
**NOAEL Maternalt.** : = 880 . mg/kg bw
**NOAEL Teratogen** : = 880 . mg/kg bw
**Protocol Guideline** : OECD Guideline 414 "Teratogenicity"
**Year of Study** : 1988
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Propylene glycol n-butyl ether (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | XZ 95420.00 |
| Purity: | "> 98%" |
| Specific Gravity: | 0.88 kg/l |
| Solubility: | 6% in water; soluble in propylene glycol |
| Storage: | Ambient temperature in the dark. |
| Stability: | "stable up to 200°C" |
| Administered as: | Dilution in propylene glycol. |

**Method** : Propylene glycol n-butyl ether (PnB) (or the negative control, propylene glycol) was applied daily on gestation days 6 through 15 to the shaved skin of three groups of pregnant Wistar rats (>20/sex/dose level) at various dilutions in propylene glycol (PG) equivalent to doses of 0 (PG-only; 1.5 ml/kg-day), 0.3 or 1.0 ml PnB/kg-day. These doses equate to 0, 264, or 880 mg PnB/kg-day. Treatment solutions were applied to the shaved dorsal trunk of each rat. Dilutions of PnB in PG resulted in applied volumes of 1.5, 1.8, or 2.5 ml test solution per kg body weight. Rats wore neck collars to prevent grooming and ingestion of test material. Solutions were applied unoccluded since the low vapor pressure of PnB and PG was considered to preclude evaporative loss.

Rats were observed for clinical signs of toxicity and skin reactions on a daily basis (week days). Individual body weights were recorded on days 0, 6, 16, and 21 of pregnancy and food consumption was monitored over days 0 – 6, 6 – 16, and 16 – 21 of pregnancy. At sacrifice, all animals were subjected to necropsy and examined for gross abnormalities. The ovaries, uterus, kidneys, and livers were removed and weighed. The number of corpora lutea was counted. Fetuses were removed from the uterus, weighed, lengths recorded, and examined for gross abnormalities. Early and late resorptions and live and dead fetuses were counted. Implantation sites in both uterine horns were counted and the empty uterus weighed. Half the fetuses from each litter were eviscerated, skinned and stripped of most subcutaneous tissue, then fixed in 96% ethanol. These fetuses were then stained with Alizarin Red S and examined for skeletal anomalies. The remaining fetuses were fixed in Bouin's fluid, transferred to 70% ethanol and sectioned into slices (after Wilson) for soft tissue analysis.

| Group | PnB Dose (ml/kg-d) | PnB Dose (mg/kg-d) | No./♀/Dose Group | Treatment Period (days) |
|---|---|---|---|---|
| Group 1 | 0 | 0 | 22 | 6 thru 15 gest. |
| Group 2 | 0.3 | 264 | 22 | 6 thru 15 gest. |
| Group 3 | 1.0 | 880 | 20 | 6 thru 15 gest. |

Percentages of pre- and post-implantation loss were calculated as was the degree of ossification for each fetus. Soft tissue and skeletal anomalies or abnormalities were recorded.

**Results** : Slight skin reactions were found in the dams from all treatment groups and thus, were not considered to be treatment related. No maternal toxicity was found: clinical signs and organ or body weights did not differ between treatment and controls groups. No deaths occurred in any groups over the course of the study. No embryo- or fetotoxicity was evident since pre- and post-implantation losses were comparable between treatment and control groups. PnB did not cause frank developmental toxicity in skeletal or soft tissue. The high dose group did exhibit a slight statistical increase in the incidence of unilateral supernumerary rudimentary thoracic ribs when compared to controls. The incidence bilaterally was not elevated. This finding was not considered biologically significant by the authors of the study who considered the incidence within normal limits for these species.

**Conclusions** : PnB is not maternally toxic, embryo- or fetotoxic, or teratogenic in Wistar rats receiving dermal doses up to 1.0 ml/kg-d during organogenesis (days 6 – 15). The NOAEL for maternal toxicity, embryo- or fetal toxicity, or developmental toxicity is 1.0 ml/kg-d (880 mg/kg-d) and a LOAEL was not established.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report followed OECD Protocol 414: "Teratogenicity" (12 May 1981), the numbers and type of test animals used and their husbandry conditions were as prescribed in the aforementioned guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the treatment period (organogenesis) was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

**References** : Waalkens-Berendsen, D.H., Koeter, H.B.W.M., van Marwijk, M.W., (1988). Dermal embryotoxicity/teratogenicity study with propyleneglycol n-butyl ether (PnB) in rats. CIVO/TNO Study No. 991. September 1988.

**Other** : Because of its low vapor pressure, PnB was not considered to evaporate and, consequently, dermal applications were not occluded. To prevent oral intake, rats wore Elizabethan collars.

**Source** : Dow Deutschland Inc Stade 5

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**Species** : Rabbit
**Sex** : Female
**Strain** : New Zealand white virgin females

| | |
|---|---|
| Age at dosing: | Approximately 6 months of age. |
| Source: | Hazleton Research animals (Denver, PA). |
| Acclimation period: | 32 Days. |
| Average weight at start of study: | Females: Group 0 controls, 3.89 ± 0.25 kg; Group 2 (10 mg/kg), 3.83 ± 0.36 kg; Group 3 (40 mg/kg), 3.92 ± 0.26 kg, Group 4 (100 mg/kg), 3.75 ± 0.22 kg. |
| Assignment to groups: | Not specified. |
| Diet: | Certified Rabbit Chow no. 5322 (Ralston, Purina). |
| Access to food: | Available ad libitum. |
| Access to water: | Available ad libitum. |
| Method of Identification: | Not specified. |
| Housing: | Individually in stainless steel cages with wire-mesh bottoms. |
| Environmental Conditions (for non-exposure periods): | |
| Temperature: | 18 - 22 °C. Recording frequency not reported. |
| Humidity: | 50 - 72%. Recording frequency not reported. |
| Air changes: | 10 air changes per hour. |
| Photoperiod: | 12 hr light/12 hr dark. |

**Route of admin.** : Dermal
**Exposure period** : Days 7-18 of gestation
**Frequency of treatment** : Daily
**Duration of test** : 29 d
**Doses** : 0, 10, 40, or 100 mg/kg bw d
**Control group** : Yes

| | | |
|---|---|---|
| **NOAEL Maternaltox.** | : | > 100 . mg/kg bw |
| **NOAEL Teratogen** | : | > 100 . mg/kg bw |
| **Protocol Guideline** | : | OECD Guideline 414 "Teratogenicity" (Although these guidelines were not specified in this peer-reviewed paper, the reported methodology satisfies the criteria described in these guidelines) |
| **Year of Study** | : | 1989 |
| **GLP** | : | Yes |
| **Test substance** | : | |

| | |
|---|---|
| Identity: | Propylene glycol n-butyl ether (1-butoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 29387-86-8 (also 5131-66-8) |
| Batch No.: | Not reported. |
| Purity: | 95% 1-n-butoxy-2-propanol (alpha isomer)<br>5% 2-n-butoxy-1-propanol (beta isomer) |
| Specific Gravity: | 0.88 kg/l (from other reports). |
| Solubility: | 6% in water (from other reports). |
| Storage: | Not reported. |
| Stability: | Stable up to 200°C (from other reports). |
| Administered as: | Dilution in water. |

**Method** : Propylene glycol n-butyl ether (PnB) was applied daily on gestation days 7 through 18 to the clipped, unabraded skin of four groups of pregnant New Zealand White rabbits (# of pregnant females/dose level are shown in table below) at various dilutions in water equivalent to doses of 0 , 10, 40, or 100 mg PnB/kg body weight/day. Dilutions of PnB in water resulted in applied volumes of 2.0 ml test solution per kg body weight. Treatment solutions were applied to the shaved dorsal trunk (area of 10 x 20 cm) of each rabbit for a period of 6 hours per day, whereafter residual material was removed with warm water. Rabbits wore neck collars to prevent grooming and ingestion of test material during the daily 6-hour exposure periods. The day of artificial insemination was designated Day 0. Solutions were applied unoccluded since the low vapor pressure of PnB was considered to preclude evaporative loss.

| Group | PnB Dose (mg/kg-d) | No. ♀/Dose Treated | No. ♀/Dose Pregnant | Treatment Period (days) |
|---|---|---|---|---|
| Group 1 | 0 | 17 | 15 | 7 thru 18 gest. |
| Group 2 | 10 | 19 | 16 | 7 thru 18 gest. |
| Group 3 | 40 | 19 | 16 | 7 thru 18 gest. |
| Group 4 | 100 | 19 | 16 | 7 thru 18 gest. |

Rabbits were observed for clinical signs of toxicity, abortion, delivery, and skin reactions several times per day over the exposure and post-exposure periods. Individual body weights and feed consumption were recorded daily during pregnancy. At sacrifice (day 29 of pregnancy), all animals were subjected to necropsy and examined for gross abnormalities. The ovaries, uterus, kidneys, and livers were removed and weighed. The number of corpora lutea were counted in each ovary. Early and late resorptions and live and dead fetuses were counted. Implantation sites in both uterine horns were counted and the empty uterus weighed. Fetuses were removed from the uterus, weighed, lengths recorded, and examined for gender and external and internal gross abnormalities, according to the method of Staples. All the fetuses from each litter were eviscerated, skinned and stripped of most subcutaneous tissue, then fixed in 96% ethanol. These fetuses were then stained with Alizarin Red S for examination for skeletal anomalies. Percentages of pre- and post-implantation loss were calculated as was the degree of ossification for each fetus. Soft tissue and skeletal anomalies or abnormalities were recorded.

**Results** : No maternal deaths occurred in any of the groups and no clinical signs of toxicity correlated with PnB treatment. Pregnancy and abortion rates were comparable among all groups. Erythema of the skin at the site of application occurred at a greater incidence and severity in does from the high exposure group. No effect upon body weights or food consumption was noted in the does. The pregnancy rate was 15/17 (88%) in water-treated negative controls and 16/19 (84%) in all PnB-treated groups. One doe from the low exposure group spontaneously aborted but, absent this effect at higher doses, this was not considered treatment related.

No effects were noted from PnB treatment on the number of live fetuses, fetal weights, sex ratio, or early or late resorptions. No fetal variation or abnormalities was found to occur at a greater incidence in PnB treated subjects.

**Conclusions** : PnB did not cause maternal toxicity, embryo- or fetal toxicity, or developmental abnormalities in fetuses at any dose level. The NOAEL for these effects is > 100 mg/kg and the LOAEL is > 100 mg/kg.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study report). The report was a peer reviewed journal article and thus did not included GLP and Quality Assurance statements. The article described study parameters that satisfied OECD Protocol 414: "Teratogenicity" (12 May 1981), including the numbers and type of test animals used and their husbandry conditions. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the treatment period (organogenesis) was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

**References** : Gibson, W.B., Nolen, G.A., Christian, M.S., (1989). Determination of the developmental toxicity potential of butoxypropanol in rabbits after topical administration. Fund. Appl. Toxicol. 13:359-365.

**Other** : Although tested at lower doses, this study is consistent with the PnB dermal developmental toxicity study in rats, which also showed no maternal or fetal effects at doses up to 880 mg/kg.

**Source** : Dow Deutschland Inc Stade 5

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## 5.10 OTHER RELEVANT INFORMATION

**Remark** : No other relevant information
**Source** : Dow Deutschland Inc Stade 5

## 5.11 EXPERIENCE WITH HUMAN EXPOSURE

**Remark** : Study classification: 4a (Secondary literature)
The exposure to organic solvents among 12 graffiti removers was studied. Health effects were also assessed in structured interview and a symptom questionnaire. Blood and urine samples were collected at the end of the day of air sampling. The concentrations of dichloromethane, glycol ethers, trimethylbenzenes, and N-methyl-2-pyrrolidinone in the breathing zone of each worker were measured during one working day. The 8-h TWA exposures to glycol ethers were low or not detectable. Irritative symptoms of the eyes and upper respiratory tract were more prevalent than in the general population.
**Source** : Dow Deutschland Inc Stade 5

(1)

**Remark** : Despite the high volume production in use no complaints have reached the producing company.
**Source** : Dow Deutschland Inc Stade 5

(1) Anundi H. et al. (1993) Int. Arch. Occup. Environ. Health, 65: 247-251.

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# Dipropylene Glycol n-Butyl Ether
# CAS No. 29911-28-2

# IUCLID with Robust Summaries (Dossier)

| | | |
|---|---|---|
| **Existing Chemical** | : | ID: 29911-28-2 |
| **CAS No.** | : | 29911-28-2 (alpha, alpha ether linkage) (also refers to commercial mixture)<br>35884-42-5 (unspecified) |
| **EINECS Name** | : | 1-(2-butoxy-1-methylethoxy)propan-2-ol |
| **EINECS No.** | : | 249-951-5 |
| **Molecular Weight** | : | 190.28 |
| **Structural Formula** | : | C4-H9-O-(C3-H6-O)2-H |
| **Molecular Formula** | : | C10H22O3 |

**Producer Related Part**

| | | |
|---|---|---|
| **Company** | : | American Chemistry Council |
| **Creation date** | : | 01.08.2002 |

**Substance Related Part**

| | | |
|---|---|---|
| **Company** | : | American Chemistry Council |
| **Creation date** | : | 01.08.2002 |
| **Memo** | : | |
| **Printing date** | : | 30.08.2002 |
| **Revision date** | : | 30.08.2002 |
| **Date of last Update** | : | 30.08.2002 |
| **Number of Pages** | : | 87 |
| **Chapter (profile)** | : | Chapter: 1, 2, 3, 4, 5, 7 |
| **Reliability (profile)** | : | Reliability: without reliability, 1, 2, 3, 4 |
| **Flags (profile)** | : | Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS |

### 1.0.1 OECD AND COMPANY INFORMATION

| | | |
|---|---|---|
| **Type** | : | |
| **Name** | : | Dow Deutschland Inc |
| **Partner** | : | |
| **Date** | : | |
| **Street** | : | Werkstade PO Box 1120 |
| **Town** | : | 21677 Stade 5 |
| **Country** | : | Germany |
| **Phone** | : | +49.414.6910 |
| **Telefax** | : | +49.414.6912600 |
| **Telex** | : | |
| **Cedex** | : | |

| | | |
|---|---|---|
| **Type** | : | |
| **Name** | : | Union Carbide Benelux |
| **Partner** | : | |
| **Date** | : | |
| **Street** | : | Norderlaan 147 |
| **Town** | : | 2030 Antwerpen |
| **Country** | : | Belgium |
| **Phone** | : | |
| **Telefax** | : | |
| **Telex** | : | |
| **Cedex** | : | |

### 1.0.2 LOCATION OF PRODUCTION SITE

### 1.0.3 IDENTITY OF RECIPIENTS

### 1.1 GENERAL SUBSTANCE INFORMATION

| | | |
|---|---|---|
| **Substance type** | : | Organic chemical. Commercial product is a mixture consisting of predominantly (>95%) secondary alcohol (alpha isomer) with less than 5% primary alcohol (beta isomer). Unless otherwise stated, results in this dossier pertain to commercial mixture. |
| **Physical status** | : | Liquid |
| **Purity** | : | % w/w |

### 1.1.0 DETAILS ON TEMPLATE

### 1.1.1 SPECTRA

### 1.2 SYNONYMS

2-Propanol, 1-(2-butoxy-1-methylethoxy)-
**Source** : Union Carbide Benelux Antwerpen

Dipropylene glycol n-butyl ether

**Source** : Dow Deutschland Inc Stade 5

Dowanol* DPnB
**Source** : Dow Deutschland Inc Stade 5

DPnB
**Source** : Dow Deutschland Inc Stade 5

n-Butoxy-methylethoxy-propanol
**Remark** : * Trademark of The Dow Chemical Company
**Source** : Dow Deutschland Inc Stade 5

n-Butoxy-propoxy-propanol
**Source** : Dow Deutschland Inc Stade 5

## 1.3 IMPURITIES

Currently, DPnB (mixed alpha & beta isomers) consists of greater than 98.5% purity. Water may be present at a maximum of 0.30%.

## 1.4 ADDITIVES

## 1.5 QUANTITY

Worldwide production (1999): 4.8 thousand tonnes (10.5 million pounds).

## 1.6.1 LABELLING

## 1.6.2 CLASSIFICATION

## 1.7 USE PATTERN

DPnB has many performance characteristics that are similar to lower molecular weight homologs but with lower volatility and higher viscosity. Uses for DPnB include: coupling agent (i.e., blending facilitator) for cleaners such as degreasers, paint removers, metal cleaners, and hard surface cleaners; coalescent for lowering minimum film formulation temperature (MFFT) in latex coatings; solvent for water-reducible coatings; chemical intermediate for production of epoxides, acid ester derivatives, solvents, and plasticizers.

## 1.7.1 TECHNOLOGY PRODUCTION/USE

## 1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

**Remark** : None established.
**Source** : Dow Deutschland Inc Stade 5

## 1.9 SOURCE OF EXPOSURE

**Remark** : Occupational exposure to DPnB is limited due to the enclosed systems in which this chemical is manufactured. End use consumers may be exposed

during the application of coatings in which DPnB is used. For such use, exposure would be by inhalation or dermal exposure. After application of coatings, DPnB would evaporate slowly from the coating and escape at low concentrations into the atmosphere. Spills of small quantities (e.g., 1 gallon or less) into the environment could occasionally be expected during coating applications.

**Source** : Dow Deutschland Inc Stade 5

**1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES**

**1.10.2 EMERGENCY MEASURES**

**1.11 PACKAGING**

**1.12 POSSIB. OF RENDERING SUBST. HARMLESS**

**1.13 STATEMENTS CONCERNING WASTE**

**1.14.1 WATER POLLUTION**

**1.14.2 MAJOR ACCIDENT HAZARDS**

**1.14.3 AIR POLLUTION**

**1.15 ADDITIONAL REMARKS**

**Source** : Union Carbide Benelux Antwerpen

**Remark** : no additional remarks
**Source** : Dow Deutschland Inc Stade 5

**1.16 LAST LITERATURE SEARCH**

**1.17 REVIEWS**

**1.18 LISTINGS E.G. CHEMICAL INVENTORIES**

## 2.1 MELTING POINT

**Value** : < -75°C (Critical Value)
**Decomposition** :
**Sublimation** :
**Method** : Not specified
**Year** :
**GLP** : no data
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : DPnB
**Source** : Staples & Davis (2002)

(31)

**Value** : < -75 ° C
**Decomposition** : no at ° C
**Sublimation** : No
**Method** : Other
**Year** :
**GLP** : no data
**Test substance** :
**Source** : Dill & Davis (1997)

(29)

## 2.2 BOILING POINT

**Value** : = 230°C (446°F) (Critical Value)
**Decomposition** : No
**Method** : Other
**Year** :
**GLP** : no data
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** :
**Source** : Dow Chemical Company MSDS

(30)

## 2.3 DENSITY

**Type** : Specific Gravity (Critical Value)
**Value** : = 0.910 at 25°/25°C
**Method** : Other
**Year** :
**GLP** : no data
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** :
**Source** : Dow Chemical Company MSDS

(30)

### 2.3.1 GRANULOMETRY

## 2.4 VAPOUR PRESSURE

**Value** : = 9.1 Pa at 20° C (or 0.091 hPa) (Critical Value)

| | | |
|---|---|---|
| **Decomposition** | : | |
| **Method** | | Other (calculated) |
| **Year** | : | |
| **GLP** | : | no data |
| **Reliability** | : | Assigned Klimisch score of 4 since methodology not available. |
| **Test substance** | : | DPnB |
| **Source** | : | Staples & Davis (2002) |

(31)

## 2.5 PARTITION COEFFICIENT

| | | |
|---|---|---|
| **Log Pow** | : | = 1.523 (Critical Value) |
| **Method** | | Other (calculated) |
| **Year** | : | |
| **GLP** | : | no data |
| **Reliability** | : | Assigned Klimisch score of 2 since methodology available. |
| **Test substance** | : | |
| **Remark** | : | Method: pomona-medchem structural fragment method |
| **Source** | : | Staples & Davis (2002) |

(31)

## 2.6.1 WATER SOLUBILITY

| | | |
|---|---|---|
| **Value** | : | 45,000 mg/liter @ 20°C (Critical Value)<br>55,000 mg/liter @ 25°C (Critical Value) |
| **Qualitative** | : | |
| **Pka** | : | |
| **PH** | : | |
| **Method** | : | Not specified |
| **Reliability** | : | Assigned Klimisch score of 4 since methodology not available. |
| **Year** | : | |
| **GLP** | : | no data |
| **Test substance** | : | DPnB |
| **Source** | : | Staples and Davis (2002) |

(31)

| | | |
|---|---|---|
| **Value** | : | 4.5 vol% at 20 ° C |
| **Qualitative** | : | |
| **Pka** | : | at 25 ° C |
| **PH** | : | at and ° C |
| **Method** | : | Other |
| **Year** | : | |
| **GLP** | : | no data |
| **Test substance** | : | |
| **Source** | : | Dill & Davis (1997) |

(29)

## 2.6.2 SURFACE TENSION

## 2.7 FLASH POINT

| | | |
|---|---|---|
| **Value** | : | = 100.4 ° C (Critical Value) |
| **Type** | : | Other |
| **Method** | : | Other: SETA |

**Year** :
**GLP** : no data
**Reliability** : Assigned Klimisch score of 2 since methodology was reported.
**Test substance** : DPnB
**Source** : Dow Chemical Company MSDS, and Staples and Davis (2002)

(30,31)

## 2.8 AUTO FLAMMABILITY

**Value** : = 194°C (381°F) (Critical Value)
**Method** : Other: DIN 51794
**Year** : 1989
**GLP** : no data
**Reliability** : Assigned Klimisch score of 2 since methodology was reported.
**Test substance** : DPnB
**Source** : Dow Chemical Company MSDS & Staples and Davis (2002)

(30, 31)

## 2.9 FLAMMABILITY

**Remark** : Lower flammability limit 0.6 %v/v at 145 deg. Celsius
Upper flammability limit 20.4 %v/v at 180 deg. Celsius
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Source** : Dow Chemical Company MSDS

(30)

## 2.10 EXPLOSIVE PROPERTIES

**Result** : not explosive
**Method** : Other
**Year** :
**GLP** : no data
**Test substance** :
**Remark** : DPnB is stable under normal storage condition
**Source** : Dow Chemical Company MSDS

(30)

## 2.11 OXIDIZING PROPERTIES

**Result** : no oxidizing properties
**Method** : Other
**Year** :
**GLP** : no data
**Test substance** :
**Remark** : Material to avoid oxidising agents
**Source** : Dow Chemical Company MSDS

(30)

## 2.12 ADDITIONAL REMARKS

**Remark** : No additional remarks
**Source** : Dow Deutschland Inc Stade 5

### 3.1.1 PHOTODEGRADATION

| | | |
|---|---|---|
| **Photodegradation OH radical rate constant** | : | 49.7 x 10-12 cm3/molecule-sec |
| **Half-life** | : | 0.215 days or 2.58 hours (assumes 12 hr of light per day and an hydroxy radical concentration of 1.5 x 106 OH/cm3) |
| **Remark** | : | These modeled values represent an estimation based on the molecular structure of the alpha, alpha isomer of this chemical. (AOP version 1.90) |
| **Source** | : | EPIWIN/AOP (v3.10) Program (43) |
| **Remark** | : | Half-life = 2.6 hours (according to Atkinson estimation methodology, based on hydroxyl radical reaction in the atmosphere)<br>No relevant data identified from literature searched. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

### 3.1.2 STABILITY IN WATER

| | | |
|---|---|---|
| **Remark** | : | Ether functions are generally stable in water under neutral conditions at ambient temperatures. DPnB is chemically stable under a variety of conditions. |
| **Source** | : | Dow MSDS; Fieser and Fieser, 1960 |

(30, 40)

### 3.1.3 STABILITY IN SOIL

| | | |
|---|---|---|
| **Remark** | : | No relevant data identified from literature searched. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

### 3.2 MONITORING DATA

| | | |
|---|---|---|
| **Remark** | : | No relevant data identified from literature searched. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

### 3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

| | | |
|---|---|---|
| **Type** | : | Fugacity Model Level III |
| **Method** | : | Mackay Level III (Equal releases to all media assumed) |
| **Year** | : | 2002 |
| **Input Parameters and Results** | : | CHEMICAL PROPERTIES AND OTHER INPUT PARAMETERS<br><br>Where input parameters were estimated, the alpha, alpha isomer was used, Where input parameters were measured, commercial mixture was used (> 95% secondary alcohol)<br><br>INPUT PARAMETERS<br><br>Chemical Type: 1<br>Molecular Mass (g/mol): 190.28<br>Data Temperature (Degrees Celsius): 25 |

LogKow: 1.523
Water Solubility (g/m3): 45000
Water Solubility (mol/m3): 236.4936
Henry's Law Constant (Pa.m3/mol): 3.847884E-02
Vapour Pressure (Pa): 9.1
Melting Point (Degrees Celsius): -75

RESULTS (HALF-LIVES)

Half-Life in Air (h): 7.6
Half-Life in Water (h): 672
Half-Life in Soil (h): 672
Half-Life in Sediment (h): 672
Half-Life in Suspended Sediment (h): 672
Half-Life in Fish (h): 24
Half-Life in Aerosol (h): 24

PARTITION COEFFICIENTS (RESULTS)
(All amounts are dimensionless, except where noted)

Log Octanol-Water Partition Coefficient: 1.523
Octanol-Water Partition Coefficient: 33.34264
Organic Carbon-Water Partition Coefficient (L/kg): 13.67048
Air-Water Partition Coefficient: 1.55230554055104E-05
Soil-Water Partition Coefficient: 0.656183173769318
Soil-Water Partition Coefficient (L/kg): 0.273409655737216
Sediment-Water Partition Coefficient: 1.31236634753864
Sediment-Water Partition Coefficient (L/kg): 0.546819311474432
Suspended Sediment-Water Partition Coefficient: 6.56183203126347
Suspended Sediment-Water Partition Coefficient (L/kg): 2.73409667969311
Fish-Water Partition Coefficient: 1.600447
Fish-Water Partition Coefficient (L/kg): 1.6004467010498
Aerosol-Water Partition Coefficient: 0
Aerosol-Air Partition Coefficient: 659340.668804316

**Reliability** : (1) Valid without restriction
**Source** : Mackay Level III Modeling

### 3.3.2 DISTRIBUTION

**Distribution at Equilibrium** : See EPIWIN modeling results below
**Air** : 0.827%
**Water** : 50.9%
**Soil** : 48.2%
**Sediment** : 0.0947%
**Remark** : Results are estimates based on the Mackay Level III fugacity model (part of EPIWIN Suite)
**Source** : EPIWIN (v3.10) Program (43)

**Remark** : Henry's Law Constant = 2.79E-07 atm-m3/mol.
(VP/Wsol estimate using EPI values)

HLC = 2.68E-9 atm-m3/mol ("Bond Method")
HLC = 2.45E-10 atm-m3/mol ("Group Method")

Results are estimates based on the HENRYWIN V3.10 module of the

EPIWIN Suite
**Source** : EPIWIN (v3.10) Program (43)

## 3.4 MODE OF DEGRADATION IN ACTUAL USE

**Remark** : No relevant data identified from literature searched; chemically stable for intended end uses.
**Source** : Dow Deutschland Inc Stade 5

## 3.5 BIODEGRADATION

**Type** : Aerobic (Closed Bottle Test)
**Inoculum** : Domestic sewage
**Concentration** : 0, 1.86, or 9.29 mg DPnB/liter.
**Contact time** : 28 days
**Degradation** : = 0.% after 28 day
**Result** : Under test conditions no biodegradation observed
**Deg. Product** : N/A
**Protocol Guideline** : OECD Guideline 301 D "Ready Biodegradability: Closed Bottle Test"
**Year of Study** : 1987
**GLP** : Yes
**Test substance** : Identity: Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2
Batch No.: XZ 95411.00
Purity: "More than 95%"
Supplied as: Not reported.
Appearance: Clear liquid.
Administered as: Solution in water.
Specific Gravity: 0.91 kg/liter.
Solubility: 5% in water.
Stability: Stable up to 200°C.
Storage: At ambient temperature in the dark.

**Method** : To test for its ready biodegradability potential, DPnB was incubated for 28 days in continuously agitated closed bottles in the dark at two concentrations with inoculum (secondary effluent) collected from a local municipal sewage treatment facility. The incubation temperature of the water was 19.7-20.0°C, pH ranged from 7.2 to 7.4, hardness was not reported, and the concentration of inoculum was one droplet per liter of test solution. Oxygen concentration was the measured variable. The concentrations of DPnB were: 0 (oxygen control with inoculum), 1.86, or 9.29 mg/liter. Other controls were: sodium acetate at 4.14 mg/liter with inoculum (positive or reference control), DPnB and sodium acetate with inoculum (to determine if DPnB inhibited NaAc degradation), an oxygen blank (no DPnB or inoculum), and an inoculum blank (same as oxygen blank but with inoculum). Degradation of DPnB was monitored by assessing the dissipation of oxygen in the test solution over time (i.e., measuring dissolved oxygen content with an oxygen electrode at various time points). Oxygen content was measured (in duplicate bottles) on days 0, 5, 15, and 28. Degradation was calculated by dividing the biochemical oxygen demand (BOD) expressed as mg O2 per mg DPnB, by the theoretical oxygen demand (ThOD).

| | | |
|---|---|---|
| **Results** | : | DPnB did not show biodegradation over the 28-day course of the study. The sodium acetate positive control chemical reached 64% biodegradation, indicating active inoculum. Oxygen depletion in the oxygen and inoculum blanks did not exceed test parameters. |
| **Conclusions** | : | DPnB is not readily biodegradable under the conditions of this closed bottle test. |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 301 D "Ready Biodegradability: Closed Bottle Test" was followed. Specifically, the incubation conditions and the inoculum used were as prescribed in the guidance. Test material characterization was adequate. The concentrations tested, the length of the monitoring period (28 days), and method for measuring test compound degradation, were typical for this type assay and were adequately recorded. |
| **References** | : | Cardinaals, J.M., de Crom, P.J.W., (1987). Assessment of the biodegradability of Dowanol DPnB in the closed bottle test. NOTOX Study No. 0481/C 239. February 1987. Unpublished study. |
| **Other** | : | For testing, six glass cylinders were prepared: 1 oxygen blank, 1 inoculation blank, 1 reference substance (4.14 mg/l of sodium acetate), 1 test substance at 9.29 mg/l, 1 test substance at 1.86 mg/l and 1 inhibition control (4.14 mg/l sodium acetate, 1.86 mg/l test substance). From these glass cylinders, the appropriate closed bottles (in duplicate) were prepared. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(3)

| | | |
|---|---|---|
| **Type** | : | Aerobic (CO2 Evolution or Modified Sturm Test) |
| **Inoculum** | : | Sediment and activated sludge (acclimated) from a domestic sewage treatment plant. |
| **Concentration** | : | 0, 10.25, or 20.50 mg DPnB/liter |
| **Contact time** | : | 28 days |
| **Degradation** | : | High concentration (20.50 mg/liter) = 49.8.% after 28 days<br>Low concentration (10.25 mg/liter) = 42.4% after 28 days |
| **Kinetics of test substance** | : | For the high DPnB concentration:<br>4 day = 20.8.%<br>8 day = 41.%<br>18 day = 44.6.%<br>22 day = 45.%<br>28 day = 50% |
| **Deg. Product** | : | N/A |
| **Protocol Guideline** | : | OECD Guideline 301 B "Ready Biodegradability: Modified Sturm Test" (since designated “CO2 Evolution Test“). |
| **Year of Study** | : | 1987 |
| **GLP** | : | Yes |

| | | | |
|---|---|---|---|
| **Test substance** | : | Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| | | Batch No.: | XZ 95411.00 |
| | | Purity: | "More than 95%" |
| | | Supplied as: | Not reported. |
| | | Appearance: | Clear liquid. |
| | | Administered as: | Solution in water. |
| | | Specific Gravity: | 0.91 kg/liter. |
| | | Solubility: | 5% in water. |
| | | Stability: | Stable up to 200°C. |
| | | Storage: | At ambient temperature in the dark. |

**Method** : To test for its biodegradability potential, DPnB was incubated for 28 days in continuously agitated closed bottles in the dark at two concentrations with an acclimated inoculum originally collected from a local municipal sewage treatment facility (this inoculum also contained freshly collected activated sludge and sediment). The incubation temperature of the water was 20±1°C; the pH ranged from 5.8 to 6.3; water hardness was not reported; O2 concentration was not reported although the water was aerated. The concentration of inoculum was approximately 3 x 108 microorganisms per 3 liters of test solution. The concentrations of DPnB were: 0 (control with inoculum), 10.25, or 20.50 mg/liter. Other controls were: sodium acetate at 21.53 mg/liter with inoculum (positive or reference control) and inoculum alone (to determine CO2 production without an exogenous organic substrate and correct the samples with organic substrate by this amount). Degradation of DPnB was monitored by assessing the evolution of CO2 gas from mineralization of the exogenous organic substrate by the inoculum. CO2 was trapped with barium hydroxide (as a barium carbonate precipitate) and the remaining Ba(OH)2 was titrated with HCl, using phenolphthalein as an indicator, to determine the amount of CO2 evolved. CO2 was measured as it evolved, approximately every other day for the first 10 days and every 5th day until the 28th day. Degradation was calculated by dividing the amount of CO2 evolved by the theoretical CO2 (ThCO2).

**Results** : The low concentration of DPnB (10.25 mg/l) showed 42.4% degradation after 28 days and the high concentration (20.50 mg/l) showed 49.8% degradation (see above for intermediate time periods). The sodium acetate reference compound showed 63.5% degradation, indicating that the inoculum was appropriately active. The negative control blanks showed appropriate levels of CO2 production.

**Conclusions** : DPnB did not meet the criteria of at least 60% degradation within 28 days (and in a window of 10 days) at either of the concentrations tested. Pre-adapted (acclimated) microorganisms did show an ability to degrade DPnB significantly within 28 days.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

| | | |
|---|---|---|
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 301 B "Ready Biodegradability: Modified Sturm Test" (since designated “CO2 Evolution Test“) was followed. Specifically, the incubation conditions and the inoculum used were mostly as prescribed in the guidance. An exception was that the inoculum was “pre-adapted“ or “acclimated,“ which consists of exposing the test material to the microorganisms for a period of time prior to the test. Acclimation is intended, through adaptation of the microorganisms, to facilitate or enhance the microorganisms’ ability to metabolize, and thereby, degrade the test material. This is not permitted under today’s guidelines in order for a chemical to qualify as “readily biodegradable“ although it is widely recognized that this commonly used procedure may show that a compound does have an inherent ability to biodegrade. Test material characterization was adequate. The concentrations tested, the length of the monitoring period (28 days), and the method for measuring test compound degradation, were typical for this type assay and adequately recorded. |
| **Reference** | : | Cardinaals, J.M., de Crom, P.J.W., (1987). Assessment of the ultimate biodegradability of Dowanol DPnB in the modified Sturm test. NOTOX Study No. not reported. July 1987. Unpublished study. |
| **Other** | : | Inoculum was acclimated with DPnB for a period of 16 days to facilitate microorganism metabolism of the test compound. According to the OECD guidelines, to show ready biodegradability, acclimated inoculum should not be used. This was a test for ultimate biodegradability and indicated an ability of pre-adapted (acclimated) microorganisms to degrade DPnB. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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| | | |
|---|---|---|
| **Type** | : | Aerobic (Modified OECD Screening Test) |
| **Inoculum** | : | activated sludge, domestic |
| **Concentration** | : | 100 mg DPnB/liter (40mg/l as DOC – Dissolved Organic Carbon) |
| **Contact time** | : | 28 days |
| **Degradation** | : | = 91.% after 28 day |
| **Result** | : | Readily biodegradable |
| **Kinetics of test substance** | : | 7 day = 22.%<br>14 day = 80.%<br>21 day = 83.%<br>28 day = 91.% |
| **Deg. Product** | : | Not determined |
| **Protocol Guideline** | : | OECD Guideline 301 E "Ready biodegradability: Modified OECD Screening Test" (since designated: “301E Modified OECD Screening Test“) |
| **Year of Study** | : | 1993 |
| **GLP** | : | Yes |

| | | | |
|---|---|---|---|
| **Test substance** | : | Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| | | Batch No.: | Not reported. |
| | | Purity: | Not reported. |
| | | Supplied as: | Liquid in amber bottle. |
| | | Appearance: | Colorless liquid. |
| | | Administered as: | Solution in water. |
| | | Specific Gravity: | Not reported. |
| | | Solubility: | Not reported. |
| | | Stability: | Not reported. |
| | | Storage: | At ambient temperature in the dark. |

**Method** : To test for its biodegradability potential, DPnB was incubated for 28 days in continuously agitated 2 liter open beakers (in duplicate) in the dark with an inoculum originally collected from a local municipal sewage treatment facility. Dissolved organic carbon (DOC) was measured at 0, 7, 14, 21, 27, and 28 days. The incubation temperature was 24°C; pH did not drop below 5.1 on sampling days (& were then adjusted to 7.3); O2 concentration remained approximately 7.8 mg/L on samping days. The concentration of inoculum was 0.5 ml inoculum per liter of test solution. The concentration of DPnB was 100 mg DPnB/liter (corresponding to 40 mg DOC/liter) (see comment below under “Other”). Controls included: 1) sodium benzoate at 35 mg/liter (20 mg DOC/liter) with inoculum (constituting the positive or reference control) and 2) inoculum alone (to determine disappearance of DOC without an exogenous organic substrate and correct the samples with organic substrate by this amount). Degradation of DPnB was monitored by assessing the removal of DOC (as supplied either by DPnB or sodium benzoate – the exogenous substrate) by the inoculum. DOC was analyzed in triplicate at each time point using a Dorhmann DC 190 Analyser. Degradation was calculated by subtracting the amount of DOC in the negative (inoculum only) control from that in the test material or positive control sample at any given time point and dividing by the initial DOC concentration at time 0.

**Results** : DPnB biodegradation, monitored as DOC removal, was 22% by day 7, 80% by day 14, 83% by day 21, 91% by day 27, and, again, 91% by day 28. Biodegradation of sodium benzoate, the positive control reference, was 93%, 96%, 98%, 102%, and 102% at the same time points, respectively, indicating a valid test.

**Conclusions** : Results indicated that DPnB is readily biodegradable under the criteria specified for this test. DPnB achieved >60% degradation within 28 days and within a 10-day window.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

| | | |
|---|---|---|
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 301 E "Modified OECD Screening Test" was followed. Specifically, the incubation conditions and the inoculum used were as prescribed in the guidance. Test material characterization was not adequately described in the report. The concentrations tested, the length of the monitoring period (28 days), and the method for measuring test compound degradation, were typical for this type assay and adequately recorded. |
| **References:** | : | Handley, J.W., Mead, C., (1993). Dowanol DPnB: Assessment of Ready Biodegradability (Modified OECD Screening Test). Safepharm Laboratories Study No. not reported. January 14, 1993. Unpublished study. |
| **Other** | : | Unlike the Closed Bottle Test, this test showed that DPnB was readily biodegradable. The figure of 40 mg/liter DOC from 100 mg DPnB/liter presumably is derived from the proportion of the mass of carbon in the DPnB molecule compared to the entire mass of DPnB. Since the molecular weight of DPnB is ~190 g/mole and there are 10 carbon atoms in DPnB (~120 g/mole), 120/190 would comprise approximately 63% of the DPnB molecule or 63% DOC (rather than 40%). The authors of the report may have assumed only 7 carbon atoms comprised DPnB (i.e., 44% DOC). Presumably, this miscalculation would not change the percentage disappearance of carbon over time. |
| **Source** | : | Dow Deutschland Inc Stade 5 (26) |
| **Type** | : | Aerobic (Zahn-Wellens/EMPA Test for “Ultimate Biodegradability“) |
| **Inoculum** | : | Activated sludge, domestic |
| **Concentration** | : | Two sets of DPnB solutions were tested.<br>Test Set #1: 230.5 mg DPnB/liter of test solution (or 145.6mg/liter as DOC - Dissolved Organic Carbon).<br>Test Set #2: 235.5 mg DPnB/liter of test solution (or 154.2mg/liter as DOC - Dissolved Organic Carbon).<br>Note: Proportions of DOC to total compound vary slightly for the two test concentrations. |
| **Contact time** | : | Up to 28 days. |
| **Degradation** | : | = 96.% after 28 day |
| **Result** | : | other: ultimate biodegradation |
| **Kinetics of test substance** | : | The following represent the average of the two DPnB test solutions.<br>7 days = 6.%<br>14 days = 78.%<br>21 days = 93.%<br>28 days = 96% |
| **Deg. Product** | : | Not characterized. |
| **Protocol Guideline** | : | OECD Guideline 302 B "Inherent biodegradability: Modified Zahn-Wellens Test" |
| **Year of Study** | : | 1992 |
| **GLP** | : | Yes |

**Test substance** : Identity: Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2
Batch No.: EB 910420
Purity: > 98%
Organic Carbon Contnt: 64.3 mgC/100 mg.
Supplied as: Not reported.
Appearance: Colorless liquid.
Specific Gravity: Not specified. (0.91 kg/liter from other reports).
Solubility: 5% in water.
Stability: Stable up to 200°C.
Stability in water: At least 30 days.
Storage: Room temperature in the dark.

**Method** : To test for its biodegradability potential, DPnB was incubated in the dark at 20.5-22.5°C for 28 days in continuously agitated in aerated 2.5 liter open beakers containing 2 liters of test solution with an inoculum originally collected from the secondary effluent of a local municipal sewage treatment facility. Two sets of DPnB solutions were evaluated. In the first, the concentration of DPnB was 230.5 mg DPnB/liter (corresponding to 145.6 mg DOC/liter). In the second, DPnB was dissolved at a concentration of 235.5 mg/liter (corresponding to 154.2 mg DOC/liter). The concentration of inoculum was ~4 grams of inoculum (dry wt) per liter of test solution. The O2 concentration ranged from 8.3 to 8.9 mg/L and pH ranged from 6.4 to 8.5.

To assess biodegradability, dissolved organic carbon (DOC) was measured at 0, 7, 14, 21, 27, and 28 days. Controls included: 1) aniline at 102 mg/liter (79.2 mg DOC/liter) with inoculum (constituting the positive or reference control) and 2) inoculum alone (to determine disappearance of DOC without an exogenous organic substrate and to correct the samples with organic substrate by this amount). Degradation was monitored by assessing the removal of DOC (as supplied either by DPnB or aniline – the exogenous substrate) by the inoculum. DOC was analyzed in triplicate at each time point using a Shimadzu TOC 500 Analyser. Degradation was calculated by subtracting the amount of DOC in the negative (inoculum only) control from that in the test material or positive control sample at any given time point and dividing by the initial DOC concentration at time 0.

**Results** : DPnB biodegradation, monitored as DOC removal, was 6% by day 7, 78% by day 14, 93% by day 21, 96% by day 28. Biodegradation of aniline, the positive control reference, was 92%, 96%, 96%, and 97%, at the same time points, respectively, indicating a valid test.

**Conclusions** : Results from this test indicate that DPnB is inherently biodegradable under the conditions employed in this test.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 302 B "Zahn/Wellens/EMPA Test" was followed. Specifically, the incubation conditions and the inoculum used were as prescribed in the guidance. Test material characterization was adequately described in the report. The concentrations tested, the length of the monitoring period (28 days), and the method for measuring test compound degradation, were typical for this type assay and adequately recorded.

**References** : Wuthrich, V., (1992). Dowanol DPNB: Inherent Biodegradability: "Modified Zahn-Wellens Test." RCC Project No. 314054. March 27, 1992. Unpublished report.

**Other** In a test with high inoculum content DPnB is biodegradable. Biodegradation of DPnB reached 96% after 28 days. The standard, aniline, was degraded within 7 days by 92% (97% after 28 days). Study classification: 1a

**Source** : Dow Deutschland Inc Stade 5

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## 3.6 BOD5, COD OR BOD5/COD RATIO

**Remark** : No relevant data identified from literature searched.
**Source** : Dow Deutschland Inc Stade 5

## 3.7 BIOACCUMULATION

**Modeling results** : EPIWIN
**Estimated log BCF** : 0.168
**Estimated BCF** : 1.473
**Source** : EPIWIN Program (v3.10) BCFWIN module (v2.14) (43)

## 3.8 ADDITIONAL REMARKS

**Remark** : No additional remarks
**Source** : Dow Deutschland Inc Stade 5

## 4.1 ACUTE/PROLONGED TOXICITY TO FISH

| | | |
|---|---|---|
| **Type** | : | Static (fresh water) |
| **Species** | : | Poecilia reticulata (guppy) |
| **Exposure Period** | : | 96 hour(s) |
| **Unit** | : | mg/liter |
| **Analytical Monitoring** | : | Nominal concentrations were used. |
| **NOEC** | : | = 180 mg DPnB/liter |
| **LC50** | : | = 841 mg DPnB/liter (at 96 hours). |
| **EC50** | : | = 180 - 320 mg DPnB/liter (at 96 hours) |
| **Protocol Guideline** | : | OECD Guideline 203 "Fish, Acute Toxicity Test" |
| **Year of Study** | : | 1987 |
| **GLP** | : | Yes |
| **Test Substance** | : | |

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Batch No.: | XZ 95411.00 |
| Purity: | “More than 95%” |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Solution in water. |
| Specific Gravity: | 0.91 kg/liter. |
| Solubility: | 5% in water. |
| Stability: | Stable up to 200°C. |
| Storage: | At ambient temperature in the dark. |

**Method** : Young Poecilia reticulata (guppies) were exposed for 96 hours to concentrations of 0, 100, 180, 320, 560, or 1000 mg DPnB/liter. These concentrations were selected from a previously conducted range-finding study. Ten guppies were exposed at each concentration in duplicate batches under static conditions for a total of 20 guppies per concentration.

Exposures were conducted in 1-liter glass vessels maintained at a temperature of 21-22°C. Two vessels were employed at each concentration (i.e., exposures were conducted in duplicate). Ten guppies of 1-3 cm length were exposed in each test vessel. Fish were not fed one day prior to exposure or throughout the 96-hour exposure period. Oxygen concentration (pO2) and pH were recorded at the initiation of exposure and every 24 hours thereafter. O2 concenrations ranged from 7.8 to 9.2 mg/L, pH from 8.2 to 8.3, and water hardness was 11.7°DH. The water of each vessel was renewed midway through the exposure period.

Fish were observed for mortality and clinical signs at 3, 24, 48, 72, and 96 hours. Clinical signs included: loss of equilibrium, changes in swimming behavior, respiratory behavior, and pigmentation. At the end of the 96-hour test period, the LC50 (with confidence limits and concentration-response slope), the EC50 (concentration at which 50% of the subjects showed clinical signs of toxicity), and NOEC (no observed effect concentration) were determined for each time point.

**Results** : No mortality was observed at concentrations up to and including 560 mg DPnB/liter. Mortality occurred only at the highest concentration tested. At 1000 mg/liter, half the guppies (5) died by 24 hours in both vessels. By 48 hours 2 more had died in both vessels, and by 72 hours, 2 more had died but in only one of the duplicate vessels. Three guppies in the first vessel and 1 guppy in the second vessel survived the 96-hour exposure to 1000 mg/liter.

No clinical signs were observed at concentrations of 180 mg/liter or less. At 320 mg/liter, all guppies showed an inhibition of swimming ability and a small number (no more than 4 of 20 total at this concentration) showed increased pigmentation. At 560 mg/liter, all subjects showed increased pigmentation and reduced swimming ability at all time points. Swimming ability was progressively inhibited to the point of immobilization and in a progressively increasing proportion of the subjects over the exposure period; touching the caudal peduncle stimulated reaction. In survivors at any concentration, no loss of equilibrium was observed.

In the negative control, mortality was zero and no clinical signs were observed.

**Conclusions** : The LD50s and EC50's at the observed time points, calculated after Finney, 1971, Probit Analysis, Cambridge U Press, 3rd Ed.), are listed in the table below.

| | 24 hr | 48 hr | 72 hr | 96 hr |
|---|---|---|---|---|
| LD50 | 1000 | 886 | 841 | 841 |
| LC50 95%CL | 882-1250 | 813-1016 | 781-945 | 781-945 |
| LC50 Slope | 7.8 | 9.9 | 11.2 | 11.2 |
| EC50 | 180-320 | 180-320 | 180-320 | 180-320 |
| EC50 95% CL | * | * | * | * |
| EC50 Slope | * | * | * | * |

* Could not be calculated.

The clinical signs NOEC level is 180 mg DPnB/liter. The lethality NOEC level is 560 mg DPnB/liter.

These results indicate that DPnB is not highly toxic to this freshwater fish species.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 203 "Fish, Acute Toxicity Test" was followed. Specifically, the fish breeding and maintenance conditions were as prescribed in the guidance. Test material characterization was adequately described in the report. The concentrations tested, the length of the exposure and observation period (96 hours), and methods for calculating results were typical for this type assay and adequately recorded.

**References** : Van der Hoeven, J.C.M, Welboren, G.T.G., (1987). Assessment of the acute toxicity of Dowanol-DPnB in Poecilia reticulata. NOTOX Report No. not reported. July 1987. Unpublished report.

**Other** : The authors speculated that the immobilization observed might have been due to a paralysis since some apparently dead fish revived when placed into fresh tap water.

No actual concentrations were measured. Completeness of dissolution of test substance in the water environment of the fish was made only on a visual basis. Since the water solubility of DPnB is ~50,000 mg/liter or about 5%, the test material is easily theoretically soluble at the highest concentration tested. Moreover, because of its low Henry's Law Constant of 3.85E-02 Pa-m3/mol (reflecting its relatively low vapor pressure and high hydrophilicity), DPnB will not have a propensity to evaporate from the water into air. Finally, the high chemical stability of DPnB suggests that this chemical will not break down spontaneously over the 4 day exposure period. The mortality observed in the highest exposure group indicates that the test material had not degraded chemically and was soluble and stable enough to exert toxic effects.

**Source** : Dow Deutschland Inc Stade 5

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## 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

**Type** : Static
**Species** : Daphnia magna (Crustacea)
**Exposure period** : 48 hour(s)
**Unit** : mg/liter
**Analytical Monitoring** : Nominal concentrations used.
**NOEC** : = 1000 mg DPnB/liter.
**Protocol Guideline** : OECD Guideline 202, part 1 "Daphnia sp., Acute Immobilisation Test"
**Year of Study** : 1987
**GLP** : Yes
**Test Substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Batch No.: | XZ 95411.00 |
| Purity: | "More than 95%" |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Solution in water. |
| Specific Gravity: | 0.91 kg/liter. |
| Solubility: | 5% in water. |
| Stability: | Stable up to 200°C. |
| Storage: | At ambient temperature in the dark. |

**Method** : In a dose-range finding study, ten Daphnia magna less than 24 hours old were exposed for 48 hours to concentrations of 0, 0.01, 0.1, 1, 10, 100, or 1000 mg DPnB/liter water. Because immobilization was observed in only one daphnia at 1000 mg/liter, a limit test was conducted. In the subsequent defining limit test, 10 daphnia per glass vessel (in duplicate for a total of 20 daphnia per concentration) were exposed to 0 or 1000 mg DPnB/liter.

Exposures were conducted in 100 milliliter glass vessels maintained at a temperature of 19±1°C. Two vessels were employed at each concentration (i.e., exposures were conducted in duplicate). Daphnia were not fed during the 48-hour exposure period. Oxygen concentration (pO2) ranged from 8.2 to 8.9 mg/L and pH ranged from 8.2 to 8.3; both parameters were recorded at the initiation of exposure and at 48 hours. Water hardness was 11.7°DH. Water was not changed or aerated during the 48-hour exposure period.

Daphnia were observed for immobilization at 24 and 48 hours. The criterion for determining immobilization consisted of a lack of movement by the daphnia within 15 seconds after gentle agitation of the test water. At 24 and 48 hours, the EC50 were determined (with, where possible, confidence limits and concentration-response slope).

**Results** : Two of twenty daphnia exhibited immobilization when exposed to 1000 mg DPnB/liter in the limit test (each of the two duplicate flasks with 10 daphnia contained one immobilized subject). Immobilization occurred only after 48 hours and was not present at 24 hours. The 48-hour EC50 was concluded to be greater than 1000 mg/liter. Results did not permit calculation of an actual EC50 with 95% confidence limits and a slope.

**Conclusions** : These results indicate that DPnB is not toxic to daphnia under the conditions of this test.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 202 "Daphnia sp., Acute Immobilization Test and Reproduction Test" was followed. Specifically, the breeding and maintenance conditions were as prescribed in the guidance. Test material characterization was adequately described in the report. The concentrations tested, the length of the exposure and observation period (48 hours), and methods for calculating results were typical for this type assay and adequately recorded.

**References** : Borgers, M., Welboren, G.T.G., (1987). Assessment of the acute effects of Dowanol-DPnB on the mobility of Daphnia magna. NOTOX Report No. not provided. July 1987. Unpublished report.

**Other** : Oxygen and pH ranges were determined to be within predefined safe limits. A K2Cr2O7 positive control group showed immobilization at the expected concentrations.

The arguments cited in this segment for the previous study indicate that nominal concentrations reflect actuals despite the latter not having been measured.

**Source** : Dow Deutschland Inc Stade 5

(9)

## 4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

**Remark** : The EPIWIN suite of models is able to predict toxicity values for chemicals based on their physicochemical characteristics of Kow, molecular weight, molecular structure, etc. The ECOSAR program module (v0.99g) of EPIWIN (v3.10) predicted a Green Algae 96-hour EC50 of 556 mg/L and a ChV of 33.65 mg/L.

**Source** : ECOSAR Module (v0.99g) of U.S. EPA's EPIWIN Modeling Suite™ (2000)

(43)

## 4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

**Remark** : No data available.

### 4.5.1 CHRONIC TOXICITY TO FISH

**Remark** : No relevant data identified from literature searched.
**Source** : Dow Deutschland Inc Stade 5

### 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

**Remark** : No relevant data identified from literature searched.
**Source** : Dow Deutschland Inc Stade 5

### 4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

**Remark** : No relevant data identified from literature searched.
**Source** : Dow Deutschland Inc Stade 5

### 4.6.2 TOXICITY TO TERRESTRIAL PLANTS

**Species** : Terrestrial plants: monocotyledonous species (corn, wheat)
**Endpoint** : Visible damage, growth rates (height), & fresh weights
**Exposure period** : Single spraying at early growth stage (2 to 3 leaf sprout)
**Unit** : Liter per hectare equivalents
**NOEC** : 25.% or 50 liters per hectare
**Year** : 1990

| | | |
|---|---|---|
| **GLP** | : | No |
| **Test substance** | : | Dowanol-DPnB |
| **Method** | : | To assess DPnB's ability to act as a solvent for pesticide formulations, various concentrations of DPnB were sprayed on sprouts of the monocotyledons, corn (Zea mays) and wheat (Triticum aestivum). The corn and wheat were in the 2 to 3 leaf sprout stage at the time of application and the concentrations sprayed onto them (in pentuplicate) were 0% (Polyglycol P26-2 or water), 6.25%, 12.5%, 25%, 50%, or 100%. These solutions were sprayed once only (overhead) at a rate equivalent to 200 liters/hectare.<br><br>Toxicity was assessed for 21 days by monitoring 1) visible damage (e.g., lack of leaf unfolding, leaf scorching, necrotic spotting, inter-venal necrosis, plant death), expressed as percent of plants affected, 2) growth rate, in millimeters, measured weekly for three weeks following application as height of the plant from the soil to the meristem or tallest leaf, and 3) fresh weights (i.e., vegetable mass) measured on day 21 post-treatment. |
| **Results** | : | At concentrations of 25% or less damage from DPnB to wheat was minimal. For corn, DPnB was least toxic. At concentrations of 25% and higher, DPnB scorched corn leaves. |
| **Conclusions** | : | DPnB caused no damage to wheat and corn at concentrations that would be used in field applications |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 2. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). Although not a GLP study following prescribed guidelines (as yet, there are no published EPA or OECD protocol guidelines for this assay), methods were thoroughly described and results comprehensively reported. |
| **References** | : | Hart, D., Verschuuren, H.G., (1990). Report on the phytotoxicity of Dowanol DPnB following foliar spray application. Letcome Laboratories Report No. not reported. October 1990. Unpublished report. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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| | | |
|---|---|---|
| **Species** | : | Terrestrial plants: dicotyledonous species (oilseed rape, soybeans, cotton, vines, tomatoes) |
| **Endpoint** | : | Visible damage, growth rates (height), & fresh weights |
| **Exposure period** | : | Single spraying at early growth stage (2 to 5 leaf sprout) |
| **Unit** | : | Liter per hectare equivalents |
| **NOEC** | : | < 12,5 liters/hectare. |
| **Protocol Guideline** | : | None available. |
| **Year of Study** | : | 1990 |
| **GLP** | : | No |
| **Test substance** | : | Dowanol-DPnB |

**Method** : To assess DPnB's ability to act as a solvent for pesticide formulations, various concentrations of DPnB were sprayed on sprouts of the dicotyledons, cotton (Gossypium hirsutum), oilseed rape (Brassica napus), soybean (Glycine max), cotton (Gossypium hirsutum), vines (Vitis vinifera), and tomatoes (Lycopersicon esculentum). Plants were in the 2 to 5 leaf sprout stage at the time of application and the concentrations sprayed onto them (in pentuplicate) were 0% (Polyglycol P26-2 or water), 6.25%, 12.5%, 25%, 50%, or 100%. These solutions were sprayed once only (overhead) at a rate equivalent to 200 liters/hectare.

Toxicity was assessed for 21 days by monitoring 1) visible damage (e.g., lack of leaf unfolding, leaf scorching, necrotic spotting, inter-venal necrosis, plant death), expressed as percent of plants affected, 2) growth rate, in millimeters, measured weekly for three weeks following application as height of the plant from the soil to the meristem or tallest leaf, and 3) fresh weights (i.e., vegetable mass) measured on day 21 post-treatment.

**Results** : Visible damage occurred at even the lowest concentrations (increasing with concentration) for DPnB. Growth rates were likewise affected by DPnB at all concentrations.

**Conclusions** : All concentrations of DPnB caused unacceptable damage to dicotyledonous species. At realistic (i.e., lower) field concentrations, less damage would be expected from DPnB.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 2.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). Although was not a GLP study following prescribed guidelines (there are no published EPA or OECD protocol guidelines for this assay), methods were thoroughly described and results comprehensively reported.

**References** : Hart, D., Verschuuren, H.G., (1990). Report on the phytotoxicity of Dowanol DPnB following foliar spray application. Letcome Laboratories Report No. not reported. October 1990. Unpublished report.

**Other** : At 6.25% only cotton had reduced fresh weight after 21 days. All dicotyledonous species were unacceptably affected by DPnB.

**Source** : Dow Deutschland Inc Stade 5

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### 4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

**Remark** : No relevant data identified from literature searched.
**Source** : Dow Deutschland Inc Stade 5

### 4.7 BIOLOGICAL EFFECTS MONITORING

**Remark** : No relevant data identified from literature searched.
**Source** : Dow Deutschland Inc Stade 5

## 4.8 BIOTRANSFORMATION AND KINETICS

**Type** : Animal
**Remark** : Biotransformation data in animals are available (see section 5.10)
**Source** : Dow Deutschland Inc Stade 5

## 4.9 ADDITIONAL REMARKS

**Remark** : no additional remarks
**Source** : Dow Deutschland Inc Stade 5

### 5.1.1 ACUTE ORAL TOXICITY

| | | |
|---|---|---|
| **Type** | : | LD50 |
| **Species** | : | Rat |
| **Strain** | : | Wistar |
| **Sex** | : | Males and females |
| **Number of animals** | : | 5 per sex |
| **Vehicle** | : | No vehicle; test material was tested undiluted. |
| **Value** | : | LD50 for both sexes: 4000 .mg/kg bw (95% conf lim: 3200-4600 mg/kg)<br>LD50 for males alone: 4400 mg/kg (95% conf lim: could not be calculated)<br>LD50 for females alone: 3700 mg/kg (95% conf lim: 2500-4800 mg/kg) |
| **Protocol Guideline** | : | OECD Guideline 401 "Acute Oral Toxicity" |
| **Year of Study** | : | 1988 |
| **GLP** | : | Yes |
| **Test substance** | : | |

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Batch No.: | XZ 95411.00 |
| Purity: | “More than 95%” |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Undiluted liquid. |
| Specific Gravity: | 0.91 kg/liter. |
| Solubility: | 5% in water. |
| Stability: | Stable up to 200°C. |
| Storage: | At ambient temperature in the dark. |

**Method** : Three groups of Wistar rats (5/sex/dose level) received single oral doses of 3200, 4200, or 5600 mg/kg dipropylene glycol n-butyl ether (DPnB), administered undiluted using a stainless steel stomach cannula attached to a syringe. Animals were fasted overnight prior to dosing and were not allowed food until 4.5-5.0 hr after dosing. Subjects were observed for mortality and signs of toxicity several times on the day of dosing (Day 0) and on weekdays thereafter for up to 14 additional days. Body weights were recorded prior to dosing, at death, or weekly thereafter. Non-survivors were necropsied as soon as possible and surviving animals were sacrificed by CO2 asphyxiation and subjected to necropsy on day 15.

**Results** : At the low dose of 3200 mg/kg DPnB, one male died on day 0 and one female died on day one (total mortality 2/10). At 4200 mg/kg, two males and two females died on day 0 and two additional females died on day 1 (total mortality 6/10). At 5600 mg/kg, four males and four females died on day 0 and one additional female died on day 1 (total mortality 9/10). The calculated oral LD50 for males alone was 4400 mg/kg (no 95% confidence limits), for females alone was 3700 mg/kg (95% CL: 2500 - 4800 mg/kg), and for both sexes combined was 4000 mg/kg (95% CL: 3200 - 4600 mg/kg).

All deaths occurred within two days of dosing. Females were affected more than males. Adverse signs included weight loss, lethargy, coma, hypopnea, hyperpnea, dacryorrhea, blood around the eyes, rough coat, and ataxia. Surviving rats showed no adverse signs by day 2. Weight gain appeared normal in survivors. At necropsy, (presumably non-surviving) rats showed 1) enlargement, hemorrhage, and hyperemia of the stomach, 2) hemorrhage of the thymus, 3) dark red lungs, 4) dark red liver, and 5) gas accumulation, bloody content, and watery content of the small intestine.

**Conclusions** : With an LD50 of 4000 mg/kg, dipropylene glycol n-butyl ether has a low degree of acute toxicity by the oral route of exposure.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 401: "Acute Oral Toxicity" was followed. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The dose level tested satisfied the appropriate OECD upper limit (i.e., 2 gm/kg), the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded.

**References** : Reijnders, J.B.J., Zucker-Keizer, A.M.M., (1987). Evaluation of the acute oral toxicity of Dowanol-DPnB in the rat. NOTOX Report No. 0481/703. July 1987. Unpublished study.

**Other** : The oral LD50 found in this study is consistent with other published values for CAS# 29911-28-2.

**Source** : Dow Deutschland Inc Stade 5

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**Type** : LD50
**Species** : Rat
**Strain** :
**Sex** :
**Number of animals** :
**Vehicle** :
**Value** : ca. 1850 . mg/kg bw
**Method** : other: see reference
**Year** : 1947
**GLP** : No
**Test substance** : other TS: Di-propylene glycol, n-butyl
**Remark** : The boiling point of the test material was 228 deg. Celsius at 1013 hPa. The undiluted material was fed to rats in single oral doses.
**Source** : Dow Deutschland Inc Stade 5

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**Type** : LD50
**Species** : Mouse
**Strain** :
**Sex** :
**Number of animals** :
**Vehicle** :
**Value** : = 2160 . mg/kg bw
**Protocol Guideline** : OECD Guideline 401 "Acute Oral Toxicity"
**Year of Study** : 1988
**GLP** : Yes
**Test substance** : as prescribed by 1.1 - 1.4
**Remark** : Result: Death occurred within 30 minutes at the 10 ml and 3.16 ml dose group. One animal died between 2.5 and 5 hours in the 3.16 ml/kg group. No further deaths were observed during 7 days. Effects observed included signs of CNS and respiratory depression and hunched body carriage. The

LD50 value was calculated as 2.37 ml/kg (2.16 g/kg).
Test condition: CD-1 mice were used; groups of 4 males were given acute oral doses of 0.1, 0.316, 1.0, 3.16 and 10 ml of DPnB; observation period was 7 days.

**Source** : Dow Deutschland Inc Stade 5

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### 5.1.2 ACUTE INHALATION TOXICITY

**Type** : LC50 (Limit Test)
**Species** : Rat
**Strain** : Fischer 344
**Sex** : Males and females
**Number of animals** : 5 per sex
**Vehicle** : None
**Exposure time** : 4 hours
**Value** : > 42.1 .ppm (>328 mg/m3)
**Protocol Guideline** : Protocol guideline not specified in report. However, protocol meets criteria in OECD 403 “Acute Inhalation Toxicity.“
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Batch No.: | XZ 95411.00 |
| Purity: | see below |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Vapor |
| Vapor pressure: | 0.06 mmHg at 25°C (79 ppm at 1 atm) |
| Specific Gravity: | 0.91 g/ml. |
| Solubility: | 5% in water. |
| Stability: | Stable up to 200°C. |

Dipropylene glycol n-butyl ether: 99.33%
Propylene glycol n-butyl ether: 0.49%
Water: 0.18%
Peroxides (as hydrogen peroxide): 134 ppm

Dipropylene glycol n-butyl ether (DPnB) is a mixture of 4 possible isomers with the major isomers being 1-(1-n-butoxy-2-propoxy)-2-propanol and 2-(1-n-butoxy-2-propoxy)-1-propanol.

**Method** : A single group of Fischer 344 rats (5/sex) was exposed in a whole-body inhalation chamber for 4 hours to vapors of dipropylene glycol n-butyl ether at a measured concentration of 42.1 ppm (328 mg/m3). Chambers were 112 liters in volume and airflow was 30 liters/min. Animals were observed for mortality and overt signs of toxicity during the exposure period (day 1) and after for 14 additional days. Rats were weighed prior to exposure and on days 2, 4, 8, 11 and 15. All animals were subjected to gross necropsy.

**Results** : No rats died when exposed to 42.1 ppm (328 mg/m3) dipropylene glycol n-butyl ether for 4 hours. No signs of toxicity during or after exposure were noted and no lesions were observed at necropsy.

**Conclusions** : The LC50 of the test material is greater than 42.1 ppm (328 mg/m3). As a vapor, dipropylene glycol n-butyl ether does not represent a vapor hazard at ambient temperatures.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although the study report did not specify that OECD Protocol 403: "Acute Inhalation Toxicity" was followed, the study satisfied the methods stipulated in Protocol 403. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The dose level tested (in this limit test) satisfied the appropriate OECD upper limit (i.e., the maximum practically attainable), the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded.

**References** : Gushow, T.S., Phillips, J.E., Lomax, L.G., Verschuuren, H.G. (1987). Dipropylene glycol n-butyl ether: An acute vapor inhalation study in Fischer 344 rats. Report No. not specified. December 8, 1987. Unpublished report.

**Other** : The measured or actual concentration was 42.1ppm. Higher concentrations resulted in condensation on the hair of the subjects. Thus, this concentration represented the practical upper limit for vapor exposure to this test material at ambient temperatures. A theoretical limit, based upon the vapor pressure, was 79 ppm (615 mg/m3), which was not attainable without condensation. The concentration of 42.1 ppm is equivalent to 328 mg/m3. The nose-only aerosol 4 hr acute inhalation toxicity study (see next), tested a concentration over 6 times higher (i.e., 2040 mg/m3).

**Source** : Dow Deutschland Inc Stade 5

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**Type** : LC50 (Limit Test)
**Species** : Rat
**Strain** : Fischer 344
**Sex** : Males and females
**Number of animals** : 5 per sex
**Vehicle** : None
**Exposure time** : 4 hours
**Value** : LC50 > 2.04 .mg/l or > 2040 mg/m3 (no deaths at this concentration); this is equivalent to > 262 ppm
**Protocol Guideline** : Protocol guideline not specified in report. However, protocol meets criteria in OECD 403 "Acute Inhalation Toxicity."
**Year of Study** : 1990
**GLP** : Yes

**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Batch No.: | EB 891115 |
| Purity: | 99.7% (0.17% dipropylene glycol) |
| Appearance: | Clear liquid. |
| Administered as: | Aerosol |
| Vapor pressure: | 0.06 mmHg at 25°C (79 ppm at 1 atm) |
| Specific Gravity: | 0.91 g/ml. |
| Solubility: | 5% in water. |
| Stability: | Stable up to 200°C. |

Dipropylene glycol n-butyl ether (DPnB) is a mixture of 4 possible isomers with the major isomers being 1-(1-n-butoxy-2-propoxy)-2-propanol and 2-(1-n-butoxy-2-propoxy)-1-propanol.

**Method** : In an acute inhalation toxicity study, a single group of 5 male and 5 female young adult Fischer 344 rats were exposed to an aerosol atmosphere of DPnB, at a concentration of 2040 mg/m3 (262 ppm), by nose-only exposure for a period of 4 hours. Rats were observed for mortality and clinical signs of toxicity on the day of exposure (day 1) and 14 days thereafter. The subjects were weighed on days 1, 2, 4, 8, 11, and 15 of the study. All animals were subjected to gross necropsy.

Polycarbonate tubes containing the subjects (nose cones) were attached to a 42-liter ADG nose-only inhalation chamber (30 x 60 cm) with an airflow of 30 liters/min. Aerosol was generated by metering DPnB into a stainless steel ¼ J spray nozzle using a FMI pump. DPnB was mixed with air in the spray nozzle and test material was sprayed into the chamber as an aerosol. Aerosol total mass concentrations were measured gravimetrically five times over the 4-hour exposure. Aerodynamic particle size was characterized using a 6-stage cascade impactor with increasingly diminishing pore sizes in the 6 stages. Temperature and humidity were monitored at ½ hour intervals over the 4-hour exposure.

**Results** : All rats survived the first day of exposure as well as the subsequent 14-day observation period (i.e., until the scheduled sacrifice on day 15). Immediately after exposure, rats were soiled with urine and feces from being in the nose cones. Body weights for both sexes were slightly decreased (3%) on the day after exposure but gained weight steadily thereafter (not unusual with nose-only exposures). No gross pathological changes were noted in any subjects at necropsy.

Characterization of the aerosol atmosphere: The time weighted average concentration of the aerosol over the 4-hour exposure period was 2.04 mg/liter or 2,040 mg/m3 (262 ppm). Forty-eight percent of the aerosol had an aerodynamic mass median diameter of less than 3 microns, indicating that a high percentage of the aerosol was respirable within the deep lung.

**Conclusions** : The lethal concentration of DPnB is greater than 2.04 mg/liter (2,040 mg/m3). If DPnB had sufficient vapor pressure, this concentration would correspond to 262 ppm.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although the study report did not specify that OECD Protocol 403: "Acute Inhalation Toxicity" was followed, the study satisfied the methods stipulated in Protocol 403. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The dose level tested (in this limit test) satisfied the appropriate OECD upper limit, the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded.

**References** : Cieszlak, F.S., Yano, B.L., Verschuuren, H.G. (1990). Dowanol DPnB: Acute aerosol LC50 study in Fischer 344 rats. Report No. not specified. November 6, 1990. Unpublished report.

**Other** : Rats were acclimated to the nose-only polycarbonate tubes for four hours the day prior to exposure. Rats showed typical transient weight loss due to stress from being confined in the tubes.

**Source** : Dow Deutschland Inc Stade 5

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### 5.1.3 ACUTE DERMAL TOXICITY

**Type** : LD50 (Limit Test)
**Species** : Rat
**Strain** : Wistar
**Sex** : Male and female
**Number of animals** : Five per sex
**Vehicle** : No vehicle (tested undiluted)
**Value** : > 2000 . mg/kg bw
**Protocol Guideline** : OECD Guideline 402 "Acute dermal Toxicity"
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Batch No.: | XZ 95411.00 |
| Purity: | More than 95% |
| Appearance: | Clear liquid. |
| Administered as: | Undiluted liquid. |
| Vapor pressure: | Not reported. |
| Specific Gravity: | 0.91 g/ml. |
| Solubility: | 5% in water. |
| Stability: | Stable up to 200°C. |

Dipropylene glycol n-butyl ether (DPnB) is a mixture of 4 possible isomers with the major isomers being 1-(1-n-butoxy-2-propoxy)-2-propanol and 2-(1-n-butoxy-2-propoxy)-1-propanol.

**Method** : A group of 5 male and 5 female Wistar rats (~7 weeks old) was treated with a single dose of 2,000 mg/kg dipropylene glycol n-butyl ether applied topically to the intact skin under occlusion for a period of 24 hours. Subjects were observed for clinical signs of toxicity and mortality during the application period and for a period of 14 days after removal of the test material. The skin of the rats at the site of application was also evaluated for signs of irritation over the course of the study. The pure test material was applied at a single dose of 2,000 mg/kg to approximately 10% of the total body surface area of skin (clipped, non-abraded) of the rats. The test material was applied to gauze patches, which were then affixed to the clipped area of the skin and covered with foil and wrapped with a bandage around the torso. The test material was held in contact with the skin for a period of 24 hours whereupon it was removed and the treated area was washed with water to remove remaining test material. On the day of treatment (day 0), animals were observed frequently for toxicity and morbidity. Thereafter, subjects were checked once daily except for weekends and holidays. Individual body weights were recorded on test days 0, 7, and 14. The treated areas of skin were examined on test days 4, 7, and 14 for signs of irritation. Animals were sacrificed on day 14 and subjected to gross necropsy.

**Results** : No deaths, clinical signs of toxicity, or skin irritation occurred over the course of the study. The dermal LD50 for dipropylene glycol n-butyl ether is greater than 2,000 mg/kg for male and female Wistar rats.

**Conclusions** : These results indicate that dipropylene glycol n-butyl ether exhibits a relatively low degree of acute dermal toxicity (EPA Category III) (achieving Category IV requires testing 5 g/kg).

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 402: “Acute Dermal Toxicity” was followed. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The dose level tested (in this limit test) satisfied the appropriate OECD upper limit (i.e., 2 gm/kg), the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded.

**References** : Reijnders, J.B.J., (1987). Evaluation of the acute dermal toxicity of Dowanol-DPnB in the rat. NOTOX C.V. Study No. not specified, July 1987. Sponsored by Dow Chemical Europe. Unpublished report.

**Other** : The dermal LD50 found in this study is consistent with published values of other propylene glycol ethers.

**Source** : Dow Deutschland Inc Stade 5

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### 5.1.4 ACUTE TOXICITY, OTHER ROUTES

**Remark** : No relevant data identified from literature searched.
**Source** : Dow Deutschland Inc Stade 5

### 5.2.1 SKIN IRRITATION

**Species** : Rabbit
**Strain** : New Zealand White
**Concentration** : Undiluted (0.5 ml)
**Exposure** : Topical on clipped dorsal back under semi-occlusive dressing
**Exposure time** : 4 hours
**Number of animals** : 3 (females)
**PDII** : 2.0
**Result** : Slightly irritating
**EC classification** : Not irritating
**Protocol Guideline** : OECD Guideline 404 "Acute Dermal Irritation/Corrosion"
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Batch No.: | XZ 95411.00 |
| Purity: | More than 95%. |
| Appearance: | Clear liquid. |
| Administered as: | Undiluted liquid under semi-occlusive dressing. |
| Vapor pressure: | 0.06 mmHg at 25°C (79 ppm at 1 atm) |
| Specific Gravity: | 0.91 kg/liter. |
| Solubility: | 5% in water. |
| Storage: | At ambient temperature in the dark. |
| Stability: | Stable up to 200°C. |

Dipropylene glycol n-butyl ether (DPnB) is a mixture of 4 possible isomers with the major isomers being 1-(1-n-butoxy-2-propoxy)-2-propanol and 2-(1-n-butoxy-2-propoxy)-1-propanol.

**Method** : In a primary dermal irritation/corrosivity test, 0.5 milliliters of undiluted dipropylene glycol n-butyl ether (DPnB) was applied to a 6 x 6 cm square gauze patch, which was then applied to an area of clipped, unabraded skin on the left flank of three young adult female New Zealand white rabbits. The test material was held in contact with the skin for a period of 4 hours under a semi-occlusive dressing. After this period, the dressing and test material were removed by washing with tissues and water. The site of application was evaluated for irritation by scoring 1) erythema/eschar and 2) edema. Both criteria were scored on a scale of 0 – 4 at approximately 30 minutes after removal of the test material, and at 24, 48, and 72 hours, and on days 7 and 14. The primary irritation index was calculated by averaging the combined scores for both criteria at 24 and 72 hours for all three animals.

**Results** : Undiluted DPnB was found to have a primary irritation index of 2.0 (1.0 for erythema/eschar plus 1.0 for edema) averaged for the three animals at 24 and 72 hours. At 30 minutes and on days 1, 2, and 3, rabbits exhibited slight erythema and edema (scores of 1.0 for each). Edema resolved in all subjects by day 7 and erythema by day 14. All three subjects had slight scaliness over a portion of the treated site over the first 3 days, which disappeared by day 7.

| | | |
|---|---|---|
| **Conclusions** | : | The authors considered undiluted dipropylene glycol n-butyl ether to be slightly irritating. Classification: According to the criteria laid down in Annex VI of the EEC Council Directive 67/548/EEC (amended by Directive 83/467/EEC), the undiluted test substance would not require labeling as a skin irritant. |
| **Data Quality** | : | The quality of the data from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 404: "Acute Dermal Irritation/Corrosion" was followed. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the observation period (14 days) was sufficient, and scoring criteria and averaging methods were typical for this type assay and adequately recorded. |
| **References** | : | Weterings, P.J.J.M., Daamen, P.A.M., (1987). Assessment of Primary Skin Irritation/Corrosion by Dowanol-DPnB in the Rabbit. NOTOX C.V. Study No. not specified, May 1987. Unpublished. |
| **Other** | : | No systemic toxicity was noted from topical application of DPnB for 4 hours. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(8)

| | | |
|---|---|---|
| **Species** | : | Rabbit |
| **Concentration** | : | |
| **Exposure** | : | |
| **Exposure time** | : | |
| **Number of animals** | : | |
| **PDII** | : | |
| **Result** | : | slightly irritating |
| **EC classification** | : | |
| **Method** | : | other: see reference |
| **Year** | : | 1947 |
| **GLP** | : | No |
| **Test substance** | : | other TS: Di-propylene glycol, n-butyl |
| **Remark** | : | Result: As far as skin irritation was concerned, the material produced only a very slight irritation.<br>Study classification: This study does not lead to any EU classification.<br>Test condition: The undiluted material was applied to the rabbit ear and belly (10 times in 2 weeks). |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(32)

### 5.2.2 EYE IRRITATION

| | | |
|---|---|---|
| **Species** | : | Rabbit |
| **Strain** | : | New Zealand White |
| **Concentration** | : | Undiluted (0.1 ml) |
| **Dose** | : | 0.1 ml instilled into the left eye conjunctival sac. |

| | | | |
|---|---|---|---|
| **Exposure Time** | : | Lids held together for a few seconds (no subsequent washing out). | |
| **Number of animals** | : | 3 (females) | |
| **Result** | : | slightly irritating | |
| **EC classification** | : | not irritating | |
| **Protocol Guideline** | : | OECD Guideline 405 "Acute Eye Irritation/Corrosion" | |
| **Year of Study** | : | 1981 | |
| **GLP** | : | Yes | |
| **Test substance** | : | Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| | | Batch No.: | XZ 95411.00 |
| | | Purity: | More than 95%. |
| | | Appearance: | Clear liquid. |
| | | Administered as: | Undiluted liquid. |
| | | Vapor pressure: | 0.06 mmHg at 25°C (79 ppm at 1 atm) |
| | | Specific Gravity: | 0.91 kg/liter. |
| | | Solubility: | 5% in water. |
| | | Storage: | At ambient temperature in the dark. |
| | | Stability: | Stable up to 200°C. |

Dipropylene glycol n-butyl ether (DPnB) is a mixture of 4 possible isomers with the major isomers being 1-(1-n-butoxy-2-propoxy)-2-propanol and 2-(1-n-butoxy-2-propoxy)-1-propanol.

**Method** : Undiluted DPnB (0.1 ml) was instilled into the conjunctival sac of the left eye of three female white rabbits. Lids were held together for a few seconds after instillation and the treatment solution was not washed out after 30 seconds. Eyes were scored for irritation (compared to the negative control right eye) at various time intervals over a period of 23 days. Readings were taken at 1 hour, 24 hours, 48 hours, 72 hours, 7 days, and 14 days after treatment. In addition at 24 hours, eyes were treated with fluorescene dye to determine the severity and areal extent of any corneal involvement that might be present. Eyes were evaluated for irritation based on 1) damage to the cornea (corneal opacity and area involved, both scored on a scale of 0 to 4) 2) damage to the iris (obvious physical damage and reaction to light, scored on a scale of 0 to 2), and 3) damage to conjunctivae (erythema [scale of 0 – 3] and chemosis [scale of 0 – 4]). Overall scores were based on observations averaged from the 24, 48, and 72-hour observation intervals.

**Results** : Instillation of 0.1 ml DPnB did not damage the corneal or iris. The conjunctivae showed slight to moderate erythema (redness) and chemosis (swelling) at 1, 24, 48, and 72 hours. Swelling resolved by day 7 but slight redness persisted through day 7, resolving by day 14. Although corneal opacity scores were rated as 0, fluorescene dye revealed some slight corneal damage (areal extent affected was 0, 20%, and 50% in the three subjects, respectively) at 24 hours. The study authors reported a “Draize score” of 12.7 at 1 hour (presumably on a total scale of 110), indicating slight irritation.

**Conclusions** : The lack of corneal and iridial involvement indicates slight eye irritation potential. Also, based on the estimated Draize score of 12.7 (1 hour) the test substance should be classified as mildly irritating according to the scheme of Kay and Calandra. According to the criteria laid down in Annex VI of the EEC Council Directive 67/548/EEC (amended by Directive 83/567/EEC), the test substance does not need to be labeled.

| | | |
|---|---|---|
| **Data Quality** | : | The quality of the data from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1. |
| **QUALITY CHECK** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 405: "Acute Eye Irritation/Corrosion" was followed. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the observation period (14 days) was sufficient, and scoring criteria and averaging methods were typical for this type assay and adequately recorded. |
| **References** | : | Weterings, P.J.J.M., Daamen, P.A.M., (1987). Assessment of acute eye irritation/corrosion by Dowanol-DPnB in the rabbit. NOTOX C.V. Study No. 0481/706, June 1987. Unpublished. |
| **Other** | : | The method to calculate the Draize score was not described in the report. |
| **Source** | : | Dow Deutschland Inc Stade 5 (6) |
| **Species** | : | Rabbit |
| **Concentration** | : | |
| **Dose** | : | |
| **Exposure Time** | : | |
| **Comment** | : | |
| **Number of animals** | : | |
| **Result** | : | slightly irritating |
| **EC classification** | : | |
| **Method** | : | other: see reference |
| **Year** | : | 1947 |
| **GLP** | : | No |
| **Test substance** | : | other TS: Di-propylene glycol, n-butyl |
| **Remark** | : | Result: As far as eye irritation was concerned, the material produced some conjunctival irritation very apparent after 24hours but probably not of lasting character. No corneal injury. Study not suitable for EC classification purpose<br>Study classification: This study does not lead to any EU classification.<br>Test condition: The undiluted material was dropped into the rabbit eye daily for 5 days. |
| **Source** | : | Dow Deutschland Inc Stade 5 (32) |

## 5.3 SENSITIZATION

| | | |
|---|---|---|
| **Type** | : | Skin sensitization |
| **Species** | : | Guinea pig |
| **Number of animals** | : | 10/sex for DPnB; 5/sex for vehicle negative control. |
| **Vehicle** | : | Propylene glycol |
| **Result** | : | Not sensitizing |
| **Classification** | : | Labeling not required for this endpoint. |
| **Protocol Guideline** | : | OECD Guideline 406 "Skin Sensitization" |
| **Year of Study** | : | 1987 |
| **GLP** | : | Yes |

**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Batch No.: | XZ 95411.00 |
| Purity: | More than 95%. |
| Appearance: | Clear liquid. |
| Administered as: | Undiluted liquid. |
| Vapor pressure: | 0.06 mmHg at 25°C (79 ppm at 1 atm) |
| Specific Gravity: | 0.91 kg/liter. |
| Solubility: | 5% in water. |
| Storage: | At ambient temperature in the dark. |
| Stability: | Stable up to 200°C. |

Dipropylene glycol n-butyl ether (DPnB) is a mixture of 4 possible isomers with the major isomers being 1-(1-n-butoxy-2-propoxy)-2-propanol and 2-(1-n-butoxy-2-propoxy)-1-propanol.

**Method** : Initially, a preliminary dose range-finding study was conducted to determine the irritation potential of the test material in order to select the appropriate treatment solution concentration for the main sensitization study. Four concentrations of dipropylene glycol n-butyl ether (DPnB) were tested (using propylene glycol as a diluent). Concentrations of 100%, 50%, 10%, and 5% were evaluated. Minimal irritation occurred at 100% and no irritation occurred at lower concentrations. Consequently, 80% DPnB was selected as an appropriate concentration to use in the induction phase. For the challenge phase, 40% DPnB was chosen as a non-irritating dose.

In the sensitization test, the backs of 20 male Hartley guinea pigs (10/sex) were clipped free of hair and 0.3 ml of the 80% DPnB test solution was topically applied to a site on the flank using a Hill Top Chamber® secured with a bandage. The test material was held in contact with the skin for 6 hours whereupon it was removed with lukewarm water. This procedure was repeated for the second and third inductions, which followed at one-week intervals. The sites were read for irritation but results were not reported. For the challenge phase, conducted 12 days after the third induction, 0.3 ml of 40% DPnB was applied to a naive site on the flank of the guinea pigs and held in place for 6 hours using a Hill Top Chamber® and then removed, as described above. A control group of five males and five females was treated similarly except that propylene glycol was applied that did not contain DPnB.

After the challenge dose, the site of skin application was depilitated using Veet cream and scored at 24 and 48 hours following removal of the test material. Responses were graded by evaluating erythema or edema on a scale that included: 0 (no reaction), ± (slight, patchy reaction), 1 (slight but confluent, or moderate but patchy reaction), 2 (moderate erythema), or 3 (severe erythema with or without edema). These responses were compared with untreated sites on the same animal and with propylene glycol-treated negative controls. Other skin reactions were recorded if present (e.g., edema, eschar, necrosis). The experimental study design is shown below.

Study Design

| Group | Test/Control Material | No. Animals | Topical Induction Dose | Challenge Dose* (Topical) |
|---|---|---|---|---|
| 1. Test Group | Dipropylene Glycol n-Butyl Ether (DPnB) | 20 (10/sex) | 0.3 ml of 80% DPnB w/v in PG, applied for 6 hr. | 0.3 ml of 40% DPnB w/v in PG, applied for 6 hr. |
| 2. Negative Control | Propylene Glycol (PG) | 10 (5/sex) | 0.3 ml of 100% pure PG, applied for 6 hr. | 0.3 ml of 100% PG, applied for 6 hr. |

Toxicity Endpoints Monitored

| | |
|---|---|
| Clinical signs: | Every 2 hours on day 0 (day of test material administration) and once daily on workdays for 14 days thereafter. |
| Morbidity/mortality: | Every 2 hours on day 0 (day of test material administration) and once daily on workdays for 14 days thereafter. |
| Body weights: | Taken on dose days –1 and post challenge day 3. |
| Food consumption: | Not recorded. |
| Necropsy: | None conducted. |
| Histopathology: | None conducted. |

**Results** : Morbidity/Mortality: All but one female survived treatment with the test compound. This female died in the restrainer over the 6-hour period of the second induction, exhibiting signs of respiratory distress.

Clinical signs: Respiratory distress in the one non-surviving female. No dermal effects reported at site of application.

Body weights: Animals appeared to gain weight normally over the course of the study.

Macroscopic Examinations: Hemorrhage of the lung was found in the single non-surviving female.

Induction reactions and duration: No effects reported.

Challenge reactions and duration:

At the 24-hour reading, all scores in treated animals were 0 for erythema or edema. Scores remained 0 at the 48-hour reading.

**Conclusions** : DPnB did not cause contact hypersensitivity under the conditions of this test.

**Data Quality** : The number of animals tested (20) meets the guidance level for the procedure. Test material application, scoring intervals, and other study parameters followed guidance. All scoring criteria recommended in the guidance were evaluated. The data quality from this study is considered acceptable. The report included documentation for methods and results although too much reliance for documentation was placed on inclusion of the study protocol appended to the report. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the

Study Director and Head of the QA Unit, respectively. While the study report did not specifically cite OECD Protocol 406: "Skin Sensitization," the numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, as did other procedures reflecting a modified Buehler assay, and findings were adequately recorded.

**References** : Vanderkom, J., (1987). Guinea pig sensitization study, Modified Buehler Method: Dipropylene glycol n-butyl ether. S.C.K.-C.E.N. Study No. not reported, June 30, 1987. Unpublished.

**Other** : This finding is consistent with propylene glycol ethers in general. This test was a Buehler-type test, rather than a Magnusson-Kligman maximization test (i.e., no adjuvant used).

**Source** : Dow Deutschland Inc Stade 5

(11)

**Type** : Patch-Test
**Species** : Human
**Number of animals** :
**Vehicle** :
**Result** : not sensitizing
**Classification** :
**Method** : other: repeat insult patch test method
**Year** : 1988
**GLP** : Yes
**Test substance** : as prescribed by 1.1 - 1.4
**Remark** : Method: A volume of 0.4 ml of DPnB was applied to a Webril disc with a diameter of 24 mm. The Webril disc, providing an occluded patch was supplied to the upper arm of 82 volunteers nine times over a period of three weeks. During this induction period each patch was left in place for 24 hours and then removed. Seventeen days after the last induction application, duplicate challenge patches were applied for 24 hours. Result: The test material showed no evidence of skin sensitization to human volunteers.
**Source** : Dow Deutschland Inc Stade 5

(16)

## 5.4 REPEATED DOSE TOXICITY

**Type** : 2-Week Vapor Inhalation (Nose-only) in Rats
**Species** : Rat
**Sex** : 5 males and 5 females per exposure level

**Strain** : Fischer 344

| | |
|---|---|
| Age at dosing: | At least 5 weeks of age. |
| Source: | Charles River Breeding Laboratory, Kingston, N.Y. |
| Acclimation period: | At least one week. |
| Weight range (start of study): | Males: 206 to 224 grams; Females: 139 to 152 grams. |
| Assignment to groups: | Computerized, weight-stratification and random number-based procedure. |
| Diet: | Purina Certified Rodent Chow #5002 (Purina Mills, Inc., Richmond, ID). |
| Access to food: | Available ad libitum in glass jars. |
| Access to water: | Available ad libitum (glass bottles). |
| Method of Identification: | Ear tags. |
| Housing: | Individually in stainless steel cages with wire-mesh bottoms during non-exposure periods. In polycarbonate tubes during daily 6-hr exposures. Animals were acclimated to the tubes 4 days prior to exposure (1 hr/ on day –4, 3 hr on day –3, and 6 hrs –2 and –1). |

Environmental Conditions (for non-exposure periods):

| | |
|---|---|
| Temperature: | Approximately 22°C (recorded at the end of each exposure period). |
| Humidity: | 50% (recorded at the end of each exposure period). |
| Air changes: | not specified. |
| Photoperiod: | 12 hr light/12 hr dark. |

Environmental Conditions (for exposure periods):

| | |
|---|---|
| Temperature: | Approximately 22°C (recorded at the end of each exposure period). |
| Humidity: | 50% (recorded at the end of each exposure period). |
| Air changes: | >25 air changes per hour. |
| Photoperiod: | 12 hr light/12 hr dark. |

**Route of admin.** : Inhalation (vapor)
**Exposure period** : 2 weeks
**Frequency of treatment** : 9 exposures, 6 h exposure
**Post obs. period** : None
**Concentrations** : 0, 20, 40 ppm (0, 0.16, 0.32 mg/l or 0, 160, 320 mg/m3)
**Control group** : Yes, air only
**NOAEL** : = 40 . ppm (320 mg/m3)
**LOAEL** : > 40 . ppm
**Protocol Guideline** : Specific protocol guideline not specified. Followed requirements of OECD Guideline 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study"
**Year of Study** : 1987
**GLP** : Yes

**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Batch No.: | XZ 95411.00. |
| Purity: | DPnB isomers 99.33%. |
| Appearance: | Clear liquid. |
| Administered as: | Vapor. |
| Vapor pressure: | 0.06 mmHg at 25°C (79 ppm at 1 atm) |
| Boiling Point: | 214-217°C. |
| Molecular Weight: | 190.2. |
| Specific Gravity: | 0.91 g/ml (from other reports). |
| Solubility: | 5% in water (from other reports). |
| Storage: | At ambient temperature in the dark. |
| Stability: | Stable up to 200°C. |

Dipropylene glycol n-butyl ether (DPnB) is a mixture of 4 possible isomers with the major isomers being 1-(1-n-butoxy-2-propoxy)-2-propanol and 2-(1-n-butoxy-2-propoxy)-1-propanol. The test material also contained 0.49% PnB, 0.18% water, and 134 ppm peroxides.

**Method** : In a 2-week inhalation toxicity study, groups of 5 male and 5 female young adult Fischer 344 rats were exposed to a vapor atmosphere of DPnB at concentrations of 0, 20, or 40 ppm (equivalent to 0, 160, or 320 mg/m3), by nose-only exposure. Rats were exposed on weekdays 6 hr/day, 5 day/wk, for total of 9 exposures over a 2-week period. Rats were observed after each exposure for mortality and clinical signs of toxicity. The subjects were weighed prior to exposure on days 1, 3, 5, and 9 of the study. Hematology, clinical chemistry, and urinalyses were conducted prior to sacrifice. All animals were subjected to gross necropsy and over 50 tissues were collected and processed into slides for histological examination.

Polycarbonate tubes containing the subjects (nose cones) were attached to a 42-liter ADG nose-only cylindrical inhalation chamber (30 x 60 cm) with an airflow of 25 liters/min. DPnB vapor was generated with the use of a J tube assembly, referenced (Miller et al. 1980. Am Ind Hyg Assc J. 41:844), but not described in this report. Atmospheres were measured hourly by GC with a flame ionization detector. Temperature and humidity were monitored at the end of each exposure period and the chamber was maintained at approximately 22°C and 50% relative humidity.

**Results** : Survival: All rats survived all nine exposures over the 14-day study period. Clinical signs: Some rats displayed porphyrin staining around the nares and were soiled with urine and feces from being in the nose cones after exposures in the first half of the study. The authors attributed this to the stress of confinement in the polycarbonate tubes. Body weights did not increase in any group, probably due to the stress of confinement. No differences were noted in body weights when DPnB-exposed rats were compared to air-only controls. No gross pathological lesions were noted at necropsy.

Organ weights: Liver weights in females were slightly increased in the mid and high exposure groups but there was no clear dose-response and there were no associated histopathological alterations in this organ or in clinical chemistry parameters indicating damage to this organ.

Hematology: DPnB-exposed males showed a statistical increase in RBCs (20 and 40 ppm), hematocrits (20 and 40 ppm), and hemoglobin (40 ppm only) when compared to controls. These findings were not considered treatment related because 1) increases were slight, 2) values were within laboratory historical control ranges, 3) no signs were evident indicating dehydration (e.g., diarrhea, abnormal electrolytes, diuresis), and 4) erythropoiesis was not evident when slides were examined of spleen, bone marrow, liver, or lymphoid tissue.

Clinical Chemistry: No changes were noted that were considered treatment-related. Males in the 40-ppm group showed a slight statistical increase in albumin that may have been related to the increased hemoconcentration discussed above. Regarding spurious changes obviously not related to treatment, males in the 20-ppm group showed a slight decrease in potassium and females in this group a slight increase in alkaline phosphatase activity.

Urinalysis: The only change noted was an increased number of males in the 40-ppm group with occult blood (3 of 5) as opposed to the control (1 of 5) and 20 ppm group (1 of 5). This finding was not considered treatment related but rather due to mild trauma of handling (pressure was applied to the abdomen to obtain urine samples).

Histopathology: No differences were noted between the 40-ppm group and controls. Consequently, the 20-ppm group was not examined.

**Conclusions** : DPnB did not cause toxicity by the inhalation (nose-only) route of exposure in Fischer 344 rats at atmospheric concentrations up to and including 40 ppm (320 mg/m3) when exposed 6 hr/day on 9 separate days (over a 2-week period). The NOAEL is 40 ppm and the LOAEL was not established.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although the study report did not specify that OECD Guideline 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study" was followed, the study satisfied the methods stipulated in this protocol. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The dose level tested (in this limit test) satisfied the appropriate OECD upper limit (i.e., the maximum practically attainable), the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded.

**Reference** : Lomax, L.G., Gushow, T.S., Hopkins, P.J., Verschuuren, H.G. (1987). Dipropylene glycol normal butyl ether: 2-Week nose-only vapor inhalation study with Fischer 344 rats. Dow Report No. DR-0287-5038-003. December 4, 1987. Unpublished report.

**Other** : DPnB at 40 ppm was considered to be the highest practical concentration that could be obtained. Nominal concentrations (calculated by dividing the amount of DPnB consumed by the volume of air that flowed through the chamber) agreed well with actual (measured) concentrations at 20 ppm but were considerably higher at 40 ppm, indicating condensation and having reached the practical maximum concentration.

Unit conversions from ppm to mg/m3 reported herein were performed by the authors. Using a molecular weight for DPnB of 190.28 and conversion factor of 24.45, 40 ppm converts to 311 ppm, according to the conversion formula used throughout the rest of this dossier: mg/m3 = ppm x (190.28/24.45). The discrepancy represents a differences of about 3% and may be accounted for by a slightly different factor than 24.45, which represents the gas law at room temperature rather than standard temperature & pressure (i.e., 20 rather than 0 degrees C).

**Source** : Dow Deutschland Inc Stade 5

(1)

**Type** : 2-Week Aerosol Inhalation (Nose-only) in Rats
**Species** : Rat
**Sex** : Male/female

**Strain** : Fischer 344

| | |
|---|---|
| Age at dosing: | 6 weeks of age. |
| Source: | Charles River Breeding Laboratory, Kingston, N.Y. |
| Acclimation period: | At least one week. |
| Weight range (start of study): | Males: 166 to 188 grams; Females: 110 to 122 grams. |
| Assignment to groups: | Computerized, weight-stratification and random number-based procedure. |
| Diet: | Purina Certified Rodent Chow #5002 (Purina Mills, Inc., Richmond, ID). |
| Access to food: | Available ad libitum except during exposures. |
| Access to water: | Available ad libitum except during exposures. |
| Method of Identification: | Ear tags. |
| Housing: | Individually during non-exposure periods (type housing not specified). In polycarbonate tubes during daily 6-hr exposures. Animals were acclimated to the tubes 2 days prior to exposure for 2 to 4 hrs. |
| Environmental Conditions (for non-exposure periods): | |
| Temperature: | Not specified. |
| Humidity: | Not specified. |
| Air changes: | Not specified. |
| Photoperiod: | 12 hr light/12 hr dark. |
| Environmental Conditions (for exposure periods): | |
| Temperature: | 22.5 - 24.5°C (recorded at the end of each exposure period). |
| Humidity: | 34-60% (recorded at the end of each exposure period). |
| Airflow: | 30 liters/min. |
| Air changes: | >25 air changes per hour. |
| Photoperiod: | 12 hr light/12 hr dark. |

**Route of admin.** : Inhalation (nose-only)
**Exposure period** : 2 weeks
**Frequency of treatment** : 6 h/d, 5 d/w (9 exposures)
**Post obs. Period** : No
**Concentrations** : 0, 0.20, 0.81, 2.01 mg/l (0, 200, 810, 2010 mg/m3)
**Control group** : Air-only
**NOAEL** : = .20. mg/l (200 mg/m3)
**LOAEL** : = .81. mg/l (810 mg/m3)
**Protocol Guideline** : Specific protocol guideline not specified. Followed requirements of OECD Guideline 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study"
**Year of Study** : 1991
**GLP** : Yes

**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Batch No.: | EB 891115 |
| Purity: | see below |
| Supplied as: | Not reported. |
| Appearance: | Colorless liquid. |
| Administered as: | Aerosol |
| Vapor pressure: | 0.06 mmHg at 25°C (79 ppm at 1 atm) |
| Specific Gravity: | 0.91 g/ml. |
| Solubility: | 5% in water. |
| Stability: | Stable up to 200°C. |

Dipropylene glycol n-butyl ether isomers: 99.70%
Dipropylene glycol: 0.17%

Dipropylene glycol n-butyl ether (DPnB) is a mixture of 4 possible isomers with the major isomers being 1-(1-n-butoxy-2-propoxy)-2-propanol and 2-(1-n-butoxy-2-propoxy)-1-propanol.

**Methods** : Groups of 5 male and 5 female young adult Fischer 344 rats were exposed to an aerosol atmosphere of DPnB, at concentrations of 0, 200, 810, or 2010 mg/m3 (0, 25, 100, or 250 ppm), by nose-only exposure, 6 hr/day, 5 d/wk over a 2 week period for a total of 9 exposures. Rats were observed after each exposure for mortality and clinical signs of toxicity. The subjects were weighed on days 1, 3, 5, 8, and 11 of the study. Ophthalmic examination was conducted prior to the first exposure and at sacrifice. Hematology, clinical chemistry, and urinalyses were conducted prior to sacrifice. All animals were subjected to gross necropsy, major organs were weighed, and over 50 tissues were collected and processed into slides for histological examination.

: Polycarbonate tubes containing the subjects (nose cones) were attached to a 42-liter ADG nose-only conical inhalation chamber (30 x 60 cm) with an airflow of 30 liters/min. Aerosol was generated by metering DPnB into a stainless steel ¼ J spray nozzle using a FMI pump. DPnB was mixed with compressed air in the spray nozzle and test material was sprayed into the chamber as an aerosol. Aerosol total mass concentrations were measured gravimetrically on pre-weighed Teflon (TE36) filters (0.45 micron pore size) at least three times per day for each chamber. Aerodynamic particle size was characterized 3 times (per exposure period or once for the study not specified) for each chamber using a 6-stage cascade impactor with increasingly diminishing pore sizes in the 6 stages. Temperature and humidity were monitored at the end of each 6-hour exposure.

**Results** : Survival: All rats survived the nine exposures over the 14-day study period.

Clinical signs: Some rats were soiled with urine and feces from being in the nose cones after exposures. This was attributed by the authors to the stress of confinement in the polycarbonate tubes. All males and some female rats in the high exposure group exhibited lethargic behavior. This behavior disappeared in most subjects after the second exposure (1 male was lethargic on test day 9) and was not evident in the low or mid-exposure groups.

Body weights: Males from the high exposure group lost significantly more body weight than controls or lower exposure groups, indicating a treatment related effect. The control, low, and mid-exposure groups lost weight during the initial phase of exposure but body weights in these groups rebounded and exceeded initial body weights by the end of the study. Male body weights from the high exposure group were statistically different from controls and were still lower than their initial weights at the end of the study. Females in all groups showed an initial body weight loss due to confinement stress in the polycarbonate tubes but no treatment related effects were evident (i.e., all paralleled air-only controls).

Ophthalmological Examination: Although some eye lesions were found, no effects attributable to treatment were noted. Specifically, two females in the high exposure group were found to have bilateral cornel opacities (total involvement) but these were not attributed to DPnB by the study authors.

Gross pathology: A few grossly observable pathological lesions were noted at necropsy but were judged to be spontaneous or incidental to the stressful regimen of nose-only treatment and not related to DPnB exposure.

**Results continued** : Organ weights: Absolute and relative liver weights in both sexes from the mid and high exposure groups were statistically increased above controls. Liver weight changes were accompanied by increased hepatocyte size but little histopathology was evident and therefore liver weight increases were considered adaptive (e.g., due to MFO induction) rather than a toxicological response to DPnB exposure. Relative kidney weights were increased in high dose males, which the authors conjectured might reflect lower body weights. No differential response existed between control and high exposure male kidney histopathology. Both sexes from the high exposure group exhibited statistically decreased absolute brain weights but males from this group also showed a significant relative brain weight increase. Relative lung weights in both sexes were statistically increased (absolute lung weights only in the mid-exposure males also were statistically increased). Statistically significant large decreases in thymus (males only; absolute and relative) and spleen weights (males only; absolute only) were also observed in the high exposure group. The authors considered organ weight changes to be related to body weight decreases and therefore secondary to the stress-related influence from confinement in the polycarbonate exposure tubes. This conclusion was supported by a lack of accompanying histopathology or correlating clinical toxicity in most of these organs.

Hematology: Both sexes in the high-exposure group showed a statistical decrease in RBCs, hematocrits, and hemoglobin when compared to controls. These findings were not considered treatment related because 1) decreases were slight, 2) values were within laboratory historical control ranges (for HGB and HCT) or nearly so (RBC), 3) erythropoiesis was not evident when slides were examined of bone marrow, and 4) no evidence of hemolysis was present.

Clinical Chemistry: Urea nitrogen was statistically increased in high-exposure males and total protein was statistically decreased in both sexes from all DPnB-exposure groups. Other parameters that were statistically different from controls were considered spurious because they did not follow a dose-response or were only slightly different from controls. These included alterations in ALT, albumin, globulin, cholesterol, potassium, and calcium.

Urinalysis: No changes were observed in any urinalysis parameters.

Histopathology: In the high-exposure group, 4 males and 1 female exhibited increased hepatocyte size across the liver lobule with a suggestion of accompanying damage (e.g., slight vacuolation or multifocal necrosis). Histological damage to this organ was considered by the authors to be related to compressive trauma during the treatment periods. Increased hepatocyte size also was noted in two males from the mid-exposure group. In the anterior nasal cavity, rats from the mid and high-exposure groups exhibited 1) multifocal epithelial hyperplasia (1 female at the mid-dose; 4 males and 3 females at the high dose) and 2) squamous metaplasia (1 male and 4 females at the mid-dose; 5 males and females at the high dose). Nasal effects were considered a direct response to irritation from DPnB typical for mucosal tissue and were sometimes accompanied by suppurative inflammation or degeneration of the olfactory epithelium. No adverse effects were noted in the deeper respiratory tract. Slight to moderate lymphoid depletion in the thymus and spleen were noted in some rats (primarily males) in the mid and high exposure groups. No evidence was present for a hemolytic effect in these or other organs/tissues and the lymphoid effect was considered secondary to weight loss in the two highest exposure groups.

**Results (continued)** : Characterization of the aerosol atmosphere: Nominal concentrations were approximately twice actual concentrations for the 200 and 810 mg/m3 exposure levels. Nominals agreed with actual at the 2010 mg/m3 level. Mass median aerodynamic diameter and the geometric standard deviation were not calculated because the aerosol particle size was not log-normally distributed. The percentage of particles under 3 microns (i.e., deep lung respirable) were 49%, 46%, and 62% for the 200, 810, and 2010 mg/m3 exposure levels, respectively.

**Conclusions** : All rats exposed to aerosols of DPnB at concentrations of 0, 200, 810, or 2010 mg/m3 survived a total of nine 6-hour exposures over a period of two weeks with minimal clinical effects (lethargy for the first few days). The primary effects from DPnB exposure were decreased body weights in rats of both sexes at 2010 mg/m3 and histopathological lesions in the liver and nasal cavities in both sexes at 810 and 2010 mg/m3. The stress of the 6-hour confinement in the polycarbonate exposure tube contributed to the body weight decreases. The liver changes, although accompanied by slight necrosis in some instances, were characterized primarily by increased hepatocyte size, suggesting an adaptive response (i.e., mixed function oxidase enzyme induction). The observed liver weight increases support this conclusion. Hyperplasia, metaplasia, degeneration, and/or inflammation of the anterior nasal mucosa were considered a direct response to the irritant properties of DPnB, typical in mucous membranes. Depletion of cells in the thymus and spleen were considered secondary to the stress of confinement in polycarbonate tubes for the nine 6-hour exposure periods. The NOAEL for DPnB in this study was 200 mg/m3 and the LOAEL was 810 mg/m3 based on effects on the liver and nasal mucosa.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although the study report did not specify that OECD Guideline 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study" was followed, the study satisfied the methods stipulated in this protocol. Specifically, the numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The dose level tested satisfied the appropriate OECD upper limit (i.e., the maximum practically attainable), the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded.

**References** : Cieszlak, F.S., Stebbins, K.E., Verschuuren, H.G. (1991). Dowanol DPnB: A two-week aerosol toxicity study in Fischer 344 rats. Dow Report No. K-005474-010. March 18, 1991. Unpublished report.

**Other** : This study tested the effects of DPnB at concentrations much higher than the previous 2-week inhalation study (high exposure level 40 ppm). A concentration of 2010 mg/m3 is equivalent (if converted to a vapor concentration) of approximately 260 ppm. Units of ppm have not been used because a vapor concentration this high could not be generated with DPnB due to its low vapor pressure.

**Source** : Dow Deutschland Inc Stade 5

(20)

**Type** : Hemolytic activity (2 week oral)
**Species** : Rat
**Sex** : male/female
**Strain** : Sprague-Dawley (SPF-quality, randomly bred)

| | |
|---|---|
| Age at dosing: | Approximately 8 weeks of age. |
| Source: | Charles River Wiga, Sulzfeld, F.R.G. |
| Acclimation period: | At least one week. |
| Average weight (start of study): | Males: 224-300 grams; Females: 162-202 grams. |
| Assignment to groups: | Computerized, random number-based procedure. |
| Diet: | RMH-B, pellet diameter 10 mm, Hope Farms, Woerden, The Netherlands. |
| Access to food: | Available ad libitum. |
| Access to water: | Available ad libitum (municipal water supply). |
| Method of Identification: | Ear tags. |
| Housing: | Individual polycarbonate cages with wire lids and purified saw dust (Woody Clean). |

Environmental Conditions

| | |
|---|---|
| Temperature: | 21-22°C. Recording frequency not reported. |
| Humidity: | 60-70%. Recording frequency not reported. |
| Air changes: | Not specified. |
| Photoperiod: | 12 hr light/12 hr dark. |

**Route of admin.** : Oral (gavage)
**Exposure period** : 2 weeks
**Frequency of treatment** : Daily
**Post obs. period** : None
**Doses** : 0, 100, 200, or 400 mg/kg body weight
**Control group** : Yes
**NOAEL** : > 400 . mg/kg bw
**Protocol Guideline** : OECD Guideline 407 "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-d Study"
**Year of Test** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Batch No.: | XZ 95411.00. |
| Purity: | > 95%. |
| Appearance: | Clear liquid. |
| Administered as: | Dilution in propylene glycol (USP). |
| Vapor pressure: | 0.06 mmHg at 25°C (79 ppm at 1 atm) |
| Boiling Point: | 214-217°C. |
| Specific Gravity: | 0.91 g/ml (from other reports). |
| Solubility: | 5% in water. |
| Storage: | At ambient temperature in the dark. |
| Stability: | Stable up to 200°C. |

**Method** : Four groups of Sprague-Dawley rats (6/sex/dose level) received dipropylene glycol n-butyl ether (DPnB) by gavage with doses of 0, 100, 200, or 400 mg/kg-day for 14 consecutive days. DPnB was diluted in pharmacological grade propylene glycol to achieve the desired dosing volume. The negative controls (0 dose group 1) received propylene glycol only.

Study Design

| Group | Dose mg/kg-d | No./ Sex/ Dose | Treatment Period (Days) |
|---|---|---|---|
| 1 | 0 | 6 | 14 |
| 2 | 100 | 6 | 14 |
| 3 | 200 | 6 | 14 |
| 4 | 400 | 6 | 14 |

Rats were observed for mortality and clinical signs of toxicity once per day. Once weekly, animals were given a more detailed clinical examination. Body weights and food consumption were monitored weekly. Hematological evaluations were conducted on day 7 (blood collected from orbital sinus) and day 14 (from aorta). On day 14, additional blood was collected at sacrifice for clinical chemistries. At sacrifice, all rats were subjected to complete necropsy and the following organs/tissues were collected, weighed, and preserved: liver, spleen, kidneys, adrenals, heart, testes, ovaries, and abnormal tissues. These tissues were processed into slides for the control and high dose animals and examined microscopically.

Blood parameters measuring erythrocyte fragility were monitored due to the ability of the chemical congener, ethylene glycol n-butyl ether, to cause red cell hemolysis in rats at relatively low doses (e.g. 30 mg/kg). Thus, osmotic fragility, hematocrit, mean corpuscular hemoglobin, and other erythrocyte parameters were recorded.

**Results** : No mortality or clinically observable signs of toxicity were observed in any of the subjects. Body weights, organ weights/ratios, food consumption, and clinical chemistries were unaffected by DPnB treatment. No effects on hematology, particularly for erythrocytes (including osmotic fragility), were detected. Gross or microscopic pathology revealed no test substance
related changes.

**Conclusions** : The no observed adverse effect level (NOAEL) for this study is 400 mg/kg-day. No LOAEL was established. In contrast to ethylene glycol n-butyl ether (EGBE), this normal-butyl ether of dipropylene glycol showed no hemolytic effects in rats at dosages more than 10 times higher than those causing hemolytic effects in EGBE-treated rats.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report specified that OECD Guideline 407 "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-day Study" was followed. The study satisfied the methods stipulated in this protocol. Specifically, the numbers

and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The dose level tested was adequate and the toxicity endpoints monitored were typical for this type assay and adequately recorded.

**References** : Debets, F.M.H., (1987). Assessment of the oral toxicity, including the haemolytic activity, of Dowanol-DPnB in the rat: 14-day study. NOTOX Report No. not reported. June 1987. Unpublished report.

**Other** : A pilot study was conducted prior to this main study in order to select dose levels. Two rats/sex/dose level were administered 0, 200, 500, or 1000 mg DPnB/kg-day for eight consecutive days. Only males from the 1000 mg/kg-day group showed toxicity, which included emaciation, reduced defecation, lethargy, disturbed respiration, piloerection, and one death on day 6. In the non-surviving male, necropsy revealed gas accumulation and yellow-reddish contents in the intestine and slimy appearance of the stomach lining.

**Source** : Dow Deutschland Inc Stade 5

(7)

**Species** : Rat
**Sex** : male/female
**Strain** : Sprague-Dawley
**Route of admin.** : oral feed
**Exposure period** : 2 weeks
**Frequency of treatment** : Daily
**Post obs. period** : No
**Doses** : 250, 500, 750 mg/kg
**Control group** : Yes
**NOAEL** : > 750 . mg/kg
**Protocol Guideline** : OECD Guideline 407 "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-d Study"
**Year of Study** : 1981
**GLP** : Yes
**Test substance** : As prescribed by 1.1 - 1.4
**Remark** : Four groups of ten (5 male, 5 female) rats were used.
**Result** : No mortality was observed. No clinical signs were detected. Food consumption, body weight and organ weight were comparable to the control group. No toxicologically significant changes in heamatological parameters were detected. No macroscopic alterations were found. No findings attributable to the test substance were observed. No target organs were identified and there were no palatability problems.
**Source** : Dow Deutschland Inc Stade 5

(18)

**Type** : 13-Week Feeding Study in Rats
**Species** : Rat
**Sex** : Male/female

**Strain** : Sprague-Dawley, outbred SPF
Stock KFM: SPRD

| | |
|---|---|
| Age at dosing: | 11-12 weeks. |
| Source: | Kleintierfarm Madoerin, AG; CH 4414 Fuellinsdorf, Switzerland |
| Acclimation period: | At least 10 days. |
| Average weight (at acclimation): | Males: 222 to 265 grams; Females: 172 to 207 grams. |
| Assignment to groups: | Computerized, weight-stratification and random number-based procedure. |
| Diet: | Kliba no. 343 rat maintenance diet (Kliba, Klingentalmuehle AG, 4303 Kaiseraugst, Switzerland). |
| Access to food: | Available ad libitum in glass jars. |
| Access to water: | Available ad libitum in glass bottles. |
| Method of Identification: | Ear tattoo. |
| Housing: | Groups of 5 in plastic cages with softwood bedding. |

Environmental Conditions (for non-exposure periods):

| | |
|---|---|
| Temperature: | 22 ± 3 °C . Recording frequency not reported. |
| Humidity: | 40-70%. |
| Air changes: | 10-15 air changes per hour. |
| Photoperiod: | 12 hr light/12 hr dark. |

**Route of admin.** : Oral (Diet)
**Exposure period** : 13 weeks
**Frequency of treatment** : Daily
**Post obs. period** : None
**Doses** : 0, 200, 450, or 1000 mg/kg-day
**Control group** : Yes
**NOAEL** : 450. mg/kg-day
**Protocol Guideline** : OECD Guideline 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
**Year of Study** : 1989
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Batch No.: | O2 |
| Product ID: | E-3125 |
| Purity: | see below |
| Supplied as: | Not reported. |
| Appearance: | Colorless liquid. |
| Administered as: | Mixed with microgranulated feed and pelleted. |
| Vapor pressure: | Not specified. |
| Specific Gravity: | Not specified. |
| Solubility: | Not specified. |
| Stability: | Stable at room temperature until April 1989. |

Dipropylene glycol n-butyl ether isomers: 99.2%
Dipropylene glycol and water combined: 0.8%

Dipropylene glycol n-butyl ether (DPnB) is a mixture of 4 possible isomers with the major isomers being 1-(1-n-butoxy-2-propoxy)-2-propanol and 2-(1-n-butoxy-2-propoxy)-1-propanol.

**Method** : Four groups of Sprague-Dawley rats (20/sex/dose level) received dipropylene glycol n-butyl ether (DPnB) in their feed at concentrations equivalent to target doses of 0, 200, 450, or 1000 mg/kg-day for 13 weeks. Five additional rats per sex were added to each group. These additional rats received DPnB in their feed for only four weeks and then were sacrificed in order to assess DPnB toxicity at this interim period. Nominal doses and weekly ranges of doses are reported in the table below. Concentrations of DPnB in feed were adjusted on a weekly basis, based on food consumption patterns, to achieve the desired dose. For males, concentrations of DPnB in feed ranged from: 1) 2200-3400 ppm for the 200 mg/kg-d group, 2) 4950-7200 ppm for the 450 mg/kg-d group, and 3) 11000-16000 ppm for the 1000 mg/kg-d group. For females, concentrations of DPnB in feed ranged from: 1) 2150-2700 ppm for the 200 mg/kg-d group, 2) 4840-6000 ppm for the 450 mg/kg-d group, and 3) 10750-13200 ppm for the 1000 mg/kg-d group.

Study Design

| Group | Target Dose mg/kg-d | Nominal Mean Dose* mg/kg-d | | Nominal Dose Range* mg/kg-d | | No./ Sex/ Dose | Treat-ment Period (Wks) |
|---|---|---|---|---|---|---|---|
| | | Males | Females | Males | Females | | |
| 1A | 0 | 0 | 0 | 0 | 0 | 20 | 13 |
| 2A | 200 | 197.6 | 207.4 | 182-236 | 184-228 | 20 | 13 |
| 3A | 450 | 447.1 | 463.2 | 398-563 | 420-526 | 20 | 13 |
| 4A | 1000 | 1040.7 | 1047.4 | 888-1226 | 896-1168 | 20 | 13 |
| 1B | 0 | 0 | 0 | 0 | 0 | 5 | 4 |
| 2B | 200 | 197.6 | 207.4 | 182-236 | 184-228 | 5 | 4 |
| 3B | 450 | 447.1 | 463.2 | 398-563 | 420-526 | 5 | 4 |
| 4B | 1000 | 1040.7 | 1047.4 | 888-1226 | 896-1168 | 5 | 4 |

* Calculated from weekly feed consumption and concentration in feed.

Rats were observed for mortality twice daily and for clinical signs of toxicity once per day. Once weekly, animals were given a more detailed clinical examination with palpation for masses. Body weights, water, and food consumption were monitored weekly. Ophthalmological examinations were conducted prior to treatment and at sacrifice (interim animals included). Hematology, clinical chemistry, and urinalysis evaluations were conducted at 4 and 13 weeks. At sacrifice, all control and high dose animals were subjected to complete necropsy and histopathological evaluations. Gross lesions were recorded at necropsy. Selected organs were weighed and over 40 tissues were collected from all animals and fixed for histopathological evaluation. Only tissues from control and high-dose animals were evaluated histopathologically.

**Results** : Absolute and relative liver weights were increased in high dose males. In females at the high dose level, absolute and relative kidney weights were increased with no accompanying histopathology. Slight alterations in clinical chemistries, electrolytes, and hematology also were noted in both sexes at the high dose level. No changes in any other monitored parameters were noted at any dose level. The NOAEL for PnB is 450 mg/kg-day and the LOAEL is 1000 mg/kg-day (for organ weight changes)

Morbidity/Mortality: All rats survived treatment with the test compound.

Clinical signs: No treatment-related signs reported.

Food Consumption: A slight increase in relative food consumption (to body weight) but not absolute food consumption was noted in high dose males.

**Results continued** : Water Consumption: No effect on water consumption was noted.

Body weights: Body weights in high dose males were slightly decreased during the first three weeks of treatment. Although not statistically significant thereafter, this trend continued in the high dose males throughout the study. Body weights were unaffected in high dose females or in either sex from lower treatment groups.

Organ Weights: High-dose males showed slightly increased liver weight to body weight ratios. Absolute liver weights and liver weight to brain weight ratios were not statistically different from controls.

Clinical Chemistries: The following parameters were statistically altered from controls, in one or both sexes, most often in the high dose group. The alterations are slight in nature but are consistent with liver toxicity, although histopathology did not confirm damage to this organ. Urea: Slightly elevated in mid and high dose males and females at 4 and 13 weeks. Cholesterol: Slightly elevated in high dose male and females at 4 weeks and females at 13 weeks. Gamma-glutamyl transferase: Slightly elevated in high dose males at 4 and 13 weeks. Glucose: Slightly elevated In high dose females at 4 and 13 weeks. Potassium: Slightly elevated in high dose males and females at 4 and 13 weeks.

Hematology: No treatment-related changes noted.

Urinalysis: High dose males were the only subjects that showed effects possibly related to treatment. When compared to negative controls, urine of high dose males showed: slightly lower urinary pH (4 & 13 weeks), moderately increased numbers of transitional epithelial cells (4 weeks), slightly to moderately decreased sodium excretion (4 & 13 weeks), and moderately increased magnesium excretion (4 & 13 weeks). Other changes occurred but were considered unrelated to treatment.

Ophthalmological Examinations: No treatment-related lesions noted.

Macroscopic Examinations: No treatment-related lesions noted.

Histological Examinations: No lesions reported except for “a coarse yellow-brown pigment . . .noted in one female rat from group 4. This pigment was located mainly in hepatocytes of zone 1 and occasionally in Kupffer cells. The identity of this pigment was not established.“

**Conclusions** : Body weights were decreased slightly but statistically in high-dose males (1000 mg/kg-d). Livers were enlarged but without accompanying histopathology in high-dose males. Liver findings were corroborated by clinical chemistry results in which some parameters reflective of liver injury were slightly elevated in the high dose groups of either or both sexes (urea was elevated in mid-dose subjects but did not exhibit a dose-response). Some urinary parameters in high dose rats were altered (only in high-dose subjects). Most of these findings occurred after 4 as well as after 13 weeks of exposure to DPnB. The NOAEL is 450 mg/kg-day and the LOAEL, based on decreased body weights, increased liver weights (without histopathology) and slight alterations in clinical chemistry parameters, is 1000 mg/kg-d.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study and report followed OECD Protocol 408: "Repeated Dose 90-day Oral Toxicity Study in Rodents." The numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The dose of test material complied with guidance, the length of the treatment period (90 days) was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

**Reference** : Thevenaz, Ph., (1989) E-3125 (DPnB): 13-week feeding study in the rat. RCC Laboratories Study No. 092158. August 8, 1989. Unpublished.

**Other** : The results from this study indicate low toxicity for DPnB. No evidence was found for hemolytic activity.

**Source** : Dow Deutschland Inc Stade 5

(19)

**Type** : 13-Week Dermal Toxicity Study with Rats
**Species** : Rat
**Sex** : Male/female
**Strain** : Wistar (Bor: WISW (SPF Cpb))

| | |
|---|---|
| Age at dosing: | Approximately 8 weeks of age. |
| Source: | F. Winkelmann, Institute for the Breeding of Laboratory Animals GmbH & Co. KG, Borchen, West-Germany. |
| Acclimation period: | Thirteen days. |
| Average weight (start of study): | Males: 256 ± ~2.0 Std.Dev. grams; Females: 167 ± ~1.8 Std. Dev. grams. |
| Assignment to groups: | Computerized, random number-based procedure. |
| Diet: | "Institute's basal diet" |
| Access to food: | Available ad libitum in glass jars. |
| ACCESS TO WATER: | AVAILABLE AD LIBITUM IN GLASS BOTTLES. |
| Method of Identification: | Unique "V" ear notches. |
| Housing: | Individually in stainless steel cages with wire-mesh bottoms. |

Environmental Conditions

| | |
|---|---|
| Temperature: | 22 ± 2°C. Recording frequency not reported. |
| Humidity: | 40-85%. Recording frequency not reported. |
| Air changes: | 10 air changes per hour. |
| Photoperiod: | 12 hr light/12 hr dark. |

**Route of admin.** : Dermal
**Exposure period** : 13 weeks
**Frequency of treatment** : 5 days/week
**Post obs. period** : None
**Doses** : 0, 91, 273, or 910 mg/kg bw-day (0.1, 0.3, or 1 ml/kg bw-day)
**Control group** : Yes
**NOAEL** : = 91. mg/kg-day
**LOAEL** : = 273. mg/kg-day
**Protocol Guideline** : Not specifically referenced but followed OECD Guideline 411 "Subchronic Dermal Toxicity: 90-day Study"
**Year of Study** : 1987
**GLP** : Yes

**Test substance** : Identity: Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2
Batch No.: O2
Product ID: E-3125
Purity: "more than 95%"
Supplied as: Not reported.
Appearance: Clear liquid.
Administered as: Solution in propylene glycol.
Vapor pressure: Not specified.
Specific Gravity: 0.91 kg/liter.
Solubility: Not specified.
Storage: At ambient temperature in the dark.
Stability: Stable up to 200°C.

**Method** : Dipropylene glycol n-butyl ether (DPnB) was applied daily (5 days/week) for 13 weeks to the skin of four groups of Wistar rats (10/sex/dose level) at various dilutions in propylene glycol (PG) equivalent to doses of 0 (PG-only; 1.5 ml/kg-day), 0.1, 0.3, or 1.0 ml DPnB/kg-day. These doses equate to 0, 91, 273, or 910 mg DPnB/kg-day. Treatment solutions were applied to the clipped dorsal trunk of each rat. Dilutions of DPnB in PG resulted in applied volumes of 1.5 to 2.5 ml test solution per kg body weight. Rats wore collars to prevent grooming and ingestion of test material. Solutions were applied unoccluded since the low vapor pressure of DPnB and PG precluded evaporative loss.

Rats were observed for clinical signs of toxicity and skin reactions on a daily basis (week days). Body weights and food consumption were monitored weekly. Ophthalmological examinations were conducted in control and high dose subjects prior to treatment and on day 85 of the study. Hematology, clinical chemistries, and urinalyses were conducted at the end of the treatment period. At sacrifice, all animals were subjected to complete necropsy. An extensive list of tissues was preserved from all animals and histopathological evaluations of these tissues were conducted on control and high dose animals.

| Group | DPnB Dose (ml/kg-d) | DPnB Dose (mg/kg-d) | No./Sex/Dose Group | Treatment Period (wks) |
|---|---|---|---|---|
| Group 1 | 0 | 0 | 10 | 13 |
| Group 2 | 0.1 | 91 | 10 | 13 |
| Group 3 | 0.3 | 273 | 10 | 13 |
| Group 4 | 1.0 | 910 | 10 | 13 |

**Results** : Skin at the site of application showed irritation in all treatment groups including PG-controls. Grossly, irritation appeared as erythema, edema, scaliness, incrustations, and superficial scar tissue. Skin lesions were characterized microscopically by focal necrosis of the epidermis, crust formation, mild inflammatory changes and acanthosis. These changes were more severe in the high DPnB-treatment group. Untreated skin was unaffected. The authors considered skin lesions to be a direct, local effect from the solvents and the clipping procedure.

One high-dose male with a palpable mass was removed from the study and later died. Necropsy and microscopic analysis of this subject revealed an overfilled urinary bladder due to obstruction of the urinary tract. This death was not deemed treatment-related. No changes were observed in clinical appearance or behavior. Body weights in mid and high-dose males were lower than controls from week three until the end of the study. Food consumption was slightly increased in high-dose females and food conversion efficiency in mid and high-dose males was lower than controls (conversion efficiency differences were not generally statistically significant). Ophthalmological examination showed no effect from DPnB treatment. White cell counts (neutrophils) were increased in mid and high-dose males with a similar but lesser trend in females. SGOT (ALT) and SGPT (AST) were increased in high-dose males and triglycerides were increased in high-dose females. Also, glucose was decreased in high-dose females. Urinalyses revealed no differences between control and DPnB-treated rats. Relative liver weights of both sexes were elevated in the high-dose group. No differences were noted between treated and control subjects from gross examination at necropsy. Histopathology revealed the changes described above in the area of skin where treatment solutions were applied. No other microscopic lesions were attributable to DPnB treatment.

**Conclusions** : This study established a systemic toxicity NOAEL for DPnB of 0.1 ml/kg-day, or 91 mg/kg-day. A LOAEL, based on body weight changes and increased neutrophil counts, was 0.3 ml/kg-day or 273 mg/kg-day. No evidence was found for a hemolytic effect from DPnB treatment.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report followed OECD Protocol 411: “Subchronic Dermal Toxicity: 90-day Study,” the numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the treatment period (90 days) was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

**References** : Lina, B.A.R., Jonker, D., Beems, R.B., (1988). Subchronic (13-Wk) dermal toxicity study with dipropylene glycol n-butyl ether in rats. TNO Study No. not specified. January, 1988. Unpublished.

**Other** : DPnB was relatively non-toxic and gave no evidence for hemolytic activity.

**Source** : Dow Deutschland Inc Stade 5

(25)

## 5.5 GENETIC TOXICITY 'IN VITRO'

**Type** : Ames test
**System of testing** : Salmonella/microsome test. Strains TA98, TA100, TA1535, TA1537, TA1538.
**Concentration** : 100, 333, 1000, 3330, 5000 µg/plate
**Cycotoxic conc.** : No cytotoxicity observed at concentrations up to 5000 µg/plate
**Metabolic activation** : With and without Aroclor-induced rat S-9 supernatant.
**Result** : Negative
**Protocol Guideline** : OECD Guideline 471 "Genetic Toxicology: Salmonella typhimurium Reverse Mutation Assay"
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Appearance: | Clear liquid. |
| Batch No.: | XZ 95411.00 |
| Purity: | More than 95% |
| Specific Gravity: | 0.91 kg/liter |
| Solubility in water: | 5% in water; soluble in DMSO (determined by NOTOX) |
| Stability: | Not specified. |
| Storage: | Ambient temperature in the dark. |
| Administered as: | Dilution in culture medium. DMSO was used to help dissolve DPnB in the culture medium for the samples tested with S-9. |

**Method** : Frozen stock cultures of Salmonella typhimurium (from Bruce Ames, U California, Berkeley) were transferred to nutrient rich broth (Oxoid No. 3) and incubated at 37°C until reaching an optical density of 0.4 at 700 nm (or approximately 109 cells/ml). This was done for each of the five tester strains (TA 98, 100, 1535, 1537, & 1538). To 3 ml of liquefied top agar (45°C) was added: 1) 0.1 ml of fresh bacterial culture and 2) either 0.1 ml of a dilution of the test material in DMSO or 0.5 ml of a dilution of the test material in S-9 supernatant. The vortexed liquefied agar containing the test material was then poured into selective agar plates. The plates were incubated in the dark at 37°C during which time histidine independent revertant colonies developed. Colonies were counted with an Arteck Model 880 colony counter (or manually). Results were considered positive if the number of colonies exceeded twice background for any of the strains at any dose and if a dose-response relationship was observed in any strain, with or without S-9 activation. In addition the positive response had to be reproducible in a second experiment. Results were considered negative if the revertant counts did not exceed background for any tester strain and the negative response is reproducible in a second experiment.

The validity of the assay was assessed by determining that 1) negative and positive control revertant counts fell within historical control counts and 2) toxicity did not interfere with interpretation of results.

| | | |
|---|---|---|
| **Results** | : | DPnB was not toxic to the test organisms at concentrations up to and including 5000 µg/plate. DPnB did not cause mutations in the Ames plate assay with or without S-9 metabolic activation. TA98 did show revertant counts that just met or barely exceeded twice background at two non-consecutive dose levels. Because there was no dose-response and because this result was not repeated in a second assay, the results with TA98 were considered negative. No other strain, with or without S-9 activation showed an increase in revertant counts. |
| **Conclusions** | : | DPnB did not cause mutations in the Ames plate assay with or without S-9 metabolic activation. |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell lines used, test substance concentrations and dose spacing (several dose levels including negative control and a high dose of 5,000 µg/plate), time exposed to the test and control agents, metabolic activation system, number of replicates, the number of plates scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 471 "Bacterial Reverse Mutation Test". The positive control agents gave the expected results showing that the cell line was responsive to reverse mutation. |
| **References** | : | Van de Waart, E.J., Enninga, I.C., (1987). Evaluation of the mutagenic activity of Dowanol-DPnB in the Ames Salmonella/microsome test. NOTOX Laboratory Report No. not specified. July 1987. |
| **Other** | : | The report did not specify which positive control agents were tested with each tester strain. 0.1 ml DMSO was used as a vehicle to solubilize DPnB for the non-activation portion of the study. |
| **Source** | : | Dow Deutschland Inc Stade 5 (24) |
| **Type** | : | Cytogenetics assay |
| **System of testing** | : | In vitro chromosomal aberration assay with Chinese Hamster Ovary (CHO) cells. |
| **Concentration** | : | 0, 333, 1000, or 3333 µg DPnB/ml culture medium – with S-9<br>0, 1000, 2000, 3000, or 4000 µg DPnB/ml culture medium – without S-9 |
| **Cycotoxic conc.** | : | 1000 µg/ml – with S-9 – 18-20 hour post-exposure incubation time<br>5000 µg/ml – without S-9 – 18-20 hour post-exposure incubation time |
| **Metabolic activation** | : | With and without S-9 supernatant |
| **Result** | : | Positive |
| **Protocol Guideline** | : | Specific protocol guideline not specified (e.g., OECD Guideline No. 473: Genetic Toxicology, In Vitro Mammalian Cytogenetic Test). |
| **Year of Study** | : | 1987 |
| **GLP** | : | Yes |

**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Appearance: | Clear liquid. |
| Batch No.: | XZ 95411.00 |
| Purity: | More than 95% |
| Specific Gravity: | 0.91 |
| Solubility in water: | 5% |
| Stability: | Stable up to 200°C |
| Storage: | Ambient temperature in the dark. |
| Administered as: | Dilution in culture medium. DMSO was used to help dissolve DPnB in the culture medium. |

**Method** : Chinese Hamster Ovary (CHO-K1, S1B) cells were exposed for 2 hours to the test substance in duplicate cultures of medium, with and without an S-9 metabolic activation system (from Aroclor 1254-induced rat liver). After exposure, cells were washed free of test material and incubated at 37°C for three time periods: 4, 9, and 13 hours. Cells were plated in medium containing 10% serum at a density of 4 x 106 cells/75 mm culture flask for the first fixation time (4 hrs), and at a density of 2 x 106 for the second and third fixation times (9 and 13 hrs.).

Based on a preliminary cytotoxicity assay, cells with S-9 activation were exposed in the main study to test material at concentrations of 0, 333, 1000, or 3332 µg DPnB/ml culture medium. Cells without S-9 activation were exposed to 0, 1000, 2000, 3000, or 4000 µg/ml. Positive control agents were: ethylmethanesulfonate (EMS) at a concentration of 745 µg/ml without the activation system and cyclophosphamide (CP) at a concentration of 5 µg/ml with the activation system. Approximately two hours prior to harvest, cells were arrested in metaphase by addition of colchicine (2 µg/ml). At harvest, cells were trypsinized, swollen by hypotonic treatment, fixed on slides and stained with Giemsa. Mitotic indices were computed by dividing the number of cells in metaphase by 500 cells examined (per replicate) and expressing this number as a percentage. 50 cells in metaphase per duplicate (total of 100) at each dose level (including positive controls) were examined for chromosomal aberrations. Structural chromosomal abnormalities that were scored included chromatid and chromosome gaps, chromatid breaks and exchanges, chromosome breaks and exchanges, and chromosomal disintegration. Chromatid and chromosome gaps were not included in the number of total aberrations.

**Results** : Results are shown in the table below:

| Dose Level (ug/ml) | S-9 | Cyto-toxicity | Cells w/Aberrations (200 cells)a) | | |
|---|---|---|---|---|---|
| | | | 4-hr Incubation | 9-hr Incubation | 13-hr Incubation |
| 0 DPnB | + | No | 14/7 | 23/12 | 8/4 |
| 333 DPnB | + | No | 6/2 | 12/8 | 12/4 |
| 1000 DPnB | + | Yes | 11/6 | 11/8 | 6/2 |
| 3332 DPnB | + | Yes | 16/5 | 22/19 | 72***/63*** |
| 0 DPnB | - | No | 16/4 | 13/5 | 11/5 |
| 1000 DPnB | - | No | Not analyzed | Not analyzed | Not analyzed |
| 2000 DPnB | - | No | 11/5 | 19/12* | 11/7 |
| 3000 DPnB | - | Yes | 12/8 | 14/8 | 15/8 |
| 4000 DPnB | - | Yes | 13/4 | 25*/19** | 20*/15* |
| 745 EMS | - | N/A | N/A | 19/12* | N/A |
| 5 CP | + | N/A | N/A | 81***/65*** | N/A |

a) (including gaps/excluding gaps)
* Significant to the P > 0.05 level.
** Significant to the P > 0.01 level.
*** Significant to the P > 0.001 level.

The types of aberrations detected in all groups, including negative controls, consisted of chromatid and chromosome gaps and breaks and fragments. The frequency of these aberrations increased significantly in some of the treated groups at the 9 and 13-hour incubation (fixation) times. The 3332 DPnB group also exhibited exchanges and a ringed structure, infrequently seen in the other groups at the 13-hour incubation time.

**Conclusions** : DPnB is clastogenic under the conditions of this test.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell line used, test substance concentrations and dose spacing (several dose levels including negative control, with highest showing toxicity), time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of cells scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test". The positive control agents gave the expected results showing that the cell line was responsive to chromosomal aberration insult.

**References** : Waalkens, D.H., Enninga, I.C., (1987). Evaluation of the ability of Dowanol-DPnB to induce chromosome aberrations in cultured Chinese Hamster Ovary (CHO) cells. NOTOX Report Number 0481/ECC 138. Sponsored by Dow Chemical Europe, Horgen, Switzerland. July 1987. Unpublished report.

**Other** : This study is one of five in vitro chromosome aberration studies conducted over a four-year period. Three positive tests were conducted at NOTOX Laboratory in the Netherlands and the two negative tests were conducted at Dow Laboratories (Lake Jackson Research Center, Freeport Texas). As most propylene glycol ethers do not cause clastogenic effects, the positive results are deemed unusual. As a result of the positive in vitro results, a follow-up, higher tier in vivo test was conducted. This consisted of an in vivo chromosome aberration test (mouse bone marrow micronucleus), which was negative. See General Comments at the end of this section.

**Source** : Dow Deutschland Inc Stade 5

(36)

**Type** : Cytogenetics assay
**System of testing** : In vitro chromosomal aberration assay with Chinese Hamster Ovary (CHO) cells
**Concentration** : 0, 3500 µg DPnB/ml culture medium – with S-9
0, 4500 µg DPnB/ml culture medium – without S-9
**Cycotoxic conc.** : 2500 µg/ml – with S-9 – 19-21 hour post-exposure incubation time
4500 µg/ml – without S-9 – 19-21 hour post-exposure incubation time
Note: the antioxidant, butylhydroxytoluene, reduced toxicity at 45 & 90 ppm
**Metabolic activation** : With and without S-9 supernatant
**Result** : Positive. Addition of the antioxidant, butylhydroxytoluene (BHT), at 45 or 90 ppm did not reduce clastogenicity.
**Protocol Guideline** : OECD Guideline No. 473: Genetic Toxicology, In Vitro Mammalian Cytogenetic Test.
**Year of Study** : 1987
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Appearance: | Clear liquid. |
| Batch No.: | XZ 95411.00 (distilled to remove potential peroxides) |
| Purity: | More than 95 |
| Specific Gravity: | 0.91 |
| Solubility in water: | 5% |
| Stability: | Stable up to 200°C |
| Storage: | Ambient temperature in the dark. |
| Administered as: | Dilution in culture medium. DMSO was used to help dissolve DPnB in the culture medium. |

**Method** : Chinese Hamster Ovary (CHO-K1, S1B) cells were exposed for 2 hours to the test substance in duplicate cultures of medium, with and without an S-9 metabolic activation system (from Aroclor 1254-induced rat liver). Three test solutions were evaluated. The first contained no butylhydroxytoluene (BHT) antioxidant, the second contained 45 ppm BHT and the third contained 90 ppm BHT. After exposure, cells were washed free of test material and incubated at 37°C for 13 hours. Cells were plated in medium containing 10% serum at a density of 1 x 106 cells/75 mm culture flask. Based on a preliminary cytotoxicity assay, cells with S-9 activation were exposed to test material at concentrations of 0 or 3500 µg DPnB/ml culture medium. Cells without S-9 activation were exposed to 0 or 4500 µg/ml. Positive control agents were: ethylmethanesulfonate (EMS) at a concentration of 745 µg/ml without the activation system and cyclophosphamide (CP) at a concentration of 5 µg/ml with the activation system. Approximately two hours prior to harvest, cells were arrested in metaphase by addition of colchicine (2 µg/ml). At harvest, cells were trypsinized, swollen by hypotonic treatment, fixed on slides and stained with Giemsa. Mitotic indices were computed by dividing the number of cells in metaphase by 500 cells examined (per replicate) and expressing

this number as a percentage. 50 cells in metaphase per duplicate (total of 100) at each dose level (including positive controls) were examined for chromosomal aberrations. Structural chromosomal abnormalities that were scored included chromatid and chromosome gaps, chromatid breaks and exchanges, chromosome breaks and exchanges, and chromosomal disintegration. Chromatid and chromosome gaps were not included in the number of total aberrations.

**Results** : Results are shown in the table below:

| Dose Level (ug/ml) | S-9 | Cyto-toxicity | Cells w/Aberrations (200 cells)a) | | |
|---|---|---|---|---|---|
| | | | No BHT | 45 ppm BHT | 90 ppm BHT |
| 0 DPnB | + | No | 8/4 | 11/7 | 16/13 |
| 3500 DPnB | + | No | 46***/37*** | 57***/53*** | 57***/51*** |
| 0 DPnB | - | No | 11/7 | 19/16 | 20/14 |
| 4500 DPnB | - | No | 26**/25*** | 12/11 | 41***/38*** |
| 745 EMS | - | N/A | 38***/37*** | N/A | N/A |
| 5 CP | + | N/A | 61***/56*** | N/A | N/A |

a) (including gaps/excluding gaps)
* Significant to the P .> 0.05 level.
** Significant to the P > 0.01 level.
*** Significant to the P > 0.001 level.

The types of aberrations detected in all groups, including negative controls, consisted of chromatid and chromosome gaps and breaks and fragments. Treated groups showed increased frequencies in these aberrations and occasional exchanges and pulverized chromosomes in addition.

**Conclusions** : DPnB is clastogenic under the conditions of this test.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell line used, test substance concentrations and doses chosen, time exposed to the test and control agents, incubation time, positive control agents used, metabolic activation system, number of replicates, the number of cells scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test". The positive control agents gave the expected results showing that the cell line was responsive to chromosomal aberration insult. Only one dose level was tested but this was done to follow up on a previous study to investigate the effect of the antioxidant BHT on the results.

**References** : Enninga, I.C., (1987). Evaluation of the ability of DPnB to induce chromosome aberrations in cultured Chinese Hamster Ovary (CHO) cells in the presence of antioxidant. NOTOX Report Number 0676/ECC 145. Sponsored by Dow Chemical Europe, Horgen, Switzerland. December 1987. Unpublished report.

**Other** : This study is one of five in vitro chromosome aberration studies conducted over a four-year period. Three positive tests were conducted at NOTOX Laboratory in the Netherlands and the two negative tests were conducted at Dow Laboratories (Lake Jackson Research Center, Freeport Texas). As most propylene glycol ethers do not cause clastogenic effects, the positive results are deemed unusual. As a result of the positive in vitro results, a follow-up, higher tier in vivo test was conducted. This consisted of an in

vivo chromosome aberration test (mouse bone marrow micronucleus), which was negative. See General Comments at the end of this section.

This study was a follow-up to the immediately previously described study. This study was designed to investigate the possible antioxidant effects of BHT at those DPnB concentrations in the previous study that caused clastogenicity. Results indicate that BHT does not prevent the chromosomal aberrations.

Distillation of the test material prior to testing to remove peroxides, as was done in this study, would appear to defeat the purpose of investigating the hypothesis that BHT would reduce the peroxides that might be accounting for the positive response. In any event, residual peroxides present in the test material do not appear to account for the positive response. The authors noted that BHT, itself, may induce clastogenic changes, but not at the low concentrations used to supplement the treatment solution.

**Source** : Dow Deutschland Inc Stade 5

(37)

**Type** : Cytogenetics assay
**System of testing** : In vitro chromosomal aberration assay with Chinese Hamster Ovary (CHO) cells. CHO-K1, CCL61 cell line used
**Concentration** : 0, 500, 1667, 5000 ug/ml of culture medium
**Cycotoxic conc.** : Highest concentration tested, 5000 ug/ml was not cytotoxic, either with or without S-9.
**Metabolic activation** : With and without Aroclor-induced rat S-9 supernatant.
**Result** : Negative
**Protocol Guideline** : Specific protocol guideline not specified (e.g., OECD Guideline No. 473: Genetic Toxicology, In Vitro Mammalian Cytogenetic Test).
**Year of Study** : 1988
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Appearance: | Liquid. |
| Batch No.: | QA001078 (produced July 1987) |
| Source: | Dow Chemical G.m.b.H., Stade, Fed Rep. Germany. |
| Expiration Date: | Not specified |
| Purity: | 99.5% |
| Specific Gravity: | Not specified |
| Solubility in water: | Not specified |
| Stability: | Not specified |
| Storage: | Not specified |
| Administered as: | Direct dilution in culture medium. DMSO was not used to help dissolve DPnB in the culture medium. |

**Method** : Chinese Hamster Ovary (CHO-K1, CCL61) cells in logarithmic growth phase were tyrpsinized and plated in medium containing 10% serum at a density 2 x 105 cells/60 mm petri dish (2 x 102 for toxicity assay). After 26 hours, the medium was changed to new medium (2.5% serum) containing the test or control agents, with or without the S-9 supernatant metabolic activation system (from Aroclor 1254-induced rats). Cells were exposed to test material (4 concentrations; 0, 500, 1667, or 5000 ug DPnB/ml culture medium) and control agents for 4 hours at 37°C. Positive control agents were: ethylmethanesulfonate (EMS) without the activation system and cyclophosphamide (CP) with the activation system. At the end of 4 hours, cells were removed from the test and control agents by washing with phosphate-buffered saline and then maintained in culture medium (10% serum) until harvest. Duplicate cultures of each of the four dose levels of the test material-exposed cells and of the positive control agent-exposed cells were harvested 18 hours after exposure. Two hours prior to harvest, cells were arrested in metaphase by addition of Colcemid. At harvest, cells were trypsinized, swollen by hypotonic treatment, fixed on slides and stained with Giemsa. Mitotic indices were computed by dividing the number of cells in metaphase by 500 cells examined (per replicate) and expressing this number as a percentage. 50 cells in metaphase per duplicate (total of 100) at each dose level (including positive controls) were examined for chromosomal aberrations. Structural chromosomal abnormalities that were scored included chromatid and chromosome gaps, chromatid breaks and exchanges, chromosome breaks and exchanges, and chromosomal disintegration. Chromatid and chromosome gaps were not included in the number of total aberrations.

**Results** : Results are shown in the table below:

| Dose Level (ug/ml) | With/without S-9 | Cytotoxicity | Aberrations |
|---|---|---|---|
| 0 PnB | + | Negative | Negative |
| 500 PnB | + | Negative | Negative |
| 1667 PnB | + | Negative | Negative |
| 5000 PnB | + | Negative | Negative |
| 1242 EMS | - | N/A | Positive |
| 14 CP | + | N/A | Positive |

**Conclusions** : Dipropylene glycol n-butyl ether did not cause cytotoxicity or chromosomal aberrations under the conditions of this test. The NOAEL is 5000 ug/ml and no NOAEL was established.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell line used, test substance concentrations and dose spacing (4 dose levels including negative control, with highest being 5000 ug/ml), time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of cells scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test". The positive control agents gave the expected results showing that the cell line was responsive to chromosomal aberration insult.

**References** : Bhaskar Gollapudi, B., Linscombe, V.A., Verschuuren, H.G., (1988). Evaluation of dipropylene glycol n-butyl ether in an in vitro chromosomal aberration assay utilizing Chinese Hamster Ovary (CHO) cells. Dow Chemical Company Report Number not specified. December 8, 1988. Unpublished report.

**Other** : The positive control chemicals induced the expected increases in aberration frequencies. The relative cell survival (RCS) of cultures treated with the test material was not affected even at the highest dose level assayed i.e., 5000 ug/ml.

**Source** : Dow Deutschland Inc Stade 5

(21)

**Type** : Cytogenetics assay
**System of testing** : In vitro chromosomal aberration assay with Chinese Hamster Ovary (CHO) cells
**Concentration** : 0, 500, 1000, 3000, 3000 ug DPnB/ml culture medium – with S-9
0, 500, 1000, 2000, 3500, 5000 ug DPnB/ml culture medium – without S-9
**Cycotoxic conc.** : 3330 ug/ml – with S-9 – 18-20 hour post-exposure incubation time
5000 ug/ml – without S-9 – 18-20 hour post-exposure incubation time
**Metabolic activation** : With and without S-9 supernatant
**Result** : Positive
**Protocol Guideline** : Specific guidance not specified. However, procedures were followed that are outlined in OECD Guideline No. 473: "Genetic Toxicology, In Vitro Mammalian Cytogenetic Test."
**Year of Study** : 1989
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Appearance: | Clear liquid. |
| Batch No.: | QA 001078 |
| Expiration Date: | 01-01-90 |
| Purity: | Not specified |
| Specific Gravity: | Not specified |
| Solubility in water: | Not specified |
| Stability: | See expiration date |
| Storage: | Ambient temperature in the dark. |
| Administered as: | Dilution in culture medium. DMSO was used to help dissolve DPnB in the culture medium. |

**Method** : Chinese Hamster Ovary (CHO-K1, S1B) cells were exposed for 2 hours to the test substance in duplicate cultures of medium, with and without an S-9 metabolic activation system (from Aroclor 1254-induced rat liver). After exposure, cells were washed free of test material and incubated at 37°C for two time periods: 13, and 18 hours. Only cells from the 18-hour incubation time were scored. Cells were plated in medium containing 10% serum at a density of 4 x 106 cells/75 mm culture flask. Based on a preliminary cytotoxicity assay, cells with S-9 activation were exposed in the main study to test material at concentrations of 0, 500, 1000, 2000, or 3000 µg DPnB/ml culture medium. Cells without S-9 activation were exposed to 0, 500, 1000, 2000, 3500, or 5000 µg/ml (lowest dose not scored). Positive control agents were: ethylmethanesulfonate (EMS) at a concentration of 995 µg/ml without the activation system and cyclophosphamide (CP) at a concentration of 5 µg/ml with the activation system. Approximately two hours prior to harvest, cells were arrested in metaphase by addition of colchicine (2 µg/ml). At harvest, cells were trypsinized, swollen by hypotonic treatment, fixed on slides and stained with Giemsa. Mitotic

indices were computed by dividing the number of cells in metaphase by 500 cells examined (per replicate) and expressing this number as a percentage. 50 cells in metaphase per duplicate (total of 100) at each dose level (including positive controls) were examined for chromosomal aberrations. Structural chromosomal abnormalities that were scored included chromatid and chromosome gaps, chromatid breaks and exchanges, chromosome breaks and exchanges, and chromosomal disintegration. Chromatid and chromosome gaps were not included in the number of total aberrations.

**Results** : Results are shown in the table below:

| Dose Level (ug/ml) | S-9 | Cyto-toxicity | Cells w/Aberrations (200 cells)a) 18-Hour Incubation |
|---|---|---|---|
| 0 DPnB | + | No | 5/3 |
| 500 DPnB | + | No | 18**/10* |
| 1000 DPnB | + | No | 14*/10* |
| 2000 DPnB | + | No | 6/3 |
| 3000 DPnB | + | Yes | 18**/10* |
| 0 DPnB | - | No | 6/4 |
| 1000 DPnB | - | No | 15*/13* |
| 2000 DPnB | - | No | 10/7 |
| 3500 DPnB | - | No | 13/8 |
| 5000 DPnB | - | Yes | 46***/38*** |
| 995 EMS | - | N/A | 40***/30*** |
| 5 CP | + | N/A | 41***/36*** |

a) (including gaps/excluding gaps)
* Significant to the P .> 0.05 level.
** Significant to the P > 0.01 level.
*** Significant to the P > 0.001 level.

The types of aberrations detected in all groups, including negative controls, consisted of chromatid and chromosome gaps and breaks and fragments. In the cells with the activation system, an increase in aberrations was seen at most of the dose levels. However, a dose-response increase was not evident and one intermediate dose did not show an increase. The cells without the metabolic activation system showed a more pronounced increase, significant to a higher p value at the highest dose. But a dose-response still was not readily apparent with intermediate doses not achiving statistical significance.

**Conclusions** : DPnB is clastogenic under the conditions of this test.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were well documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell line used, test substance concentrations and dose spacing (several dose levels including negative control, with highest showing toxicity), time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of cells scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test". The positive control agents gave the expected results showing that the cell line was responsive to chromosomal aberration insult.

**References** : Enninga, I.C., van de Waart, E.J., (1989). Evaluation of the ability of Dowanol-DPnB to induce chromosome aberrations in cultured Chinese Hamster Ovary (CHO) cells. NOTOX Report Number 1321/ECC 174.

Sponsored by Dow Chemical Europe, Horgen, Switzerland. July 1989. Unpublished report.

**Other** : This study is one of five in vitro chromosome aberration studies conducted over a four-year period. Three positive tests were conducted at NOTOX Laboratory in the Netherlands and the two negative tests were conducted at Dow Laboratories (Lake Jackson Research Center, Freeport Texas). As most propylene glycol ethers do not cause clastogenic effects, the positive results are deemed unusual. As a result of the positive in vitro results, a follow-up, higher tier in vivo test was conducted. This consisted of an in vivo chromosome aberration test (mouse bone marrow micronucleus), which was negative. See General Comments at the end of this section.

**Source** : Dow Deutschland Inc Stade 5

(38)

**Type** : Cytogenetic assay
**System of testing** : In vitro chromosomal aberration assay with Chinese Hamster Ovary (CHO) cells. CHO-K1, S1B cell line used
**Concentration** : 0, 500, 1667, 5000 ug/ml of culture medium
**Cycotoxic conc.** : Some toxicity was seen at highest dose tested (5000 ug/ml) with (53% survival compared to controls) and without (32% survival) S-9
**Metabolic activation** : With and without Aroclor-induced rat liver S-9
**Result** : Negative
**Protocol Guideline** : Specific protocol guideline not specified (e.g., OECD Guideline No. 473: Genetic Toxicology, In Vitro Mammalian Cytogenetic Test).
**Year of Study** : 1991
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 (also 35884-42-5) |
| Appearance: | Liquid. |
| Batch No.: | QA001078 (produced July 1987) |
| Source: | Dow Chemical G.m.b.H., Stade, Fed Rep. Germany. |
| Expiration Date: | Not specified |
| Purity: | 99.5% (total isomers) |
| Specific Gravity: | Not specified |
| Solubility in water: | Not specified |
| Stability: | Not specified |
| Storage: | Not specified |
| Administered as: | Direct dilution in culture medium. DMSO was not used to help dissolve DPnB in the culture medium. |

**Method** : Chinese Hamster Ovary (CHO-K1, S1B) cells in logarithmic growth phase were tyrpsinized and plated in medium containing 10% serum at a density 2 x 105 cells/60 mm petri dish. After approximately 24 hours, the medium was changed to new medium (2.5% serum) containing the test or control agents, with or without the S-9 supernatant metabolic activation system (from Aroclor 1254-induced rats). Cells were exposed to test material (4 concentrations; 0, 500, 1667, or 5000 µDPnB/ml culture medium) and control agents for 4 hours at 37°C. Positive control agents were: ethylmethanesulfonate (EMS) without the activation system and cyclophosphamide (CP) with the activation system. At the end of 4 hours, cells were removed from the test and control agents by washing with phosphate-buffered saline and then maintained in culture medium (10% serum) until harvest. Duplicate cultures of each of the four dose levels of the test material-exposed cells and of the positive control agent-exposed cells were harvested 18 hours after exposure. Two hours prior to harvest, cells were arrested in metaphase by addition of Colcemid. At harvest, cells were trypsinized, swollen by hypotonic treatment, fixed on slides and stained with Giemsa. Mitotic indices were computed by dividing the number of cells in metaphase by 500 cells examined (per replicate) and expressing this number as a percentage. 50 cells in metaphase per duplicate (total of 100) at each dose level (including positive controls) were examined for chromosomal aberrations. Structural chromosomal abnormalities that were scored included chromatid and chromosome gaps, chromatid breaks and exchanges, chromosome breaks and exchanges, and chromosomal disintegration. Chromatid and chromosome gaps were not included in the number of total aberrations.

**Results** : Results are shown in the table below:

| Dose Level (ug/ml) | With/without S-9 | Cytotoxicity* | Aberrations |
|---|---|---|---|
| 0 DPnB | + | Negative | Negative |
| 500 DPnB | + | Negative | Negative |
| 1667 DPnB | + | Negative | Negative |
| 5000 DPnB | + | 21% RCS (both +) | Negative |
| 1242 EMS | - | N/A | Positive |
| 14 CP | + | N/A | Positive |

* Cytotoxicity was greater at 5000 DPnB in this main assay than in the preliminary cytotoxicity assay. No cytotoxicity occurred at doses lower than 5,000 µg/ml in this main assay.

**Conclusions** : Dipropylene glycol n-butyl ether did not cause cytotoxicity or chromosomal aberrations under the conditions of this test. The NOAEL is 5000 µg/ml and no LOAEL was established.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were well documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell line used, test substance concentrations and dose spacing (4 dose levels including negative control, with highest being 5000 µg/ml), time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of cells scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test". The positive control agents gave the expected results showing that the cell line was responsive to chromosomal aberration insult.

**References** : Linscombe, V.A., Verschuuren, H.G., (1991). Evaluation of dipropylene glycol n-butyl ether in an in vitro chromosomal aberration assay utilizing Chinese Hamster Ovary (CHO-K1, S1B) cell line. Report No. not specified. February 20, 1991. Unpublished report.

**Other** : Instead of their usual cell line, in this assay Dow used the same strain as NOTOX laboratory in an attempt to more closely duplicate test conditions. This change did not produce a positive response as had been found in the 3 NOTOX lab assays. A remaining difference between the protocols of the two laboratories was that NOTOX used DMSO to solubilize DPnB whereas Dow diluted the test material directly into the culture medium without the aid of DMSO. Because DPnB is soluble in water up to 5% (i.e., ~50,000 µg/ml), DPnB should be adequately soluble to mix well with the incubation medium at the concentrations tested such that target cells would be exposed.

The positive control chemicals induced the expected increases in aberration frequencies. In the main assay, the relative cell survival (RCS) of cultures treated with 5000 ug/ml in the absence and presence of S-9 was 20.9% and 20.8%, respectively. This cytotoxicity was higher than in the preliminary toxicity assay but the next lower dose evaluated for toxicity (3750 ug/ml), showed no toxicity (note that this dose level was not evaluated for cytogenic damage). However, there were no statistically significant increases in the incidence of cells with aberrations in cultures treated with any of the three
concentrations of DPnB, either in the presence or absence of S-9, as compared to the negative controls.

**Source** : Dow Deutschland Inc Stade 5

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**Type** : In vitro CHO/HGPRT forward mutation test
**System of testing** : Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase assay
**Concentration** : 279 - 5000 microG/ml
**Cycotoxic conc.** : 2500 ug/ml and above.
**Metabolic activation** : With and without Aroclor-induce rat S-9 supernatant.
**Result** : Negative
**Protocol Guideline** : Specific guidance OECD No. 476 “In Vitro Mammalian Cell Gene Mutation Test” was referenced.
**Year of Study** : 1995
**GLP** : Yes

**Test substance** :

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Appearance: | Liquid. |
| Batch No.: | MM940207. |
| Source: | Dow Chemical Co., Midland, MI. |
| Expiration Date: | Not specified |
| Purity: | 98.97% |
| Specific Gravity: | Not specified |
| Solubility in water: | Not specified |
| Stability: | Not specified |
| Storage: | Not specified |
| Administered as: | Direct dilution in culture medium. DMSO was not used to help dissolve DPnB in the culture medium. |

**Method** : Stock cells were grown in Ham's serum containing F-12 nutrient mix, which also contained hypoxanthine required by the cell line. Cells in logarithmic growth phase, grown to a density of 3 x 106 cells/T-25 flask (for gene mutation assay; 1 x 106 cells/T-25 flask for toxicity assay), were trypsinized and plated. Approximately 24 hours after plating, medium was replaced with 1) fresh medium without serum, 2) the test material, negative control solvent (DMSO), or positive controls, 3) with or without S-9 supernatant. Cells incubated with the test material at 37°C for approximately 4 hours, then cells were washed with phosphate-buffered saline to terminate treatment. Subsequently, cultures were trypsinized and re-plated at a density of 1 x 106 cells per 100 mm dish (2 dishes per replicate) in medium still containing hypoxanthine for 6 to 8 days for phenotypic expression. At the end of the 6-8 day expression period, cultures were trypsinized and plated at a density of 2 x 105 cells/100 mm dish (10 dishes/replicate) in the selection medium (Ham's 12 without hypoxanthine and with 6-thioguanine) for selection of HGPRT- mutants. During this selection period, dishes were incubated at 37°C for 8-10 days to allow for colony formation. At the end of this time, the cells were fixed with methanol and stained with crystal violet. Mutant frequency was determined from the number of colonies formed in the dishes, taking into account cloning efficiency. 3-Methylcholanthrene (4 ug/ml) was the positive control agent with S-9 and ethylmethanesulfonate (621 ug/ml) was the positive control agent without S-9. DMSO at 1% was the negative control.

**Results** : In the toxicity assay, doses up to and including 1250 ug DPnB/ml culture medium were without effect. Without S-9, doses of 2500 and 5000 ug/ml showed Relative Cell Survival (RCS) of 61% and 56%, respectively. With S-9, toxicity occurred only at 5000 ug/ml (38%). In the mutation assay itself, toxicity was less as evidenced by higher RCS at higher dose levels.

In the first mutation assay, doses ranged slightly below target of 5000 ug/ml. Specifically doses ranged from 279 to 4467 ug/ml. No toxicity was seen without S-9 at the highest dose level. With S-9, toxicity was seen at the highest dose only (4467 ug/ml) with 48% RCS in one replicate and 36% in another. In this first mutation assay, mutation frequencies were not different from controls either with or without S-9 metabolic activation. Negative and positive controls fell within laboratory historical limits.

In the second mutation assay, doses ranged from 312 up to 5000 ug/ml. Without S-9, cytotoxicity occurred only at the highest dose tested, 84% in one duplicate and 66% in the second. With S-9, toxicity was seen at 2500 ug/ml (75% & 90%) and 5000 ug/ml (62% & 80%). In this second assay, mutation frequencies were not different from controls either with or without S-9 metabolic activation. Negative and positive controls fell within laboratory historical limits.

**Conclusions** : DPnB is not mutagenic in the CHO/HGPRT forward mutation assay.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were well documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell line used, test substance concentrations and dose spacing (4 dose levels including negative control, with highest being 5000 ug/ml), time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of cells scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 476 “In Vitro Mammalian Cell Gene Mutation Test.“ The positive control agents gave the expected results showing that the cell line was responsive to forward mutation insult.

**References** : Linscombe, V.A., Okowit, D.W., Kropscott, B.E., (1995). Evaluation of Dowanol DPnB in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) forward mutation assay. Report No. not specified. March 2, 1995. Unpublished report.

**Other** : Unlike the cytogenietics studies conducted by Dow that used no vehicle solvent, DMSO was used as a diluent for DPnB in this assay. DMSO served as the negative control at 1% concentration within the media.

**Source** : Dow Deutschland Inc Stade 5

(2)

**General Remark for the Genetic Toxicity (In Vitro) Section** : A summary report, compiled by NOTOX Laboratory, discusses the results of 5 genotoxicity studies: 1) three in vitro CHO chromosome aberration studies carried out under varying conditions by RCC-NOTOX, 2) one in vitro CHO chromosome aberration study conducted by Dow and 3) one in vivo mouse bone marrow micronucleus test conducted by Dow. A fifth in vitro chromosome aberration study conducted by DOW in 1991, which was negative, was not discussed in this report.

Three out of the four in vitro chromosome aberration (cytogenetics) assays conducted in NOTOX Laboratories and carried out with DPnB in Chinese Hamster Ovary cells, showed positive results. One in vitro chromosome aberration assay, conducted in Dow Laboratories was negative. A later assay at Dow (not discussed in the NOTOX summary report), repeated with another sample of DPnB, confirmed the negative result in the CHO chromosome aberration assay. This second Dow study used the same strain of cells as NOTOX. Thus, three in vitro CHO chromosome aberration studies were positive and two were negative. The defining in vivo micronucleus test with DPnB was negative.

In vitro chromosome aberration assays using CHO cells are reported to produce false positive results with certain compounds due to changes in pH or osmolarity of the culture medium. However, in the present studies with DPnB no changes in pH or osmolarity of the culture medium were observed. The presence of peroxides in the samples testing positive also was hypothesized potentially to account for the positive response. Consequently, one of the cytogenetics studies added an antioxidant butylhydroxytoluene (BHT) to reduce the presence of peroxides but BHT (at a concentration low enough to not produce aberrations itself) did not eliminate the clastogenic effects of the sample. Distilling the sample to further remove peroxides also did not eliminate the positive response. The activity of a powerful solvent like DPnB on the cell membrane of sensitive cells could constitute another condition for a false positive. In addition, the discrepancy in results of the in vitro assays at the two laboratories involved could be due to differences in characteristics of the CHO cell lines used, including the sensitivity towards the solvent properties, or to slight differences in the test protocols. Finally, NOTOX used DMSO to solubilize the test material while Dow diluted the test material directly in the culture medium (i.e., did not use DMSO). The combined solvent effects of DMSO and DPnB may have contributed to the positive results in the NOTOX assays.

It also should be noted that two other in vitro genotoxicity studies, also not discussed in the NOTOX summary report, were negative for DPnB. These consisted of an Ames assay and an in vitro CHO/HGPRT forward mutation test. Finally, in the in vivo mouse micronucleus test, distribution studies with radiolabeled material show the presence of DPnB in bone marrow. The inability of DPnB to induce micronuclei in the bone marrow of mice indicates that DPnB is not clastogenic in vivo. The table below summarizes all genotoxicity results.

| Test | Type | Lab. | Results |
|---|---|---|---|
| Ames Salmonella | In Vitro | NOTOX | Negative |
| CHO/HGPRT Forward Mutation | In Vitro | Dow | Negative |
| Chromosome Aberration 1 | In Vitro | NOTOX | Positive |
| Chromosome Aberration 2 | In Vitro | Dow | Negative |
| Chromosome Aberration 3 | In Vitro | NOTOX | Positive |
| Chromosome Aberration 4 | In Vitro | NOTOX | Positive |
| Chromosome Aberration 5 | In Vitro | Dow | Negative |
| Mouse Micronucleus | In Vivo | Dow | Negative |

Because the results of the in vitro assays were equivocal and because propylene glycol ethers are rarely genotoxic, the in vivo mouse bone marrow test becomes definitive in assessing the genotoxic potential of DPnB. Since this in vivo test was negative (see next section), it may be concluded that DPnB does not present a genotoxicity hazard.

**Source** : Dow Deutschland Inc Stade 5

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## 5.6 GENETIC TOXICITY 'IN VIVO'

| | | |
|---|---|---|
| **Type** | : | Micronucleus assay |
| **Species** | : | Mouse |
| **Sex** | : | Male/female |
| **Strain** | : | CD-1 (ICR) BR |
| **Route of admin.** | : | Gavage |
| **Exposure period** | : | Single administration. |
| **Doses** | : | 0, 250, 833, 2500 mg/kg bw |
| **Result** | : | Negative |
| **Protocol Guideline** | : | No specific protocol guideline cited (e.g., OECD 475: "Mammalian Erythrocyte Micronucleus Test"). General guidelines cited: 40 CFR Part 160, OECD ISBN 92-64-12367-9. |
| **Year of Study** | : | 1988 |
| **GLP** | : | Yes |
| **Test substance** | : | |

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 |
| Appearance: | Liquid. |
| Batch No.: | QA001078 (produced in July 1987). |
| Source: | Dow Chemical Europe, Stade, Federal Republic of Germany. |
| Expiration Date: | Not specified |
| Purity: | 99.5% |
| Specific Gravity: | Not specified |
| Solubility in water: | Not specified |
| Stability: | Not specified |
| Storage: | Not specified |
| Administered as: | Dilution in 1% Methocel and water. |

| | | |
|---|---|---|
| **Method** | : | Groups of CD-1 (ICR) BR mice (5/sex/dose/sacrifice time) were administered single doses (by gavage) of 0, 250, 833, or 2500 mg DPnB/kg body weight. The positive control chemical was cyclophosphamide (120 mg/kg). The negative control chemical (i.e., the diluent for DPnB) was 1% methocel (10 ml/kg). Groups of animals were sacrificed by cervical dislocation at three time intervals: 24, 48, and 72 hours after treatment. Bone marrow was collected from the femur of each animal. Cells from the bone marrow were transferred to slides, fixed in methanol, and stained in 5% Giemsa. One thousand polychromatic erythrocytes were evaluated from each animal and the frequencies of micronucleated polychromatic erythrocytes were recorded. |
| **Results** | : | There were no significant increases in the frequencies of micronucleated polychromatic erythrocytes (MN-PCE) in any of the groups treated with the test chemical compared to negative controls at any dose or time point. The positive control mice showed significant increases in MN-PCE. |
| **Conclusions** | : | Under the experimental conditions used, the test chemical was negative in the mouse bone marrow micronucleus test. |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1. |

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were well documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell line used, test substance concentrations and dose spacing (4 dose levels including negative control, with highest being 2500 mg/kg), positive control agent used, the number of cells scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 475 "Mammalian Erythrocyte Micronucleus Test." The positive control agents gave the expected results showing that the animals were responsive to clastogenic insult.

**References** : McClintock, M.L., Bhaskar Gollapudi, B., Verschuuren, H.G., (1988). Evaluation of dipropylene glycol-n-butyl ether in the mouse bone marrow micronucleus test. Report No. not specified. December 12, 1988. Unpublished Report.

**Other** : Other metabolism studies show that DPnB reaches the bone marrow of mice. This in vivo assay confirms that that DPnB is not clastogenic to chromosomal material. See also General Remark above in the In Vitro Genotoxicity section.

**Source** : Dow Deutschland Inc Stade 5

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## 5.7 CARCINOGENITY

Propylene glycol methyl ether (surrogate chemical)

**Type** : Chronic Toxicity/Carcinogenicity

**Species** : Rats and mice

Fischer 344 Rats

| | |
|---|---|
| Age at dosing: | 6-8 weeks. |
| Source: | Charles River (Portage, MI). |
| Acclimation period: | 7 days. |
| Weight at start of study: | 143 g (males); 117 g (females). |
| Assignment to groups: | Randomized by weight. |
| Diet: | Certified Rodent Chow #5002 (Purina Mills, Inc., St Louis, MO). |
| Access to food: | Ad libitum except during inhalation exposures. |
| Access to water: | Ad libitum. |
| Method of Identification: | Implanted microchip. |
| Housing: | 2 per stainless steel wire-mesh cage. |

Environmental Conditions (for non-exposure periods):

| | |
|---|---|
| Temperature: | 22 ± 2°C. |
| Humidity: | 40-60%. |
| Air changes: | 12/hr. |
| Photoperiod: | 12 hr light/12 hr dark. |

B6C3F1 Mice

| | |
|---|---|
| Age at dosing: | 6-8 weeks. |
| Source: | Charles River (Portage, MI). |
| Acclimation period: | 14 days. |
| Weight at start of study: | 24 g (males); 17 g (females). |
| Assignment to groups: | Randomized by weight. |
| Diet: | Certified Rodent Chow #5002 (Purina Mills, Inc., St Louis, MO). |
| Access to food: | Ad libitum except during inhalation exposures. |
| Access to water: | Ad libitum. |

Method of Identification: Implanted microchip.
Housing: 2 per stainless steel wire-mesh cage.
Environmental Conditions (for non-exposure periods):
Temperature: 22 ± 2°C.
Humidity: 40-60%.
Air changes: 12/hr.
Photoperiod: 12 hr light/12 hr dark.

**SEX** : Males and females
: Rats: Fischer 344
Mice: B6C3F1
**Type** : Vapor Inhalation (whole-body)
**Species** : Lifetime with interim sacrifices
**FREQUENCY** : 6 hr/day, 5 days/week
**Strain** : None
**Route of admin.** : 0, 300, 1000, or 3000 ppm
**Control group** : Air-only
**NOAEL** : Rats: 300 ppm based on altered hepatocellular foci in males.
Mice: 1000 ppm based on slight body weight decreases in both sexes.
**LOAEL** : Rats: 1000 ppm based on altered hepatocellular foci in males.
Mice: 3000 ppm based on slight body weight decreases in both sexes.
**Protocol Guideline** : Meets requirements of US EPA Health Effects Test Guidelines OPPTS 870.4300: "Combined Chronic Toxicity/Carcinogenicity" and OECD Guideline for Testing of Chemicals 453 "Combined Chronic Toxicity/Carcinogenicity Studies"
**Year of Study** : 1999 (in-life completion)
**GLP** : Yes
**Test substance** : Propylene glycol methyl ether (PGME) as surrogate for dipropylene glycol n-butyl ether

Identity: 1-methoxy-2-hydroxypropane or propylene glycol methyl ether. CAS # 107-98-2
Source: Dow Chemical Company (Midland, MI)
Lot No.: Not specified.
Purity: >97% 1-methoxy-2-propanol: <3% 2-methoxy-1-propanol (> 99.96% both isomers combined).

**Method:** : In a chronic toxicity/carcinogenicity study, Fischer rats and B6C3F1 mice (50/sex/exposure level) were exposed to vapor concentrations of propylene glycol methyl ether (PGME) at concentrations of 0, 300, 1000, or 3000 ppm 6 hr/day, 5 days/wk for 2 years. Over the course of the study, these subjects were evaluated for clinical signs and body weights. At the end of two years, survivors were subjected to clinical chemistry and hematological examinations, urinalyses, determination of body organ weights, and histopathological examination of a large number of tissues.

In order to evaluate potential toxicity at interim time intervals during the exposure period, additional subjects were exposed to PGME vapors and subjected to routine and specialized toxicological tests at the times shown in the experimental design table below. Subchronic toxicity (at 13 weeks) was evaluated in 5 to 10 mice/sex/exposure level that included clinical chemistry and hematology evaluations, urinalyses, and determination of histopathological changes.

Specialized tests conducted in both mice and rats at the time intervals shown in the table included evaluation of 1) cell proliferation in liver and kidneys, 2) hepatic mixed function oxidase (MFO) activity, and 3) α2μ-globulin nephropathy.

Study Design:

Summary Chronic Study (with mechanistic substudies), Number of Rats (R) and Mice (M) per exposure level (males/ females)

| | | 6 mos | | 12 mos | | 18 mos | | 24 mos | |
|---|---|---|---|---|---|---|---|---|---|
| ppm | Group* | R | M | R | M | R | M | R | M |
| 0 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | D | 5/0 | -- | 5/0 | -- | -- | -- | | |
| 300 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | -- | -- | -- | -- | -- | -- | -- | -- |
| | D | 5/0 | -- | 5/0 | -- | -- | -- | -- | -- |
| 1000 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | -- | -- | -- | -- | -- | -- | -- | -- |
| | D | 5/0 | 5/0 | 5/0 | -- | -- | -- | -- | -- |
| 3000 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | D | 5/0 | -- | 5/0 | -- | -- | -- | -- | -- |

* Group A: routine study, Group B: cell proliferation in liver and kidneys, Group C: Hepatic MFO induction, Group D: α2μ-g nephropathy evaluation.

Table reproduced from chronic portion of Spencer et al. (39)

**Methods (continued)** : Atmospheres of PGME were generated by metering the test material into a glass J-tube assembly through which compressed, heated air was channeled. Evaporated PGME in the heated air was diluted with room temperature air to the desired concentration at a flow rate of 2900 liters per minute into whole-body inhalation chambers. Airflow in the chambers was maintained at a level that provided approximately 12 changes/hour and normal oxygen concentration. PGME concentrations were measured from the breathing zone of the animals inside the chambers two times per hour using a Miran 1A infrared spectrophotometer. Analytical concentrations were within 0.5% of nominal concentrations throughout the study.

**Results** : Some results from additional, shorter-term studies are discussed in Spencer et al. (46), and not in this chronic toxicity/carcinogenicity section.

At 3000 ppm, both mice and rats exhibited decreased activity, incoordination, and transient sedation during the first week of exposure. Subjects recovered 1-2 hours after removal from the chambers. These signs disappeared in both species after the second week but returned in rats 12-18 months into the study. Mortality was unaffected until 18 months when males but not females of both species showed higher mortality rates that were not ascribable to any particular cause. During the course of the study, body weights in both species were decreased at the 3000 ppm exposure level. These decreases were not large but were statistically significant in all but male rats. Decreased body weights also occurred in mice at the 1000 ppm level. Despite changes during the study, body weights were not statistically different from controls at terminal sacrifice.

No clinical chemistry changes were evident in the subchronic mouse evaluation. In the chronic study, no hematology or urinalysis changes were evident in either species. However, several clinical chemistry parameters in male rats exposed to 3000 ppm PGME were altered at the 24 month sacrifice: creatinine increased 78% and urea nitrogen increased 100%.

Serum alkaline phosphatase was increases as well and earlier, at 6 through 24 months at the 3000 ppm level, and at 1000 ppm, at 24 months in male rats. Changes in SGOT (AST) and SGPT (ALT), which could be associated with liver injury, were mildly and inconsistently increased in male rats during the first year of exposure at 3000 ppm but not after. No histological changes accompanied these effects. Liver weights were increased at 3000 ppm in both sexes of both species. Kidney weights were increased at this exposure level only in rats.

**Results (continued)** : Dark foci in the liver were grossly observable in male rats exposed to 1000 and 3000 ppm PGME after 24 months. These subjects also exhibited eosinophilic hepatocellular foci and cystic degeneration microscopically that was not reported in female rats or mice of either sex. Male rats and, to a lesser extent, male mice showed increased S-phase DNA synthesis when exposed to 3000 ppm PGME. This effect was not pronounced (reported in a separate, 2-week study), and was evident to a lesser extent in female rats. MFO activity was increased in the livers of rats and mice exposed to 3000 ppm PGME.

In the kidney, histopathology revealed that male rats had α2μ-globulin nephropathy as is typical for this strain. The incidence and severity of this condition was increased in males exposed to 1000 and 3000 ppm PGME compared to controls. No increase in renal epithelial tumors was observed in rats or mice.

**Conclusions** : The major changes seen in this study were 1) decreased body weights in both species, 2) liver effects including increased weight, increased MFO activity and increased cell proliferation primarily in males of both species, 3) kidney effects (in rats) of α2μ-globulin nephropathy typical of the Fischer 344 strain, and 4) slightly increased mortality occurring only after 18 months of exposure in males of both species. Clinical chemistry parameters reflected and corroborated these effects.

Rats exhibited a NOAEL of 300 ppm based on altered hepatocellular foci in males. Mice showed a NOAEL of 1000 ppm based on slight body weight decreases in both sexes. The LOAELS were correspondingly higher.

No carcinogenic effect as evidenced by any increase in tumor incidence, even in kidneys of the male rats, occurred from exposure to PGME at any concentration in either species.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were well documented in the pre-print paper for publication). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The test system used, test substance concentrations and dose spacing (3 dose levels including negative control), time exposed to the test agent, the number of subjects used, the toxicity endpoints monitored, and scoring criteria all followed or exceeded guidance as specified in US EPA Health Effects Test Guidelines OPPTS 870.4300: “Combined Chronic Toxicity/Carcinogenicity” and OECD Guideline for Testing of Chemicals 453 “Combined Chronic Toxicity/Carcinogenicity Studies.”

**References** : Spencer, P.J., Crissman, J.W., Stott, W.T., Corley, R.A., Cieszlak, F.S., Schumann, A.M., Hardisty, J.F. (2002). Propylene glycol monomethyl ether (PGME): Inhalation toxicity and carcinogenicity in Fischer 344 rats

and B6C3F1 mice. Accepted for publication in Toxicologic Pathology, January 2002.

**Other** : Since no chronic or carcinogenicity studies have been conducted with PnB, PGME is used in this report as a representative surrogate chemical.

**Source** : Dow Chemical Company

(39)

## 5.8 TOXICITY TO REPRODUCTION

Propylene glycol methyl ether (surrogate chemical)

| | | |
|---|---|---|
| **Study Type** | : | 2-Generation Reproduction |
| **Species/strain** | : | Mouse/CD-1 |
| **Sex** | : | Male and Female |
| **Route of Admin.** | : | Oral (drinking water) |
| **Exposure Period** | : | Before mating, through gestation, and post-birth. |
| **Treatment Frequency** | : | Daily |
| **Post-exposure observ.** | : | Not reported. |
| **Premating exposure** | : | 7 days for males and females. |
| **Exposure Levels** | : | 0, 0.5, 1.0, or 2.0 percent in drinking water |
| **Control Group** | : | Yes, water |
| **NOAEL Patenal** | : | 1% |
| **NOAEL F1 Offspring** | : | 1% |
| **NOAEL F2 Offspring** | : | 1% |
| **Protocol Guideline** | : | Not specified. |
| **Year of Study** | : | 1997 |
| **GLP** | : | Not specified. |
| **Test Substance** | : | Details not provided. |
| **Method** | : | Details not provided. The publication describing results was a summary of 90 studies on a variety of chemical substances conducted by the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP). Only a two-page summary of results was provided for PM. The methodology cited was the “RACB protocol” after Morrissey et al., Fundam Appl Toxicol. 13:747-777. |
| **Results** | : | The referenced study is an abstract. There were no changes in body weight or food consumption in any of the first generation exposure groups except for a 4% reduction in pup weight at the highest dose tested. In the second generation exposure groups, reductions in male and female body weight were noted (14% reduction during nursing; 8% reduction in body weight in males during and after mating, and epididymus and prostate weights were 9 and 8% below controls in males, respectively). There was no evidence of reproductive toxicity; mating and fertility indices, and the number and viability of F1 and F2 offspring were not affected. Among F1 offspring, mean pup weight was decreased in the 2% group. F2 offspring from the 2% group displayed reduced pup weight at birth, which continued postnatally during nursing. At sacrifice, female body weights in the 2% group were lower than controls; absolute testis, and relative epididymis and prostate weights were also reduced. F1 female body-weight-adjusted liver weights were increased. |
| **Conclusions** | : | NOAELs occurred at the 1% level. Effects seen did not include reproductive toxicity related to mating, fertility indices, or offspring viability. The effects on parental organ weights (epididymis and prostate) may have been secondary to body weight decreases which paralleled these decreases in magnitude. |

| | | |
|---|---|---|
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1. |
| **Quality Check** | : | This study appeared to follow modern guidance. |
| **Reference** | : | Chapin, R.E., Sloane, R.A., (1997). Reproductive assessment by continuous breeding: Evolving Study Design and Summaries of Ninety Studies; Propylene glycol monomethyl ether. Environ Health Perspect. 105 (Suppl 1), 233-234. |
| **Other** | : | N/A |
| **Source** | : | Dow Chemical Co. (41) |
| | | Propylene glycol methyl ether (surrogate chemical) |
| **Study Type** | : | 2-Generation Reproduction |
| **Species/strain** | : | Rat/Sprague-Dawley |
| **Sex** | : | Male and Female |
| **Route of Admin.** | : | Inhalation (whole-body) |
| **Exposure Period** | : | Before mating, through gestation, and post-birth. |
| **Treatment Frequency** | : | 6 hr/day |
| **Post-exposure observ.** | : | Not reported. |
| **Premating exposure** | : | 5 days/week prior to mating; 7 days/week post mating |
| **Exposure Levels** | : | 0, 300, 1000, or 3000 ppm |
| **Control Group** | : | Yes, air-only. |
| **NOAEL Patenal** | : | 300 ppm |
| **NOAEL F1 Offspring** | : | 1000 ppm |
| **NOAEL F2 Offspring** | : | 1000 ppm |
| **Protocol Guideline** | : | OECD 416. |
| **Year of Study** | : | 1997. |
| **GLP** | : | Yes. |
| **Test Substance** | : | Identity: 97.99% - 98.07% 1-methoxy-2-hydroxypropane or propylene glycol methyl ether (alpha isomer). CAS # 107-98-2<br>1.86% –1.90% 2-methoxy-1-hydroxypropane or propylene glycol methyl ether (beta isomer).<br><br>Source: Dow Chemical Company (Midland, MI)<br>Lot No.: MM950417.<br>Purity: See above. Impurities: none detected at >0.1% |
| **Method** | : | In a 2-generation reproductive toxicity study by Carney et al. (1999) exposed Sprague-Dawley rats (30/sex/exposure level) to 0, 300, 1000, or 3000 ppm PM 6 hr/day, 5 days/wk prior to mating and 7 days/week during mating, gestation and lactation, for two generations. |
| **Results** | : | At 3000 ppm, toxicity in the P1 and P2 adults was marked, as evidenced by sedation during and after exposure for several weeks, and mean body weights which were as much as 21% lower than controls. This marked parental toxicity was accompanied by lengthened estrous cycles, decreased fertility, decreased ovary weights, reduced pup survival and litter size, slight delays in puberty onset, and histologic changes in the liver and thymus of the F1 and F2 offspring. At 3000 ppm, there was an increase in histologic ovarian atrophy in P1 and P2 females, and at 1000 ppm, there was a decrease in pre-mating body weight in the P1 and P2 females. No treatment-related differences in sperm counts or motility were observed among the P1 or P2 males. |
| **Conclusions** | : | The NOAEL for paternal toxicity is 300 ppm and for offspring toxicity is |

1000 ppm. Effects appear secondary to parental weight loss.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : The protocol followed OECD 416.

**Reference** : Liberacki AB et al. (1997) Propylene glycol monomethyl ether: Two-generation inhalation reproduction study in Sprague-Dawley rats. Dow Chemical Company. Unpublished report

Carney, E.W., Crissman, J.W., Liberacki, A.B., Clements, C.M., Breslin, W.J., (1999). Assessment of adult and neonatal reproductive parameters in Sprague-Dawley rats exposed to propylene glycol monomethyl ether vapors for two generations. Toxicol. Sci. 50:249-258.

**Other** : The nature of the reproductive/neonatal effects and their close individual correlation with decreased paternal body weights suggest that these effects were secondary to general toxicity and/or nutritional stress. No such effects were observed at 1000 ppm, a concentration which caused less marked, but significant body weights effects without sedation.

**Source** : Dow Chemical Company.

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## 5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

**Type** : Developmental Toxicity by Dermal Application in the Rat
**Species** : Rat
**Sex** : Female
**Strain** : Wistar derived SPF-bred albino rats (Bor;WISW, SPF TNO)

| | |
|---|---|
| Age at dosing: | Approximately 12 weeks (females) and 13 weeks (males) of age. |
| Source: | F. Winkelmann Versuchstierzucht GmbH & Co. KG, Borchen, West-Germany. |
| Acclimation period: | Approximately 1 week. |
| Average weight (start of study): | Males: not specified; Females: 186 – 209 grams. |
| Assignment to groups: | Computerized, random number-based procedure. |
| Diet: | “Basal Diet“ (analysis provided in report. |
| Access to food: | Available ad libitum. |
| ACCESS TO WATER: | AVAILABLE AD LIBITUM. |
| Method of Identification: | “V” notches on ears. |
| Housing: | Prior to mating: males - individually, females - 5 per group in stainless steel cages with wire-mesh bottoms. After mating: housing-type for females not specified. |

Environmental Conditions:

| | |
|---|---|
| Temperature: | 22 ± 2°C. Recording frequency not reported. |
| Humidity: | At least 40%. Range & recording frequency not reported. |
| Air changes: | 8-10 air changes per hour. |
| Photoperiod: | 12 hr light/12 hr dark. |

**Route of admin.** : Dermal

| | | | |
|---|---|---|---|
| **Exposure period** | : | Days 6-15 of gestation (day plug found was Day 0) | |
| **Frequency of treatment** | : | Daily | |
| **Duration of test** | : | until day 21 of pregnancy | |
| **Doses** | : | 273 or 910 mg/kg | |
| **Control group** | : | yes, concurrent vehicle (propylene glycol) | |
| **NOAEL Maternalt.** | : | = 910 .mg/kg bw | |
| **NOAEL Teratogen** | : | = 910 .mg/kg bw | |
| **Protocol Guideline** | : | OECD Guideline 414 "Teratogenicity" | |
| **Year of Study** | : | 1987 | |
| **GLP** | : | Yes | |
| **Test substance** | : | Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2. |
| | | Appearance: | Clear, colorless liquid. |
| | | Batch No.: | XZ451100. |
| | | Source: | Dow Chemical Europe, Horgen, Switzerland. |
| | | Expiration Date: | None specified. |
| | | Purity: | >95%. |
| | | Specific Gravity: | 0.91 kg/liter. |
| | | Solubility in water: | 5%. |
| | | Stability: | Stable up to 200°C. |
| | | Storage: | Ambient temperature in dark. |
| | | Administered as: | Dilution in 1% Methocel and water. |

**Method** : Dipropylene glycol n-butyl ether (DPnB) was applied daily to the skin of pregnant rats on gestation days 6 through 15 (detection of sperm in vaginal smears was designated day 0). DPnB was applied to the clipped skin of two groups of Wistar rats (>20/sex/dose level) at various dilutions in propylene glycol (PG) equivalent to doses of 0 (PG-only; 1.5 ml/kg-day), 0.3 or 1.0 ml DPnB/kg-day. These doses equate to 0, 273, or 910 mg DPnB/kg-day. Treatment solutions were applied to the clipped dorsal trunk of each rat over an area of about 20 cm2. Dilutions of DPnB in PG resulted in applied volumes of 1.5 ml (PG-only), 1.8 ml (1.5 ml PG & 0.3 ml DPnB), or 2.5 ml (1.5 ml PG & 1.0 ml DPnB) test solution per kg body weight. Rats wore neck collars to prevent grooming and ingestion of test material. Solutions were applied unoccluded since the low vapor pressure of DPnB and PG precluded evaporative loss. The experimental design is shown in the table below.

| *Group* | DPnB Dose (ml/kg-d) | Vehicle PG Dose (ml/kg-d) | DPnB Dose (mg/kg-d) | No.♀/Dose Group | Treatment Period (days) |
|---|---|---|---|---|---|
| 1 | 0 | 1.5 | 0 | 22 | 6 thru 15 gest. |
| 2 | 0.3 | 1.5 | 273 | 21 | 6 thru 15 gest. |
| 3 | 1.0 | 1.5 | 910 | 25 | 6 thru 15 gest. |

Rats were observed for clinical signs of toxicity and skin reactions on a daily basis (week days). Individual body weights were recorded on days 0, 6, 16, and 21 of pregnancy and food consumption was monitored over days 0 – 6, 6 – 16, and 16 – 21 of pregnancy. At sacrifice, all animals were subjected to necropsy and examined for gross abnormalities. The ovaries, uterus, kidneys, and livers were removed and weighed. The number of corpora lutea was counted. Fetuses were removed from the uterus, weighed, lengths recorded, and examined for gross abnormalities. Early and late resorptions and live and dead fetuses were counted. Implantation sites in both uterine horns were counted and the empty uterus weighed. Half the fetuses from each litter were eviscerated, skinned and stripped of most subcutaneous tissue, then fixed in 96% ethanol. These fetuses were then stained with Alizarin Red S for examination for skeletal anomalies. The remaining fetuses were fixed in Bouin's fluid, transferred to 70% ethanol and sectioned into slices (after Wilson) for soft tissue examination.

Percentages of pre- and post-implantation loss were calculated, as was the degree of ossification for each fetus. Soft tissue and skeletal anomalies or abnormalities were recorded.

**Results** : Slight skin reactions were found in the dams from all treatment groups and thus were not considered to be treatment related. No maternal toxicity was found: clinical signs and organ or body weights did not differ between treatment and controls groups. No deaths occurred in any groups over the course of the study. Fecundity was comparable among groups. No embryo- or fetotoxicity was evident since pre- and post-implantation loss, number of viable fetuses, and fetal weights and lengths were comparable between treatment and control groups. DPnB did not cause frank developmental toxicity in skeletal or soft tissue. Frank skeletal malformations were observed only in the control group (6 fetuses from 2 litters). Skeletal variants were observed in all dose groups. The high dose group did exhibit a slight increase (not statistically significant) in the incidence of supernumerary rudimentary thoracic ribs when compared to controls. However, this finding was not considered biologically significant by the authors of the study since the incidence was within normal limits for these species.

**Conclusions** : DPnB is not maternally toxic, embryo- or fetotoxic, or teratogenic in Wistar rats receiving dermal doses up to 1.0 ml/kg-d during organogenesis (days 6 – 15). The NOAEL for maternal toxicity, embryo- or fetal toxicity, or developmental toxicity is 1.0 ml/kg-d (910 mg/kg-d) and a LOAEL was not established.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report followed OECD Protocol 414: “Teratogenicity” (12 May 1981), the numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the treatment period (organogenesis) was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

**References** : Wilmer, J.W.G.M., van Marwijk, M.W., (1988). Dermal embryotoxicity/ teratogenicity study with dipropyleneglycol n-butyl ether (DPnB) in rats. Final report. CIVO/TNO Report No. B87-0509. April 1988. Unpublished report.

**Other** : In a pilot study 0, 0.1, 0.3 or 1 ml DPnB was applied dermally to Wistar rats during gestation day 6 till 16. No mortalities were observed. The reproduction and litter data did not reveal any treatment related effect. From this study it was concluded that DPnB at levels up to 1 ml (910 mg/kg bw) was not embryo/fetotoxic to rats.

Wilmer JW, Marwijk MW and Verschuuren HG, "Pilot dermal embryotoxicity/teratogenicity study with Dowanol DPnB in rats". Internal report of Dow Europe, 1988

**Source** : Dow Deutschland Inc Stade 5

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## 5.10 OTHER RELEVANT INFORMATION

| | | |
|---|---|---|
| **Type** | : | Other: Disposition and Metabolism |
| **Species** | : | Rat |
| **Strain** | : | Fischer-344 |
| **Sex** | : | Males (4 per dose level) |
| **Route of admin.** | : | Oral (via gavage) |
| **Frequency of treatment** | : | Single dose |
| **Duration of test** | : | 48 hours |
| **Doses** | : | 0.4 or 4.4 mmol DPnB/kg body weight |
| **Control group** | : | None |
| **Protocol guideline** | : | None specified although complies with OECD 417 “Toxicokinetics“ and OPPTS 870.7485 “Metabolism and Pharmacokinetics“ |
| **Test substance** | : | The specific activity of [14C]-DPnB was 10.9 mCi/mmole, with a radiochemical purity of 99%. Two carbon atoms of DPnB were radiolabeled, one each (a terminal carbon) on either of the two propylene glycol moieties. |

| | |
|---|---|
| Identity: | Dowanol-DPnB (n-butoxypropoxypropanol or dipropylene glycol normal-butyl ether). CAS # 29911-28-2 or 35884-42-5 |
| Appearance: | Clear, colorless liquid. |
| Batch No.: | Radiolabeled (C14) sample synthesized from batch XZ 95411.00 by Wizard Laboratories. |
| Source: | Dow Chemical Europe, Horgen, Switzerland. |
| Expiration Date: | None specified. |
| Purity: | >99.5% for 4 possible DPnB isomers. Radiochemical purity was 98.3±1%. |
| Specific Gravity: | 0.91 kg/liter (from other reports). |
| Solubility in water: | 5% (from other reports). |
| Stability: | Stable up to 200°C (from other reports). |
| Boiling point: | 229°C/101.3 kPa. |
| Vapor pressure: | 0.08 kPa/20°C. |
| Storage: | Ambient temperature in dark. |
| Administered as: | Dilution in 1% methocellulose and water. |

| | | |
|---|---|---|
| **Method** | : | After an initial pilot study to select doses, 4 male rats were administered oral doses via gavage of 0.4 or 4.4 mmole of C14-radiolabelled DPnB/kg body weight. These doses correspond to approximately 75 or 840 mg DPnB/kg body weight. Rats were housed in metabolism cages where urine, feces, and expired air were collected in varying time increments over a total period of 48 hours and monitored for radioactivity. Urine was collected in 12 hour increments, feces in 24 hour increments, and expired air was collected at 6, 12, 24, 36, and 48 hours. In addition, at the end of 48 hours, brain, muscle, peri-renal fat, skin, kidneys, liver and the remaining carcass were analyzed for total radioactivity. Urine samples were fractionated using liquid chromatography and fractions containing radioactivity were analyzed to identify the structures of the metabolites. In a separate study, the kinetics of DPnB in the blood over time was evaluated in 4 male rats, which had patent indwelling jugular catheters. Blood was collected at 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hours. |
| **Results** | : | After 48 hrs, 42% of the dose was excreted in urine and 42% as C14-CO2 at 0.4 mmol/kg BW; while the high dose rats excreted 51% in urine and 35% as C14-CO2. Fecal excretion accounted for 4% of the dose at the low dose and 11% at the high dose. Less than 1% of the dose was eliminated as expired volatile organics at both dose levels. Tissues and carcass retained 11% of the dose 48 hrs after 0.4 mmol DPnB/kg bw and 7% after |

4.4 mmol/kg bw. The distribution of C14-activity in tissues was similar between dose groups with liver, bone marrow and kidneys retaining the highest percentage. Peak blood levels of C14-activity occurred at 0.5 hrs after dosing with 0.4 mmol/kg bw and at 4.0 hrs after 4.4 mmol/kg bw. Profiles of urinary C14-activity were qualitatively similar between dose levels. After 48 hours, radioactivity in all measured tissues was less than 1% of the original dose (for either the low or high dose). These tissues included blood, bone marrow, brain, carcass, fat, kidney, liver, muscle, and skin.

The following urinary metabolites were identified:
- sulfate conjugate of DPnB
- propylene glycol n-butyl ether
- dipropylene glycol
- propylene glycol
- parent material

**Conclusions** : DPnB shows similar absorption, distribution, metabolism and elimination patterns as other propylene glycol ethers.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although not explicitly identified in the report, this study followed guidance provided in OECD Protocol 417: “Toxicokinetics.” The numbers and type of test animals used and their husbandry conditions were as prescribed in the guidance. Test material characterization was adequate. The amount of test material administered complied with guidance, the length of the treatment period was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

**References** : Zemple, J.A., Campbell, R.A., Verschuuren, H.G., (1991). Metabolism and disposition of diproplylene glycol n-butyl ether in male Fischer-344 rats. Dow Laboratory Study No. not reported. July 9, 1991. Unpublished report.

**Other** : No butoxydi- or mono-propionic acid metabolites were identified, indicating a lack of production of potentially toxic metabolites.

**Source** : Dow Deutschland Inc Stade 5

(35)

## 5.11 EXPERIENCE WITH HUMAN EXPOSURE

**Remark** : No relevant data identified from literature searched
**Source** : Dow Deutschland Inc Stade 5

(1) "Dipropylene glycol n-butyl ether; 2 weeks nose-only vapour inhalation study with Fischer 344 rats." L.G. Lomax, T.S. Gushow, P.J. Hopkins and H.G. Verschuuren. Internal report of The Dow Chemical Company, 1987.

(2) "Evaluation of Dowanol* DPnB in the Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay". Unpublished report of The Dow Chemical Company, March 2, 1995

(3) Cardinaals J.M and Verschuuren H.G. (1987) Assessment of the biodegradability of DOWANOL DPnB in the closed bottle test. Internal report of Dow Europe, November 20, 1987

(4) Cardinaals J.M., Verschuuren H.G. (1987) Assessment of the ultimate biodegradability of DOWANOL DPnB in the modified Sturm test. Internal report of Dow Chemical Europe. Nov. 1987.

(5) Dow internal report. "Phytotoxicity of Dowanol DPnB following foliar spray application." D. Hart and H.G. Verschuuren. Confidential report of Dow Chemical Europe, Oct. 1990.

(6) Dow internal report: "Assessment of acute eye irritation/corrosion by DOWANOL DPnB in the rabbit." P.J.J.M. Weterings, P.A.M. Daamen, and H.G. Verschuuren. Confidential report of Dow Chemical Europe. Nov. 1987.

(7) Dow internal report: "Assessment of oral toxicity, including haemolytic activity of DOWANOL DPnB in the rat: 14-day study." F.M.H. Debets and H.G. Verschuuren. Confidential report of the Dow Chemical Europe. Nov. 1987.

(8) Dow internal report: "Assessment of primary skin irritation/corrosion by DOWANOL DPnB in the rabbit". P.J.J.M. Weterings, P.A.M. Daamen, and H.G. Verschuuren. Confidential report of Dow Chemical Europe. Nov. 1987.

(9) Dow internal report: "Assessment of the acute effects of DOWANOL DPnB in the mobility of Daphnia magna." M. Bogers, G.T.G. Welboren, and H.G. Verschuuren. Confidential report of Dow Chemical Europe. Nov. 1987.

(10) Dow internal report: "Assessment of the acute toxicity of DOWANOL DPnB in Poecilia reticulata." J.C.M. v.d. Hoeven, G.T.G. Welboren, and H.G. Verschuuren. Confidential report of Dow Chemical Europe. Nov. 1987.

(11) Dow internal report: "Dipropylene glycol n-butyl ether: Guinea-pig sensitization study, with modified Buehler method." J. Vanderkom and H.G. Verschuuren. Confidential report of Dow Chemical Europe. Dec. 1987.

(12) Dow internal report: "Dipropylene glycol n-butyl ether: an acute vapour inhalation study in Fischer 344 rat." T.S. Gushow, J.E. Philips, L.G. Lomax, and H.G. Verschuuren. Confidential report of The Dow Chemical Company. Dec. 1987.

(13) Dow internal report: "DOWANOL DPnB: Acute aerosol LC50 study in Fischer 344 rats. F.S. Cieslak, B.L. Yano, and H.G. Verschuuren. Confidential report of the Dow Chemical Company. Nov. 1990.

(14) Dow internal report: "Evaluation of the acute dermal toxicity of DOWANOL DPnB in the rat." J.B.J. Reijnders, and H.G. Verschuuren. Confidential report of Dow Chemical Europe. Nov. 1987.

(15) Dow internal report: "Evaluation of the acute oral toxicity of DOWANOL DPnB in the rat." J.B.J. Reijnders, A.M.M. Zucker-Keizer, and H.G. Verschuuren. Confidential report of Dow Chemical Europe. Nov. 1987.

(16) Dow internal report: "Human repeat insult patch test with dipropylene glycol n-butyl ether." A. Maclennon, J. Hedgecock, and H.G. Verschuuren. Confidential report of Dow Chemical Europe. Oct. 1988.

(17) Dow internal report: "Pharmacological screen of dipropylene glycol n-butyl ether in mice." D.R. Algate, P.L. Munt, S.S. Rowton, and H.G. Verschuuren. Confidential report of Dow Chemical Europe. Oct. 1988.

(18) Dow internal report: "Two-week dietary toxicity study in rats with dipropylene glycol n-butyl ether." P.H. Thevenaz, H. Luetkemeier, P. Mladenovic, and H.G. Verschuuren. Confidential report of The Dow Chemical Company. Dec. 1987.

(19) Dow internal report: 13-week dietary toxicity study in rats with dipropylene glycol n-butyl ether. Ph. Thevenaz, H. Luetkemeier, W. Vogel, B. Schlotke, Ch. Terrier, and H.G. Verschuuren. 1988.

(20) Dow internal report: DOWANOL DPnB: Two-week aerosol toxicity study in Fischer 344 rats. F.S. Cieslak, K.E. Stebbins, and H.G. Verschuuren. 1990.

(21) Dow internal report: Evaluation of dipropylene glycol n-butyl ether in an in-vitro chromosomal aberration assay utilizing Chinese hamster ovary (CHO) cells. B. Bhaskar Gollapudi, V.A. Linscombe, and H.G. Verschuuren.

(22) Dow internal report: Evaluation of dipropylene glycol n-butyl ether in an in-vitro chromosomal assay utilizing Chinese hamster ovary (CHO-K1-S1B) cell line. V.A. Linscombe and H.G. Verschuuren.

(23) Dow internal report: Evaluation of the clastogenic properties of dipropylene glycol n-butyl ether. I.C. Enninga and H.G. Verschuuren. 1990.

(24) Dow internal report: Evaluation of the mutagenic activity of DOWANOL DPnB in the Ames salmonella/microsome test. E.J. van de Waart, I.C. Enninga, and H.G. Verschuuren. 1987.

(25) Dow internal report: Subchronic (13-week) dermal toxicity study with dipropylene glycol n-butyl ether in rats. B.A.R. Lina, D. Jonker, R.B. Beems, and H.G. Verschuuren. 1988.

(26) Handley J.W., Verschuuren H.G. (1993) Dowanol DPnB: Assessment of the ready biodegradability in the modified OECD screening test. Internal report of Dow Europe, January 22, 1993.

(27) I.C. Enninga (1990) Evaluation of the clastogenic properties of dipropylene glycol-n-butyl ether. (Summary report of three NOTOX Laboratory in vitro cytogenetics studies – NOTOX studies 0481/ECC 138, 0676/ECC 145, & 1321/ECC 174 - and comparison with one Dow Laboratory study, with NOTOX study reports appended). 12 January 1990.

(28) McClintock ML, Gollapudi BB, Verschuuren HG (1988) Evaluation of dipropylene glycol-n-butyl ether in the mouse bone marrow micronucleus test. Internal report of The Dow Chemical Company, December 12, 1988.

(29) Dill, D.C., Davis, J.W., (1997). Environmental assessment of the Dowanol glycol ethers P-series product family. Dow Chemical Company Study ID ES-3186. August 12, 1997. Unpublished Report.

(30) MSDS (Material Safety Data Sheet), 2000. Dowanol DPNB Glycol Ether High Purity.

(31) Staples, C.A., Davis, J.W., (2002). An examination of the physical properties, fate, ecotoxicity and potential environmental risks for a series of propylene glycol ethers. Chemosphere 49:61-73.

(32) V.K. Rowe, The Dow Chemical Company, unpublished report, 1947.

(33) Wilmer J.W. and Marwijk M.W (1988) Dermal Embryotoxicity/teratogenicity study with dipropyleneglycol-n-butyl ether (DPnB) in rats. Internal report of Dow Europe, June 2, 1988.

(34) Wuethrich V, Verschuuren H.G (1993) Dowanol DPnB: Inherent biodegradability in the modified Zahn-Wellens test. Internal report of Dow Europe, February 16, 1993.

(35) Zempel, J.A., Campbell, R.A., Verschuuren, H.G. (1991) Metabolism and disposition of dipropylene glycol n-butyl ether in male Fischer-344 rats, unpublished report of The Dow Chemical Company, July 9, 1991.

(36) Waalkens, D.H., Enninga, I.C., (1987). Evaluation of the ability of Dowanol-DPnB to induce chromosome aberrations in cultured Chinese Hamster Ovary (CHO) cells. NOTOX Report Number 0481/ECC 138. Sponsored by Dow Chemical Europe, Horgen, Switzerland. July 1987. Unpublished report.

(37) Enninga, I.C., (1987). Evaluation of the ability of DPnB to induce chromosome aberrations in cultured Chinese Hamster Ovary (CHO) cells in the presence of antioxidant. NOTOX Report Number 0676/ECC 145. Sponsored by Dow Chemical Europe, Horgen, Switzerland. December 1987. Unpublished report.

(38) Enninga, I.C., van de Waart, E.J., (1989). Evaluation of the ability of Dowanol-DPnB to induce chromosome aberrations in cultured Chinese Hamster Ovary (CHO) cells. NOTOX Report Number 1321/ECC 174. Sponsored by Dow Chemical Europe, Horgen, Switzerland. July 1989. Unpublished report.

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(41) Chapin, R.E., Sloane, R.A., (1997). Reproductive assessment by continuous breeding: Evolving Study Design and Summaries of Ninety Studies; Propylene glycol monomethyl ether. Environ Health Perspect. 105 (Suppl 1), 233-234.

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# Dipropylene Glycol Methyl Ether Acetate
# CAS No. 88917-22-0

# IUCLID with Robust Summaries
# (Dossier)

| | | |
|---|---|---|
| **Existing Chemical** | : | ID: 88917-22-0 |
| **CAS No.** | : | 88917-22-0 (unspecified as to alpha or beta isomer, or commercial mixture) |
| **EINECS Name** | : | 1-(2-methoxy-1-propoxy)-1-propan-2-ol |
| **EINECS No.** | : | |
| **Molecular Weight** | : | 190.2 |
| **Structural Formula** | : | CH3-O-(C3-H6-O)2-OOCH2-CH3 |
| **Molecular Formula** | : | C9H18O4 |
| **Source** | : | American Chemistry Council |

**Producer Related Part**

| | | |
|---|---|---|
| **Company** | : | American Chemistry Council |
| **Creation date** | : | 30.08.2002 |

**Substance Related Part**

| | | |
|---|---|---|
| **Company** | : | American Chemistry Council |
| **Creation date** | : | 30.08.2002 |
| **Memo** | : | |
| **Printing date** | : | 30.08.2002 |
| **Revision date** | : | 30.08.2002 |
| **Date of last Update** | : | 30.08.2002 |
| **Number of Pages** | : | 53 |
| **Chapter (profile)** | : | Chapter: 1, 2, 3, 4, 5, 7 |
| **Reliability (profile)** | : | Reliability: without reliability, 1, 2, 3, 4 |
| **Flags (profile)** | : | Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS |

### 1.0.1 OECD AND COMPANY INFORMATION

| | | |
|---|---|---|
| **Type** | : | |
| **Name** | : | CHEMOXY INTERNATIONAL PLC |
| **Partner** | : | |
| **Date** | : | |
| **Street** | : | ALL SAINTS REFINERY, CARGO FLEET ROAD |
| **Town** | : | TS3 6AF MIDDLESBROUGH, CLEVELAND |
| **Country** | : | United Kingdom |
| **Phone** | : | 44 0642 248555 |
| **Telefax** | : | 44 0642 244340 |
| **Telex** | : | 587185 CEMINT G |
| **Cedex** | : | |

| | | |
|---|---|---|
| **Type** | : | |
| **Name** | : | Dow Deutschland Inc |
| **Partner** | : | |
| **Date** | : | |
| **Street** | : | Werkstade PO Box 1120 |
| **Town** | : | 21677 Stade 5 |
| **Country** | : | Germany |
| **Phone** | : | +49.414.6910 |
| **Telefax** | : | +49.414.6912600 |
| **Telex** | : | |
| **Cedex** | : | |

### 1.0.2 LOCATION OF PRODUCTION SITE

### 1.0.3 IDENTITY OF RECIPIENTS

### 1.1 GENERAL SUBSTANCE INFORMATION

| | | |
|---|---|---|
| **Substance type** | : | Organic chemical. Commercial product is a mixture consisting of predominantly (>95%) secondary alcohol (alpha isomer) with less than 5% primary alcohol (beta isomer). Unless otherwise stated, results in this dossier pertain to commercial mixture. |
| **Physical status** | : | Clear colorless liquid with sweet ether odor |
| **Purity** | : | 99 % w/w |
| **Source** | : | (2,3) |

### 1.1.0 DETAILS ON TEMPLATE

### 1.1.1 SPECTRA

### 1.2 SYNONYMS

2-propanol, 1-methyl-(1-propoxy), acetate

| | | |
|---|---|---|
| **Source** | : | CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND<br>Dow Deutschland Inc Stade 5 |

Dipropylene glycol methyl ether acetate

**Source** : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND
Dow Deutschland Inc Stade 5

Dowanol DPMA
**Source** : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND
Dow Deutschland Inc Stade 5

**Source** : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND
Dow Deutschland Inc Stade 5

## 1.3 IMPURITIES

Currently, DPnB (mixed alpha & beta isomers) consists of greater than 98.0% purity. DPM may be present at a maximum of 0.50% and water at a maximum of 0.05%.

## 1.4 ADDITIVES

## 1.5 QUANTITY

U.S. production (1993): 900-1,800 tonnes (2-3 million pounds)

## 1.6.1 LABELLING

## 1.6.2 CLASSIFICATION

## 1.7 USE PATTERN

DPMA has uses similar to monopropylene glycol methyl ether acetate for applications requiring lower evaporation and flammability. Because of it's high solvency and coalescing abilities, it's high dilution ratio, moderate evaporation rate and viscosity control, DPMA is used as an active solvent in solvent-based coatings, solvent-based silkscreen printing inks, and as a tailing solvent in coatings.

## 1.7.1 TECHNOLOGY PRODUCTION/USE

## 1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

**Remark** : None established.
**Source** : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND

**Remark** :
**Source** : Dow Deutschland Inc Stade 5

## 1.9 SOURCE OF EXPOSURE

**Remark** : Occupational exposure to DPMA is limited due to the enclosed systems in which this chemical is manufactured. End use consumers may be exposed during the application of coatings and other uses for which DPMA is used. In such instances, exposure would be by inhalation or dermal exposure.

After application of coatings, DPMA would evaporate slowly from the coating and escape at low concentrations into the atmosphere. Spills of small quantities (e.g., 1 gallon or less) into the environment could occasionally be expected during coating applications.

**Source** : Dow Deutschland Inc Stade 5

**1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES**

**1.10.2 EMERGENCY MEASURES**

**1.11 PACKAGING**

**1.12 POSSIB. OF RENDERING SUBST. HARMLESS**

**1.13 STATEMENTS CONCERNING WASTE**

**1.14.1 WATER POLLUTION**

**1.14.2 MAJOR ACCIDENT HAZARDS**

**1.14.3 AIR POLLUTION**

**1.15 ADDITIONAL REMARKS**

**Remark** : Disposal:
- incineration
- industrial effluent treatment.

**Source** : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND

**Remark** : Disposal:
- incineration
- industrial effluent treatment

**Source** : Dow Deutschland Inc Stade 5

**1.16 LAST LITERATURE SEARCH**

**1.17 REVIEWS**

**1.18 LISTINGS E.G. CHEMICAL INVENTORIES**

## 2.1 MELTING POINT

**Value** : -25.2.°C (Critical Value)
**Decomposition** :
**Sublimation** :
**Method** : Other
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : DPMA
**Source** : Dill & Davis (1997) & Staples and Davis (2002)

(1,4)

## 2.2 BOILING POINT

**Value** : = 208.9.° C
**Decomposition** : No
**Method** : other
**Year** :
**GLP** : No
**Test substance** :
**Source** : 3M MSDS

(2)

**Value** : = 209.°C, 408°F (Critical Value)
**Decomposition** : No
**Method** : other
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : DPMA
**Source** : Dow Chemical Company MSDS & Staples & Davis (2002)

(3,4)

## 2.3 DENSITY

**Type** : Specific Gravity (Critical Value)
**Value** : = 0.976. at 25° C /25°C (water = 1)
**Method** : other:
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** :
**Source** : Dow & 3M MSDS's; Dow study

(2,3,8)

### 2.3.1 GRANULOMETRY

## 2.4 VAPOUR PRESSURE

**Value** : = 0.13 mm Hg. at 25° C

**Decomposition** :
**Method** Other
**Year** :
**GLP** : No
**Test substance** :
**Source** : Dow Chemical Company

(1)

**Value** : < 1 mm Hg at 20° C
**Decomposition** :
**Method** Other
**Year** :
**GLP** : No data
**Test substance** :
**Source** : 3M MSDS

(2)

**Value** : 0.0836 mm Hg at 20° C
**Decomposition** :
**Method** Other
**Year** :
**GLP** : No data
**Test substance** :
**Source** : Dow Chemical Company MSDS

(3)

**Value** : 17 Pa or 0.17 hPa @ 25°C (Critical Value)
**Decomposition** :
**Method** Other
**Year** :
**GLP** : No data
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : DPMA
**Source** : Staples and Davis (2002)

(4)

## 2.5 PARTITION COEFFICIENT

**Log Pow (Log Kow)** : = 0.803. (Critical Value)
**Method** Other
**Year** :
**GLP** : no data
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : DPMA
**Remark** : Reference material does not specify whether this value was measured or estimated.
**Source** : Dill and Davis, 1997, Staples and Davis (2002), Gonsior and Bailey (1983)

(1,4,8)

## 2.6.1 WATER SOLUBILITY

**Value** : = 16.0 wt% or 160,000 mg/liter (Critical Value)
**Qualitative** :
**Pka** : At ° C
**PH** : at and ° C

**Method** : other
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** :
**Source** : Dill and Davis (1997), Staples and Davis (2002)

(1,4)

**Value** : = 19.4 g./100 gr
**Qualitative** :
**Pka** : At °C
**PH** : at and ° C
**Method** : other
**Year** : 1983
**GLP** : No data
**Test substance** :
**Source** : 3M & Dow MSDS's, Dow report

(2,3,8)

### 2.6.2 SURFACE TENSION

### 2.7 FLASH POINT

**Value** : = 85.6°C
**Type** : Tag closed cup (TCC)
**Method** : other:
**Year** : 1998
**GLP** : No
**Test substance** :
**Remark** : Method:
**Source** : 3M MSDS

(2)

**Value** : = 186°F, 86°C (Critical Value)
**Type** : Tag closed cup (TCC)
**Method** : other:
**Year** : 1999
**GLP** : No
**Reliability** : Assigned Klimisch score of 2 since methodology available.
**Test substance** : DPMA
**Remark** :
**Source** : Dow Chemical Company MSDS, Staples & Davis (2002)

(3, 4)

### 2.8 AUTO FLAMMABILITY

**Value** : Approximately 321.°C (autoignition temperature) (Critical Values
**Method** : Not reported
**Year** : 1999
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : DPMA

**Source** : 3M MSDS

(2)

## 2.9 FLAMMABILITY

**Remark** : Lower Explosive Limit (%): 1.21% by volume @ 150°C.
Upper Explosive Limit (%): 5.35% by volume @ 150°C.
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Source** : 3M & Dow MSDSs

(2, 3)

## 2.10 EXPLOSIVE PROPERTIES

**Result** : Stable
**Method** : other
**Year** :
**GLP** : No
**Test substance** :
**Remark** : “Stable. Hazardous polymerization will not occur.” & “DPMA is stable under normal storage conditions.”
**Source** : 3M & Dow MSDSs

(2, 3)

## 2.11 OXIDIZING PROPERTIES

**Result** : no oxidizing properties
**Method** : other
**Year** :
**GLP** : No
**Test substance** :
**Source** : Dow Chemical Company MSDS

(3)

## 2.12 ADDITIONAL REMARKS

**Remark** : Disposal considerations
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Incinerate under controlled conditions according to local and national regulations.
**Source** : Dow Chemical Company MSDS

(3)

### 3.1.1 PHOTODEGRADATION

| | | |
|---|---|---|
| **Photodegradation OH radical rate constant** | : | 33.6 x 10-12 cm3/molecule-sec |
| **Half-life** | : | 0.318 days or 3.82 hours (assumes 12 hr of light per day and an hydroxy radical concentration of 1.5 x 106 OH/cm3) |
| **Remark** | : | These modeled values represent an estimation of the rate of photodegradation in the the atmosphere, based on the molecular structure of the alpha isomer. (AOP version 1.90) |
| **Source** | : | EPIWIN/AOP (v3.10) Program |

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### 3.1.2 STABILITY IN WATER

| | | |
|---|---|---|
| **Remark** | : | The acetate moiety may be cleaved to yield the parent ether and acetic acid. DPMA will cleave most likely under alkaline conditions whereas it should be stable at neutral or acidic pH. The ether linkage of this molecule is stable in water under neutral conditions at ambient temperatures. |
| **Source** | : | Fieser and Fieser, 1960; Dow MSDS |

(3, 21)

### 3.1.3 STABILITY IN SOIL

| | | |
|---|---|---|
| **Remark** | : | no data available |
| **Source** | : | |

### 3.2 MONITORING DATA

| | | |
|---|---|---|
| **Remark** | : | no studies |
| **Source** | : | Dow Deutschland Inc Stade 5 |

### 3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

| | | |
|---|---|---|
| **Type** | : | Fugacity Model Level III |
| **Method** | : | Mackay Level III |
| **Year** | : | 2002 |
| **Input Parameters and Results** | : | CHEMICAL PROPERTIES AND OTHER INPUT PARAMETERS<br>Where input parameters were estimated, alpha isomer was used, Where input parameters were measured, commercial mixture was used (>95% alpha isomer)<br><br>INPUT PARAMETERS<br><br>Chemical Type: 1<br>Molecular Mass (g/mol): 190.2388<br>Data Temperature (Degrees Celsius): 25<br>Log Kow: 0.803<br>Water Solubility (g/m3): 160000<br>Water Solubility (mol/m3): 841.0482<br>Henry's Law Constant (Pa.m3/mol): 2.021287E-02<br>Vapour Pressure (Pa): 17<br>Melting Point (Degrees Celsius): -25.2 |

RESULTS (HALF-LIVES)

Half-Life in Air (h): 7.6
Half-Life in Water (h): 672
Half-Life in Soil (h): 672
Half-Life in Sediment (h): 672
Half-Life in Suspended Sediment (h): 672
Half-Life in Fish (h): 24
Half-Life in Aerosol (h): 24

PARTITION COEFFICIENTS (RESULTS)
(All amounts are dimensionless, except where noted)

Log Octanol-Water Partition Coefficient: 0.803
Octanol-Water Partition Coefficient: 6.353309
Organic Carbon-Water Partition Coefficient (L/kg): 2.604857
Air-Water Partition Coefficient: 8.15423494360427E-06
Soil-Water Partition Coefficient: 0.125033117022759
Soil-Water Partition Coefficient (L/kg): 5.20971320928162E-02
Sediment-Water Partition Coefficient: 0.250066234045518
Sediment-Water Partition Coefficient (L/kg): 0.104194264185632
Suspended Sediment-Water Partition Coefficient: 1.25033122805708
Suspended Sediment-Water Part. Coefficient (L/kg): 0.520971345023784
Fish-Water Partition Coefficient: 0.3049589
Fish-Water Partition Coefficient (L/kg): 0.30495885014534
Aerosol-Water Partition Coefficient: 0
Aerosol-Air Partition Coefficient: 352941.185986284

**Remark** : The air/water partition coefficient for DPM acetate was determined to be <1 x 10-4, which indicates that the product will tend to remain in a water solution.
**Reliability** : (1) Valid without restriction
**Source** : Mackay Fugacity Model, Level 3

### 3.3.2 DISTRIBUTION

**Distribution at Equilibrium** : See EPIWIN modeling results below
**Air** : 1.07%
**Water** : 52.0%
**Soil** : 46.8%
**Sediment** : 0.0902%
**Remark** : Results are estimates based on the Mackay Level III fugacity model (part of EPIWIN Suite)
**Source** : EPIWIN (v3.10) Program (23)

**Remark** :

Henry's Law Constant = 1.99E-07 atm-m3/mol
(VP/Wsol estimate using EPI values)

HLC = 7.46E-8 atm-m3/mol ("Bond Method")
HLC = 2.94E-9 atm-m3/mol ("Group Method")

**Source** : EPIWIN (HENRYWIN Module) (23)

**Remark** : Henry's Law Constant = 2.03E-07 atm-m3/mol (or 2.03E-02 Pa-m3/mol).
(1,4)

## 3.4 MODE OF DEGRADATION IN ACTUAL USE

**Remark** : Biodegradable with industrial and municipal seeds.
**Source** : Dow Report
(8)

## 3.5 BIODEGRADATION

| | | |
|---|---|---|
| **Type** | : | Aerobic (Ready Biodegradability) |
| **Inoculum** | : | Sediment and activated sludge from a domestic sewage treatment plant. |
| **Concentration** | : | 0 or 100 mg/L |
| **Contact time** | : | 28 days |
| **Degradation** | : | O2 consumption = 16.% after 28 days<br>DPMA→DPM = 100% after 28 days |
| **Result** | : | DPMA is not readily biodegradable |
| **Kinetics of test substance (high dose)** | : | Based on O2 consumption<br>Day 7 = 12.%<br>Day 14 = 15.%<br>Day 21 = 16.%<br>Day 28 = 16.%Day 22 = 65.8%<br>Day 28 = 67.0% |
| **Deg. Product** | : | DPM |
| **Protocol Guideline** | : | Japanese Guidelines "Biodegradation test of chemical substance by microorganisms etc." stipulated in the Order Prescribing the Items of the Test Relating to the New Chemical Substance (KANHOGYO Notification No. 5, YAKUHATSU Notification No. 615 and 49 KIKYOKU Notification No. 392, dated July 13, 1974. |
| **Year of Study** | : | 2000 |
| **GLP** | : | Yes |
| **Test substance** | : | Identity: Propylene glycol methyl ether acetate, DPMA. CAS # 770-35-4 (also 88917-22-0)<br>Lot No.: MK13011TD1<br>Purity: 99% w/w<br>Appearance: Colorless transparent liquid<br>Solubility: 16% w/v in water.<br>Storage: Room temperature.<br>Stability: Stable; IR spectra similar before & after study. |

**Method** : To test for its biodegradability potential, DPMA was incubated with activated inoculum for 28 days in sealed, continuously agitated closed bottles at 25±1°C in triplicate at a concentration of 100 mg DPMA/liter. The concentration of suspended solids was 30 mg/liter and the pH was 7.2 to 7.6. Controls were single flasks of: 1) water and test substance, 2) control blank (inoculum alone) and 3) inoculum and aniline (positive control). Degradation of DPMA was monitored by assessing 1) the disappearance of O2 and 2) determination of disappearance of DPMA and appearance of DPM by GC analysis. O2 was measured at weekly intervals throughout the 28 day incubation period. For oxygen uptake, biodegradation was calculated by dividing the biological oxygen demand (BOD – mg O2 uptake by DPMA minus O2 uptake by blank) divided by the theoretical oxygen demand (ThOD), times 100. DPMA and DPM were measured using a gas chromatograph equipped with a flame ionization detector. O2 concentration (depletion) was one of the measured variables. The pH ranged from 6.93 to 7.15 after 28 days. Water hardness was not reported.

**Results** : Incubation of DPMA with inoculum resulted in: 1) 16% degradation after 28 days based on O2 consumption and near 100% conversion of DPMA to DPM. DPM did not appear to further biodegrade. The aniline reference compound showed appropriate degradation. The negative control blanks showed expected levels of O2 consumption.

**Conclusions** : With a BOD of 16%, DPMA did not meet the criteria of "readily biodegradable." While the acetate appeared to be quantitatively hydrolyzed to yield DPM, this by-product did not appear to further degrade. The acetate moiety appeared to completely mineralize.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that Japanese guidelines were followed. Specifically, the incubation conditions and the inoculum used, followed guidance. Test material characterization was adequate. The concentrations tested, the length of the monitoring period (28 days), and methods for measuring test compound degradation were typical for this type assay and adequately recorded.

**References** : Matsue, H., (2000). Final report: Ready Biodegradability Study of DPMA. Hodogaya Contract Laboratory Study No. 9933D. January 25, 2000. Unpublished study.

**Other** : The amount of acetic acid theoretically produced (assuming 100% conversion of DPMA to DPM) by hydrolysis of the acetate from DPM, and subsequently mineralized, was calculated to produce a theoretical oxygen demand of 17%. This agreed with the measured oxygen demand as BOD degradation of 16%. It is surprising that further biodegradation of the parent ether did not take place.

**Source** : Dow Chemical Japan, Inc.

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**Type** : Aerobic (Ultimate Biodegradability)
**Inoculum** : Acclimated activated sludge from a domestic sewage treatment plant.
**Concentration** : 0, 3.75, or 7.5 mg carbon/liter

| | | |
|---|---|---|
| | | or 0, 7.92, or 15.8 mg DPMA/liter |
| **Contact time** | : | 28 days |
| **Degradation** | : | At 3.75 mg carbon/liter<br>O2 consumption = 84.4.% after 28 days<br>O2 consumption = 94.0.% after 43 days<br>At 7.50 mg carbon/liter<br>O2 consumption = 58.% after 28 days<br>O2 consumption = 73.3.% after 43 days |
| **Result** | : | DPMA is biodegradable with acclimated sludge |
| **Kinetics of test substance (high dose)** | : | Based on O2 consumption & DPMA concentration of 3.75 mg carbon/liter (or 7.92 mg DPMA/liter)<br>Day 7 = 21.2.%<br>Day 15 = 67.7.%<br>Day 21 = 79.5.%<br>Day 28 = 84.4.%Day 22 = 65.8%<br>Day 28 = 67.0%<br>Day 43 = 90.0% |
| **Deg. Product** | : | Not determined. |
| **Protocol Guideline** | : | Similar to OECD ready biodegradability tests (e.g., 301D Closed Bottle Test). Does not qualify, however, because acclimated (i.e., pre-adapted) sludge was used wherein the sludge was pre-exposed to the test material to facilitate its metabolism during the actual test. |
| **Year of Study** | : | 1996 |
| **GLP** | : | No data. |
| **Test substance** | : | DPMA |
| **Method** | : | DPMA was incubated with previously acclimated (for 10 days), activated inoculum for up to 43 days in sealed, continuously agitated closed bottles at 25±1°C in triplicate at concentrations of 3.75 or 7.50 mg carbon/liter (7.92 or 15.8 mg DPMA/liter). The concentration of suspended solids was 30 mg/liter and the pH was 7.2 to 7.6. Water hardness was not reported. O2 concentration was a measured variable used to assess biodegradation. Controls were single flasks of: 1) water and test substance, 2) control blank (inoculum alone) and 3) inoculum and sodium benzoate (positive control). Degradation of DPMA was monitored by assessing 1) the disappearance of O2. O2 was measured on days 0, 3, 5, 7, 9. 12, 13, 15, 17, 21, 27, 28, 35, and 43. For oxygen uptake, biodegradation was calculated by dividing the biological oxygen demand at a particular time point (BOD – mg O2 uptake by DPMA minus O2 uptake by blank) divided by the theoretical oxygen demand (ThOD), times 100. |
| **Results** | : | DPMA was 84.4% biodegraded within 28 days at a concentration of 3.75 mg carbon/liter and was 58% biodegraded within 28 days at a concentration of 7.50 mg carbon/liter. At the lower concentration, 60% biodegradation was achieved in 28 days (after reaching 10% within a 10 day window). |
| **Conclusions** | : | With sludge that has been acclimated for a period of time to the test material, DPMA is extensively biodegraded, which appears to go beyond simple hydrolysis of the acetate moiety to yield a non-biodegradable DPM. This is because degradation continued beyond the theoretical limit of 11% for mineralization of only the acetate group and not the other by-product, DPM. Overall, these results cannot be interpreted to mean DPMA is “readily biodegradable” as defined by the OECD, since acclimated inoculum may not be used in such an assay. It is, however, “ultimately biodegradable” under the conditions of this test, which used acclimated inoculum. |

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 2.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report did not include signed GLP and Quality Assurance statements. The study report did provide documentation that procedures were followed, which were similar to those recommended in OECD 302D: "Closed Bottle Test," except that acclimated inoculum was used. Specifically, the incubation conditions and the inoculum used, followed guidance. Test material characterization was adequate. The concentrations tested, the length of the monitoring period (>28 days), and methods for measuring test compound degradation were typical for this type assay and adequately recorded.

**References** : Wu, H., Crapo, K.C., Doi, J.D., (1996). Ultimate biochemical oxygen demand (BODu) test: PM;, PM Acetate; PNP: DPNP; DPM Acetate; TPM. Roy F. Weston study no. 95-079. ARCO Chemical Co sponsor. May 9, 1996. Unpublished report.

**Other** : Unlike the previous assay (see immediately above), these results show that DPMA may be biodegraded beyond DPM to completely mineralize when incubated under conditions simulating a sewage treatment environment with acclimated inoculum and at a lower test material concentration than in the previous assay.

**Source** : ARCO Chemical Company

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## 3.6 BOD5, COD OR BOD5/COD RATIO

**BOD5** : 1% of TOD
**BOD20** : 22% for municipal seed
**BOD20** : 58% for industrial seed
**Source** : Dow Chemical Company

(7)

**BOD5** : 2% of TOD
**BOD28** : 67% with industrial seed
**BOD28** : 9% with municipal seed
**Source** : Dow report

(8)

## 3.7 BIOACCUMULATION

**Modeling results** : EPIWIN
**Estimated log BCF** : 0.5000
**Estimated BCF** : 3.162
**Source** : EPIWIN/AOP (v3.10) Program

**Remark** : Low potential for bioaccumulation based on high water solubility.
**Source** : Dow Report

(8)

## 3.8 ADDITIONAL REMARKS

## 4.1 ACUTE/PROLONGED TOXICITY TO FISH

**Type** : Static (fresh water)
**Species** : Pimephales promelas Rafinesque (Fathead minnow)
**Exposure period** : 96 hour(s)
**Unit** : Mg DPMA/liter
**Analytical monitoring** : Nominal concentrations were used.
**NOEC** : = 125 mg/L
**LC50** : = 151 mg/L (139 mg/L < 95% Conf. Limit < 161 mg/L)
**EC50** : Not determined
**Protocol Guideline** : Specific guidance not referenced. However, OECD Guideline 203 "Fish, Acute Toxicity Test" was followed.
**Year of Study** : 1983
**GLP** : Yes
**Test substance** : Identity: 1-methoxy-(2-propoxy)-2-hydroxypropane acetate (or dipropylene glycol methyl ether acetate). CAS # 88917-28-2
Lot No.: XA-10865.00 (DPC 291-110)
Purity: 99.4% (all isomers)
Appearance: Not specified.
Solubility: 19.4 g/100 ml (water)
Storage: Not specified.
Stability: Not specified.

**Method** : Fathead minnow fish (Pimephales promelas Rafinesque) were exposed under static (slightly aerated) conditions to dipropylene glycol methyl ether acetate (DPMA) at nominal concentrations of 0, 100, 125, 160, 200, 250, or 320 mg/liter for periods extending up to 96 hours (survival permitting). Actual concentrations were not determined. Each exposure group was comprised of 10 fish (sex unspecified). Fish were observed for mortality and signs of toxicity at 24, 48, 72, and 96 hours after exposure to the test material. The design is shown with some results in the table below.

Exposures were conducted in large glass vessels containing 10 liters of filtered UV irradiated Saginaw Bay, Lake Huron water maintained within a temperature range of 16.4-18.0°C. Water was carbon filtered, had a pH of 7.7 to 8.1, a hardness of 98-100 mg/L (as CaCO3), and dissolved oxygen content > 57% saturation. Ten fish of mean length 3.0 (2.5-3.5) cm length and mean weight of 0.57 grams were exposed in each test vessel. Loading was 0.57 g/liter. Fish were not fed throughout the 96-hour exposure period. Oxygen concentration (pO2), pH, and temperature were recorded at the initiation of exposure and every 24 hours thereafter in the control, low, mid-, and high dose groups, survival permitting.

| Group | DPMA Conc (mg/L)* | #/Conc .** | %Dead @ 24 hr | %Dead @ 48 hr | %Dead @ 72 hr | %Dead @ 96 hr |
|---|---|---|---|---|---|---|
| 1 | 0 | 10 | 0 | 0 | 0 | 0 |
| 2 | 100 | 10 | 0 | 0 | 0 | 0 |
| 3 | 125 | 10 | 0 | 0 | 0 | 0 |
| 4 | 160 | 10 | 0 | 50 | 70 | 80 |
| 5 | 200 | 10 | 60 | 100 | 100 | 100 |
| 6 | 250 | 10 | 60 | 100 | 100 | 100 |
| 7 | 320 | 10 | 100 | 100 | 100 | 100 |

* Nominal concentration (actual concentration not determined).
** Sex not specified.

**Results** : An overview of the results is shown in the preceding table. Using moving averages method, the LC50 was calculated to be 151 mg/liter with 95% confidence intervals ranging from 139 to 161 mg/liter. At the highest concentrations, all fish died during the first 24 hours. At the next two lower concentrations, mortality was 60% after 24 hours and 100% after 48 hours. At 160 mg/liter, mortality was 50% at 48 hours, 70% at 72 hours, and 80% after 96 hours. In the control and lowest two exposure groups (0, 100 and 125 mg/liter), no deaths were observed over the 96 hour exposure period.

**Conclusions** : The 96-hr LC50 for DPMA was calculated to be 151 mg/l (139 < 95% CL < 161 mg/l). The NOEC for mortality is 125 mg/l. The approximate 2-fold difference in the concentration causing no mortality and that causing 100% mortality indicates a steep dose-response curve. These results indicate that, under the conditions of this test, DPMA is moderately toxic to this freshwater aquatic species and has a steep dose-response curve.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 2.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included signed GLP and Quality Assurance statements. The report did not specifically reference OECD Protocol 203 "Fish, Acute Toxicity Test." However, the fish maintenance conditions followed guidance. Test material characterization was adequately described in the report. The number of concentrations tested, their spacing, and magnitudes, the length of the exposure period (96 hours), and methods for calculating results were typical for this type assay and adequately recorded.

**References** : Dill, D.C., Applegath, S.L., (1983). Evaluation of the toxicity of DPM Acetate (XA-10856.00) to representative aquatic organisms. Dow Report No. ES-595. April 7, 1983. Unpublished report.

**Other** : No actual concentrations were measured. Completeness of dissolution of the test substance in the water environment of the fish was made only on a visual basis. Since the water solubility of DPMA is ~194,000 mg/liter, the test material is easily theoretically soluble at the highest concentration tested. Moreover, DPMA is not volatile and is fairly stable in aqueous solution. Tthe acetate moiety may hydrolyze to yield DPM, however, hydrolysis in this test of the acetate to the parent ether is considered unlikely since strongly alkaline pH would be required. Presumably, the alkalinity required for hydrolysis would be toxic to the test organisms. Thus, the nominal concentrations presumably are representative of the actual concentrations. The mortality in the four highest exposure groups indicates that the test material was soluble enough to exert toxic effects. The loading factor of 0.57 grams fish to 1 liter water is within the recommended value in the OECD guidance of 1.0 gram/liter (OECD Protocol 203).

**Source** : Dow Chemical Company

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## 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

**Type** : Static
**Species** : Daphnia magna (Crustacea)
**Exposure period** : 48 hour(s)
**Unit** : mg/liter
**Analytical monitoring** : Nominal concentrations used.
**NOEC** : 160. mg/liter
**Protocol Guideline** : Specific guidance not referenced. However, OECD Guideline 202 "Daphnia sp., Acute Immobilisation Test and Reproduction Test" was followed.
**Year of Study** : 1983
**GLP** : Yes
**Test substance** : Identity: 1-methoxy-(2-propoxy)-2-hydroxypropane acetate or (dipropylene glycol methyl ether acetate). CAS # 88917-28-2
Lot No.: XA-10865.00 (DPC 291-110)
Purity: 99.4% (all isomers)
Appearance: Not specified.
Solubility: 19.4 g/100 ml (water)
Storage: Not specified.
Stability: Not specified.

**Method** : Thirty Daphnia magna (first instar) per level were exposed for 48 hours to concentrations of 160, 250, 400, 630, 1000, 1600, or 2500 mg DPMA/liter water. Ten daphnids (in triplicate for a total of 30 daphnids) were exposed to each concentration of DPMA. Daphnia were observed only for mortality at 24 and 48 hours (i.e., EC50 based on immobilization was not reported). At these time points, the LC50 (with confidence limits) was determined.

**Results** : No mortality occurred at the lowest concentration of 160 mg DPMA/liter after 48 hours. At the next highest concentration of 250 mg/liter, 1 of 30 daphnids died within 24 hours and the remainder survived the entire 48 hour exposure period. Mortality for these and the groups exposed to higher DPMA concentrations are shown in the table below. Water was carbon filtered, had a pH of 8.1 to 8.3, a hardness of 98-100 mg/L (as CaCO3), and dissolved oxygen content > 91% saturation.

| Concentration | # Exposed | %Dead - 24 hr | %Dead - 48 hr |
|---|---|---|---|
| 0 mg/l | 30 | 0 | 0 |
| 160 mg/l | 30 | 0 | 0 |
| 250 mg/l | 30 | 3 | 3 |
| 400 mg/l | 30 | 7 | 10 |
| 630 mg/l | 30 | 13 | 17 |
| 1000 mg/l | 30 | 10 | 20 |
| 1600 mg/l | 30 | 70 | 80 |
| 2500 mg/l | 30 | 77 | 100 |

The 48-hour LC50 was 1090 mg/liter with 95% confidence limits ranging from 957 to 1260 mg/liter. The NOEC is 160 mg/liter for mortality.

**Conclusions** : These results indicate that DPMA is “slightly toxic” to “practically non-toxic” to daphnia under the conditions of this test. Various ranking criteria for this conclusion include toxicity categories established by U.S. EPA Office of Prevention and Toxic Substances (Report EPA 738-R-94-035) and the U.S. Fish and Wildlife Service, Research Information Bulletin No. 84-78.

**Data Quality** : The data quality from this study is considered acceptable with limitations. The report included limited documentation for methods and results. This study reaches Klimisch Level 2.

| | | |
|---|---|---|
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included signed GLP and Quality Assurance statements. The study report did not specifically reference OECD Protocol 202 " Daphnia sp., Acute Immobilisation Test and Reproduction Test." However, the daphnia maintenance conditions followed guidance. Test material characterization was adequately described in the report. The number of concentrations tested, their spacing, and magnitudes, the length of the exposure period (48 hours), and methods for calculating results were typical for this type assay and adequately recorded. |
| **References** | : | Dill, D.C., Applegath, S.L., (1983). Evaluation of the toxicity of DPM Acetate (XA-10856.00) to representative aquatic organisms. Dow Report No. ES-595. April 7, 1983. Unpublished report. |
| **Other** | : | No actual concentrations were measured. Completeness of dissolution of test substance in the water environment of the daphnia was made only on a visual basis. Since the water solubility of DPMA is ~194,000 mg/liter, the test material is easily theoretically soluble at the highest concentration tested. Moreover, DPMA is not volatile and is fairly stable in aqueous solution. Tthe acetate moiety may hydrolyze to yield DPM, however, hydrolysis in this test of the acetate to the parent ether is considered unlikely since strongly alkaline pH would be required. Presumably, the alkalinity required for hydrolysis would be toxic to the test organisms. Thus, the nominal concentrations presumably are representative of the actual concentrations. The mortality in the higher exposure groups indicates that the test material was soluble enough to exert toxic effects. |
| **Source** | : | Dow Chemical Company |

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### 4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

| | | |
|---|---|---|
| **Remark** | : | The EPIWIN suite of models is able to predict toxicity values for chemicals based on their physicochemical characteristics of Kow, molecular weight, molecular structure, etc. The ECOSAR program module (v.0.99) of EPIWIN (v3.10) predicted a Green Algae 96-hour EC50 of 11.37 mg/L and a ChV of 8.565 mg/L. |
| **Source** | : | ECOSAR Module of EPIWIN Modeling Suite |

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Surrogate Chemical: Propylene Glycol Methyl Ether Acetate

| | | |
|---|---|---|
| **Type** | : | Static |
| **Species** | : | Selenastrum capricornutum ATCC22662 (from ATCC) |
| **Exposure period** | : | 72 hours |
| **Unit** | : | mg/liter |
| **Concentrations Tested** | : | Nominal: 0, 95, 171, 309, 556, or 1000 mg PMA/liter<br>Actual (at test start): <0.5, 93.4, 167.8, 305.4, 533.8, or 995.0 mg/L<br>Actual (at test end): <0.5, 81.5, 145.0, 266.8, 466.1, or 863.3 mg/L |
| **Analytical monitoring** | : | Yes, measured by gas chromatography at start and end of test (72 hr). |
| **Toxicity Endpoint** | : | Growth inhibition, expressed as EC50s and NOECs and measured by a) comparison of area under the growth curve and b) comparison of growth rates. |
| **NOEC** | : | > 1000 mg/liter (nominal) |
| **Protocol Guideline** | : | OECD TG 201 |
| **Year of Study** | : | 1998 |
| **GLP** | : | Yes |

**Test substance** : Identity: 1-Methoxy-2-propanol acetate CAS # 108-65-6
Batch No.: Lot No. WTH 5725.
Purity: > 97%
Storage: Room temperature in dark.
Stability: Confirmed by GC.

**Method** : Test Conditions
· Test temperature range: 23±2 °C
· Growth/test medium: OECD medium.
· Shaking: 100 rpm
· Dilution water source: OECD medium.
· Exposure vessel type: 100 mL OECD medium in a 300 mL Erlenmeyer flask with a silicon cap which allows ventilation.
· Water chemistry in test (pH) in at least one replicate of each concentration (at start and end of the test): pH=7.4-7.5 at start and 7.0-9.4 at end of the test (72 h).
· Stock solutions preparation : No stock solution was prepared. Test chemical was diluted to 2.0 wt.% with OECD medium and sterilised with filter before use.
· Light levels and quality during exposure: 4,000-5,000 lux, continuous illumination.

Test design:
· Number of replicates: Triplicate
· Concentrations: 0,95, 171, 309, 556 and 1,000 mg/L
· Initial cell number in cells/mL: 1x104

Method of calculating mean measured concentrations:
· Geometric mean.

**Results** : - Unit : Cell density (cells/mL)
- Results: (calculated based on nominal concentrations)
(1) Growth inhibition (comparison of area under growth curve)
EC50 (0-72 h) > 1,000 mg/L
NOEC (0-72 h)> 1,000 mg/L
(2) Growth inhibition (comparison of growth rates)
EC50 (24-48) > 1,000 mg/L
EC50 (24-72) > 1,000 mg/L
NOEC (24-72) > 1,000 mg/L

- Was control response satisfactory:
Yes: Mean cell density increased to 2.25x106 cells/mL (225-fold increase) after 72 hr.
- Statistical results as appropriate:
Significant difference in the growth curve was not observed between values at 1,000 mg/L and in control.

Biological observations
· Cell density at each flask at each measuring point:

Nominal Concentration (mg/L) Cell Density (x104 cells/mL)

| | 0 hr | 24 hr | 48 hr | 72 hr |
|---|---|---|---|---|
| Control | 1.0 ± 0.00 | 9.4 ± 0.84 | 62.8 ± 25.82 | 224.6 ±45.58 |
| 95 | 1.0 ± 0.00 | 15.5 ±6.63 | 42.8 ± 4.49 | 229.4 ±7.67 |
| 171 | 1.0 ± 0.00 | 8.7 ± 1.39 | 44.7 ± 2.18 | 211.7 ±25.87 |
| 309 | 1.0 ± 0.00 | 11.7 ± 8.63 | 46.7 ± 16.28 | 232.5 ±10.34 |
| 556 | 1.0 ± 0.00 | 7.2 ±1.18 | 40.7 ± 2.21 | 224.1 ±16.55 |
| 1,000 | 1.0 ± 0.00 | 5.8 ± 0.88 | 37.7 ± 14.69 | 209.6 ±13.89 |

(Each value represents the mean of three sample counts.)

Growth curves: Logarithmic growth until end of the test (72 h).

- Percent biomass/growth rate inhibition per concentration: Not described.
- Observations:All test groups (95-1,000 mg/L) showed normal and similar growth to that of control (210-232-fold increase after 72 hr).

**Conclusions** : PMA is relatively non-toxic to this algal species.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included a study review statement, signed by the Study Director and laboratory supervisory personnel indicating that a quality assurance inspection had been performed. The study report provided documentation that OECD Protocol 201 "Alga, Growth Inhibition Test" was followed. Specifically, the microorganism growth and maintenance conditions were as prescribed in the aforementioned guidance. Test material characterization was described in the report. The concentrations tested, the length of the exposure and observation period (72 hours), and methods for calculating results were typical for this type assay and adequately recorded.

**References** : Environment Agency of Japan, 1998.

**Other** : Low toxicity of PMA in this test is consistent with the low toxicity observed with other divergent organisms and other propylene glycol ethers.

**Source** : Dow Deutschland Inc Stade 5

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### 4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

**Remark** : No studies found.
**Source** :

### 4.5.1 CHRONIC TOXICITY TO FISH

**Remark** : No studies found.
**Source** :

### 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

**Remark** : No studies found.
**Source** :

### 4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

**Remark** : No studies found.
**Source** :

### 4.6.2 TOXICITY TO TERRESTRIAL PLANTS

**Remark** : No studies found.
**Source** :

### 4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

**Remark** : No studies found.
**Source** :

### 4.7 BIOLOGICAL EFFECTS MONITORING

No studies found.
**Source** :

### 4.8 BIOTRANSFORMATION AND KINETICS

**Source** : Dow Deutschland Inc Stade 5

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### 4.9 ADDITIONAL REMARKS

**Remark** : No remarks.
**Source** :

### 5.1.1 ACUTE ORAL TOXICITY

| | | | |
|---|---|---|---|
| **Type** | : | LD50 | |
| **Species** | : | Rat | |
| **Strain** | : | Fischer 344 | |
| **Sex** | : | males and females | |
| **Number of animals** | : | 6 per sex | |
| **Vehicle** | : | No vehicle; test material was tested undiluted. | |
| **Concentrations tested** | : | See methods below | |
| **Protocol Guideline** | : | Federal Register 43:163.81-1, 1978 specifically referenced. Generally follows OECD Guideline 401 "Acute Oral Toxicity" | |
| **Year of Study** | : | 1982 | |
| **GLP** | : | Unknown | |
| **Test substance** | : | Identity: | Dowester A50B or Dipropylene glycol methyl ether acetate (CAS# 88917-22-0) |
| | | ID Code: | “Herb Jackson, 1710”. |
| | | Appearance: | Clear liquid. |
| | | Purity: | Not specified. |
| | | Source: | Organic Chemicals Research Laboratory, Midland MI. |
| | | Administered as: | Undiluted. |

**Method** : Adult male and female Fischer 344 rats (6/sex/group) were administered single gavage doses of 630, 1300, 2500, 5000 or 10000 mg/kg (only females were treated at this high dose) of undiluted DPMA in an olive oil vehicle. Rats were observed for mortality and signs of toxicity for 14 days after administration of the test material and survivors were subjected to complete necropsy at the end of the observation period.

Rats were administered a single gavage dose of the test compound during the morning of day 1 after being fasted for 16 hours over the previous night. After dosing, signs and symptoms were monitored several times on the first day and at least daily thereafter on workdays. Animals were checked for morbidity and mortality twice per day on workdays and once per day on holidays. Rats were fasted for 16 hours prior to final sacrifice with CO2 on day 14 and were subjected to gross necropsy. The experimental design is shown in the table below along with mortality results.

| Group | DPMA Dose (mg/kg) | #/Sex/ Dose | No. Males Dead | No. Females Dead | Total Dead |
|---|---|---|---|---|---|
| 1 | 630 | 6 | 0/6 | 0/6 | 0/12 |
| 2 | 1300 | 6 | 0/6 | 0/6 | 0/12 |
| 3 | 2500 | 6 | 0/6 | 0/6 | 0/12 |
| 4 | 5000 | 6 | 0/6 | 2/6 | 2/12 |
| 5 | 10000 | 6* | N/A | 6/6 | 6/6 |

* Only females were tested at 10000 mg/kg.

| | | |
|---|---|---|
| **Results** | : | No rats died that were treated with 2500 mg/kg DPMA or less. Two females but no males died that were treated with 5000 mg/kg DPMA. All 6 females treated with 10000 mg/kg DPMA died. All non-surviving rats succumbed within 3 days. No signs of toxicity were evident in rats treated with 630 mg/kg. Incoordination and decreased activity were observed at 1300 mg/kg, which increased in severity to lethargy and semi-consciousness as the dose level increased. Labored respiration, lethargy, watery eyes, and unconsciousness were observed at 5000 and 10000 mg/kg. Surviving rats gained weight steadily throughout the observation period. No grossly observable lesions were reported in the remaining subjects that survived until terminal sacrifice. |
| **Conclusions** | : | The oral LD50 exceeds 5000 mg/kg in rats of both sexes. In males, the oral LD50 is greater than 5000 mg/kg. In females, the LD50 is 5448 mg/kg (4071 – 7635 95% confidence limits), with a dose-response slope of 5.1. These results indicate low acute oral toxicity for DPMA. |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 2. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). While the report did not include signed GLP and Quality Assurance statements, it did provide documentation that the requirements of OECD Protocol 401: "Acute Oral Toxicity" were followed. Specifically, the numbers and type of test animals used and their husbandry conditions followed guidance. The dose levels tested satisfied the appropriate OECD upper limit (i.e., 2 gm/kg or greater), the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded. |
| **References** | : | Carreon, R.E., Yakel, H.O., Eisenbrandt, D.L., Wall, J.M., (1982). Dipropylene glycol monomethyl ether acetate: Acute toxicological properties and industrial handling hazards. Dow report HET K-6410-(3). May 17, 1982. Unpublished report. |
| **Other** | : | The oral LD50s found in this study is consistent with other published values for this chemical. No explanation was given for why only females were administered the high dose of 10000 mg/kg. |
| **Source** | : | Dow Chemical Company |

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### 5.1.2 ACUTE INHALATION TOXICITY

| | | |
|---|---|---|
| **Type** | : | LC50 (vapor exposure) |
| **Species** | : | Rat |
| **Strain** | : | Fischer 344 (~12 weeks old) |
| **Sex** | : | Males only |
| **Number of animals** | : | 6 |
| **Vehicle** | : | None |
| **Exposure time** | : | 4 hours |
| **Concentration(s) tested** | : | 5.7 mg/liter or 5,700 mg/cubic meter (734 ppm).. |
| **Protocol Guideline** | : | Though not specifically referenced, OECD 403 "Acute Inhalation Toxicity" was generally followed. |

**Year of Study** : 1982.
**GLP** : Unknown.
**Test substance** : Identity: Dowester A50B or Dipropylene glycol methyl ether acetate (CAS# 88917-22-0)
ID Code: "Herb Jackson, 1710".
Appearance: Clear liquid.
Purity: Not specified.
Source: Organic Chemicals Research Laboratory, Midland MI.
Administered as: Undiluted.

**Method** : Animals were assigned to the test group noted in Table 1 below. Six male rats were exposed to 0 and 5.7 mg/liter DPMA for 4 hours in 112-liter, stainless steel and glass whole-body inhalation chambers. The test atmosphere was not analyzed. Rather, the exposure concentration was calculated (as nominal) from the amount of DMPA used divided, by the air flow. Rats were observed for mortality and signs of toxicity over the course of exposure and the 2-week observation period. After 24 hours, one control and one DPMA-exposed rat were sacrificed and subjected to gross necropsy. After 14 days of observation, the remaining animals were sacrificed and a necropsy was performed.

Table 1. Concentrations, exposure conditions, mortality/animals treated.

| Nominal Conc. | Analy-tical Conc. | MMAD * (□m) | GSD** (□m) | No. dead/total (Males) | No. dead/total (Females)* | No. dead/total (Combined) |
|---|---|---|---|---|---|---|
| 0 mg/L | N/A | N/A | N/A | 0/6 | N/A | 0/6 |
| 5.7 mg/L | N/A | N/A | N/A | 0/6 | N/A | 0/6 |

* MMAD = Mass Median Aerodynamic Diameter (in micrometers).
** GSD= Geometric Standard Deviation (in micrometers).
*** Females were not used in this study.

Generation of the test atmosphere and description of the chamber

Vapor Generation: The vapor atmosphere was generated by metering DPMA into a J tube into which heated air (100°C) was directed. The resulting vapor was diluted to the desired concentration with room temperature air.

**Results** : No mortalities occurred as a result of exposure to the test material.

The LC50 for males is > 5.7 mg/L (5,700 mg/m3) or > 734 ppm DPMA.

No abnormal clinical signs were noted in any of the test subjects. No changes in body weights were noted over the course of the study. No adverse findings attributable to DPMA were reported when animals were necropsied at 24 hours post-exposure (1 rat/concentration) or at the end of the 14-day observation period (5 rats/concentration).

**Conclusions** : The DPMA 4-hour inhalation LC50 for males is greater than 5.7 mg/l (or > 5,700 mg/m3). No deaths occurred in 6 males at this exposure level so the actual LC50 may be considerably higher than this value. Actual concentrations were not measured and the calculated vapor concentration is greater than the theoretical maximum (see comment below). However, no condensation was reported on the chamber walls so a supersaturated condition may have existed.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 2.

| | | |
|---|---|---|
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). While the report did not include GLP and Quality Assurance statements and did not specifically reference OECD Protocol 403: "Acute Inhalation Toxicity," the standards specified in this guidance were generally followed. Specifically, the numbers and type of test animals used and their husbandry conditions followed guidance. Test material characterization was adequate except for the use of only nominal concentrations (acceptable for an acute test). The dose level tested (in this limit test) satisfied the appropriate OECD upper limit, the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded. |
| **Reference** | : | Carreon, R.E., Yakel, H.O., Eisenbrandt, D.L., Wall, J.M., (1982). Dipropylene glycol monomethyl ether acetate: Acute toxicological properties and industrial handling hazards. Dow report HET K-6410-(3). May 17, 1982. Unpublished report. |
| **Other** | : | The low acute inhalation toxicity found in this study for DPMA is consistent with other propylene glycol ethers. No explanation was given for why only males were evaluated<br><br>The authors noted that the tested concentration of DPMA might have represented a supersaturated concentration since the theoretical maximum calculated by the Antoine equation would be 135 ppm. The concentrations were not verified by chemical analysis and, therefore, could have been less than the calculated nominal concentration. |
| **Source** | : | Dow Chemical Company<br>(10) |
| **Type** | : | LC50 (vapor exposure) |
| **Species** | : | Rat |
| **Strain** | : | Not specified |
| **Sex** | : | Not specified |
| **Number of animals** | : | 5 males? (based on another compound tested in the same study). |
| **Vehicle** | : | None |
| **Exposure time** | : | 7 hours |
| **Concentration(s) tested** | : | 4000 ppm (nominal) (equivalent to 31,125 mg/m3) |
| **Protocol Guideline** | : | Pre-guideline |
| **Year of Study** | : | 1949 |
| **GLP** | : | Pre-GLP |
| **Test substance** | : | Propylene glycol methyl ether acetate (DPMA) |
| **Method** | : | Using a vacuum pump, vapors of DPMA from a heated source was directed into a 19 liter bell jar containing the rats. Airflow was regulated using a rotameter. Actual concentrations were not measured; rather nominal concentrations were calculated based on airflow rate and amount of test material consumed. By these means, rats were estimated to have been exposed to 4000 ppm (31,125 mg/m3) DPMA for 7 hours. |
| **Results** | : | A thick fog was noticed in the exposure jar indicating the presence of aerosol. Rats exhibited nasal irritation by rubbing their noses and sneezing. Salivation occurred throughout the 7 hour exposure period and slight inebriation was noticed at the end of the exposure. Rats lost weight on the following day but had recovered by the third day following exposure. |
| **Conclusions** | : | It is difficult to quantify acute inhalation toxicity from this older study since |

exposure concentrations were not measured. Actual concentrations may have been substantially less than nominals since the latter level, 4000 ppm (31,125 mg/m3), was far higher than the theoretical maximum vapor concentration of 135 ppm. However, due to the visual observation of a thick fog within the exposure chamber, rats were probably exposed to heavy aerosol concentrations, as well as vapor, far excess of 135 ppm. Condensation of aerosol was not reported but the existence of such a fog would render this possibility highly likely. Consequently, atmospheric concentrations of DMBA could have been substantially less than nominals due to condensing-out of DMBA on the walls of the exposure chamber and fur of the test subjects.

**Data Quality** : Klimisch level 4.

**Quality Check** : The report relating the methods and results of this study is very cursory as sometimes occurs for such an old study. For example, not even the number of rats per exposure group was specified for DPMA.

**Reference** : Hollingsworth, R.L., (1949). Results of range finding acute vapor toxicity tests on Dowesters A33B, A50B, and A62B. Dow file K-6410-(2). April 28, 1949. Unpublished report.

**Other** : The amount of aerosol formed and the possible loss due to condensation was not characterized. The nominal concentration of 4,000 ppm is much higher than the theoretical maximum (135 ppm – see above study).

**Source** : Dow Chemical Company.

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### 5.1.3 ACUTE DERMAL TOXICITY

**Type** : LD50 (Limit Test)
**Species** : Rabbit
**Strain** : New Zealand White
**Sex** : Males and females
**Number of animals** : 2 per sex
**Vehicle** : Test material was tested undiluted.
**Concentration(s) tested** : 5000 .mg/kg bw for 24 hours
**Protocol Guideline** : Though not specifically referenced, OECD Guideline 402 "Acute Dermal Toxicity" was followed.
**Year of Study** : 1982
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowester A50B or Dipropylene glycol methyl ether acetate (CAS# 88917-22-0) |
| ID Code: | “Herb Jackson, 1710”. |
| Appearance: | Clear liquid. |
| Purity: | Not specified. |
| Source: | Organic Chemicals Research Laboratory, Midland MI. |
| Administered as: | Undiluted. |

| | | |
|---|---|---|
| **Method** | : | A group of 2 male and 2 female New Zealand albino rabbits was treated with a single application of 5,000 mg/kg undiluted DPMA applied topically to the clipped, intact skin under occlusion for a period of 24 hours. Subjects were observed for clinical signs of toxicity and mortality during the application period and for a period of 14 days after removal of the test material. The skin of the rabbits at the site of application was also evaluated for signs of irritation over the course of the study. Over the course of the study, animals were routinely observed for toxicity and morbidity. Individual body weights were recorded on test days 0, 7, and 14. Animals were sacrificed on day 14 and subjected to gross necropsy. |
| **Results** | : | No deaths occurred during the study. Other than a transient lethargy, no signs of systemic toxicity were observed. No local dermal responses to treatment were recorded. All subjects gained weight normally and revealed no abnormalities upon necropsy. The dermal LD50 for DPMA is greater than 5000 mg/kg. |
| **Conclusions** | : | These results indicate that DPMA exhibits a relatively low degree of acute dermal toxicity. |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 2. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). While the report did not include signed GLP and Quality Assurance statements and did not specifically reference OECD Protocol 402: "Acute Dermal Toxicity," the numbers and type of test animals used and their husbandry conditions followed guidance. Test material characterization was adequate. The dose level tested (in this limit test) satisfied the appropriate OECD upper limit (i.e., 2 gm/kg or greater), the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded. |
| **References** | : | Carreon, R.E., Yakel, H.O., Eisenbrandt, D.L., Wall, J.M., (1982). Dipropylene glycol monomethyl ether acetate: Acute toxicological properties and industrial handling hazards. Dow report HET K-6410-(3). May 17, 1982. Unpublished report. |
| **Other** | : | The low acute dermal toxicity found in this study for DPMA is consistent with other propylene glycol ethers. |
| **Source** | : | Dow Chemical Company |

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### 5.1.4 ACUTE TOXICITY, OTHER ROUTES

| | | |
|---|---|---|
| **Remark** | : | No studies found. |
| **Source** | : | |

### 5.2.1 SKIN IRRITATION

| | | |
|---|---|---|
| **Species** | : | Rabbit |
| **Strain** | : | New Zealand White |
| **Concentration** | : | Two 0.5 ml aliquots/rabbit, undiluted (one aliquot to an abraded and the second aliquot to an unabraded site); total dose 1.0 ml/rabbit |

**Exposure** : Topical on clipped dorsal back under semi-occlusive dressing.
**Exposure time** : 24 hours
**Number of animals** : Six females
**PDII** : 0.04 out of a possible 8.0
**Result** : Non-irritating
**EC classification** : Non-irritating
**Protocol Guideline** : U.S. Federal Register, 38:187, Part II, Section 1500.41, 1973. Although not specifically referenced, OECD Guideline 404 "Acute Dermal Irritation/Corrosion" was followed.
**Year of Study** : 1982
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowester A50B or Dipropylene glycol methyl ether acetate (CAS# 88917-22-0) |
| ID Code: | "Herb Jackson, 1710". |
| Appearance: | Clear liquid. |
| Purity: | Not specified. |
| Source: | Organic Chemicals Research Laboratory, Midland MI. |
| Administered as: | Undiluted. |

**Method** : The dorso-lumbar region of six albino rabbits (sex not specified) was clipped free of hair 24 hours prior to application of the test material. On the day of treatment, 0.5 ml of undiluted DPMA was applied to an abraded area of skin and another 0.5 ml was applied to an unabraded area of skin; both application sites were then covered with surgical gauze patches overlaid with a piece of heavy-gauge SARAN film to preclude evaporation. After 24 hours, covers were removed, residual DMBA washed off with mild soap and water, and the sites were scored for irritation. Rabbits were fitted with Elizabethan collars immediately after removal of the test material to prevent oral ingestion of any residues. Collars remained in place for a period of at least 72 hours thereafter. The site of application was scored for irritation by assessing the amount of erythema and edema. Both criteria were judged on a scale of 0 – 4. Initially, the sites were scored immediately after test sample removal (24 hrs from initiation of treatment) and again 48 hours after removal of the test material (or 72 hours after initiation of treatment). The overall irritation score was an average of the scores for all six test subjects from both the 24 and 72-hour observation intervals.

**Results** : DPMA was practically nonirritating as shown by the scores in the table below. When the scores for the 24 and 72 hour observation periods were averaged, the mean score was 0.04 for erythema and 0.00 for edema. The only irritation score exceeding 0 was observed immediately after removal of the test material in one animal, which exhibited a score of 1 (very slight) for erythema (and 0 for edema). The remaining five subjects had scores of 0 both for erythema and edema at this and the 72 hour time point.

| Rabbit | | Dose (ml) * | 24-hr Score Abraded | | 24-hr Score Non-abraded | | 72-hr Score Abraded | | 72-hr Score Non-abraded | |
|---|---|---|---|---|---|---|---|---|---|---|
| No. | Sex | | Erythema | Edema | Erythema | Edema | Erythema | Edema | Erythema | Edema |
| 1 | F | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | F | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | F | 1.0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 4 | F | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | F | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | F | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

* 0.5 ml applied to abraded site and 0.5 ml applied to non-abraded site.

**Conclusions** : Results from this study indicate that DPMA has low potential for dermal irritation.

| | | |
|---|---|---|
| **Data Quality** | : | The quality of the data from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 2. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). Although the report did not include signed GLP and Quality Assurance statements, it did provide documentation that OECD Protocol 404: "Acute Dermal Irritation/Corrosion" was followed. Specifically, the numbers and type of test animals used and their husbandry conditions followed guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the observation period (14 days) was sufficient, and scoring criteria and averaging methods were typical for this type assay and adequately recorded. |
| **References** | : | Carreon, R.E., Yakel, H.O., Eisenbrandt, D.L., Wall, J.M., (1982). Dipropylene glycol monomethyl ether acetate: Acute toxicological properties and industrial handling hazards. Dow report HET K-6410-(3). May 17, 1982. Unpublished report. |
| **Other** | : | These results are consistent with other propylene glycol ethers. |
| **Source** | : | Dow Chemical Company |

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### 5.2.2 EYE IRRITATION

| | | |
|---|---|---|
| **Species** | : | Rabbit |
| **Strain** | : | New Zealand White |
| **Concentration** | : | Undiluted |
| **Dose** | : | 0.1 ml |
| **Exposure** | : | Conjunctival sac of right eye |
| **Exposure time** | : | Group 1 (6 rabbits): Unwashed<br>Group 2 (3 rabbits): Washed after 30 second exposure, with tepid, flowing tap water. |
| **Number of animals** | : | Group 1: 6 females<br>Group 2: 2 females and 1 male |
| **Primary Irritation Index (PII) score** | : | Unwashed group (six rabbits)<br>Day 1: 1.0 out of a possible 110<br>Day 2: 0.3 out of a possible 110<br>Days 3 and following, 0.0<br><br>Washed group (three rabbits)<br>out of a possible 110 at all time points. |
| **Result** | : | Non-irritating |
| **EC classification** | : | Non-irritating |
| **Protocol Guideline** | : | U.S. Federal Register, 43:163.81-4, 1978. Although not specifically referenced, OECD Guideline 405 "Acute Eye Irritation/Corrosion" was followed. |
| **Year of Study** | : | 1982 |
| **GLP** | : | Unknown |

| | | | |
|---|---|---|---|
| **Test substance** | : | Identity: | Dowester A50B or Dipropylene glycol methyl ether acetate (CAS# 88917-22-0) |
| | | ID Code: | “Herb Jackson, 1710”. |
| | | Appearance: | Clear liquid. |
| | | Purity: | Not specified. |
| | | Source: | Organic Chemicals Research Laboratory, Midland MI. |
| | | Administered as: | Undiluted. |

**Method** : In a primary eye irritation test, 0.1 milliliters of undiluted DPMA was instilled into the conjunctival sac of the right eye of six female New Zealand white rabbits. The test material was not washed out from the eyes of these animals. A second group of 2 females and one male received identical treatment except that after 30 seconds, the test material was washed out of the eyes of the treated animals using flowing tepid tap water. Eyes were read for irritation at various time intervals over a period of 7 days. Readings were made at 24 hours, 48 hours, 72 hours, 96 hours, and 7 days after treatment. The left eye was used as an untreated control for comparison purposes. Eyes were evaluated for irritation based on 1) damage to the cornea (corneal opacity and area involved, both scored on a scale of 0 to 4) 2) damage to the iris (obvious physical damage and reaction to light, scored on a scale of 0 to 2), and 3) damage to conjunctivae (erythema [scale of 0 – 3] and chemosis [scale of 0 – 4]). The maximum score per animal or per group (as a group mean) was 110.

**Results** : In the unwashed group after 24 hours, DPMA produced an average score of 1.0. This was based on moderate erythema (scores of 2.0) in 3 of the 6 subjects (no corneal or iritic damage occurred in any subject). After 48 hours, only one subject had conjunctival erythema and this resolved by day 3. In the unwashed group, no irritation was observed at any time point.

**Conclusions** : Results indicate that DPMA has a very low potential for eye irritation.

**Data Quality** : The quality of the data from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 2.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). Although the report did not include signed GLP and Quality Assurance statements, documentation was provided that satisfied the requirements of OECD Protocol 405 "Acute Eye Irritation/Corrosion." Specifically, the numbers and type of test animals used and their husbandry conditions followed or exceeded guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the observation period (7 days) met guidance in light of the minimal response, and scoring criteria and averaging methods were typical for this type assay and adequately recorded.

**Reference** : Carreon, R.E., Yakel, H.O., Eisenbrandt, D.L., Wall, J.M., (1982). Dipropylene glycol monomethyl ether acetate: Acute toxicological properties and industrial handling hazards. Dow report HET K-6410-(3). May 17, 1982. Unpublished report.

**Other** : N/A

**Source** : Dow Chemical Company

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## 5.3 SENSITIZATION

Surrogate Chemical (Dipropylene glycol methyl ether)

| | | |
|---|---|---|
| **Type** | : | Sensitization |
| **Species** | : | Human |
| **Number of animals** | : | |
| **Vehicle** | : | |
| **Result** | : | Not sensitizing |
| **Classification** | : | |
| **Method** | : | Other |
| **Year of Study** | : | 1954 |
| **GLP** | : | No |
| **Test substance** | : | Surrogate Chemical (Dipropylene glycol methyl ether). |
| **Remark** | : | Undiluted DPM was applied to the backs of 200 human subjects, 100 males and 100 females, and remained in direct contact with the skin for a period of 5 days. Three weeks later, DPM was applied again to the backs of the same subjects and allowed to remain in contact with the skin for a period of 48 hours.<br><br>DPM was tested by a repeated insult method on 50 human subjects, 25 males and 25 females. The material was applied to the back of the subjects for 4 to 8 hours every other day until 10 applications had been made. After a lapse of 3 weeks, the material was reapplied for a period of 24 to 48 hours. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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## 5.4 REPEATED DOSE TOXICITY

Surrogate Chemical (Dipropylene glycol methyl ether)

| | | |
|---|---|---|
| **Type** | : | Oral repeated-dose toxicity study |
| **Species** | : | Rat |
| **Sex** | : | male/female |
| **Strain** | : | Sprague-Dawley |
| **Route of admin.** | : | Oral (gavage) |
| **Exposure period** | : | 28 days |
| **Frequency of treatment** | : | Daily |
| **Post obs. period** | : | None |
| **Doses** | : | 0, 40, 200, 1000 mg/kg bw d |
| **Control group** | : | Yes, concurrent vehicle |
| **NOAEL** | : | 200 mg/kg |
| **Protocol Guideline** | : | Kanpogyo 700, Yakuhatsu 1039, Kikyoku 1014 |
| **Year of Study** | : | 2000 |
| **GLP** | : | Yes |
| **Test substance** | : | Dipropylene glycol methyl ether or DPM. |

**Method** : Four groups of Sprague-Dawley rats (5/sex/dose level) were treated with dipropylene glycol methyl ether by gavage at doses of 0, 40, 200, or 1000 mg/kg-day for 28 consecutive days. Five additional animals per sex were treated for 28 days with DPM and then observed for an additional 14 days without treatment to assess reversibility of potential toxic effects. The negative controls (group 1; 0 mg/kg) received only water.

Study Design

| Group | Dose* mg/kg-d | No./ Sex/ Dose | Treat-ment Period (Days) | Recovery Period (Days) |
|---|---|---|---|---|
| 1 | 0 | 10 | 28 | 14 (5/sex) |
| 2 | 40 | 5 | 28 | None |
| 3 | 200 | 5 | 28 | None |
| 4 | 1000 | 10 | 28 | 14 (5/sex) |

* Calculated from weekly feed consumption and concentration in feed.

Rats were observed for mortality and clinical signs of toxicity three times per day. Body weights were monitored weekly. Hematological evaluations were conducted. At sacrifice, all rats were subjected to complete necropsy and the following organs/tissues were collected (some were weighed, and all were preserved): brain, pituitary, thyroid, heart, thymus, esophagus, stomach, duodenum, ileum, colon, kidneys, adrenals, urinary bladder, testes, epididymis, prostate, ovaries, uterus, femoral bone, spinal cord, sciatic nerve, and lymph nodes. These tissues were processed into slides and examined microscopically.

**Results** : NOAEL (NOEL): 200 mg/kg
LOAEL (LOEL): 1000 mg/kg
Toxic response/effects by dose level:
1000 mg/kg: tentative salivation, significantly increased relative liver weight, centrilobular hypertrophy

No effects were noted on body weight or survival. No hematological effects were reported. Tentative salivation was noted immediately after exposure beginning on day 11. Evidence of hepatotoxicity also was noted at the highest dose. Liver weight (absolute and relative) remained significantly elevated in male rats following a two week recovery period. No other treatment related effects were observed.

**Conclusions** : A subchronic dose of 200 mg DPM/kg-day represents a NOAEL in rats under the conditions of this oral study.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. This study followed Kanpogyo 700, Yakuhatsu 1039, Kikyoku 1014. Although not specifically referenced in the report, generally the study followed EPA Protocol Guideline 870.3200 "21/28-Day dermal toxicity." Specifically, the numbers and type of test animals used and their husbandry conditions followed guidance. The dosages of test material complied with guidance, the length of the treatment period was sufficient for this type of test, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

**References** : Anonymous. (2000). Dow Chemical Japan. Unpublished Report #FBM 99-2691.

**Other** : The results of this study should reflect the toxicity of DPMA since the only difference in the two compounds is the acetate moiety, which has been shown to rapidly hydrolyze from the parent compound in rat plasma, yielding DPM.

**Source** : Dow Chemical Japan

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Surrogate Chemical (Dipropylene glycol methyl ether)

**Type** : Inhalation repeated-exposure toxicity study
**Species** : Rat
**Sex** : Male/female
**Strain** : Fischer 344
**Route of admin.** : Inhalation
**Exposure period** : 90 days
**Frequency of treatment** : 6 h/d 5 d/w
**Post obs. period** : None
**Doses** : 0, 15, 50, or 200 ppm (0, 91, 303, or 1,212 mg/m3)
**Control group** : Yes, room air.
**NOAEL** : 200 ppm (1,212 mg/m3)
**LOAEL** : > 200 ppm (1,212 mg/m3)
**Protocol Guideline** : Not specified. Generally follows EPA Protocol Guideline 870.3465 "90-Day inhalation toxicity"
**Year of Study** : 1984
**GLP** : Yes
**Test substance** : Dipropylene glycol methyl ether or DPM.

**Method** : Fischer 344 rats (10/sex/exposure concentration) and were exposed to 0, 15, 50, or 200 ppm (0, 91, 303, or 1212 mg/m3) of dipropylene glycol monomethyl ether (DPM) for 6 hr/day, 5 days/week for 13 weeks. Monitored toxicity endpoints included clinical signs, body weights, clinical chemistry, hematology, urinalyses, necropsy, organ weights, and histopathology.

**Results** : NOAEL (NOEL): 200 ppm (1,212 mg/m3)
LOAEL (LOEL): none established (greater than 200 ppm)
Toxic response/effects by dose level:
None noted.

No effects were noted for any of the monitored toxicity endpoints at any exposure level on male or female rats.

**Conclusions** : DPM at concentrations up to 200 ppm (1,212 mg/m3) did not cause toxicity in this study.

| | | |
|---|---|---|
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although not specifically referenced in the report, generally the study followed EPA Protocol Guideline 870.3465 "90-Day inhalation toxicity" or OECD Guideline 413: Subchronic Inhalation Toxicity: 90-day Study. Specifically, the numbers and type of test animals used and their husbandry conditions followed guidance. The number, spacing, and magnitude of the exposure levels complied with guidance. The length of the treatment period was sufficient for this type of test and evaluation criteria and statistical methods were typical for this type assay and adequately recorded. |
| **References** | : | Landry, T.D., Yano, B.L., (1984). Dipropylene glycol monomethyl ether: A 13 week inhalation toxicity study in rats and rabbits. Fund. Appl. Toxicol. 4:612-617. |
| **Other** | : | The results of this study on DPM should reflect the toxicity of DPMA since the only difference between the two compounds is the acetate moiety, which has been shown to rapidly hydrolyze from DPMA in rat plasma, yielding DPM.<br><br>Concentrations of 15, 50 and 200 ppm DPGME correspond to 91, 303, and 1212 mg/m3 DPM respectively. 200 ppm was approximately 40% of a saturated DPGME atmosphere. |
| **Source** | : | Dow Chemical (15) |
| | | Surrogate Chemical (Dipropylene glycol methyl ether) |
| **Type** | : | Inhalation repeated-exposure toxicity study |
| **Species** | : | Rabbit |
| **Sex** | : | Male/female |
| **Strain** | : | New Zealand White |
| **Route of admin.** | : | Inhalation |
| **Exposure period** | : | 90 days |
| **Frequency of treatment** | : | 6 h/d 5 d/w |
| **Post obs. period** | : | None |
| **Doses** | : | 0, 15, 50, or 200 ppm (0, 91, 303, or 1,212 mg/m3) |
| **Control group** | : | Yes, room air |
| **NOAEL** | : | 200 ppm (1,212 mg/m3) |
| **LOAEL** | : | > 200 ppm (1,212 mg/m3) |
| **Protocol Guideline** | : | Not specified. Generally follows EPA Protocol Guideline 870.3465 "90-Day inhalation toxicity." |
| **Year of Study** | : | 1984 |
| **GLP** | : | Yes |
| **Test substance** | : | Dipropylene glycol methyl ether or DPM. |
| **Method** | : | New Zealand White rabbits (7/sex/exposure concentration) and were exposed to 0, 15, 50, or 200 ppm (0, 91, 303, or 1212 mg/m3) of dipropylene glycol monomethyl ether (DPM) for 6 hr/day, 5 days/week for 13 weeks. Monitored toxicity endpoints included clinical signs, body weights, clinical chemistry, hematology, urinalyses, necropsy, organ weights, and histopathology. |

| | | |
|---|---|---|
| **Results** | : | NOAEL (NOEL): 200 ppm (1,212 mg/m3)<br>LOAEL (LOEL): none established (greater than 200 ppm)<br>Toxic response/effects by dose level:<br>None noted.<br><br>No effects were noted for any of the monitored toxicity endpoints at any exposure level on male or female rabbits. |
| **Conclusions** | : | DPM at concentrations up to 200 ppm (1,212 mg/m3) did not cause toxicity in this study. |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although not specifically referenced in the report, generally the study followed EPA Protocol Guideline 870.3465 "90-Day inhalation toxicity" or OECD Guideline 413: Subchronic Inhalation Toxicity: 90-day Study. Specifically, the numbers and type of test animals used and their husbandry conditions followed guidance. The number, spacing, and magnitude of the exposure levels complied with guidance. The length of the treatment period was sufficient for this type of test and evaluation criteria and statistical methods were typical for this type assay and adequately recorded. |
| **References** | : | Landry, T.D., Yano, B.L., (1984). Dipropylene glycol monomethyl ether: A 13 week inhalation toxicity study in rats and rabbits. Fund. Appl. Toxicol. 4:612-617. |
| **Other** | : | The results of this study on DPM should reflect the toxicity of DPMA since the only difference between the two compounds is the acetate moiety, which has been shown to rapidly hydrolyze from DPMA in rat plasma, yielding DPM.<br><br>Concentrations of 15, 50 and 200 ppm DPGME correspond to 91, 303, and 1212 mg/m3 DPM respectively. 200 ppm was approximately 40% of a saturated DPGME atmosphere. |
| **Source** | : | Dow Chemical |

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## 5.5 GENETIC TOXICITY 'IN VITRO'

| | | |
|---|---|---|
| **Type** | : | Bacterial mutagenicity (Ames test) (preincubation method) |
| **System of testing** | : | Salmonella typhimurium (strains TA98, TA100, TA1535 and TA1537) |
| **Concentration** | : | Dose range-finding study: 0, 19.5, 78.1, 313, 1250, or 5000 ug/plate<br>Main study: 0, 313, 635, 1250, 2500, or 5000 ug/plate |
| **Cycotoxic conc.** | : | Not toxic at highest concentration. |
| **Metabolic activation** | : | With and without Aroclor 1254-induced rat S-9 microsomal fraction |
| **Result** | : | Negative |
| **Protocol Guideline** | : | KIHATSU No 603; Test guidelines for bacterial mutagenic testing, (Notice No 77, 1 September 1988, Ministry of Labour, amended subsequently by Notice No 67, 2 June 1997, and KIHATSU No 413, 2 June 1997). |
| **Year of Study** | : | 2000 |

**GLP** : Yes

**Test substance** :

| | |
|---|---|
| Identity: | Dipropylene glycol methyl ether acetate. CAS # 88917-22-0 |
| Lot No.: | MK 13011TD1 |
| Purity: | >99% |
| Supplied as: | Brown bottle. |
| Vapor Pressure: | Not specified. |
| Specific Gravity: | Not specified. |
| Appearance: | Clear, transparent liquid. |
| Administered as: | Dilution in water. |

**Method** : Frozen stock cultures of Salmonella typhimurium were transferred to nutrient rich broth and incubated at 37°C until reaching a cell density between 1 and 2 x 109 cells/ml for each of the four tester strains (TA98, TA100, TA1535, & TA1537).

Results were considered positive if the number of colonies exceeded twice background for any of the strains at any dose and if a dose-response relationship was observed in any strain, with or without S-9 activation. In addition the positive response had to be reproducible in a second experiment. Results were considered negative if the revertant counts did not exceed twice background for any tester strain and the negative response was reproducible in a second experiment.

The validity of the assay was assessed by determining that 1) negative and positive control revertant counts fell within historical control counts and 2) toxicity did not interfere with interpretation of results.

**Results** : DPMA did not induce a mutagenic response in any tester strain at any concentration, with or without S-9 metabolic activation. Toxicity did not interfere with the assay and negative and positive controls fell within historical control limits.

**Conclusions** : DPMA is not mutagenic in the Ames Salmonella typhimurium assay under the conditions of this test.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell lines used, test substance concentrations and dose spacing (several dose levels including negative control, with highest at 5000 ug/plate showing no toxicity), time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of plates scored, and scoring criteria all followed or exceeded guidance as specified in KIHATSU No 603; Test guidelines for bacterial mutagenic testing, (Notice No 77, 1 September 1988, Ministry of Labour, amended subsequently by Notice No 67, 2 June 1997, and KIHATSU No 413, 2 June 1997). The positive control agents gave the expected results showing that the cell line was responsive to reverse mutation.

**References** : Sakata, T., (2000). DPMA: Bacterial Mutation Assay. Fuji Biomedix Study Number FBM 00-8048. May 31, 2000. Dow Chemical Japan Limited. Unpublished study.

**Other** : A negative response for mutagenicity in this Ames and other in vitro tests is consistent with results with other propylene glycol ethers.

**Source** : Dow Chemical Japan

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**Type** : Bacterial mutagenicity with E. coli (preincubation method)
**System of testing** : Escherichia coli (strain WP2uvrA)
**Concentration** : Dose range-finding study: 0, 19.5, 78.1, 313, 1250, or 5000 ug/plate
Main study: 0, 313, 635, 1250, 2500, or 5000 ug/plate
**Cycotoxic conc.** : Not toxic at highest concentration.
**Metabolic activation** : With and without Aroclor 1254-induced rat S-9 microsomal fraction
**Result** : Negative
**Protocol Guideline** : KIHATSU No 603; Test guidelines for bacterial mutagenic testing, (Notice No 77, 1 September 1988, Ministry of Labour, amended subsequently by Notice No 67, 2 June 1997, and KIHATSU No 413, 2 June 1997).
**Year of Study** : 2000
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dipropylene glycol methyl ether acetate. CAS # 88917-22-0 |
| Lot No.: | MK 13011TD1 |
| Purity: | >99% |
| Supplied as: | Brown bottle. |
| Vapor Pressure: | Not specified. |
| Specific Gravity: | Not specified. |
| Appearance: | Clear, transparent liquid. |
| Administered as: | Dilution in water. |

**Method** : Frozen stock cultures were transferred to nutrient rich broth and incubated at 37°C until reaching a cell density between 1 and 2 x 109 cells/ml for the Escherichia coli tester strain (WP2uvrA).

Results were considered positive if the number of colonies exceeded twice background for any of the strains at any dose and if a dose-response relationship was observed in any strain, with or without S-9 activation. In addition the positive response had to be reproducible in a second experiment. Results were considered negative if the revertant counts did not exceed twice background for any tester strain and the negative response was reproducible in a second experiment.

The validity of the assay was assessed by determining that 1) negative and positive control revertant counts fell within historical control counts and 2) toxicity did not interfere with interpretation of results.

**Results** : DPMA did not induce a mutagenic response in Escherichia coli strain WP2uvrA at any concentration, with or without S-9 metabolic activation. Toxicity did not interfere with the assay and negative and positive controls fell within historical control limits.

**Conclusions** : DPMA is not mutagenic under the conditions of this in vitro bacterial mutation assay.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The cell lines used, test substance concentrations and dose spacing (several dose levels including negative control, with highest at 5000 ug/plate showing no toxicity), time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of plates scored, and scoring criteria all followed or exceeded guidance as specified in KIHATSU No 603; Test guidelines for bacterial mutagenic testing, (Notice No 77, 1 September 1988, Ministry of Labour, amended subsequently by Notice No 67, 2 June 1997, and KIHATSU No 413, 2 June 1997). The positive control agents gave the expected results showing that the cell line was responsive to reverse mutation.

**References** : Sakata, T., (2000). DPMA: Bacterial Mutation Assay. Fuji Biomedix Study Number FBM 00-8048. May 31, 2000. Dow Chemical Japan Limited. Unpublished study.

**Other** : A negative response for mutagenicity in this in vitro bacterial test is consistent with results with other propylene glycol ethers.

**Source** : Dow Chemical Japan

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## 5.6 GENETIC TOXICITY 'IN VIVO'

**Type** : No data

## 5.7 CARCINOGENITY

Surrogate Chemical (Propylene glycol methyl ether – PM)

**Type** : Chronic Toxicity/Carcinogenicity
**Species** : Rats and mice

Fischer 344 Rats

| | |
|---|---|
| Age at dosing: | 6-8. |
| Source: | Charles River (Portage, MI). |
| Acclimation period: | 7 days. |
| Weight at start of study: | 143 g (males); 117 g (females). |
| Assignment to groups: | Randomized by weight. |
| Diet: | Certified Rodent Chow #5002 (Purina Mills, Inc., St Louis, MO). |
| Access to food: | Ad libitum except during inhalation exposures. |
| Access to water: | Ad libitum. |
| Method of Identification: | Implanted microchip. |
| Housing: | 2 per stainless steel wire-mesh cage. |

Environmental Conditions (for non-exposure periods):

| | |
|---|---|
| Temperature: | 22 ± 2°C. |
| Humidity: | 40-60%. |
| Air changes: | 12/hr. |
| Photoperiod: | 12 hr light/12 hr dark. |

B6C3F1 Mice

| | |
|---|---|
| Age at dosing: | 6-8 weeks. |

| | | |
|---|---|---|
| Source: | | Charles River (Portage, MI). |
| Acclimation period: | | 14 days. |
| Weight at start of study: | | 24 g (males); 17 g (females). |
| Assignment to groups: | | Randomized by weight. |
| Diet: | | Certified Rodent Chow #5002 (Purina Mills, Inc., St Louis, MO). |
| Access to food: | | Ad libitum except during inhalation exposures. |
| Access to water: | | Ad libitum. |
| Method of Identification: | | Implanted microchip. |
| Housing: | | 2 per stainless steel wire-mesh cage. |
| Environmental Conditions (for non-exposure periods): | | |
| Temperature: | | 22 ± 2°C. |
| Humidity: | | 40-60%. |
| Air changes: | | 12/hr. |
| Photoperiod: | | 12 hr light/12 hr dark. |

**Sex** : Males and females

**Strain** : Rats: Fischer 344
Mice: B6C3F1

**Type** : Vapor Inhalation (whole-body)

**Species** : Lifetime with interim sacrifices

**Frequency** : 6 hr/day, 5 days/week

**Route of admin.** : 0, 300, 1000, or 3000 ppm

**Control group** : Air-only.

**NOAEL** : Rats: 300 ppm based on altered hepatocellular foci in males.
Mice: 1000 ppm based on slight body weight decreases in both sexes.

**LOAEL** : Rats: 1000 ppm based on altered hepatocellular foci in males.
Mice: 3000 ppm based on slight body weight decreases in both sexes.

**Protocol Guideline** : Meets requirements of US EPA Health Effects Test Guidelines OPPTS 870.4300: “Combined Chronic Toxicity/Carcinogenicity” and OECD Guideline for Testing of Chemicals 453 “Combined Chronic Toxicity/Carcinogenicity Studies”

**Year of Study** : 1999 (in-life completion)

**GLP** : Yes

**Test substance** : Propylene glycol methyl ether (PGME) as surrogate for dipropylene glycol methyl ether acetate

| | |
|---|---|
| Identity: | 1-methoxy-2-hydroxypropane or propylene glycol methyl ether. CAS # 107-98-2 |
| Source: | Dow Chemical Company (Midland, MI) |
| Lot No.: | Not specified. |
| Purity: | >97% 1-methoxy-2-propanol: <3% 2-methoxy-1-propanol (> 99.96% both isomers combined). |

**Method:** : In a chronic toxicity/carcinogenicity study, Fischer rats and B6C3F1 mice (50/sex/exposure level) were exposed to vapor concentrations of propylene glycol methyl ether (PGME) at concentrations of 0, 300, 1000, or 3000 ppm

6 hr/day, 5 days/wk for 2 years. Over the course of the study, these subjects were evaluated for clinical signs and body weights. At the end of two years, survivors were subjected to clinical chemistry and hematological examinations, urinalyses, determination of body organ weights, and histopathological examination of a large number of tissues.

In order to evaluate potential toxicity at interim time intervals during the exposure period, additional subjects were exposed to PGME vapors and subjected to routine and specialized toxicological tests at the times shown in the experimental design table below. Subchronic toxicity (at 13 weeks) was evaluated in 5 to 10 mice/sex/exposure level that included clinical chemistry and hematology evaluations, urinalyses, and determination of histopathological changes.

Specialized tests conducted in both mice and rats at the time intervals shown in the table included evaluation of 1) cell proliferation in liver and kidneys, 2) hepatic mixed function oxidase (MFO) activity, and 3) α2μ-globulin nephropathy.

Study Design:

Summary Chronic Study (with mechanistic substudies), Number of Rats (R) and Mice (M) per exposure level (males/ females)

| | | 6 mos | | 12 mos | | 18 mos | | 24 mos | |
|---|---|---|---|---|---|---|---|---|---|
| ppm | Group* | R | M | R | M | R | M | R | M |
| 0 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | D | 5/0 | -- | 5/0 | -- | -- | -- | | |
| 300 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | -- | -- | -- | -- | -- | -- | -- | -- |
| | D | 5/0 | -- | 5/0 | -- | -- | -- | -- | -- |
| 1000 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | -- | -- | -- | -- | -- | -- | -- | -- |
| | D | 5/0 | 5/0 | 5/0 | -- | -- | -- | -- | -- |
| 3000 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | D | 5/0 | -- | 5/0 | -- | -- | -- | -- | -- |

* Group A: routine study, Group B: cell proliferation in liver and kidneys, Group C: Hepatic MFO induction, Group D: α2μ-g nephropathy evaluation.

Table reproduced from chronic portion of Spencer et al. (17)

**Methods (continued)** : Atmospheres of PGME were generated by metering the test material into a glass J-tube assembly through which compressed, heated air was channeled. Evaporated PGME in the heated air was diluted with room temperature air to the desired concentration at a flow rate of 2900 liters per minute into whole-body inhalation chambers. Airflow in the chambers was maintained at a level that provided approximately 12 changes/hour and normal oxygen concentration. PGME concentrations were measured from the breathing zone of the animals inside the chambers two times per hour using a Miran 1A infrared spectrophotometer. Analytical concentrations were within 0.5% of nominal concentrations throughout the study.

**Results** : Some results from additional, shorter-term studies are discussed in Spencer et al. (46), and not in this chronic toxicity/carcinogenicity section.

At 3000 ppm, both mice and rats exhibited decreased activity, incoordination, and transient sedation during the first week of exposure. Subjects recovered 1-2 hours after removal from the chambers. These

signs disappeared in both species after the second week but returned in rats 12-18 months into the study. Mortality was unaffected until 18 months when males but not females of both species showed higher mortality rates that were not ascribable to any particular cause. During the course of the study, body weights in both species were decreased at the 3000 ppm exposure level. These decreases were not large but were statistically significant in all but male rats. Decreased body weights also occurred in mice at the 1000 ppm level. Despite changes during the study, body weights were not statistically different from controls at terminal sacrifice.

No clinical chemistry changes were evident in the subchronic mouse evaluation. In the chronic study, no hematology or urinalysis changes were evident in either species. However, several clinical chemistry parameters in male rats exposed to 3000 ppm PGME were altered at the 24 month sacrifice: creatinine increased 78% and urea nitrogen increased 100%. Serum alkaline phosphatase was increases as well and earlier, at 6 through 24 months at the 3000 ppm level, and at 1000 ppm, at 24 months in male rats. Changes in SGOT (AST) and SGPT (ALT), which could be associated with liver injury, were mildly and inconsistently increased in male rats during the first year of exposure at 3000 ppm but not after. No histological changes accompanied these effects. Liver weights were increased at 3000 ppm in both sexes of both species. Kidney weights were increased at this exposure level only in rats.

**Results (continued)** : Dark foci in the liver were grossly observable in male rats exposed to 1000 and 3000 ppm PGME after 24 months. These subjects also exhibited eosinophilic hepatocellular foci and cystic degeneration microscopically that was not reported in female rats or mice of either sex. Male rats and, to a lesser extent, male mice showed increased S-phase DNA synthesis when exposed to 3000 ppm PGME. This effect was not pronounced (reported in a separate, 2-week study), and was evident to a lesser extent in female rats. MFO activity was increased in the livers of rats and mice exposed to 3000 ppm PGME.

In the kidney, histopathology revealed that male rats had α2μ-globulin nephropathy as is typical for this strain. The incidence and severity of this condition was increased in males exposed to 1000 and 3000 ppm PGME compared to controls. No increase in renal epithelial tumors was observed in rats or mice.

**Conclusions** : The major changes seen in this study were 1) decreased body weights in both species, 2) liver effects including increased weight, increased MFO activity and increased cell proliferation primarily in males of both species, 3) kidney effects (in rats) of α2μ-globulin nephropathy typical of the Fischer 344 strain, and 4) slightly increased mortality occurring only after 18 months of exposure in males of both species. Clinical chemistry parameters reflected and corroborated these effects.

Rats exhibited a NOAEL of 300 ppm based on altered hepatocellular foci in males. Mice showed a NOAEL of 1000 ppm based on slight body weight decreases in both sexes. The LOAELS were correspondingly higher.

No carcinogenic effect as evidenced by any increase in tumor incidence, even in kidneys of the male rats, occurred from exposure to PGME at any concentration in either species.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

| | | |
|---|---|---|
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The test system used, test substance concentrations and dose spacing (3 dose levels including negative control), time exposed to the test agent, the number of subjects used, the toxicity endpoints monitored, and scoring criteria all followed or exceeded guidance as specified in US EPA Health Effects Test Guidelines OPPTS 870.4300: "Combined Chronic Toxicity/Carcinogenicity" and OECD Guideline for Testing of Chemicals 453 "Combined Chronic Toxicity/Carcinogenicity Studies." |
| **References** | : | Spencer, P.J., Crissman, J.W., Stott, W.T., Corley, R.A., Cieszlak, F.S., Schumann, A.M., Hardisty, J.F. (2002). Propylene glycol monomethyl ether (PGME): Inhalation toxicity and carcinogenicity in Fischer 344 rats and B6C3F1 mice. Accepted for publication in Toxicologic Pathology, January 2002. |
| **Other** | : | Since no chronic or carcinogenicity studies have been conducted with DPMA, PGME is used in this report as a representative surrogate chemical. |
| **Source** | : | Dow Chemical Company |

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## 5.8 TOXICITY TO REPRODUCTION

Surrogate Chemical (Propylene glycol methyl ether acetate – PMA)

| | | |
|---|---|---|
| **Type** | : | OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test |
| **Species** | : | Rat |
| **Sex** | : | Males and females |
| **Strain/Husbandry** | : | Crj:CD (SD) |
| **Conditions** | | Age at study initiation: 9 week old for males, 8 week old for females<br>Weight at study initiation: 388-436 g for males, 217-239 g for females<br>No. of animals per sex per dose: 10 per sex per dose group |
| **Route of admin.** | : | Oral (gavage) |
| **Exposure period** | : | Males: 44 days total, starting 2 weeks prior to mating.<br>Females: 41-45 days, starting 2 weeks prior to mating to day 3 postpartum (throughout mating and pregnancy). |
| **Frequency of treatment** | : | Once daily |
| **Duration of test** | : | From 2 weeks prior to mating, through mating & pregnancy, until 3 days postpartum. Males were treated for 44 days and females for 41-45 days. |
| **Doses** | : | 0, 100, 300, 1000 mg/kg bw d |
| **Control group** | : | Yes, concurrent vehicle (purified water) |
| **NOAEL Maternal Tox** | : | = 1000 mg/kg bw for parental generation (both sexes) |
| **NOAEL Feto/-embryotoxicity** | | = 1000 mg/kg bw for both sexes |
| **NOAEL Teratogen** | : | = 1000 mg/kg bw for both sexes |
| **Protocol Guideline** | : | OECD Guideline 422 "Combined Repeated Dose toxicity Study with the Reproduction/Developmental toxicity Screening Test" |
| **Year of Study** | : | 1997 |
| **GLP** | : | Yes |
| **Test substance** | : | 1-Methoxy-2-propanol acetate (CAS No. 108-65-6)<br>Purity > 99.9% |
| **Method** | : | Dams were sacrificed on day 4 of lactation. Non-pregnant females were |

killed 4 days after the expected delivery date (1/10 in control and 1/10 in 300mg/kg group).

Vehicle: Purified water
Satellite groups and reasons they were added: None
Mating procedures: Male/female per cage; 1/1, length of cohabitation; at the most 3 days, until proof of pregnancy (formation of vaginal closing or sperm detection in vagina).
Clinical observations performed and frequency:
Parent: General appearance once a day
Fetus: General appearance once a day after birth
Hematology and biochemistry for males conducted only at time of necropsy after 44 days of chemical exposure. Urinalysis was done on day 40 of administration for males.
Organs examined at necropsy:
Parent: organ weight: brain, pituitary gland, thyroid gland, heart, liver, kidney, spleen, adrenal, thymus and for males, testes and epididymis.
Microscopic: all animals in control and 1,000 mg/kg group, and unfertilized animals in other groups: brain, spinal cord, pituitary gland, eyeball, thyroid gland (including parathyroid gland), thymus, heart, trachea, lung, liver, kidney, adrenal, spleen, stomach, small intestine, large intestine, pancreas, urinary bladder, bone marrow, sciatic nerve, lymph node, testes, epididymis, prostate, seminal vesicle, ovary, uterus, vagina, mammary gland. All pregnant males and females in 100 and 300 mg/kg group: kidney and any organs, which might be expected to have histopathological changes at the higher doses.
Fetal: full macroscopic examinations on all of pups.

Parameters assessed during study:
Body wt. (for males, once a week, and the first, the last day of administration, the day sacrificed, and for pregnant females, days 0, 14 and 20 of gestation and days 0 and 4 of lactation), food/water consumption (once a week, and on the same day when body wt. determined), No. of pairs with successful copulation, copulation index (No. of pairs with successful copulation/No. of pairs mated x 100), pairing days until copulation, No. of pregnant females, fertility index = (No. of pregnant animals/No. of pairs with successful copulation x 100), No. of corpora lutea, No. of implantation sites, implantation index (No. of implantation sites/No. of corpora lutea x 100), No. of living pregnant females, No. of pregnant females with parturition, gestation length, No. of pregnant females with live pups on day 0, gestation index (No. of females with live pups/No. of living pregnant females x 100), No. of pregnant females with live pups on day 4, delivery index (No. of pups born/No. of implantation sites x 100), No. of pups alive on day 0 of lactation, live birth index (No. of live pups on day 0/No. of pups born x 100), sex ratio (Total No. of male pups/Total No. of female pups), No. of pups alive on day 4 of lactation, viability index (No. of live pups on day 4/No. of live pups on day 0 x 100), body wt. of live pups (on day 0 and 4).

**Results** : NOAEL and LOAEL maternal toxicity: NOAEL: 1,000 mg/kg/day
NOAEL and LOAEL fetal toxicity: NOAEL: 1,000 mg/kg/day
Actual dose received by dose level by sex if available: 0, 100, 300, 1,000 mg/kg/day for both sexes.
Maternal data with dose level: No effects related to chemical exposure were observed at 1,000 mg/kg, although there was a single unsuccessful copulation at this dose level that was not statistically significantly different from the control ($p<0.05$).
Fetal data with dose level: At 1,000 mg/kg, no effects related to chemical exposure were observed, although there was 1 pup without tail in 1,000 mg/kg group.

REMARKS FIELD FOR RESULTS.
Mortality and day of death: None.
Body weight: Low body weight gain during the premating period in females at 1,000 mg/kg (Dunnets test p< 0.05).
Food/water consumption: For males, a tendency for decrease in food consumption during administration period was observed at 1,000 mg/kg, and statistical significant difference from controls was noticed on day 29(Dunnets test p< 0.05) and 36(Dunnets test p< 0.01) of the administration. For females, no statistical significant difference from controls was observed.
Reproductive data: No statistical significant difference from controls.
Fetal data: No statistical significant difference from controls.
Grossly visible abnormalities, external, soft tissue and skeletal abnormalities: No statistically significant effects were observed except 1 pup of no tail in 1,000 mg/kg group.

Results continued:

Reproduction results of rats treated orally with PMA

| Dose level (mg/kg/day) | 0 | 30 | 100 | 1,000 |
|---|---|---|---|---|
| No. of pairs mated | 10 | 10 | 10 | 10 |
| No. of pairs mated with successful copulation | 10 | 10 | 10 | 9 |
| Copulation index (%) | 100 | 100 | 100 | 90 |
| No. of pregnant females | 9 | 10 | 9 | 9 |
| Fertility index (%) | 90 | 100 | 90 | 100 |
| Pairing days until copulation (Mean ± S.D.) | 2.9±1.1 | 2.3±0.9 | 2.4±0.7 | 3.1±0.8 |
| No. of corpora lutea (Mean ± SD) | 18.2±3.6 | 16.8±2.0 | 18.9±3.8 | 17.4±1.3 |
| No. of implantation sites (Mean ± S.D.) | 17.0±1.9 | 16.2±1.9 | 17.7±1.7 | 17.1±0.9 |
| Implantation index (%, Mean ± S.D.) | 94.7±9.2 | 96.7±7.2 | 95.2±10.2 | 98.3±5.0 |
| No. of preg fem with parturition (Mean ± S.D.) | 9 | 10 | 9 | 9 |
| Gestation length (days, Mean ± SD) | 22.6±0.5 | 22.6±0.5 | 22.4±0.5 | 22.8±0.4 |
| No. of pregnant females with live pups on day 0 | 9 | 10 | 9 | 9 |
| Gestation index (%) | 100 | 100 | 100 | 100 |
| No. of pregnant females with live pups on day 4 | 9 | 10 | 9 | 9 |

Copulation index (%)= (No. of pairs with successful copulation / No. of pairs mated)x100
Fertility index (%) =(No. of pregnant females / No. of pairs with successful copulation)x100
Gestation index (%)=(No. of females with live pups / No. of pregnant females)x100

Results continued:

Litter results of rats treated orally with PMA

| Dose level (mg/kg/day) | 0 | 30 | 100 | 1,000 |
|---|---|---|---|---|
| No. of pups born | 15.8±3.2 | 15.0±2.2 | 16.1±2.6 | 16.3±1.0 |
| Delivery index (%) | 91.9±12.0 | 92.4±5.7 | 91.0±9.4 | 95.5±3.9 |
| No. of pups alive on day 0 of lactation | | | | |
| Total | 15.7±3.2 | 14.7±1.9 | 15.8±2.7 | 15.9±1.4 |
| Male | 6.7±1.4 | 7.5±2.0 | 7.9±2.1 | 7.3±1.9 |
| Female | 9.0±2.7 | 7.2±2.0 | 7.9±2.9 | 8.6±2.4 |
| Live birth index (%) | 99.4±1.9 | 98.3±2.8 | 97.9±4.5 | 97.2±4.5 |
| Sex ratio (Male/Female) | 0.73 | 1.05 | 1.01 | 0.86 |
| No. of pups alive on day 4 of lactation | | | | |
| Total | 15.6±3.1 | 14.5±1.7 | 15.6±3.0 | 15.8±1.4 |
| Male | 6.7±1.4 | 7.4±2.1 | 7.8±2.2 | 7.3±1.9 |
| Female | 8.9±2.6 | 7.1±1.9 | 7.8±3.1 | 8.4±2.3 |
| Viability index (%) | 99.3±2.0 | 98.8±3.7 | 98.3±3.4 | 99.3±2.1 |
| Body weight of live pups (g) | | | | |
| (On day 0 ) | | | | |
| Male | 7.0±0.8 | 7.4±0.5 | 7.2±0.9 | 7.1±0.6 |
| Female | 6.7±0.8 | 7.0±0.4 | 6.6±0.8 | 6.6±0.5 |
| (On day 4 ) | | | | |
| Male | 11.3±2.1 | 11.9±1.1 | 11.9±1.8 | 10.9±1.4 |
| Female | 11.0±2.1 | 11.3±0.9 | 11.2±1.6 | 10.3±1.3 |

Delivery index (%) = (No. of pups born/ No. of implantation sites)x100
Live birth index (%) =(No. of live pups on day 0 / No. of pups born)x100
Viability index (%) =(No. of live pups on day 4/ No. of live pups on day 0)x100
Sex ratio =Total No. of male pups/ Total No. of female pups
Values are expressed as Mean±S.D. Except sex ratio.

**Conclusions** : Reproductive/developmental toxicity in rats by oral administration is not observed at the highest dose. A NOAEL was established at 1,000 mg/kg bw/day.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report followed OECD Protocol 422 "Combined Repeated Dose toxicity Study with the Reproduction/Developmental toxicity Screening Test." The numbers and type of test animals used and their husbandry conditions followed guidance. Test material characterization was adequate. The amount of test material administered complied with guidance, the length of the treatment period was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

**References** : Anon, (1998). Ministry of Health and Welfare: Japan, Toxicity testing reports of environmental chemicals 6, 205-223.

**Other** : Well conducted study, carried out by Research Institute for Animal Science in Biochemistry and Toxicology (Japan).

This study was conducted to examine both repeated dose toxicity and reproductive/developmental toxicity as an OECD screening combined study. Estrus cycle length and pattern, and anogenital distances were not performed because the test was conducted by the TG adopted in 1990.

**Source** : Japanese Ministry of Health and Welfare

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## 5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Surrogate Chemical (Propylene glycol methyl ether acetate – PMA)

| | | |
|---|---|---|
| **Type** | : | Developmental Toxicity Study |
| **Species** | : | Rat |
| **Sex** | : | Female |
| **Strain/Husbandry** | : | Sprague-Dawley |
| **Conditions** | | Age at study initiation: 9-12 Weeks of age.<br>Weight at study initiation: 229-233 g at Day 0 of gestation.<br>No. of animals per dose: 23 Pregnant rats in all groups except the 4,000 ppm (21,600 mg/m3) exposure group, which contained 20. |
| **Route of admin.** | : | Inhalation |
| **Exposure period** | : | Days 6 through 15 of gestation. |
| **Frequency of treatment** | : | Daily; 6 hr/day |
| **Duration of test** | : | 21 d |
| **Exposure Levels** | : | 0, 500, 2000, 4000 ppm (0, 2700, 10800, 21600 mg/m3) |
| **Control group** | : | Yes, room air |
| **NOAEL Maternal Tox** | : | = 500 ppm (2,700 mg/m3) |
| **NOAEL Embryo/Feto-toxicity** | : | = 4000 ppm (21,600 mg/m3) |
| **NOAEL Teratogen** | : | = 4000 ppm (21,600 mg/m3) |
| **Protocol Guideline** | : | Although not specifically stated, the protocol generally follows OECD Guideline 414 "Teratogenicity." |
| **Year of Study** | : | 1988 |
| **GLP** | : | Yes |
| **Test substance** | : | 1-Methoxy-2-propanol acetate (CAS No. 108-65-6)<br>Lot No. 870916, Purity : 97.3%, Impurity: 1-Methoxy-2-methylethyl acetate; 2.0 %. |

**Method** : Study design
The animals were sacrificed on Day 20 of gestation. In order to avoid large time differentials between groups, a single dam from each exposure group was removed sequentially and euthanized.

Vehicle: Room air
Satellite groups and reasons they were added: None
Mating procedures: Male/female per cage; 1/1, length of cohabitation; not specified, but until proof of pregnancy (sperm plug observed on the pad or sperm detection in vagina)

Clinical observations performed and frequency:
Dams: Daily for changes in appearance and behavior, gross structural abnormalities or pathological changes at necropsy.
Fetuses: External and visceral abnormalities at necropsy.
Hematology, biochemistry and urinalysis: Not done.
Organs examined at necropsy:
Dams: Organ weight: Brain, liver, uterus
Fetuses: Visceral abnormalities at necropsy, but not specified. Skeletons and heads after fixed and stained.
Parameters assessed during study:
Body wt. of dams (on gestation Days 0, 6, 10, 13, 16 and 20), fetal body wt. at necropsy, food/water consumption (daily), No. of pregnant females, fertility index = (pregnant animals/positively mated animals x 100), counts and location of corpora lutea, total implantations, resorptions, viable and nonviable fetuses, sex, gestation index = (viable litters/pregnant animals x 100), index of alive fetuses = (alive total/total total x 100), resorption index = (total No. of resorptions/total No. of implantations x 100), index of malformations = (total No. of fetuses with malformations/total No. of fetuses x 100), index of variations = (total No. of fetuses with variations/total No. of fetuses x 100), No. of runts.

**Results** : NOAEL and LOAEL maternal toxicity:

NOAEL: 500 ppm (2,700 mg/m3, nominal and measured).
LOAEL: 2,000 ppm (10,800 mg/m3, nominal) or 1,980 ppm (10,692 mg/m3, measured). In the 2,000 ppm (10,800 mg/m3) exposure group, one dam exhibited dyspnea, one had a ruffled pelt and two had red discharges from the eyes or mouth. No toxic signs were observed in the 500 ppm (2,700 mg/m3) exposure group.

NOAEL and LOAEL fetal toxicity:

NOAEL: 4,000 ppm (21,600 mg/m3, nominal) or 4,160 ppm (22,464 mg/m3, measured).
LOAEL: Not determined under the conditions tested.

Actual dose received by dose level by sex if available: 500, 1,980, 4,160 ppm (2,700, 10,692, 22,464 mg/m3 for the mean time weighted average concentrations) for dams.

Maternal data with dose level: Although there were some effects on food consumption, body weight gains for dams, there were no differences in relative organ weight (liver and uterus) between dams in the exposure and control group whether ratios were calculated for body weight or brain weights. NOAEL was determined as 500 ppm (2,700 mg/m3) for dams.

**Results continued** : Litter and Fetal data with dose level: No teratological or other developmental effects were seen in fetuses in all exposure groups tested (500, 2,000 and 4,000 ppm or 2,700, 10,800 and 21,600 mg/m3, respectively). NOAEL was determined as 4,000 ppm (21,600 mg/m3) for fetuses.

Toxic signs: Nearly half of the 20 dams in the 4,000 ppm (21,600 mg/m3) exposure group exhibited dyspnea at various times throughout the exposure period (Days 6 through 15). Breathing returned to normal soon after the dams were returned to their boxes. In the 4,000 ppm (21,600 mg/m3) exposure group, half had red to reddish brown discharges from the nose and/or eyes on Days 8 and 10 through 15. Four dams were observed to have yellow staining in the fur of the urogenital area ranging from slight to marked on days 6, 8, 13 and 14. Reduced muscle tone was observed during handling in 15 dams on two separate occasions. In the 2,000 ppm (10,800 mg/m3) exposure group, one dam exhibited dyspnea, one had a ruffled pelt and two had red discharges from the eyes or mouth. No toxic signs were observed in the 500 ppm (2,700 mg/m3) exposure group.

Mortality and day of death: No mortalities were reported. On Day 20 of gestation, each female was euthanized. To avoid a large time differential between groups, one dam from each exposure or control was euthanized.

Body weight: Maternal body weights were lower in the 2,000 and 4,000 ppm (10,800 and 21,600 mg/m3, respectively) exposure group on Day 16 only. Mean dam body weight gains in the 2,000 and 4,000 ppm (10,800 and 21,600 mg/m3, respectively) exposure group were lower on Day 10 through Day 13 and Day 10 through Day 16, respectively (Duncan's test $p < 0.05$) and less overall. However, maternal body weight and weight gains in the 500 ppm (2,700 mg/m3) exposure group were the same as control.

Food/water consumption: A reduction of food consumption as a percentage of maternal body weight was observed in all exposure groups (500, 2,000, 4,000 ppm or 2,700, 10,800, 21,600 mg/m3). (Student-Newman-Keuls test $p < 0.05$). In the 4,000 ppm (21,600 mg/m3) exposure group, a reduction of food consumption as a percentage of maternal body weight coincided with exposure to PMA. A similar pattern was seen in the 2,000 ppm (10,800 mg/m3) exposure group where food consumption was lower on Day 7, Days 11 through 13 and Day 15. In the 500 ppm (2,700 mg/m3) exposure group, food consumption was lower on Days 7 and 11.

Maternal organ weight ratio: There were no differences in relative liver or uterus weight between dams in control group and dams in any exposure group whether ratios were calculated for body weight or brain weights.

Corpora lutea, implantation, litter size, resorption and fetal death: No statistically significant difference from controls. The number of corpora lutea, implantation sites and live total per litter was the same in the exposed groups as controls. Both the percent of conceptuses resorbed per litter and and the percent of litters which contained a resorption, were the same in the exposed groups as the controls. There were no dead in any litter.

**Results continued** : Fetal body weight and runts fetal data: No statistically significant difference from controls that showed a dose-response. There were no dose related differences in fetal body weights, The average fetal body weight in the 2,000 and 4,000 ppm (10,800 and 21,600 mg/m3, respectively) exposure groups was approximately 5 percent lower than the low and controls. This difference was statistically significant in the 2,000 ppm (10,800 mg/m3) exposure group, however, the 4,000 ppm (21,600 mg/m3) exposure group was marginally non-significant (i.e., not quite statistically significant at the 0.05 level). There were no differences in the percent of litters, which contained runts.

Fetal sex ratio: No statistically significant difference from controls.

Malformations and variations: There was no difference in the percent of foetuses per litter that were malformed, had variations or were normal. In addition, there were no differences in the percent of litters that contained a malformation, a variation, or contained all normal fetuses.

**Conclusions** : No teratological or other developmental effects were seen in total at concentrations as high as 4,160 ppm (22,464 mg/m3, measured), in spite of slight effects in dams at all concentrations tested. A NOAEL was established at 500 ppm (2,700 mg/m3, measured) for dams and 4,160 ppm (22,464 mg/m3, measured) for fetuses.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). Although not specifically referenced in the report, the study generally followed OECD Protocol 414: “Teratogenicity” (12 May 1981). The numbers and type of test animals used and their husbandry conditions followed guidance. Test material characterization was adequate. The amount of test material to which subjects were exposed complied with guidance, the length of the treatment period (organogenesis) was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

**References** : Anon. (1989). United States Army Environmental Hygiene Agency. Report USA EHA-75-51-0753-90.

**Other** : N/A
**Source** : US Army

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## 5.10 OTHER RELEVANT INFORMATION

Surrogate Chemical: PMA
**Type** : Toxicokinetics
**Results** : After a single oral dose (8.7 mmol/kg) of 14C-labelled PMA was administered to male F-344 rats, 64% of the radioactivity was eliminated via the lungs as 14CO2 and 24% via the urine in a 48 h period. Similarly, 53% of the dose was eliminated via the lungs as CO2 and 26% via the urine within 48 h after a single 6 h inhalation exposure to 3,000 ppm (16,200 mg/m3) 14C-labeled PMA. Propylene glycol, propylene glycol monomethyl ether (PM), and its sulfate and glucuronide conjugates were

identified as urinary metabolites after po dosing, as well as after inhalation exposure to PMA. However, PMA was not detected in urine. The urinary metabolite profile and disposition of 14C-labelled PMA were nearly identical to results previously obtained with PM, indicating that PMA is rapidly and extensively hydrolysed to PM in vivo.

**Remark** : Metabolism and disposition of PMA is very similar to that for PM following acute oral or inhalation exposure.

**References** : Miller et al. Toxicol. Appl. Pharm. 75 521-530 (1984)

(24)

Surrogate Chemical: PMA

**Type** : Toxicokinetics

**Results** : The blood pharmacokinetics was investigated using propylene glycol methyether (PM) and PMA in male F-344 rats after a single 6 hr dermal exposure. PM or PMA were applied to the dorsal region of the rat at 100 and 1,000 mg/kg. Blood was collected via a jugular cannula prior to dermal application (0 min) and at ~5, 10, 15, 30, and 40 min and 1,2,4, and 6 hr after dermal application. The site of application was washed following 6 hr of exposure initiation. A GC-MS method was used to quantify PM and PMA in blood from exposed rats. Following dermal application, conclusions based on statistical evaluation of AUC (or AUC normalised to the applied dose) in this study are as follows:

1) The blood AUC of PM is different following a dermal dose (100 or 1,000 mg/kg) of PM as compared with PMA.

2) The AUC for PM is linearly related to dose between the low and high PM dermal exposures.

On administration of PMA, the AUC for PM increased linearly between the low and high dose of PMA

4) From this study, the PM AUC resulting from PM application is at least 4-times higher than that resulting from PMA application. Any effects arising from administration of PMA would thus be overestimated by using PM toxicity data in place of PMA data.

**Remarks** : The American Chemistry Council (ACC) sponsored this study.

**Reference** : Susan C.J. Sumner, Blood Pharmacokinetics of Propylene Glycol Methyl Ether (PM) and Propylene Glycol Methyether Acetate (PMA) in Male F-344 Rats after Dermal Application, Final Report 98003 (1999).

(25)

Surrogate Chemical: PMA (beta isomer)

**Type** : Metabolism data (hydrolysis of acetate in rat plasma in vitro)

**Species** : Rat

**Strain** : Wistar (Chbb – THOM (SPF))

**Sex** : Not specified.

**Number of animals** : Pooled rat plasma

**Vehicle** : DPMA tested undiluted

**Concentration(s) tested** : 20 ul of PMA in 5 ml H20.

**Protocol Guidance** : None specified.

**Year of Study** : 1985

**GLP** : Not specified

**Test substance** : The 2-methoxy isomer of PMA (i.e., beta isomer). Greater than 99% purity (GLC analysis).

**Method** : Twenty microliters of PMA (beta isomer) was mixed with an equal volume of internal standard and this was diluted with water up to 5 ml. 50 µl of this stock was incubated with 500 µl rat plasma at 37°C for 2 minutes whereupon an aliquot was taken for GC analysis. Subsequent aliquots were taken at subsequent time points.

**Results** : From these data, a half-life of 0.64 minutes was calculated for the beta isomer of PMA.

**Conclusions** : PMA (beta isomer) is rapidly hydrolyzed to the free ether in rat plasma in vitro.

**Data Quality** : The data quality from this study is considered acceptable although cursory. The report included some documentation for methods and results. This study reaches Klimisch level 2.

**Quality Check** : The methods were not comprehensively documented.

**References** : Hoffmann, H.D., Jackh, R., (1985). Short communication. Cleavage of glycol ether acetates by rat plasma in vitro. BASF Department of Toxicology.

**Other** : These results are consistent with studies of other acetates of glycol ethers; i.e., hydrolysis of the acetate is rapid. This lends credibility to the conclusion that the toxicity of the acetate is similar to that of the free glycol ether.

**Source** : BASF Corporation.

(20)

**Type** : General Comment
**Remark** : Acetates of propylene glycol ethers hydrolyze rapidly in mammalian tissues and plasma due to the presence of esterases. These acetates hydrolyze to the parent ether and acetic acid.
**Reference** : Patty's Toxicology (2001).

(26)

## 5.11 EXPERIENCE WITH HUMAN EXPOSURE

**Remark** : No other relevant information

(1) Dill, D.C., Davis, J.W., (1997). Environmental assessment of the Dowanol glycol ethers P-series product family. Dow Chemical Company Study ID ES-3186. August 12, 1997. Unpublished Report.

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(3) MSDS (Material Safety Data Sheet), (1999). Dowanol DPMA Glycol Ether Acetate.

(4) Staples, C.A., Davis, J.W., (2002). An examination of the physical properties, fate, ecotoxicity and potential environmental risks for a series of propylene glycol ethers. Chemosphere 49:61-73.

(5) Matsue, H., (2000). Final report: Ready Biodegradability Study of DPMA. Hodogaya Contract Laboratory Study No. 9933D. January 25, 2000. Unpublished study.

(6) Wu, H., Crapo, K.C., Doi, J.D., (1996). Ultimate biochemical oxygen demand (BODu) test: PM;, PM Acetate; PNP: DPNP; DPM Acetate; TPM. Roy F. Weston study no. 95-079. ARCO Chemical Co sponsor. May 9, 1996. Unpublished report.

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(9) Dill, D.C., Applegath, S.L., (1983). Evaluation of the toxicity of DPM Acetate (XA-10856.00) to representative aquatic organisms. Dow Report No. ES-595. April 7, 1983. Unpublished report.

(10) Carreon, R.E., Yakel, H.O., Eisenbrandt, D.L., Wall, J.M., (1982). Dipropylene glycol monomethyl ether acetate: Acute toxicological properties and industrial handling hazards. Dow report HET K-6410-(3). May 17, 1982. Unpublished report.

(11) Hollingsworth, R.L., (1949). Results of range finding acute vapor toxicity tests on Dowesters A33B, A50B, and A62B. Dow file K-6410-(2). April 28, 1949. Unpublished report.

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(13) Rowe et al. (1954) AMA Arch Ind Hyg Occup Med 9, 509-525.

(14) Anonymous, (2000). Dow Chemical Japan. Unpublished Report #FBM 99-2691.

(15) Landry, T.D., Yano, B.L., (1984). Dipropylene glycol monomethyl ether: A 13 week inhalation toxicity study in rats and rabbits. Fund. Appl. Toxicol. 4:612-617.

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(17) Spencer, P.J., Crissman, J.W., Stott, W.T., Corley, R.A., Cieszlak, F.S., Schumann, A.M., Hardisty, J.F. (2002). Propylene glycol monomethyl ether (PGME): Inhalation toxicity and carcinogenicity in Fischer 344 rats and B6C3F1 mice. Accepted for publication in *Toxicologic Pathology*, January 2002.

(18) Anon, (1998). Ministry of Health and Welfare: Japan, Toxicity testing reports of environmental chemicals 6, 205-223.

(19) Anon. (1989). United States Army Environmental Hygiene Agency. Report USA EHA-75-51-0753-90.

(20) Hoffmann, H.D., Jackh, R., (1985). Short communication. Cleavage of glycol ether acetates by rat plasma in vitro. BASF Department of Toxicology.

(21) Fieser, L.F., and Fieser, M., (1960). Organic Chemistry. D.C. Heath and Company, Boston. P.137.

(22) Environment Agency of Japan, 1998.

(23) EPIWin (Estimation Program Interface) Suite, (2000). Suite of environmental predictive models developed by the U.S. Environmental Protection Agency, Office of Pollution Prevention Toxics and Syracuse Research Corporation.

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(26) Patty's Toxicology: Cragg, S.T., Boatman, R.J., (2001). Glycol Ethers: Ethers of Propylene, Butylene Glycols, and other Glycol Derivatives. Chapter 87 in Patty's Toxicology, Volume 7, Fifth Edition. (E. Bingham, B. Cohrssen, C. Powell, eds.). John Wiley & Sons, Inc., New York.

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# Tripropylene Glycol Methyl Ether
# CAS No. 25498-49-1

# IUCLID with Robust Summaries (Dossier)

| | | |
|---|---|---|
| **Existing Chemical** | : | ID: 25498-49-1 |
| **CAS No.** | : | 25498-49-1 isomeric mixture<br>20324-33-8 (all alpha isomer) |
| **EINECS Name** | : | [2-(2-methoxymethylethoxy)methylethoxy]propanol |
| **EINECS No.** | : | 247-045-4 |
| **Molecular Weight** | : | 206.32 |
| **Molecular Formula** | : | C10H22O4 |

**Producer Related Part**

| | | |
|---|---|---|
| **Company** | : | American Chemistry Council |
| **Creation date** | : | 30.09.2002 |

**Substance Related Part**

| | | |
|---|---|---|
| **Company** | : | American Chemistry Council |
| **Creation date** | : | 30.09.2002 |
| **Memo** | : | |
| **Printing date** | : | 30.09.2002 |
| **Revision date** | : | 30.09.2002 |
| **Date of last Update** | : | 30.09.2002 |
| **Number of Pages** | : | 57 |
| **Chapter (profile)** | : | Chapter: 1, 2, 3, 4, 5, 7 |
| **Reliability (profile)** | : | Reliability: without reliability, 1, 2, 3, 4 |
| **Flags (profile)** | : | Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS |

### 1.0.1 OECD AND COMPANY INFORMATION

| | | |
|---|---|---|
| **Type** | : | |
| **Name** | : | Dow Deutschland Inc |
| **Partner** | : | |
| **Date** | : | |
| **Street** | : | Werkstade PO Box 1120 |
| **Town** | : | 21677 Stade 5 |
| **Country** | : | Germany |
| **Phone** | : | +49.414.6910 |
| **Telefax** | : | +49.414.6912600 |
| **Telex** | : | |
| **Cedex** | : | |

| | | |
|---|---|---|
| **Type** | : | |
| **Name** | : | Shell Nederland Chemie B.V. |
| **Partner** | : | |
| **Date** | : | |
| **Street** | : | Vondelingenweg 601 |
| **Town** | : | 3196 KK Rotterdam |
| **Country** | : | Netherlands |
| **Phone** | : | |
| **Telefax** | : | |
| **Telex** | : | |
| **Cedex** | : | |

### 1.0.2 LOCATION OF PRODUCTION SITE

### 1.0.3 IDENTITY OF RECIPIENTS

### 1.1 GENERAL SUBSTANCE INFORMATION

| | | |
|---|---|---|
| **Substance type** | : | Organic chemical. Commercial product is a mixture consisting of predominantly (>95%) secondary alcohol (alpha isomer) with less than 5% primary alcohol (beta isomer). Unless otherwise stated, results in this dossier pertain to commercial mixture. |
| **Physical status** | : | liquid |
| **Purity** | : | % w/w |

### 1.1.0 DETAILS ON TEMPLATE

### 1.1.1 SPECTRA

### 1.2 SYNONYMS

DOWANOL* TPM

| | | |
|---|---|---|
| **Remark** | : | * DOWANOL is a Trademark of The Dow Chemical Company. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

Methyltripropylene glycol

**Source** : Shell Nederland Chemie B.V. Rotterdam

TPGME
**Remark** : * Trademark of The Dow Chemical Company
**Source** : Dow Deutschland Inc Stade 5

TPM
**Source** : Dow Deutschland Inc Stade 5

Tripropylene glycol methyl ether
**Source** : Dow Deutschland Inc Stade 5

Tripropylene glycol mono methyl ether
**Source** : Dow Deutschland Inc Stade 5

Tripropyleneglycol (mono)methyl ether
**Source** : Shell Nederland Chemie B.V. Rotterdam

### 1.3 IMPURITIES

Currently, TPM (mixed isomers) consists of greater than 97.5% purity. Water may be present at a maximum of 0.10%.

### 1.4 ADDITIVES

### 1.5 QUANTITY

Worldwide production (1999): 2,700 tonnes (6 million pounds)

### 1.6.1 LABELLING

### 1.6.2 CLASSIFICATION

### 1.7 USE PATTERN

Because of its high polymer solvency and low evaporation rate, TPM is used in inks for ballpoint and felt-tipped pens and inkpads to prevent drying. Because it has a high boiling point and flash point, it is used in oven cleaners and as a tailing solvent in high-solids, solvent-based coatings. It is used also in rust, paint, and varnish removers, and in penetrating oils.

### 1.7.1 TECHNOLOGY PRODUCTION/USE

### 1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

**Remark** : None established
**Source** : Shell Nederland Chemie B.V. Rotterdam

**Remark** : No occupational exposure limits established.
**Source** : Dow Deutschland Inc Stade 5

## 1.9 SOURCE OF EXPOSURE

**Remark** : Spillage during car maintenance and car repair activities; road accidents
**Source** : Shell Nederland Chemie B.V. Rotterdam

**Remark** : Occupational exposure to TPM is limited due to the enclosed systems in which this chemical is manufactured. End use consumers may be exposed during the application of coatings in which TPM is used. For such use, exposure would be by inhalation or dermal exposure. After application of coatings, TPM would evaporate slowly from the coating and escape at low concentrations into the atmosphere. Spills of small quantities (e.g., 1 gallon or less) into the environment could occasionally be expected during coating applications.
**Source** : Dow Deutschland Inc Stade 5

**Remark** : Direct exposure due to handling operations primarily through contact with the skin, in view of the low vapor pressure.
The municipal waste water treatment plants allow for biological degradation.
Theoretically, the substance could leach from the soil and partition to the ground water.
There are no reports on drinking water contamination.
There are no uses for direct contact with food.
**Source** : Dow Deutschland Inc Stade 5

**Remark** : TPM does not occur to any significant extend in the 73000 chemical products checked in Sweden.
Ref.: Gunnar Johanson and Ulf Rick
Occurrence of glycol ethers in chemical products in Sweden
Arbete och Haelsa, Vetenskaplig Skriftserie, 1986:13
**Source** : Dow Deutschland Inc Stade 5

## 1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

## 1.10.2 EMERGENCY MEASURES

## 1.11 PACKAGING

## 1.12 POSSIB. OF RENDERING SUBST. HARMLESS

## 1.13 STATEMENTS CONCERNING WASTE

## 1.14.1 WATER POLLUTION

## 1.14.2 MAJOR ACCIDENT HAZARDS

### 1.14.3 AIR POLLUTION

### 1.15 ADDITIONAL REMARKS

**Remark** : DISPOSAL OPTIONS

Dispose to licensed disposal contractor.
Recover or recycle if possible; otherwise incinerate in licensed waste incineration plant.

**Source** : Shell Nederland Chemie B.V. Rotterdam

### 1.16 LAST LITERATURE SEARCH

### 1.17 REVIEWS

### 1.18 LISTINGS E.G. CHEMICAL INVENTORIES

## 2.1 MELTING POINT

**Value** : -77.8°C (Critical Value)
**Sublimation** :
**Method** : Other
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : TPM
**Source** : Dill & Davis, 1997, Staples & Davis, 2002

(1,2)

## 2.2 BOILING POINT

**Value** : 243°C or 469°F @ 760 mmHg (1.01 bar) (Critical Value)
**Decomposition** :
**Method** :
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : TPM
**Source** : Dow Chemical Company

(6)

**Value** : 242.2°C at 1013 hPa
**Decomposition** : No
**Method** : Other
**Year** :
**GLP** : No
**Test substance** :
**Source** : ECETOC

(3)

## 2.3 DENSITY

**Type** : Density (Critical Value)
**Value** : 0.966 g/cm3 or 8.06 lb/gal at 20°C
0.962 g/cm3 or 8.03 lb/gal at 25°C
**Method** : Other
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : TPM
**Source** : Dow Chemical Company

(6)

### 2.3.1 GRANULOMETRY

## 2.4 VAPOUR PRESSURE

**Value** : 0.028 hPa @ 25°C (Critical Value)
**Decomposition** :

**Method** :
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : TPM
**Source** : Staples and Davis, 2002

(2)

**Value** : 2.1E-2 mmHg @ 25°C
**Decomposition** :
**Method** :
**Year** :
**GLP** : Unknown
**Test substance** :
**Source** : Dow Chemical Company

(1,5)

**Value** : 2.8 Pa or 0.002 kPa (1.7E-2 mmHg) @ 25°C
**Decomposition** :
**Method** :
**Year** :
**GLP** : Unknown
**Test substance** :
**Source** : Dow Chemical Company

(2,4)

**Value** : = .03 . hPa at 20° C
**Decomposition** :
**Method** : other (calculated)
**Year** :
**GLP** : No
**Test substance** :
**Source** : Dow Deutschland Inc Stade 5

## 2.5 PARTITION COEFFICIENT

**Log Kow (Log Pow)** : 0.309 (Critical Value)
**Method** Other (calculated)
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : TPM
**Source** : Dill and Davis, 1997; Staples and Davis, 2002

(1,2)

## 2.6.1 WATER SOLUBILITY

**Value** : 999999.99999 g/l at 20 ° (i.e., infinitely soluble in water) (Critical Value)
**Qualitative** : Miscible
**Pka** : at 25 ° C
**PH** : At and ° C
**Method** : other
**Year** :
**GLP** : No
**Reliability** : Assigned Klimisch score of 4 since methodology not available.
**Test substance** : TPM
**Source** : Dill and Davis, 1997; Staples and Davis, 2002

(1,2)

### 2.6.2 SURFACE TENSION

| | | |
|---|---|---|
| **Value** | : | 30.0 dynes/cm or mN/m @ 25°C |
| **Type** | : | |
| **Method** | : | |
| **Year** | : | |
| **GLP** | : | |
| **Test substance** | : | TPM |
| **Source** | : | Dow Chemical Company |

(6)

### 2.7 FLASH POINT

| | | |
|---|---|---|
| **Value** | : | 111°C |
| **Type** | : | |
| **Method** | : | Setaflash |
| **Year** | : | 1999 |
| **GLP** | : | |
| **Test substance** | : | TPM |
| **Source** | : | Dow Chemical Company |

(5)

| | | |
|---|---|---|
| **Value** | : | 121°C (Critical Value) |
| **Type** | : | |
| **Method** | : | Closed Cup |
| **Year** | : | |
| **GLP** | : | No |
| **Reliability** | : | Assigned Klimisch score of 4 since methodology not available. |
| **Test substance** | : | TPM |
| **Source** | : | Dow Chemical Company |

(6)

| | | |
|---|---|---|
| **Value** | : | 127 ° C |
| **Type** | : | open cup |
| **Method** | : | other |
| **Year** | : | |
| **GLP** | : | No |
| **Test substance** | : | |
| **Source** | : | Dow Deutschland Inc Stade 5 |

### 2.8 AUTO FLAMMABILITY

| | | |
|---|---|---|
| **Value** | : | 277°C or 531°F (Autoignition temperature) (Critical Value) |
| **Method** | : | |
| **Year** | : | |
| **GLP** | : | No |
| **Reliability** | : | Assigned Klimisch score of 4 since methodology not available. |
| **Test substance** | : | TPM |
| **Remark** | : | Method DIN 51794 |
| **Source** | : | Dow Chemical Company |

(5,6)

## 2.9 FLAMMABILITY

| | | |
|---|---|---|
| **Remark** | : | Lower and upper flammability limit of Dowanol TPM is 1.5 %vol/vol at 151 deg. C and 10.9 %vol/vol at 151 deg. C. |
| **Reliability** | : | Assigned Klimisch score of 4 since methodology not available. |
| **Source** | : | Dow Chemical Company MSDS for Dowanol TPM (1999) |

(5)

## 2.10 EXPLOSIVE PROPERTIES

| | | |
|---|---|---|
| **Result** | : | Other |
| **Method** | : | Other |
| **Year** | : | |
| **GLP** | : | No |
| **Test substance** | : | |
| **Remark** | : | Lower limit 1.1 % v/v at 145 degree C<br>Upper limit 7.0 % v/v at 180 degree C |
| **Source** | : | Dow Deutschland Inc Stade 5 |

## 2.11 OXIDIZING PROPERTIES

## 2.12 ADDITIONAL REMARKS

| | | |
|---|---|---|
| **Remark** | : | Stable under normal storage conditions. Avoid contact with oxidizing substances. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

### 3.1.1 PHOTODEGRADATION

| | | |
|---|---|---|
| **Photodegradation OH radical rate constant** | : | 63.2 x 10-12 cm3/molecule-sec |
| **Half-life** | : | 0.169 days or 2.03 hours (assumes 12 hr of light per day and an hydroxy radical concentration of 1.5 x 106 OH/cm3) |
| **Remark** | : | These modeled values represent an estimation of the rate of photodegradation in the atmosphere, based on the molecular structure of the alpha isomer. (AOP version 1.90) |
| **Source** | : | EPIWIN/AOP (v3.10) Program |

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| | | |
|---|---|---|
| **Type** | : | Air |
| **Light source** | : | |
| **Light spect.** | : | Nm |
| **Rel. intensity** | : | based on Intensity of Sunlight |
| **Remark** | : | Half life is calculated as 2.2 hours, according to Atkinson. Methodology is based on hydroxyl radical reaction in the atmosphere. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

### 3.1.2 STABILITY IN WATER

| | | |
|---|---|---|
| **Remark** | : | Ether functions are generally stable in water under neutral conditions at ambient temperatures |
| **Source** | : | Fieser and Fieser, 1960; Dow MSDS |

(5, 28)

### 3.1.3 STABILITY IN SOIL

| | | |
|---|---|---|
| **Remark** | : | Stability in soil depends on presence of microorganisms. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

### 3.2 MONITORING DATA

| | | |
|---|---|---|
| **Type of measurement** | : | Concentration at contaminated site |
| **Medium** | : | Ground water |
| **Method** | : | |
| **Concentration** | : | |
| **Remark** | : | A municipal landfill leachate was studied at the Orange County Landfill in Florida. Amongst many organic constituents of this Landfill leachate TPM was found at a<br>concentration of 21 microgram/l. No information on method of analysis or sampling was provided in this one line information.<br>Robin R. Hallbourg, J.J. Delfino and W.L. Miller, Organic priority pollutants in groundwater and surface water at three landfills in North Central Florida. Water, Air and Soil Pollution 65: 307-322, 1992. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

| | | |
|---|---|---|
| **Type of measurement** | : | Other |
| **Medium** | : | surface water |
| **Method** | : | |
| **Concentration** | : | |
| **Remark** | : | Monitoring data not available, the substance has a low vapor pressure. Reported concentrations, in forest pools after spraying of pesticide |

containing TPM as a solvent, are on the order of 1 microgram/ml.
P.-Y. Caux, Pearl Weinberger and D.B. Carlisle, Dowanol, an environmentally safe adjuvant. Environmental Toxicology and Chemistry, Vol. 5, pp. 1047-1054, 1986.

**Source** : Dow Deutschland Inc Stade 5

(10)

### 3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

**Type** : Fugacity Model Level III
**Method** : Mackay Level III
**Year** : 2002
**Input Parameters and Results** : Level 3 MODEL RESULTS
CHEMICAL PROPERTIES
Where input parameters were estimated, alpha isomer was used, Where input parameters were measured, commercial mixture was used (>95% alpha isomer)

INPUT PARAMETERS

Chemical Type: 1
Molecular Mass (g/mol): 206.32
Data Temperature (Degrees Celsius): 25
Log Kow: 0.309
Water Solubility (g/m3): 1E+09
Water Solubility (mol/m3): 4846840
Henry's Law Constant (Pa.m3/mol): 5.77696E-07
Vapour Pressure (Pa): 2.8
Melting Point (Degrees Celsius): -77.8

RESULTS (HALF-LIVES)

Half-Life in Air (h): 4.3
Half-Life in Water (h): 432
Half-Life in Soil (h): 672
Half-Life in Sediment (h): 672
Half-Life in Suspended Sediment (h): 672
Half-Life in Fish (h): 24
Half-Life in Aerosol (h): 24

PARTITION COEFFICIENTS (RESULTS)
(All amounts are dimensionless, except where noted)

Log Octanol-Water Partition Coefficient: 0.309
Octanol-Water Partition Coefficient: 2.037042
Organic Carbon-Water Partition Coefficient (L/kg): 0.8351872
Air-Water Partition Coefficient: 2.33052930541603E-10
Soil-Water Partition Coefficient: 0.040088986311709
Soil-Water Partition Coefficient (L/kg): 1.67037442965454E-02
Sediment-Water Partition Coefficient: 8.01779726234181E-02
Sediment-Water Partition Coefficient (L/kg): 3.34074885930909E-02
Suspended Sediment-Water Partition Coefficient: 0.40088985409059
Suspended Sediment-Water Part. Coefficient (L/kg): 0.167037439204412
Fish-Water Partition Coefficient: 9.777801E-02
Fish-Water Partition Coefficient (L/kg): 9.77780148386955E-02
Aerosol-Water Partition Coefficient: 0
Aerosol-Air Partition Coefficient: 2142857.19252591

**Reliability** : (1) Valid without restriction
**Source** : American Chemistry Council

### 3.3.2 DISTRIBUTION

**Distribution at Equilibrium** : See EPIWIN modeling results below
**Air** : 0.247%
**Water** : 48.5%
**Soil** : 51.1%
**Sediment** : 0.0813%
**Remark** : Results are estimates based on the Mackay Level III fugacity model (part of EPIWIN Suite)
**Source** : EPIWIN (v3.10) Program

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**Remark** : Henry's Law Constant = 5.70E-09 atm-m3/mol (or 2.72E-01 Pa-m3/mol). (VP/Wsol estimate using EPI values)

HLC = 2.36E-11 atm-m3/mol ("Bond Method")
HLC = 4.55E-13 atm-m3/mol ("Group Method")

Results are estimates based on the HENRYWIN V3.10 module of the EPIWIN Suite
**Source** : EPIWIN (v3.10) Program

(29)

**Media** : Water – air
**Method** : Other (measurement)
**Year** :
**Remark** : In a 24-h aeration test, no removal from water was detected by dichromate COD method.
Dow confidential data, Dow Ecol database.
**Source** : Dow Deutschland Inc Stade 5

### 3.4 MODE OF DEGRADATION IN ACTUAL USE

**Remark** : Chemically stable for intended end uses.
Degradation in water and soil depending on presence of microorganisms.
Propylene glycol is the main metabolite.

**Source** : Dow Deutschland Inc Stade 5

### 3.5 BIODEGRADATION

**Type** : Aerobic (Ultimate Biodegradability)
**Inoculum** : Acclimated activated sludge from a domestic sewage treatment plant. "Acclimated" indicates that the inoculum was pre-adapted to test substance.
**Concentration** : 0, 3.75, or 7.5 mg carbon/liter
or 0, 6.4, or 12.9 mg TPM/liter
**Contact time** : 28 days
**Degradation** : At 3.75 mg carbon/liter
O2 consumption = 71.6.% after 28 days
O2 consumption = 79.7.% after 43 days

| | | |
|---|---|---|
| | | At 7.50 mg carbon/liter<br>O2 consumption = 67.6.% after 28 days<br>O2 consumption = 75.4.% after 43 days |
| **Result** | : | TPM is biodegradable with acclimated sludge |
| **Kinetics of test substance** | : | Based on O2 consumption & TPM concentration of 3.75 mg carbon/liter (or 6.4 mg TPM/liter)<br>Day 7 = 3.7.%<br>Day 9 = 13.0.%<br>Day 17 = 60.8.%<br>Day 21 = 68.5.%<br>Day 28 = 71.6.%Day 22 = 65.8%<br>Day 28 = 67.0%<br>Day 43 = 79.7% |
| **Deg. Product** | : | Not determined. |
| **Protocol Guideline** | : | Similar to OECD ready biodegradability tests (e.g., 301D Closed Bottle Test). Does not qualify, however, because acclimated sludge was used (i.e., inoculum was pre-adapted to test substance before test began). |
| **Year of Study** | : | 1996 |
| **GLP** | : | No data. |
| **Test substance** | : | TPM (purity greater than 97%) |
| **Method** | : | TPM was incubated with previously acclimated (for 10 days), activated inoculum for up to 43 days in sealed, continuously agitated closed bottles at 25±1°C in triplicate at concentrations of 3.75 or 7.50 mg carbon/liter (6.4 or 12.9 mg TPM/liter). The concentration of suspended solids was 30 mg/liter and the pH was 7.2 to 7.6. Water hardness was not reported. O2 concentration was a measured variable used to assess biodegradation. Controls were single flasks of: 1) water and test substance, 2) control blank (inoculum alone) and 3) inoculum and sodium benzoate (positive control). Degradation of TPM was monitored by assessing 1) the disappearance of O2. O2 was measured on days 0, 3, 5, 7, 9. 12, 13, 15, 17, 21, 27, 28, 35, and 43. For oxygen uptake, biodegradation was calculated by dividing the biological oxygen demand (BOD – mg O2 uptake by TPM minus O2 uptake by blank) divided by the theoretical oxygen demand (ThOD), times 100. |
| **Results** | : | TPM was 71.6% biodegraded within 28 days at a concentration of 3.75 mg carbon/liter and was 67.6% biodegraded within 28 days at a concentration of 7.50 mg carbon/liter. At both concentrations, 60% biodegradation was achieved in 28 days (after reaching 10%) within a 10-day window. |
| **Conclusions** | : | With sludge that has been acclimated for a period of time to the test material, TPM was extensively biodegraded. Although meeting the criteria of >60% biodegradable in 28 days (and within a 10 day window), these results cannot be interpreted to mean TPM is “readily biodegradable” as defined by the OECD, since acclimated inoculum may not be used in such an assay. |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 2. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report did not include GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that the methods followed were similar to those recommended in OECD 302D “Closed Bottle Test,” except that acclimated inoculum was used. Specifically, the incubation conditions and the inoculum used were as recommended in the guidance. Test material characterization was adequate. The concentrations tested, the length of the monitoring period (28 days), and methods for measuring test |

compound degradation were typical for this type assay and adequately recorded.

**References** : Wu, H., Crapo, K.C., Doi, J.D., (1996). Ultimate biochemical oxygen demand (BODu) test: PM;, PM Acetate; PNP; DPNP; DPM Acetate; TPM. Roy F. Weston Study No. 95-079. ARCO Chemical Co sponsor. May 9, 1996. Unpublished report.

**Other** : These results show that TPM may biodegrade when incubated under conditions where the inoculum has been pre-exposed to the test substance.. The purpose of pre-exposure is to allow the inoculum time to adapt so that it may more easily metabolize the test substance. Pre-adaptation is not permissible in order to met the criteria of "readily biodegradable" but does provide useful information about the compound's ability to biodegrade.

**Source** : ARCO Chemical Company

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**Type** : Aerobic (OECD Method 301F: Manometric Respirometry Test)
**Inoculum** : Sediment and activated sludge from a domestic sewage treatment plant.
**Concentration** : 0 or 86.9 mg/L ThODNH3
**Contact time** : 28 days
**Degradation** : O2 consumption = 60.% after 28 days
CO2 production = 51% after 28 days
DOC removal = 66% after 28 days
**Result** : TPM is readily biodegradable based on O2 consumption.
**Kinetics of test substance (high dose)** : Based on O2 consumption
Day 12.1 = 10.%
Day 21.8 = 60%
Day 28 = 60.%Day 22 = 65.8%
Day 28 = 67.0%
**Deg. Product** : CO2
**Protocol Guideline** : OECD Guideline 301F "Manometric Respirometry Test"
**Year of Study** : 1998
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Tripropylene glycol methyl ether, TPM, CAS # 25498-49-1 (also 20324-33-8) |
| Batch No.: | MC0601B1P1 |
| Molecular Wt.: | 206.3 |
| ThODNH3: | 2.09 |
| Mol. Formula: | C10H22O4 |
| Purity: | 99% |

**Method** : To test for its biodegradability potential, TPM was incubated for 28 days in continuously agitated, closed, 1-liter bottles in the dark (in duplicate) at a concentration of 86.9 mg/L ThOD as test material with an activated inoculum originally collected from a local municipal sewage treatment facility (this inoculum was collected 1 day prior to use and aerated continuously before incubation to minimize residual carbon). The average mixed liquor suspended solids concentration (MLSS) was 2810 mg/liter. This was diluted to 30 mg/liter for the incubation with pH adjusted to 7.2 - 7.6. The incubation temperature was 22±1°C. Water hardness was not reported. Dissolved oxygen was frequently recorded as a parameter to measure biodegradation. Controls were: 1) sodium benzoate at 198.1 mg/liter with inoculum (positive or reference control), 2) inoculum alone (to determine O2 depletion, CO2 production, and organic carbon uptake without an exogenous organic substrate and correct the samples with organic substrate by this amount), and 3) killed or sterilized control with TPM to determine and correct for non-biological degradation. Degradation

of TPM was monitored by assessing: 1) the disappearance of O2, 2) the evolution of CO2 gas from mineralization of the exogenous organic substrate by the inoculum, and 3) the disappearance of organic carbon. O2 and CO2 were measured at 4-hour intervals throughout the 28-day incubation period. Dissolved organic carbon was measured at the beginning and end of this period. For oxygen uptake, biodegradation was calculated by dividing the biological oxygen demand (BOD – mg O2 uptake by TPM minus O2 uptake by blank) divided by the theoretical oxygen demand (ThOD), times 100. For CO2 evolution, biodegradation was measured by first subtracting the CO2 evolved by the blanks from the CO2 evolved by the TPM sample, then dividing the result by the theoretical CO2 (Th CO2). The resulting mineralization yield was divided by the theoretical maximum CO2 that could be evolved from TPM (i.e., ThCO2), to give the biodegradation based on CO2 evolution. A similar calculation was used to express biodegradation based on the disappearance of dissolved organic carbon.

**Results** : Incubation of TPM with inoculum resulted in: 1) 60% degradation after 28 days based on O2 consumption, 2) 51% degradation after 28 days based on CO2 evolution, and 3) 66% based on DOC removal. The sodium benzoate reference compound showed 107%, 83%, and 96% degradation, based on these endpoints, respectively. The negative control blanks showed appropriate levels of O2 consumption, CO2 production, and DOC removal.

**Conclusions** : By two of the three measures of biodegradation, including the major measure of O2 consumption, TPM meets the criteria of “readily biodegradable,” having achieved a biodegradation level of 60% or more within a 10-day window (starting on the day of reaching 10% degradation and ending before day 28).

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 301F "Manometric Respirometry Test” was followed. Specifically, the incubation conditions and the inoculum used were as recommended in the guidance. Test material characterization was adequate. The concentrations tested, the length of the monitoring period (28 days), and methods for measuring test compound degradation were typical for this type assay and adequately recorded.

**References** : Goodwin, P.A., West, R.J., (1998). Evaluation of ready biodegradability of five glycol ethers using the OECD Method 301F: Manometric Respirometry Test. Dow Chemical Company Study No. 981111. September 3, 1998. Unpublished study.

**Other** : TPM is readily biodegradable under the conditions of this test.

**Source** : Dow Chemical Company

(8)

**Contact time** :
**Degradation** : 51.7% after 20 days
**Result** :

| | | |
|---|---|---|
| **Kinetic of test substance** | : | 5 day = 0 .- 0 %<br>10 day = 2 %<br>20 day = 51.7 %<br>%<br>% |
| **Deg. Product** | : | |
| **Protocol Guideline** | : | After OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test" |
| **Year of Study** | : | 1978 |
| **GLP** | : | |
| **Test substance** | : | |
| **Remark** | : | Biodegradation reached in Closed Bottle test after 20 days: 51.7%. Dow confidential report ES-265, 1978. Evaluation in The Aquatic Environment. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(9)

## 3.6 BOD5, COD OR BOD5/COD RATIO

| | | |
|---|---|---|
| **BOD5** | | |
| **Method** | : | other |
| **Year** | : | 1978 |
| **GLP** | : | |
| **Concentration** | : | |
| **BOD5** | : | .12 mgO2/l |
| **Remark** | : | Biodegradation may increase in soil and/or water with acclimation. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

## 3.7 BIOACCUMULATION

| | | |
|---|---|---|
| **Modeling results** | : | EPIWIN |
| **Estimated log BCF** | : | 0.500 |
| **Estimated BCF** | : | 1.162 |
| **Source** | : | EPIWIN (v3.10) Program (“BCF” Module version 2.14) |

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| | | |
|---|---|---|
| **Remark** | : | Log octanol/water partition coefficient (log Pow) is calculated to be 0.309. Bioaccumulation is not indicated. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

## 3.8 ADDITIONAL REMARKS

## 4.1 ACUTE/PROLONGED TOXICITY TO FISH

| | | |
|---|---|---|
| **Type** | : | Static |
| **Species** | : | Pimephales promelas Rafinesque (Fathead minnow) |
| **Exposure period** | : | 96 hour(s) |
| **Unit** | : | mg/liter |
| **Analytical monitoring** | : | None |
| **NOEC** | : | < 5,600 mg TPM/liter |
| **LC50** | : | 11,619 .mg TPM/liter (11,562 < 95% CL > 11,713) |
| **LC100** | : | 13,500 mg TPM/liter |
| **Protocol Guideline** | : | This was a study conducted in 1978, prior to publication of guidelines. Comparison of the study report with OECD Guideline 203 "Fish, Acute Toxicity Test" does not permit an evaluation of whether guideline recommendations generally were followed because of the brevity of the report, particularly regarding description of methodology. |
| **Year of Study** | : | 1978 |
| **GLP** | : | No |
| **Test substance** | : | Identity: Dowanol TPM, tripropylene glycol methyl ether CAS # 25498-49-1 (also 20324-33-8)<br>Batch No.: Not reported.<br>Purity: 98%<br>Supplied as: Not reported.<br>Appearance: Not reported.<br>Administered as: Pure liquid.<br>Specific Gravity: Not reported.<br>Solubility: Miscible with water.<br>Storage: Not reported.<br>Stability: Stable. |
| **Method** | : | Pimephales promelas Rafinesque (Fathead minnows) were exposed to various concentrations of TPM in dechlorinated Lake Huron water for 96 hours at a temperature of 12°C ± 1°C. Water parameters such as oxygen content, pH, and hardness were not reported. The LC50 was calculated using the Thompson's method of moving averages (Thompson, W.R., 1947. Use of moving averages and interpolation to estimate median-effective dose. Bacteriological Review, 11(2):115-145). The number of subjects per exposure concentration, the concentrations of TPM used, and other methodological parameters were not described. The protocol describing the methodology was referenced as "Standard static acute fish toxicity test method – Environmental Sciences Research Laboratory, The Dow chemical Company, 1975" but this reference was not appended to the report. |
| **Results** | : | No mortality was observed at concentrations up to and including 5,600 mg TPM/liter. 100% mortality was observed at a concentration of 13,500 mg TPM/liter. The LC50 was calculated to be 11,619 mg TPM/liter with 95% confidence limits ranging from 11,562 to 11,713 mg TPM/liter. |
| **Conclusions** | : | These results indicate that TPM is of low acute toxicity to this freshwater aquatic species. |
| **Data Quality** | : | The data quality from this report is quite abbreviated, probably due to standards typical so long ago (pre-GLP). The report included only superficial documentation for methods and results. However, due to the reputation of the study director and the laboratory conducting the study, this study is assigned Klimisch Level 2. |

**Quality Check** : This study was identified as key for this toxicity endpoint. GLP and Quality Assurance statements were not included for this pre-GLP study. The report did not provide adequate documentation that OECD Protocol 203 "Fish, Acute Toxicity Test" was followed. Test material characterization was marginally adequately as described in the report. The concentrations tested, numbers of subjects per exposure level, and other critical experimental parameters were not reported. The length of the exposure and observation period (96 hours), and method for calculating results were typical for this type assay.

**References** : Dill, D.C., (1978). Evaluation of Dowanol TPM (Tripropylene glycol methyl ether) in the aquatic environment. Dow Report ES-265. December 15, 1978. Unpublished report.

**Other** : This study relied solely on nominal concentrations calculated from the quantity of chemical added to the aqueous environment of the test species. While TPM was not measured analytically in this study, this chemical is 1) highly water soluble (miscible), 2) has a very low vapor pressure and low octanol water partition coefficient (i.e., has a low Henry's Law constant), indicating that TPM would not tend to evaporate from the water into the air, and 3) is chemically stable in water. These three characteristics support the conclusion that the reported nominal concentrations accurately reflect actual concentrations to which the test species were exposed.

**Source** : Dow Chemical Company

(9)

### 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

**Type** : Acute 48-hour Lethality
**Species** : Daphnia magna Strauss (Crustacea) (water flea)
**Exposure period** : 48 hour(s)
**Unit** : mg/l
**Analytical monitoring** : None
**NOEC** : 10,000 TPM mg/liter .
**EC50** : Not monitored (lethality only)
**LC50** : > 10,000 mg TPM/liter (no mortality at this highest concentration tested)
**LC100** : > 10,000 mg TPM/liter
**Protocol Guideline** : This was a study conducted in 1978, prior to publication of guidelines. Comparison of the study report with OECD Guideline 203 "Fish, Acute Toxicity Test" does not permit an evaluation of whether guideline recommendations generally were followed because of the brevity of the report, particularly regarding description of methodology.

**Year of Study** : 1978
**GLP** : No

| | | | |
|---|---|---|---|
| **Test substance** | : | Identity: | Dowanol TPM, tripropylene glycol methyl ether CAS # 25498-49-1 (also 20324-33-8) |
| | | Batch No.: | Not reported. |
| | | Purity: | 98% |
| | | Supplied as: | Not reported. |
| | | Appearance: | Not reported. |
| | | Administered as: | Pure liquid. |
| | | Specific Gravity: | 0.88 g/ml. |
| | | Solubility: | Miscible with water. |
| | | Storage: | Not reported. |
| | | Stability: | Stable. |

**Method** : Daphnia magna Straus (water flea) were exposed to various concentrations of TPM in dechlorinated Lake Huron water for 48 hours at a temperature of 20°C ± 1°C. Water parameters such as oxygen content, pH, and hardness were not reported. The LC50 was calculated using the Thompson's method of moving averages (Thompson, W.R., 1947. Use of moving averages and interpolation to estimate median-effective dose. Bacteriological Review, 11(2):115-145). The number of subjects per exposure concentration, the concentrations of TPM used, and other methodological parameters were not described. The protocol describing the methodology was referenced as "Standard static acute daphnid toxicity test method – Environmental Sciences Research Laboratory, The Dow chemical Company, 1977" but this reference was not appended to the report.

**Results** : No mortality was observed at the highest concentration tested, 10,000 mg TPM/liter.

**Conclusions** : These results indicate that TPM presents low acute toxicity to the common water flea.

**Data Quality** : The data quality from this report is quite abbreviated, probably due to standards typical so long ago (pre-GLP). The report included only superficial documentation for methods and results. However, due to the reputation of the study director and the laboratory conducting the study, this study is assigned Klimisch Level 2.

**Quality Check** : This study was identified as key for this toxicity endpoint. GLP and Quality Assurance statements were not included for this pre-GLP study. The report did not provide adequate documentation that OECD Protocol 202 "Daphnia sp., Acute Immobilisation Test and Reproduction Test" was followed. Test material characterization was marginally adequately described in the report. The concentrations tested, numbers of subjects per exposure level, and other critical experimental parameters were not reported. The length of the exposure and observation period (48 hours), and method for calculating results were typical for this type assay.

**Reference** : Dill, D.C., (1978). Evaluation of Dowanol TPM (Tripropylene glycol methyl ether) in the aquatic environment. Dow Report ES-265. December 15, 1978. Unpublished report.

**Other** : This study relied solely on nominal concentrations calculated from the quantity of chemical added to the aqueous environment of the test species. While TPM was not measured analytically in this study, this chemical is 1) highly water soluble (miscible), 2) has a very low vapor pressure and low octanol water partition coefficient (i.e., has a low Henry's Law constant), indicating that TPM would not tend to evaporate from the water into the air, and 3) is chemically stable in water. These three characteristics support the conclusion that the reported nominal concentrations accurately reflect

actual concentrations to which the test species were exposed.

**Source** : Dow Chemical Company

### 4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

| | | |
|---|---|---|
| **Type** | : | Laboratory phytotoxicity study (static) |
| **Species** | : | Lemna minor L. (Duck weed) |
| **Exposure period** | : | 2-10 days, up to 28 days |
| **Unit** | : | µg/ml (or mg/liter) |
| **Concentrations Tested** | : | 0, 96.5, 482.5, or 965 µg/ml |
| **Analytical monitoring** | : | Gas chromatography of TPM. |
| **Toxicity Endpoint(s)** | : | Effects on biomass, photosynthesis, ATP levels, and electrical potential of the bath media. |
| **NOEC** | : | 482.5 µg/ml (mg/liter). |
| **LOEC** | : | 965 µg/ml (mg/liter) |
| **Protocol Guideline** | : | No specific guidance cited. |
| **Year of Study** | : | 1986 |
| **GLP** | : | Not reported (secondary literature) |
| **Test substance** | : | Identity: Dowanol-TPM (tripropylene glycol methyl ether). CAS# 25498-49-1 (a.k.a. 20324-33-8)<br>Batch No.: Not specified.<br>Purity: Not specified.<br>Supplied as: Not specified.<br>Appearance: Not specified. |

**Method** : TPM was incubated with Lemna minor (duck weed) fronds at concentrations of 0, 96.5, 482.5, or 965 µg/ml for 2 to 10 days, extending in some instances up to 28 days. Single fronds of Lemna minor were incubated with TPM in 3-liter flasks containing 1 liter of Bowker's medium. Water/growth medium parameters such as oxygen content, pH, and hardness were not reported.

Endpoints monitored included effects of TPM on biomass, photosynthesis, ATP levels, and electrical potential (conductivity) of the bath media. The influence of TPM on biomass was characterized by monitoring 1) frond growth rates and morphology, 2) wet and dry weights and, 3) fluorescence (a measure of photosynthesis as well as growth) using a Plant Productivity Fluorometer (model SF-20). Photosynthesis (i.e., chlorophyll content) was measured after Arnon (Plant Physiol. 24:1-15, 1949) using a Unicam SP 1800 Ultraviolet Spectrophotometer at $\lambda$ = 652 nm. ATP was determined after Gower (Bull. Environ. Contamin. Toxicol. 32:53-58, 1983) and Patterson et al. (Current Res. 4:569-575, 1970). Electropotential was assessed using a conductivity meter and TPM in plant tissues was measured using a Hewlett Packard model 5880 gas chromatograph with a flame ionization detector.

**Results** : At the highest exposure concentration of 965 µg/ml, TPM produced an initial significant functional impairment in the plants, indicted by depression of all monitored parameters except conductivity. After several days, a recovery in depressed parameters was noted. This recovery often exceeded baseline levels (overcompensation). Once removed completely from TPM following the initial depression (after 2-days exposure), plants recovered quickly. Daughter generations of mother fronds exposed to 965 µg/ml showed heritable effects. No effects were noted at lower concentrations. TPM did not accumulate in plant tissues. The LOEC for TPM is 965 µg/ml and the NOEC is 482.5 µg/ml.

**Conclusions** : Because the concentration causing effects was high, TPM may be considered relatively non-toxic to this aquatic plant species.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 2.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the type of test conducted and the methods followed. The study report provided documentation for test organism growth and maintenance conditions, exposure conditions, and methods for measuring toxicity endpoints

**References** : Caux, P.Y., Weinberger, P., Carlisle, D.B., (1986). Dowanol, an environmentally safe adjuvant. Environmental Toxicology and Chemistry. 5:1047-1054.

**Other** : TPM was tested because of its use as a non-active adjuvant in pesticide formulations (specifically, fenitrothion formulations to control Canadian Spruce budworms).

**Source** : Secondary literature

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**Remark** : The EPIWIN suite of models is able to predict toxicity values for chemicals based on their physicochemical characteristics of Kow, molecular weight, molecular structure, etc. The ECOSAR program module (v0.99) of EPIWIN (v3.10) predicted a Green Algae 96-hour EC50 of 9067 mg/L and a ChV of 254 mg/L.

**Source** : ECOSAR Module of EPIWIN Modeling Suite

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### 4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

**Remark** : No data available.

### 4.5.1 CHRONIC TOXICITY TO FISH

**Remark** : No data available.
**Source** : Dow Deutschland Inc Stade 5

### 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

**Remark** : No data available.
**Source** : Dow Deutschland Inc Stade 5

### 4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

**Remark** : No data available.
**Source** : Dow Deutschland Inc Stade 5

### 4.6.2 TOXICITY TO TERRESTRIAL PLANTS

**Remark** : No data available.
**Source** : Dow Deutschland Inc Stade 5

### 4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

**Remark** : No data available.
**Source** : Dow Deutschland Inc Stade 5

### 4.7 BIOLOGICAL EFFECTS MONITORING

**Remark** : No data available.
**Source** : Dow Deutschland Inc Stade 5

### 4.8 BIOTRANSFORMATION AND KINETICS

**Remark** : See biotransformation data in rats under section 5.10.1.
**Source** : Dow Deutschland Inc Stade 5

### 4.9 ADDITIONAL REMARKS

### 5.1.1 ACUTE ORAL TOXICITY

**Type** : LD50
**Species** : Rat
**Strain** : Sprague-Dawley CFY
**Sex** : Males and females
**Number of animals** : 5/sex/dose group
**Vehicle** : None
**Value** : Both sexes combined:
3500 .mg/kg bw (95% CL: 3100 – 3900 mg/kg)
**Protocol Guideline** : OECD Guideline 401 "Acute Oral Toxicity"
**Year of Study** : 1986
**GLP** : Yes
**Test substance** : "Dowfroth 250E" (polypropylene glycol methyl ether)

| | |
|---|---|
| Batch No.: | 120286 21.3.86 |
| Purity: | 90% polypropylene glycol methyl ether (tri- and higher). |
| Supplied as: | Metal screw-top container. |
| Appearance: | Clear brown liquid. |
| Administered as: | Pure liquid. |
| Specific Gravity: | 0.973. |
| Solubility: | Not specified. |
| Stability: | Not specified. |

**Method** : Three groups of Sprague-Dawley rats (5/sex/dose level) received single oral doses of 2300, 3000, 3900, or 5000 mg/kg polypropylene glycol methyl ether (PPM), administered undiluted using a stainless steel stomach cannula attached to a syringe. Animals were fasted overnight prior to dosing. Subjects were observed for mortality and signs of toxicity several times on the day of dosing (Day 0) and on weekdays thereafter for up to 14 additional days. Body weights were recorded prior to dosing, weekly thereafter, or at death. Non-survivors were necropsied as soon as possible and surviving animals were subjected to necropsy on day 14. LD50's and 95% confidence limits were calculated for both sexes individually and combined using the method of Weil (Biometrics 8:249, 1952).

**Results** : Mortality is shown in the table below. In non-survivors, death occurred within 4 hours of dosing and was characterized by coma and gasping respiration, and, upon necropsy, red appearance of the lungs, darkened liver, and congested small intestine.

| Dose Level (mg/kg) | Mortalities | | | |
|---|---|---|---|---|
| | Male | Female | Both Sexes | Percentage |
| 2300 | 0/5 | 0/5 | 0/10 | 0 |
| 3000 | 1/5 | 2/5 | 3/10 | 30 |
| 3900 | 3/5 | 3/5 | 6/10 | 60 |
| 5000 | 5/5 | 5/5 | 10/10 | 100 |

Combined sex Oral LD50 = 3500 mg/kg (95% CL: 3100 – 3900 mg/kg)
Male-only Oral LD50 = 3600 mg/kg (95% CL: 3100 – 4200 mg/kg)
Female-only Oral LD50 = 3400 mg/kg (95% CL: 2900 – 4100 mg/kg)

Symptoms in survivors exhibited a dose-response relationship and included hunched posture, lethargy, piloerection, decreased respiratory rate, ptosis, body tremors, and red/brown staining around the eyes or snout at all doses levels. Other more severe symptoms occurring more often at higher dose levels included coma and gasping respiration. By day 2, symptoms had disappeared in the two lower dose levels and by day 3 in

survivors from the 3900 mg/kg group. Body weights appeared to be unaffected. Necropsy of survivors revealed congested lungs in 4 males and 4 females from the 2300 mg/kg group but not in the 3000 or 3900 mg/kg groups.

**Conclusions** : With an oral LD50 of 3500 mg/kg, polypropylene glycol methyl ether shows a low degree of acute toxicity. This test material is appears to be comprised largely of tripropylene glycol methyl ether (see "Other" comment).

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 2.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The study report provided documentation that OECD Protocol 401: "Acute Oral Toxicity" was followed. Specifically, the numbers and type of test animals used and their husbandry conditions were as recommended in the guidance. Test material characterization was adequate. The dose level tested satisfied the appropriate OECD upper limit (i.e., 2 gm/kg), the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded.

**Reference** : Jones, J.R., Collier, T.A., (1986). Dowfroth 250E: Acute oral toxicity test in the rat. Safepharm Laboratories Limited. Dow confidential Report DET 781. Unpublished report.

**Other** : The test material was not pure TPM. Analysis indicated test material was 90% polypropylene glycol methyl ether (tri- and higher).

**Source** : Dow Deutschland Inc Stade 5

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**Type** : LD50
**Species** : Rat
**Strain** :
**Sex** :
**Number of animals** :
**Vehicle** :
**Value** : 3412 mg/kg (95% CL: 3377 - 4342 mg/kg)
or 3.3 ml/kg (95% CL: 3.1 – 3.5 ml/kg)
**Protocol Guideline** : Pre-guideline
**Year of Study** : 1954
**GLP** : Pre-GLP
**Test substance** : Tripropylene glycol monomethyl ether (TPM), a.k.a. "62B"
**Remark** : V. K. Rowe et. al. (1954)
**Source** : Dow Deutschland Inc Stade 5

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**Type** : LD50
**Species** : Rat
**Strain** : Wistar
**Sex** : Males only; 90-120 grams and 3 to 4 weeks of age
**Number of animals** : 5 per dose level
**Vehicle** : None
**Value** : 5.66 ml/kg bw (3.21 < 95% CL < 9.95) or 5462. mg/kg bw

| | | |
|---|---|---|
| **Protocol Guideline** | : | Pre-Guidance |
| **Year of Study** | : | 1977 |
| **GLP** | : | Pre-GLP |
| **Test substance** | : | Propasol Solvent TM<br>Amount Received: 1 pint<br>Sample No. 40-130<br>ID: 511-01-1485<br>Receipt Date: March 22, 1977 |
| **Methods** | : | Male Wistar rats were dosed orally with 2.0, 4.0, or 8.0 milliliters TPM per kg body weight and observed presumably for 14 days. |
| **Results** | : | At the high dose of 8 ml/kg (7.72 g/kg or 7720 mg/kg), four of 5 male rats died on the first day (time of survival not specified). High dose rats lost an average of 96 grams of weight and exhibited prostration for the first 15 minutes, salivation for 3 hours, and porphyria (as nasal discharge) for 2 days. At the mid-dose of 4 ml/kg (3.86 g/kg or 3860 mg/kg), one of 5 male rats died after treatment. Rats from this group exhibited sluggish behavior, piloerection for 15 minutes and, prostration, twitching 30 minutes to 3 hours (non-survivor only?) and the single death after 3 hours. After 2 ml/kg (1.93 g/kg or 1930 mg/kg), no rats died but exhibited prostration for 1.25 hours and unsteady gait for 3 hours. At necropsy, non-survivors showed petechial hemorrhage in the lungs, pale and/or mottled livers, congested, pale and/or mottled kidneys, congested adrenal glands, full bladders, liquid and gas-filled distended stomachs, white pylori, and yellow or pink liquid or gas-filled opaque intestines. Survivors exhibited “prominent” acini of the liver. |
| **Conclusions** | : | The oral LD50 for TPM is 5.66 ml/kg with 95% confidence limits ranging from 3.21 to 9.95 m/kg. This corresponds to 5462 mg/kg (3098 < 95% CL < 9600 mg/kg). TPM shows a low order of acute oral toxicity. |
| **Data Quality** | : | The data quality from this study is considered marginally acceptable. This study reaches Klimisch Level 2. |
| **Quality Check** | : | This study was performed prior to establishment of GLPs or publication of protocol guidelines. The report included very limited documentation for methods and results but the performing institution, Carnegie Mellon, was/is highly regarded. As typical for a study this old, the report did not provide sufficient documentation that elements of OECD Protocol 401: “Acute Oral Toxicity” were followed, although the numbers and type of test animals used (but not their husbandry conditions) were as recommended in the guidance. Test material characterization was not addressed other than to identify batch numbers, amount received, and receipt dates. However, the dose level tested more than satisfied the appropriate OECD upper limit (i.e., 2 gm/kg). While the length of the observation period was not explicitly stated it is presumed to have been the typical 14 days; the toxicity endpoints monitored were standard for this type assay and adequately recorded. |
| **References** | : | Kuryla, W.C., (1991). CAP 8(e) Submission from Union Carbide Corporation with cover letter dated 110791: Propasol Solvent TM: Range Finding Toxicity Studies. Chemical Hygiene Fellowship (Carnegie-Mellon) Project Report 40-117, September 9, 1977. NTIS Fiche No. OTS-0534581, 1991. |
| **Other** | : | The finding of low acute oral toxicity for TPM is consistent with other glycol ethers. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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| | | |
|---|---|---|
| **Type** | : | LD50 |
| **Species** | : | Rat |
| **Strain** | : | |
| **Sex** | : | |
| **Number of animals** | : | |
| **Vehicle** | : | |
| **Value** | : | = 3184 . mg/kg bw |
| **Method** | : | other |
| **Year** | : | 1954 |
| **GLP** | : | No |
| **Test substance** | : | |
| **Remark** | : | V.K. Rowe, D.D. McCollister, H.C. Spencer, F. Oyen, R.L. Hollingsworth and V.A. Drill Toxicology of Mono-, Di-, and Tri-Propylene Glycol Methyl Ethers. A.M.A. Archives of Industrial Hygiene and Occupational Medicine, June 1954, Vol. 9, 509-525 |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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| | | |
|---|---|---|
| **Type** | : | LD50 |
| **Species** | : | Dog |
| **Strain** | : | |
| **Sex** | : | |
| **Number of animals** | : | |
| **Vehicle** | : | |
| **Value** | : | ca. 4835 . mg/kg bw |
| **Method** | : | other |
| **Year** | : | 1951 |
| **GLP** | : | No |
| **Test substance** | : | as prescribed by 1.1 - 1.4 |
| **Remark** | : | Ref. Shideman, F.E. and Procita, L. J. Pharmacol. Exp. Therap. 102(2), 79-87, 1951 |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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### 5.1.2 ACUTE INHALATION TOXICITY

| | | |
|---|---|---|
| **Type** | : | LC0 |
| **Species** | : | Rat |
| **Strain** | : | |
| **Sex** | : | |
| **Number of animals** | : | |
| **Vehicle** | : | |
| **Exposure time** | : | 8 hour(s) |
| **Value** | : | > 30. ppm (> 253 mg/m3) |
| **Method** | : | OECD Guideline 403 "Acute Inhalation Toxicity" |
| **Year** | : | 1991 |
| **GLP** | : | Yes |
| **Test substance** | : | |
| **Remark** | : | Concentration: saturated vapor, dynamic conditions at room temperature. Concentration calculated as 30 ppm at 25 degrees C. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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| | | |
|---|---|---|
| **Type** | : | LC50 (Limit Test) |
| **Species** | : | Rat |
| **Strain** | : | Wistar albino |

| | | |
|---|---|---|
| **Sex** | : | Not specified. |
| **Number of animals** | : | 10 at the single exposure level tested |
| **Vehicle** | : | Ambient air |
| **Exposure time** | : | 1 hour |
| **Value** | : | 200 mg/liter or 200,000 mg/m3 (nominal concentration) |
| **Protocol Guideline** | : | Pre-guideline |
| **Year of Study** | : | 1975 |
| **GLP** | : | Pre-GLP |
| **Test substance** | : | Polysolv TPM (Tripropylene glycol methyl ether, CAS# 25498-49-1) Clear yellow liquid. |
| **Method** | : | Ten rats were placed into 50 liter chambers (not described) and exposed to nominal concentrations of 200 mg/liter TPM (or 200,000 mg/m3 or 23,700 ppm). Atmosphere generation methods were not described. This concentration is far in excess of the theoretical vapor concentration for TPM and, consequently, subjects were exposed to TPM as an aerosol. If the aerosol condensed within the chamber or on animal fur, the actual concentrations could have been far lower than the reported nominal concentrations. Subjects were exposed for 1 hour, then observed for 14 days for mortality and signs of toxicity. |
| **Results** | : | No deaths or signs of toxicity were observed, indicating that the inhalation LD50 exceeded the nominal exposure concentration. |
| **Conclusions** | : | Because the exposure atmosphere was not characterized (i.e., actual concentrations were not measured), the actual exposure concentrations could have been much lower than the reported nominal exposure concentration. See comment in “Other” section below. |
| **Data Quality** | : | This pre-GLP, pre-protocol guideline study is assigned Klimisch level 4 due to poor documentation. Study reports of this era often are not well documented yet results are valid. |
| **Quality Check** | : | This is a pre-GLP, pre-protocol guideline study. Results of this study were contained in an extremely abbreviated report without much detail. The atmosphere generation method and exposure chambers were not described. The test material and the test subjects were not adequately characterized in the report. Whether condensation was observed on the chamber walls or on the fur of the rats was not reported. Thus, the actual concentration of test material to which rats were exposed cannot be reliably judged. |
| **References** | : | Moreno, O.M. (1975). Report in inhalation toxicity in rats. MB Research Laboratories, Inc. Project No. MB 75-991. Olin unpublished report. TSCATS Microfiche No. OTS 0516710. |
| **Other** | : | The results of this study are worth reporting since the nominal concentrations are very high and greatly in excess of the vapor study described previously. If the test subjects were exposed to even one one hundredth of the nominal concentration reported, this would represent an exposure concentration of 2,000 mg/m3 or ~240 ppm (about 10X as high as the above vapor study). Although exposures were only 1 hour in this study (as opposed to 8 hours in the vapor study), these results suggest that the inhalation LD50 could be considerably higher than that reported in the GLP vapor study above. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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### 5.1.3 ACUTE DERMAL TOXICITY

| | | |
|---|---|---|
| **Type** | : | LD50 |
| **Species** | : | Rabbit (3 to 5 months old; weight not specified) |
| **Strain** | : | Albino (strain not specified) |
| **Sex** | : | Male only |
| **Number of animals** | : | 4 per group |
| **Vehicle** | : | None |
| **Value** | : | 16 ml/kg or 15440. mg/kg |
| **Protocol Guidance** | : | Pre-Guidance |
| **Year of Study** | : | 1977 |
| **GLP** | : | Pre-GLP |
| **Test substance** | : | Propasol Solvent TM<br>Amount Received: 1 pint<br>Sample No. 40-130<br>ID: 511-01-1485<br>Receipt Date: March 22, 1977 |
| **Methods** | : | For a period of 24 hour, TPM was applied under occlusion (impermeable wrap – polyethylene sheeting) to the clipped, intact skin of the trunk of male albino rabbits at dose levels of 8.0 or 16 milliliters TPM per kg body weight. These dose volumes correspond to 7.72 or 15.4 g/kg (7720 or 15400 mg/kg). Rabbits were restrained in an undefined manner. At the end of the 24-hour application period, excess TPM was removed and the rabbits were observed for mortality and signs of toxicity for an unspecified period thereafter (presumably up to 14 days). |
| **Results** | : | The high dose of 16 ml/kg (15400 mg/kg) caused death in 2 of 4 rabbits on days 2 and 3. Non-survivors lost 80 and 113 grams of weight and one subject from this group had an unsteady gait and another was prostrate at 24 hours. At 8 ml/kg (7720 mg/kg), no rabbits died and no symptoms were reported. All rabbits lost weight, which may have been due to stress from restraint. At necropsy, non-survivors showed mottled livers, mottled spleens, and full bladders. Survivors exhibited pale and mottled kidneys. |
| **Conclusions** | : | The dermal LD50 of TPM is 16 ml/kg or 15400 mg/kg with a very broad 95% confidence interval ranging from 4.48 to 57.2 ml/kg due, according to the authors, of the fractional mortality at the high dose. TPM shows a low order of acute dermal toxicity. |
| **Data Quality** | : | The data quality from this study is considered marginally acceptable. This study reaches Klimisch Level 3. |
| **Quality Check** | : | This study was performed prior to establishment of GLPs or publication of protocol guidelines. The report included very limited documentation for methods and results but the performing institution, Carnegie Mellon, was/is highly regarded. As typical for a study this old, the study report did not provide sufficient documentation that elements of OECD Protocol 402: “Acute Dermal Toxicity” were followed, although the numbers and type of test animals used (but not their husbandry conditions) were as recommended in the guidance. Test material characterization was not addressed other than to identify batch numbers, amount received, and receipt dates. However, the dose level tested more than satisfied the appropriate OECD upper limit. While the length of the observation period was not explicitly stated, it is presumed to have been the typical 14 days; the toxicity endpoints monitored were typical for this type assay and adequately recorded. |

| | | |
|---|---|---|
| **References** | : | Kuryla, W.C., (1991). CAP 8(e) Submission from Union Carbide Corporation with cover letter dated 110791: Propasol Solvent TM: Range Finding Toxicity Studies. Chemical Hygiene Fellowship (Carnegie-Mellon) Project Report 40-117, September 9, 1977. NTIS Fiche No. OTS-0534581, 1991. |
| **Other** | : | The finding of low acute dermal toxicity for TPM is consistent with other glycol ethers. |
| **Source** | : | Dow Deutschland Inc Stade 5 (13) |
| **Type** | : | LD50 |
| **Species** | : | Rabbit |
| **Strain** | : | |
| **Sex** | : | |
| **Number of animals** | : | |
| **Vehicle** | : | |
| **Value** | : | > 19300 . mg/kg bw |
| **Method** | : | Other |
| **Year** | : | 1954 |
| **GLP** | : | No |
| **Test substance** | : | |
| **Remark** | : | Method: Draize, Woodard and Calvery, J. Pharmacol. & Exper. Therap. Vol. 82, 377-390, 1944.<br><br>Ref.: V.K. Rowe et al. , see section 5.1.1, record 4 |
| **Source** | : | Dow Deutschland Inc Stade 5 (12) |

### 5.1.4 ACUTE TOXICITY, OTHER ROUTES

| | | |
|---|---|---|
| **Remark** | **:** | No data available. |
| **Source** | **:** | Dow Deutschland Inc Stade 5 |

### 5.2.1 SKIN IRRITATION

| | | |
|---|---|---|
| **Species** | : | Rabbit (3 to 5 months old; weight not specified) |
| **Strain** | : | Albino (strain not specified) |
| **Sex** | : | Male only |
| **Concentration** | : | Undiluted (0.010 ml) |
| **Exposure** | : | Unoccluded on intact skin |
| **Exposure time** | : | 24 hours. |
| **Number of animals** | : | 5 males |
| **PDII** | : | 1 on scale of 10 |
| **Result** | : | not irritating |
| **EC classification** | : | not irritating |
| **Protocol Guidance** | : | Pre-guidance |
| **Year of Study** | : | 1977 |
| **GLP** | : | Pre-GLP |
| **Test substance** | : | Propasol Solvent TM<br>Amount Received: 1 pint<br>Sample No. 40-130<br>ID: 511-01-1485<br>Receipt Date: March 22, 1977 |

| | | |
|---|---|---|
| **Methods** | : | TPM was applied to the intact clipped skin of the belly of 5 albino rabbits for an unspecified period of time. The application site was not covered and, presumably, subjects were restrained to prevent grooming and consequent ingestion (subjects were restrained in the dermal LD50 test by the same institution, described above, on this same batch of test material). Irritation was scored on a scale of 1 to 10, based on moderate or marked capillary injection, erythema, edema or necrosis within 24 hours. No evident injury is judged to be a Grade 1. |
| **Results** | : | Under this regimen, TPM did not cause dermal irritation and was scored as Grade 1. |
| **Conclusions** | : | TPM does not appear to be irritating to the skin of rabbits under the conditions of this test. |
| **Data Quality** | : | The data quality from this study is considered marginally acceptable. This study reaches Klimisch Level 3. |
| **Quality Check** | : | This study was performed prior to establishment of GLPs or publication of protocol guidelines. The report included very limited documentation for methods and results but the performing institution, Carnegie Mellon, was/is highly regarded. As typical for a study this old, the report did not provide sufficient documentation that elements of OECD Protocol 404: "Acute Dermal Irritation/Corrosion" were followed, although the numbers and type of test animals used (but not their husbandry conditions) were as recommended in the guidance. Remarkably, the length of time that test material was held in contact with the skin was not defined. Test material characterization was not addressed other than to identify batch numbers, amount received, and receipt dates. While the length of the observation period was not explicitly stated it is presumed to have been the typical 14 days or until all signs of irritation had regressed; the toxicity endpoints monitored were typical for this type assay and adequately recorded. |
| **References** | : | Kuryla, W.C., (1991). CAP 8(e) Submission from Union Carbide Corporation with cover letter dated 110791: Propasol Solvent TM: Range Finding Toxicity Studies. Chemical Hygiene Fellowship (Carnegie-Mellon) Project Report 40-117, September 9, 1977. NTIS Fiche No. OTS-0534581, 1991. |
| **Other** | : | This study did not employ the criteria of Draize to score dermal irritation. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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### 5.2.2 EYE IRRITATION

| | | |
|---|---|---|
| **Species** | : | Rabbit |
| **Strain** | : | Albino |
| **Sex** | : | Male |
| **Concentration** | : | Undiluted |
| **Dose** | : | 0.1 ml, and 0.02 ml |
| **Exposure Time** | : | No washing |
| **Number of animals** | : | 5 rabbits |
| **Result** | : | Moderately irritating |
| **Protocol Guidance** | : | Pre-Guidance |
| **Year of Study** | : | 1977 |
| **GLP** | : | Pre-GLP |

| | | |
|---|---|---|
| **Test substance** | : | Propasol Solvent TM<br>Amount Received: 1 pint<br>Sample No. 40-130<br>ID: 511-01-1485<br>Receipt Date: March 22, 1977 |
| **Methods** | : | Undiluted TPM was instilled into the conjunctival sac of one eye of a rabbit at doses of 0.1, 0.02, or 0.005 ml (5 rabbits per group). Eyes were scored immediately (without fluorescein) and at 24 hours (with fluorescein). Eyes were scored on a scale of 1 to 10 (criteria not specified). |
| **Results** | : | At a dose of 0.1 ml, TPM caused moderate corneal injury (presumably in all 5 rabbits) with iritis in one. At 0.02 ml, TPM caused trace corneal injury in 3 of 5 rabbits with trace iritis in 1 rabbit. A dose of 0.005 ml TPM did not cause eye irritation. On a scale of 1 to 10, the authors of the report assigned a score of Grade 4 (Moderately irritating). |
| **Conclusions** | : | Results from this study indicate that TPM has the potential to irritate or injure eyes. |
| **Data Quality** | : | The data quality from this study is considered marginally acceptable. This study reaches Klimisch Level 3. |
| **Quality Check** | : | This study was performed prior to establishment of GLPs or publication of protocol guidelines. The report included very limited documentation for methods and results but the performing institution, Carnegie Mellon, was/is highly regarded. As typical for a study this old, the study report did not provide sufficient documentation that elements of OECD Protocol 405: "Acute Eye Irritation/Corrosion" were followed, although the numbers and type of test animals used (but not their husbandry conditions) were as recommended in the guidance. Test material characterization was not addressed other than to identify batch numbers, amount received, and receipt dates. While the length of the observation period was not explicitly stated it is presumed to have been the typical 14 days or until all signs of irritation had regressed; the toxicity endpoints monitored were typical for this type assay and adequately recorded. |
| **References** | : | Kuryla, W.C., (1991). CAP 8(e) Submission from Union Carbide Corporation with cover letter dated 110791: Propasol Solvent TM: Range Finding Toxicity Studies. Chemical Hygiene Fellowship (Carnegie-Mellon) Project Report 40-117, September 9, 1977. NTIS Fiche No. OTS-0534581, 1991. |
| **Other** | : | Scoring criteria were not explained. |
| **Remark** | : | Method: Consumer Product Safety Act, Title 16 CFR 1500.42. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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## 5.3 SENSITIZATION

| | | |
|---|---|---|
| **Remark** | : | From the handling and use experience no reports have come foreword to indicate sensitizing properties. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

## 5.4 REPEATED DOSE TOXICITY

**Type** : Two-Week Aerosol Inhalation with Rat
**Species** : Rat
**Sex** : Males & Females
**Strain** : Fischer 344

| | |
|---|---|
| Age at first exposure: | 7-9 weeks of age. |
| Source: | Charles River Breeding Laboratory, Kingston, N.Y. |
| Acclimation period: | At least one week. |
| Weight range (start of study): | Males: average of 179.5 grams; Females: average of 128.4grams. |
| Assignment to groups: | Computer generated random number table. |
| Diet: | Purina Certified Rodent Chow #5002 (Ralston Purina Co., St Louis, MO). |
| Access to food: | Available ad libitum except during exposures. |
| Access to water: | Available ad libitum except during exposures. |
| Method of Identification: | Metal ear tags. |
| Housing: | Individually in stainless steel cages with wire bottoms during non-exposure periods. Same cages during daily 6-hr exposures. |

Environmental Conditions (for non-exposure periods):

| | |
|---|---|
| Temperature: | 72°F. |
| Humidity: | 50%. |
| Air changes: | Not specified. |
| Photoperiod: | 12 hr light/12 hr dark. |

Environmental Conditions (for exposure periods):

| | |
|---|---|
| Temperature: | ~70°F (recorded at the end of each exposure period). |
| Humidity: | ~50% (recorded at the end of each exposure period). |
| Airflow: | 200 liters/min. |
| Air changes: | 12 air changes per hour. |
| Photoperiod: | 12 hr light/12 hr dark. |

**Route of admin.** : Inhalation
**Exposure period** : 2 weeks (total of 9 exposures)
**Frequency of treatment** : Monday through Friday, 6 hours a day
**Post obs. Period** : None
**Exposure Levels** : 0, 0.15, 0.36, or 1.01 mg/l (0, 150, 360, or 1010 mg/m3) (0, 17.8, 42,7, or 120 ppm)
**No. Subjects/dose** : 5/sex/exposure level (including controls)
**Control group** : Yes
**NOAEL** : 0.15. mg/l (liver weight increases with no histopathology)
**LOAEL** : 0.36. mg/l (liver weight increases with no histopathology)
**Protocol Guideline** : Specific protocol guideline not specified. Followed requirements of OECD Guideline 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study"
**Year of Study** : 1985
**GLP** : Yes

**Test substance** : Identity: Tripropylene glycol methyl ether (CAS# 25498-49-1 or 20324-33-8)
Batch No.: Not specified.
Purity: 99.4% as TPM isomers
Supplied as: Production grade TPGME (Tank #56).
Appearance: Colorless liquid.
Administered as: Aerosol in air
Vapor pressure: 0.017 mmHg at 25°C
Specific Gravity: 0.961
Solubility: Not specified.
Stability: Stable up to 200°C.

**Methods** : Groups of 5 male and 5 female young adult Fischer 344 rats were exposed to an aerosol atmosphere of TPM, at measured concentrations of 0, 0.15, 0.36, or 1.01 mg/liter, 6 hr/day, 5 d/wk over a 2 week period for a total of 9 exposures. Nominal concentrations were 0, 0.58, 2.17, and 5.57 mg/liter, calculated from the amount of TPM used and the airflow rate. Rats were observed after each exposure for mortality and clinical signs of toxicity. The subjects were weighed on exposure days 1, 3, 5, and 9. Ophthalmic examination was conducted prior to the first exposure and at sacrifice. Hematology, clinical chemistry, and urinalyses were conducted prior to sacrifice. All animals were subjected to gross necropsy, major organs were weighed, and 50 tissues were collected and processed into slides for histological examination.

Rats were exposed in glass and stainless steel chambers with an internal volume of 1 cubic meter with an airflow of 200 liters/min. TPM aerosol was generated using a spray nozzle (Spraying Systems Co., Wheaton, IL). Aerosol total mass concentrations were measured gravimetrically 4 to 5 times per day. Aerodynamic particle size was characterized once per day for each chamber using an APS 33 Aerodynamic Particle Sizer and diluter (TSI Inc., St. Paul, MN). Temperature and humidity were monitored at the end of each 6-hour exposure.

**Results** : Survival: All rats survived exposure to TPM.

Clinical signs: The fur of rats in the high exposure group appeared damp following each day's exposure, due presumably to condensation of the test material. A slight nasal exudate was noted in rats from the high exposure group following the last exposure.

Body weights: Body weights were not affected by treatment with TPM.

Organ weights: Absolute and relative liver weights in both sexes from the high exposure groups and males but not females (relative liver weights only) in the mid-exposure group were statistically increased above controls ($p < 0.05$). Other measured organ weights (brain, heart, kidneys, and testes) were not affected.

Hematology: Hematology was unaffected by treatment with TPM. No evidence of hemolysis was present.

Urinalysis: The specific gravity was increased over controls in female rats from the low and high exposure groups. The mid-dose group was not statistically increased and no trend correlating with exposure concentration was evident. The authors concluded that the effect on specific gravity was not treatment-related because of this and since clinical chemistry parameters and kidney histology were normal.

Clinical Chemistry: Clinical chemistry parameters were unaffected by treatment with TPM.

Gross pathology: At necropsy, livers of some animals appeared enlarged.

Histopathology: No abnormal histology was found in rats at any exposure level.

Characterization of the aerosol atmosphere: Nominal concentrations were approximately 3 times actual concentrations for the 0.15 mg/liter group, 6 times actual concentrations in the 0.36 mg/liter group, and 5.5 times actual concentrations in the 1.01 mg/liter group. The mass median aerodynamic diameter (MMAD) ranged from 3.4 to 4.1 microns for all three exposure concentrations and the geometric standard deviation ranged from 1.6 to 1.7, indicating a deep-lung respirable particle size.

**Conclusions** : The only effect found in rats with exposure to TPM was a statistically significant increase in absolute and relative liver weights in both sexes treated with 1.01 mg/liter (high exposure group). Relative but not absolute liver weights were increased in males but not females treated with 0.36 mg/liter (mid-dose group). These changes were not accompanied by histological damage. Based on liver weight increases, the NOEL is 0.15 mg/liter and the LOEL is 0.35 mg/liter. If liver weight increases without histopathology are considered adaptive (MFO induction), the NOAEL for this study is 1.01 mg/liter.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although the study report did not specify that OECD Guideline 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study" was followed, the study satisfied the methods stipulated in this protocol. Specifically, the numbers and type of test animals used and their husbandry conditions were as recommended in the guidance. Test material characterization was adequate. The dose level tested satisfied the appropriate OECD upper limit, the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded.

**References** : Miller, R.R., Lomax, L.G., Calhoun, L.L., Kociba, R.J., (1985). Tripropylene Glycol Monomethyl Ether: 2-Week aerosol inhalation toxicity study in rats and mice. Confidential report of the Dow Chemical Company: November 12, 1985. Unpublished report.

**Other** : These results indicate low toxicity from repeated exposures to TPM aerosols.

**Source** : Dow Deutschland Inc Stade 5

(17)

**Type** : Two-Week Aerosol Inhalation with Mouse
**Species** : Mouse
**Sex** : Males & Females
**Strain** : B6C3F1

| | |
|---|---|
| Age at first exposure: | 7-9 weeks of age. |
| Source: | Charles River Breeding Laboratory, Kingston, N.Y. |
| Acclimation period: | At least one week. |
| Weight range (start of study): | Males: average of 24.9 grams; Females: average of 22.1grams. |
| Assignment to groups: | Computer generated random number table. |
| Diet: | Purina Certified Rodent Chow #5002 (Ralston Purina Co., St Louis, MO). |
| Access to food: | Available ad libitum except during exposures. |
| Access to water: | Available ad libitum except during exposures. |
| Method of Identification: | Metal ear tags. |
| Housing: | Individually in stainless steel cages with wire bottoms during non-exposure periods. Same cages during daily 6-hr exposures. |

Environmental Conditions (for non-exposure periods):

| | |
|---|---|
| Temperature: | 72°F. |
| Humidity: | 50%. |
| Air changes: | Not specified. |
| Photoperiod: | 12 hr light/12 hr dark. |

Environmental Conditions (for exposure periods):

| | |
|---|---|
| Temperature: | ~70°F (recorded at the end of each exposure period). |
| Humidity: | ~50% (recorded at the end of each exposure period). |
| Airflow: | 200 liters/min. |
| Air changes: | 12 air changes per hour. |
| Photoperiod: | 12 hr light/12 hr dark. |

| | | |
|---|---|---|
| **Route of admin.** | : | Inhalation |
| **Exposure period** | : | 2 weeks (total of 9 exposures) |
| **Frequency of treatment** | : | Monday through Friday 6 hours a day |
| **Post obs. Period** | : | None |
| **Doses** | : | 0, 0.15, 0.36, or 1.01 mg/l (0, 150, 360, or 1010 mg/m3) (0, 17.8, 42,7, or 120 ppm) |
| **No. Subjects/dose** | : | 5/sex/exposure level (including controls) |
| **Control group** | : | Yes |
| **NOAEL** | : | < 0.15. mg/liter (liver weight increases – no accompanying histopathology) |
| **LOAEL** | : | 0.15. mg/liter (liver weight increases – no accompanying histopathology) |
| **Protocol Guideline** | : | Specific protocol guideline not specified. Followed requirements of OECD Guideline 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study" |
| **Year of Study** | : | 1985 |
| **GLP** | : | Yes |
| **Test substance** | : | Identity: Tripropylene glycol methyl ether (CAS# 25498-49-1 or 20324-33-8)<br>Batch No.: Not specified.<br>Purity: 99.4% as TPM isomers<br>Supplied as: Production grade TPGME (Tank #56).<br>Appearance: Colorless liquid.<br>Administered as: Aerosol in air<br>Vapor pressure: 0.017 mmHg at 25°C<br>Specific Gravity: 0.961<br>Solubility: Not specified.<br>Stability: Stable up to 200°C. |

**Methods** : Groups of 5 male and 5 female young adult B6C3F1 mice were exposed to an aerosol atmosphere of TPM, at measured concentrations of 0, 0.15, 0.36, or 1.01 mg/liter, 6 hr/day, 5 d/wk over a 2 week period for a total of 9 exposures. Nominal concentrations were 0, 0.58, 2.17, and 5,57 mg/liter, calculated from the amount of TPM used and the airflow rate. Mice were observed after each exposure for mortality and clinical signs of toxicity. The subjects were weighed on exposure days 1, 3, 5, and 9. Hematology and clinical chemistry were conducted prior to sacrifice. All animals were subjected to gross necropsy, major organs were weighed, and 50 tissues were collected and processed into slides for histological examination.

Mice were exposed in glass and stainless steel chambers with an internal volume of 1 cubic meter with an airflow of 200 liters/min. TPM aerosol was generated using a spray nozzle (Spraying Systems Co., Wheaton, IL). Aerosol total mass concentrations were measured gravimetrically 4 to 5 times per day. Aerodynamic particle size was characterized once per day for each chamber using an APS 33 Aerodynamic Particle Sizer and diluter (TSI Inc., St. Paul, MN). Temperature and humidity were monitored at the end of each 6-hour exposure.

**Results** : Survival: One female mouse in the control group and one female in the 0.15 mg/liter groups died as a result of trauma unrelated to TPM exposure.

Clinical signs: All surviving mice survived treatment without apparent clinical signs of toxicity.

Body weights: Body weights were not affected by treatment with TPM.

Organ weights: Absolute and relative liver weights in both sexes from the high exposure groups were statistically increased above controls ($p < 0.05$). In males this effect on liver weight changes was also increased at this significance level in the 0.15 and 0.36 mg/liter group (i.e., at all exposure levels). Other measured organ weights (brain, heart, kidneys, and testes) were not affected.

Hematology: Hematology was unaffected by treatment with TPM. No evidence of hemolysis was present.

Clinical Chemistry: Clinical chemistry parameters were unaffected by treatment with TPM.

Gross pathology: At necropsy, livers of some animals appeared enlarged.

Histopathology: In the high-exposure group (1.01 mg/liter), the livers of males exhibited increased "altered tinctorial properties (increased eosinophilia) in peripheral regions of hepatic lobules. . .considered to be an adaptive response rather than a degenerative phenomenon." Hepatocytes appeared normal.

Characterization of the aerosol atmosphere: Nominal concentrations were approximately 3 times actual concentrations for the 0.15 mg/liter group, 6 times actual concentrations in the 0.36 mg/liter group, and 5.5 times actual concentrations in the 1.01 mg/liter group. The mass median aerodynamic diameter (MMAD) ranged from 3.4 to 4.1 microns for all three exposure concentrations and the geometric standard deviation ranged from 1.6 to 1.7, indicating deep-lung respirable particle size.

**Conclusions** : The only effect found with exposure to TPM was an increase in liver weights that affected male mice in all treated groups and female mice only in the high exposure group. These changes were not accompanied by histological damage in the low and mid dose group males or in the high dose females. Males but not females in the high exposure group exhibited staining changes but no frank evidence of histologic damage to hepatocytes. Based on liver weight increases, the NOEL is < 0.15 mg/liter and the LOEL is 0.15 mg/liter. If the liver weight increases without cellular damage in mice at the lower dose levels are considered adaptive in nature (i.e., MFO induction), this establishes a NOAEL of 1010 mg/m3 based on liver changes with histopathology in mice.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch Level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although the study report did not specify that OECD Guideline 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study" was followed, the study satisfied the methods stipulated in this protocol. Specifically, the numbers and type of test animals used and their husbandry conditions were as recommended in the guidance. Test material characterization was adequate. The dose level tested satisfied the appropriate OECD upper limit, the length of the observation period (14 days) was sufficient, and the toxicity endpoints monitored were typical for this type assay and adequately recorded.

**References** : Miller, R.R., Lomax, L.G., Calhoun, L.L., Kociba, R.J., (1985). Tripropylene Glycol Monomethyl Ether: 2-Week aerosol inhalation toxicity study in rats and mice. Confidential report of the Dow Chemical Company: November 12, 1985. Unpublished report.

**Other** : These results indicate low toxicity from repeated exposures to TPM aerosols.

**Source** : Dow Deutschland Inc Stade 5

(17)

**Type** : 90-Day Dermal Toxicity with Rabbit
**Species** : Rabbit
**Sex** : Male
**Strain** :
**Route of admin.** : Dermal
**Exposure period** : 90 days
**Frequency of treatment** : 5 times a week
**Post obs. period** : None
**Doses** : 0.0, 1.0, 3.0, 5.0, 10.0 ml/kg; (0, 965, 2895, 4825, 9650 mg/kg)
**Control group** : Distilled water
**NOAEL** : = 965. mg/kg
**LOAEL** : = 2895. mg/kg
**Protocol Guideline** : Pre-guideline
**Year of Study** : 1954
**GLP** : Pre-GLP
**Test substance** : Tripropylene glycol methyl ether (TPM), “62B”

| | |
|---|---|
| Batch No.: | Not reported. |
| Purity: | “Essentially 100%” |
| Supplied as: | Not reported. |
| Appearance: | Clear liquid. |
| Administered as: | Undiluted liquid. |
| Specific Gravity: | 0.967 g/ml. |
| Solubility: | Miscible. |
| Stability: | Stable. |

**Methods** : Groups of five to eight adult rabbits per dose level received topical applications of TMP at the doses shown in the table below, 5 d/wk, over 3 months (for a total of 65 applications). TPM was applied to a gauze pad (7.5x7.5 cm sq) at the appropriate dose level. This pad was applied to the clipped or shaved abdomen of the rabbit, covered with impervious saran wrap, covered with a heavy cloth, and secured to the rabbit with adhesive tape. This dosing procedure was repeated 5 times per week. Blood was collected and differential blood counts determined before the study began and on the 30th and 90th day of the study. Body weights (weekly) and organ weights were also monitored. At necropsy, samples from liver, kidneys, spleen, adrenals, heart, lungs, and G.I. tract were collected for processing into slides for histological evaluation.

| Group | TPM Dose (ml/kg-d) | # Rabbits Treated | Total # Days Treated | # Dying |
|---|---|---|---|---|
| 1 | 0 (water) | 5 | 65 | 0 |
| 2 | 1.0 | 6 | 65 | 0 |
| 3 | 3.0 | 7 | 65 | 0 |
| 4 | 5.0 | 8 | 65 | 0 |
| 5 | 10.0 | 8 | 65 | 7* |

* Weeks of death were: 1, 1, 3, 3, 3, 3, & 10.

**Results** : The highest dose, 10 ml/kg-d, produced narcosis and death in 7 of 8 of the subjects. All but one non-survivor died within 3 weeks of initiation of treatment. The remaining non-survivor died during the 10th week of exposure. Other observations in the high dose group included weight loss and increased kidney weights. Autopsy of the high dose group showed that organs appeared normal when examined grossly. Histopathology was largely normal in all organs in the high dose group with the exception that kidneys occasionally showed granular degeneration and hydropic changes. Oddly, at 1.0 and 3.0, but not at 5.0 ml/kg-d, tubular necrosis was observed in some rabbits. Hematology was normal at all dose levels. At 3.0 and 5.0 ml/kg-d, body weight loss was evident on days 84 and 90 but not at earlier exposure times. Kidney weights were increased in these two groups as well. Gross and histopathological examination of the skins of the rabbits at the site of TPM application indicated occasional erythema and “scalding” but did not reveal significant severity or incidence differences from water treated controls.

**Conclusions** : The NOAEL is 1.0 ml/kg-d and the LOAEL is 3.0 ml/kg-d based on increased kidney weights (and decreased body weights late in the study).

**Data Quality** : This study was conducted prior to GLP’s and publication of protocol guidelines. Nonetheless, the study appeared well conducted with enough animals to determine statistical significance. This study reaches Klimisch level 2.

| | | |
|---|---|---|
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were well documented in the publication). Methods were fairly well documented in the 1954 publication. Although this was an older study, conducted prior to GLP's, the numbers and type of test animals used and their husbandry conditions followed modern protocol guidance. Test material characterization was adequate. Test material application was well described and adequate. The dose levels tested were high and conducted under complete occlusion, the length of the treatment (90 days) was sufficient for evaluation of subchronic toxicity, and the toxicity endpoints monitored were typical for this type assay and adequately recorded. |
| **Reference** | : | Rowe, V.K., McCollister, D.D., Spencer, H.C., Oyen, F., Hollingsworth, R.L., Drill, V.A., (1954). Toxicology of mono-, di-, and tri-propylene glycol methyl ethers. AMA Arch. Ind. Hyg. Occ. Med. 9(1):509-525. |
| **Other** | : | This study indicates that TPM presents low toxicity upon repeated topical application. |
| **Remark** | : | Application site 7.5 x 7.5 cm, cotton pad covered by impervious saran film (13 x 13 cm) secured with adhesive tape. Hematological parameters normal. Kidney weight significant increased as from 2895 mg/kg. Death from narcoses was often related to pneumonia and emphysema. In the kidneys slight granular degeneration and hydropic changes were seen in some rabbits. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(12)

### 5.5 GENETIC TOXICITY 'IN VITRO'

| | | |
|---|---|---|
| **Type** | : | Ames test |
| **System of testing** | : | Tester strains: TA98, TA100, TA1535, TA1537, TA1538 |
| **Concentration** | : | 0, 0.01, 0.1, 1, 10, or 100 mg per plate (or 0, 10, 100, 1000, 10000, or 100000 µg/plate) |
| **Cycotoxic conc.** | : | Without activation:<br>100 mg/plate (100000 µg/plate) in all strains and at 10 mg/plate (10000 µg/plate) in strains TA98 and TA1538<br><br>With activation:<br>100 mg/plate (100000 µg/plate) in strains TA98, TA100, & TA1535 |
| **Metabolic activation** | : | With and without |
| **Result** | : | Negative |
| **Protocol Guideline** | : | Although not explicitly stated, methods generally followed OECD Guideline 471 "Genetic Toxicology: Salmonella typhimurium Reverse Mutation Assay" |
| **Year of Study** | : | 1982 |
| **GLP** | : | Yes |

**Test substance** : Identity: Dowanol TPM (tripropylene glycol methyl ether). CAS # 25498-49-1
Batch No.: QP-820427-46
Purity: >98.7%
Supplied as: Not specified.
Appearance: Not specified.
Administered as: Various dilutions (see below).
Specific Gravity: 0.965 25°C/25°C (from other reports).
Solubility: Miscible (from other reports).
Storage: Not specified.
Stability: Stable up to 200°C (from other reports).

**Method** : Frozen stock cultures of Salmonella typhimurium (from Bruce Ames, U California, Berkeley) were transferred to nutrient rich broth and incubated at 37°C until reaching a pre-specified optical density at 650 nm (108 to 109 cells/ml). This was done for each of the four tester strains (TA98, TA100, TA1535, & TA1537). To optimize contact between the bacteria and TPM, the pre-incubation modification was employed. This entailed 1) mixing TPM, the S-9 activation system (when appropriate), and the bacteria in a tightly capped culture tube, 2) incubating this mixture for 30 minutes at 30°C, 3) adding supplemental top agar, then 4) pouring the mixture onto plates. Plates were incubated at 37°C for two days during which time histidine independent revertant colonies developed. TPM concentrations of 0, 10, 100, 1000, 10000, or 100000 µg/plate in distilled water were tested.

The activation system consisted of the 9000 x G supernatant of Aroclor 1254-induced rat liver homogenate (Litton Bionetics). Positive control substances were included in the study design to verify the sensitivity of the test organisms. Under conditions without activation, positive control substances included 1) N-methyl-N'-nitro-N-nitrosoguanidine for strains TA100 and TA1535 (10 µg/plate), 2) 2-notrofluorene for strains TA98 and TA1538 (100 µg/plate), and 3) quinacrine mustard dihydrochloride for strain TA1537 (10 µg/plate). Under conditions with activation, positive control substances included 1) 2-anthramine for strains TA100 and TA1535 (10 µg/plate), 2) 2-acetylaminofluorene for strains TA98 and TA1538 (100 µg/plate), and 3) 8-aminoquinoline for strain TA1537 (25 µg/plate).

Colonies were counted with an Arteck Model 880 colony counter (or manually). Results were considered positive if the number of colonies exceeded three times background for any of the strains at any dose and if a dose-response relationship was observed over several doses in any strain, with or without S-9 activation. In addition the positive response had to be reproducible in a second experiment. Results were considered negative if the revertant counts did not exceed background for any tester strain and the negative response was reproducible in a second experiment.

The validity of the assay was assessed by determining that 1) negative and positive control revertant counts fell within historical control counts and 2) toxicity did not interfere with interpretation of results.

**Results** : Toxicity was elicited in all tester strains without activation at 100 mg/plate (100000 µg/plate) and at 10 mg/plate (10000 µg/plate) in strains TA98 and TA1538. With activation, toxicity occurred at the highest concentration only 100 mg/plate (100000 µg/plate) in strains TA98, TA100, & TA1535.

TPM did not cause mutations in the Ames plate assay with or without S-9 metabolic activation. A repeat experiment with the five tester strains confirmed these results.

**Conclusions** : TPM did not cause mutations in the pre-incubation Ames plate assay with or without S-9 metabolic activation.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included a GLP and Quality Assurance statement, signed by the Head of the QA Unit. The cell lines used, test substance concentrations and dose spacing (several dose levels including negative control, with highest showing toxicity), time exposed to the test and control agents, positive control agents used, metabolic activation system, number of replicates, the number of plates scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 471 "Bacterial Reverse Mutation Test". The positive control agents gave the expected results showing that the cell line was responsive to reverse mutation.

**References** : Mendrala, A.L., Schumann, A.M., (1982). Evaluation of Dowanol TPM in the Ames Salmonella/Mammalian in microsomal mutagenicity assay. Confidential report of the Dow Chemical Company, HET K-005534-003. November 22, 1982.

**Other** : These results are consistent with a wide variety of other glycol ethers.

**Source** : Dow Deutschland Inc Stade 5

(18)

**Type** : In Vitro Unscheduled DNA synthesis
**System of testing** : Male CDF Fischer 344 rat hepatocytes. Autoradiography method of evaluating unscheduled DNA synthesis (via increased 3H-thymidine uptake) in primary rat hepatocytes.

**Concentration** : Molar concentrations (moles/liter): 0.0001, 0.000316, 0.001, 0.00316, 0.01, 0.0316, or 0.1 Molar

Mg/liter concentrations: 0, 20.6, 65.2, 206, 652, 2063, 6520, or 20630 mg TPM/liter

**Cycotoxic conc.** : TPM concentrations of 0.001 molar (206 mg/liter) and greater were toxic.
**Metabolic activation** : Inherent in isolated hepatocyte.
**Result** : Negative
**Protocol Guideline** : Although not explicitly stated, methods generally followed OECD Guideline 482 “Genetic Toxicology: DNA Damage and Repair/Unscheduled DNA Synthesis in Mammalian Cells in vitro“ was followed (see “Quality Check“).
**Year of Study** : 1982
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | Dowanol TPM (tripropylene glycol methyl ether). CAS # 25498-49-1 |
| Batch No.: | QP-820427-46 |
| Purity: | >98.7% |
| Supplied as: | Not specified. |
| Appearance: | Not specified. |
| Administered as: | Various dilutions (see below). |
| Specific Gravity: | 0.965 25°C/25°C (from other reports). |
| Solubility: | Miscible (from other reports). |
| Storage: | Not specified. |
| Stability: | Stable up to 200°C (from other reports). |

| | | |
|---|---|---|
| **Method** | : | 5 x 10E5 cells of freshly collected rat hepatocytes were seeded onto 35 mm tissue culture dishes containing a plastic cover slip. Three replicate plates were seeded per concentration level. 2-Acetylaminofluorene (2-AAF) dissolved in DMSO was used as the positive control agent and appropriate negative solvent controls also were employed. Eight concentrations of TPM were evaluated: 0.0, 0.0001, 0.000316, 0.0010, 0.00316, 0.010, 0.0316, or 0.10 moles TPM per liter medium. Cells were exposed to TPM and 3H-thymidine for 18 hours at 37°C. Cells were then washed free of test material and free thymidine, fixed, affixed to slides, and a photosensitive emulsion was applied to detect 3H-thymidine incorporated into nuclear material. Fifteen cells per slide (x 2 slides), for a total of 30 cells were scored for UDS per test concentration using an Artek Counter (Model 880). The average net number of nuclear grain counts (minus background) per dose level were recorded. Also recorded for each dose level were the number of nuclei with 5 or more grain counts. |
| **Results** | : | Toxicity occurred at TPM concentrations of 0.001 molar (206 mg/liter) and higher as evidenced by detachment from cover slips and/or granular appearance.<br><br>Treatment with TPM did not cause unscheduled DNA synthesis. |
| **Conclusions** | : | TPM is not genotoxic in the UDS assay under the conditions of this test. |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1. |
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included a GLP and Quality Assurance statement, signed by the Head of the QA Unit. The cells used, their derivation, test substance concentrations and dose spacing, time exposed to the test and control agents, positive control agents used, number of replicates, the number of cells scored, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 482 “Genetic Toxicology: DNA Damage and Repair/Unscheduled DNA Synthesis in Mammalian Cells in vitro.“ |
| **References** | : | Mendrala, A.L., Schumann, A.M., (1982). Evaluation of Dowanol TPM in the rat hepatocyte unscheduled DNA synthesis assay. Confidential report of the Dow Chemical Company, HET K-005534-004. August 4, 1982. |
| **Other** | : | These results are consistent with other glycol ethers. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

(19)

## 5.6 GENETIC TOXICITY ‘IN VIVO‘

| | | |
|---|---|---|
| **Remark** | : | No data available. |
| **Source** | : | Dow Deutschland Inc Stade 5 |

## 5.7 CARCINOGENITY

Propylene glycol methyl ether (surrogate chemical)

| | | |
|---|---|---|
| **Type** | : | Chronic Toxicity/Carcinogenicity with Rats and Mice (Vapor Inhalation) |
| **Species** | : | Rats and mice |

Fischer 344 Rats

| | |
|---|---|
| Age at dosing: | 6-8. |
| Source: | Charles River (Portage, MI). |
| Acclimation period: | 7 days. |
| Weight at start of study: | 143 g (males); 117 g (females). |
| Assignment to groups: | Randomized by weight. |
| Diet: | Certified Rodent Chow #5002 (Purina Mills, Inc., St Louis, MO). |
| Access to food: | Ad libitum except during inhalation exposures. |
| Access to water: | Ad libitum. |
| Method of Identification: | Implanted microchip. |
| Housing: | 2 per stainless steel wire-mesh cage. |

Environmental Conditions (for non-exposure periods):

| | |
|---|---|
| Temperature: | 22 ± 2°C. |
| Humidity: | 40-60%. |
| Air changes: | 12/hr. |
| Photoperiod: | 12 hr light/12 hr dark. |

B6C3F1 Mice

| | |
|---|---|
| Age at dosing: | 6-8 weeks. |
| Source: | Charles River (Portage, MI). |
| Acclimation period: | 14 days. |
| Weight at start of study: | 24 g (males); 17 g (females). |
| Assignment to groups: | Randomized by weight. |
| Diet: | Certified Rodent Chow #5002 (Purina Mills, Inc., St Louis, MO). |
| Access to food: | Ad libitum except during inhalation exposures. |
| Access to water: | Ad libitum. |
| Method of Identification: | Implanted microchip. |
| Housing: | 2 per stainless steel wire-mesh cage. |

Environmental Conditions (for non-exposure periods):

| | |
|---|---|
| Temperature: | 22 ± 2°C. |
| Humidity: | 40-60%. |
| Air changes: | 12/hr. |
| Photoperiod: | 12 hr light/12 hr dark. |

| | | |
|---|---|---|
| **Sex** | : | Males and females |
| **Strain** | : | Rats: Fischer 344<br>Mice: B6C3F1 |
| **Route of admin.** | : | Vapor Inhalation (whole-body) |
| **Exposure period** | : | Lifetime with interim sacrifices |
| **Frequency of treatment** | : | 6 hr/day, 5 days/week |
| **Post obs. period** | : | None |
| **Exposure levels** | : | 0, 300, 1000, or 3000 ppm (0, 1106, 3686, or 11,058 mg/m3) |
| **Control group** | : | Air-only |
| **NOAEL** | : | Rats: 300 ppm based on altered hepatocellular foci in males.<br>Mice: 1000 ppm based on slight body weight decreases in both sexes. |
| **LOAEL** | : | Rats: 1000 ppm based on altered hepatocellular foci in males.<br>Mice: 3000 ppm based on slight body weight decreases in both sexes. |
| **Protocol Guideline** | : | Meets requirements of US EPA Health Effects Test Guidelines OPPTS 870.4300: “Combined Chronic Toxicity/Carcinogenicity” and OECD Guideline for Testing of Chemicals 453 “Combined Chronic Toxicity/Carcinogenicity Studies” |
| **Year of Study** | : | 1999 (in-life completion) |

**GLP** : Yes
**Test substance** : Propylene glycol methyl ether (PGME) as surrogate for tripropylene glycol methyl ether

| | |
|---|---|
| Identity: | 1-methoxy-2-hydroxypropane or propylene glycol methyl ether. CAS # 107-98-2 |
| Source: | Dow Chemical Company (Midland, MI) |
| Lot No.: | Not specified. |
| Purity: | >97% 1-methoxy-2-propanol: <3% 2-methoxy-1-propanol (> 99.96% both isomers combined). |

**Method:** : In a chronic toxicity/carcinogenicity study, Fischer rats and B6C3F1 mice (50/sex/exposure level) were exposed to vapor concentrations of propylene glycol methyl ether (PGME) at concentrations of 0, 300, 1000, or 3000 ppm 6 hr/day, 5 days/wk for 2 years. Over the course of the study, these subjects were evaluated for clinical signs and body weights. At the end of two years, survivors were subjected to clinical chemistry and hematological examinations, urinalyses, determination of body organ weights, and histopathological examination of a large number of tissues.

In order to evaluate potential toxicity at interim time intervals during the exposure period, additional subjects were exposed to PGME vapors and subjected to routine and specialized toxicological tests at the times shown in the experimental design table below. Subchronic toxicity (at 13 weeks) was evaluated in 5 to 10 mice/sex/exposure level that included clinical chemistry and hematology evaluations, urinalyses, and determination of histopathological changes.

Specialized tests conducted in both mice and rats at the time intervals shown in the table included evaluation of 1) cell proliferation in liver and kidneys, 2) hepatic mixed function oxidase (MFO) activity, and 3) α2μ-globulin nephropathy.

Study Design:

Summary Chronic Study (with mechanistic substudies), Number of Rats (R) and Mice (M) per exposure level (males/ females)

| | | 6 mos | | 12 mos | | 18 mos | | 24 mos | |
|---|---|---|---|---|---|---|---|---|---|
| ppm | Group* | R | M | R | M | R | M | R | M |
| 0 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | D | 5/0 | -- | 5/0 | -- | -- | -- | | |
| 300 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | -- | -- | -- | -- | -- | -- | -- | -- |
| | D | 5/0 | -- | 5/0 | -- | -- | -- | -- | -- |
| 1000 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | -- | -- | -- | -- | -- | -- | -- | -- |
| | D | 5/0 | 5/0 | 5/0 | -- | -- | -- | -- | -- |
| 3000 | A | -- | -- | -- | -- | -- | -- | 50/50 | 50/50 |
| | B | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | C | 5/5 | 5/5 | 5/5 | 5/5 | 10/10 | 10/10 | -- | -- |
| | D | 5/0 | -- | 5/0 | -- | -- | -- | -- | -- |

* Group A: routine study, Group B: cell proliferation in liver and kidneys, Group C: Hepatic MFO induction, Group D: $\alpha_2\mu$-g nephropathy evaluation.

Table reproduced from chronic portion of Spencer et al. (46)

**Methods (continued)** : Atmospheres of PGME were generated by metering the test material into a glass J-tube assembly through which compressed, heated air was channeled. Evaporated PGME in the heated air was diluted with room

temperature air to the desired concentration at a flow rate of 2900 liters per minute into whole-body inhalation chambers. Airflow in the chambers was maintained at a level that provided approximately 12 changes/hour and normal oxygen concentration. PGME concentrations were measured from the breathing zone of the animals inside the chambers two times per hour using a Miran 1A infrared spectrophotometer. Analytical concentrations were within 0.5% of nominal concentrations throughout the study.

**Results** : Some results from additional, shorter-term studies are discussed in Spencer et al. (46), and not in this chronic toxicity/carcinogenicity section.

At 3000 ppm, both mice and rats exhibited decreased activity, incoordination, and transient sedation during the first week of exposure. Subjects recovered 1-2 hours after removal from the chambers. These signs disappeared in both species after the second week but returned in rats 12-18 months into the study. Mortality was unaffected until 18 months when males but not females of both species showed higher mortality rates that were not ascribable to any particular cause. During the course of the study, body weights in both species were decreased at the 3000 ppm exposure level. These decreases were not large but were statistically significant in all but male rats. Decreased body weights also occurred in mice at the 1000 ppm level. Despite changes during the study, body weights were not statistically different from controls at terminal sacrifice.

No clinical chemistry changes were evident in the subchronic mouse evaluation. In the chronic study, no hematology or urinalysis changes were evident in either species. However, several clinical chemistry parameters in male rats exposed to 3000 ppm PGME were altered at the 24 month sacrifice: creatinine increased 78% and urea nitrogen increased 100%. Serum alkaline phosphatase was increases as well and earlier, at 6 through 24 months at the 3000 ppm level, and at 1000 ppm, at 24 months in male rats. Changes in SGOT (AST) and SGPT (ALT), which could be associated with liver injury, were mildly and inconsistently increased in male rats during the first year of exposure at 3000 ppm but not after. No histological changes accompanied these effects. Liver weights were increased at 3000 ppm in both sexes of both species. Kidney weights were increased at this exposure level only in rats.

**Results (continued)** : Dark foci in the liver were grossly observable in male rats exposed to 1000 and 3000 ppm PGME after 24 months. These subjects also exhibited eosinophilic hepatocellular foci and cystic degeneration microscopically that was not reported in female rats or mice of either sex. Male rats and, to a lesser extent, male mice showed increased S-phase DNA synthesis when exposed to 3000 ppm PGME. This effect was not pronounced (reported in a separate, 2-week study), and was evident to a lesser extent in female rats. MFO activity was increased in the livers of rats and mice exposed to 3000 ppm PGME.

In the kidney, histopathology revealed that male rats had α2μ-globulin nephropathy as is typical for this strain. The incidence and severity of this condition was increased in males exposed to 1000 and 3000 ppm PGME compared to controls. No increase in renal epithelial tumors was observed in rats or mice.

**Conclusions** : The major changes seen in this study were 1) decreased body weights in both species, 2) liver effects including increased weight, increased MFO activity and increased cell proliferation primarily in males of both species, 3) kidney effects (in rats) of α2μ-globulin nephropathy typical of the Fischer 344 strain, and 4) slightly increased mortality occurring only after 18 months of exposure in males of both species. Clinical chemistry

parameters reflected and corroborated these effects.

Rats exhibited a NOAEL of 300 ppm based on altered hepatocellular foci in males. Mice showed a NOAEL of 1000 ppm based on slight body weight decreases in both sexes. The LOAELS were correspondingly higher.

No carcinogenic effect as evidenced by any increase in tumor incidence, even in kidneys of the male rats, occurred from exposure to PGME at any concentration in either species.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. The test system used, test substance concentrations and dose spacing (3 dose levels including negative control), time exposed to the test agent, the number of subjects used, the toxicity endpoints monitored, and scoring criteria all followed or exceeded guidance as specified in US EPA Health Effects Test Guidelines OPPTS 870.4300: “Combined Chronic Toxicity/Carcinogenicity” and OECD Guideline for Testing of Chemicals 453 “Combined Chronic Toxicity/Carcinogenicity Studies”.

**References** : Spencer, P.J., Crissman, J.W., Stott, W.T., Corley, R.A., Cieszlak, F.S., Schumann, A.M., Hardisty, J.F. (2002). Propylene glycol monomethyl ether (PGME): Inhalation toxicity and carcinogenicity in Fischer 344 rats and B6C3F1 mice. Accepted for publication in Toxicologic Pathology, January 2002.

**Other** : Since no chronic or carcinogenicity studies have been conducted with TPM, PGME is used in this report as a representative surrogate chemical.

**Source** : Dow Chemical Company

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## 5.8 TOXICITY TO REPRODUCTION

Propylene glycol methyl ether (surrogate chemical)

**Study Type** : 2-Generation Reproduction
**Species/strain** : Mouse/CD-1
**Sex** : Male and Female
**Route of Admin.** : Oral (drinking water)
**Exposure Period** : Before mating, through gestation, and post-birth.
**Treatment Frequency** : Daily
**Post-exposure observ.** : Not reported.
**Premating exposure** : 7 days for males and females.
**Exposure Levels** : 0, 0.5, 1.0, or 2.0 percent in drinking water
**Control Group** : Yes, water
**NOAEL Patenal** : 1%
**NOAEL F1 Offspring** : 1%
**NOAEL F2 Offspring** : 1%
**Protocol Guideline** : Not specified.
**Year of Study** : 1997
**GLP** : Not specified.
**Test Substance** : Details not provided.

| | | |
|---|---|---|
| **Method** | : | Details not provided. The publication describing results was a summary of 90 studies on a variety of chemical substances conducted by the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP). Only a two-page summary of results was provided for PM. The methodology cited was the "RACB protocol" after Morrissey et al., Fundam Appl Toxicol. 13:747-777. |
| **Results** | : | The referenced study is an abstract. There were no changes in body weight or food consumption in any of the first generation exposure groups except for a 4% reduction in pup weight at the highest dose tested. In the second generation exposure groups, reductions in male and female body weight were noted (14% reduction during nursing; 8% reduction in body weight in males during and after mating, and epididymus and prostate weights were 9 and 8% below controls in males, respectively). There was no evidence of reproductive toxicity; mating and fertility indices, and the number and viability of F1 and F2 offspring were not affected. Among F1 offspring, mean pup weight was decreased in the 2% group. F2 offspring from the 2% group displayed reduced pup weight at birth, which continued postnatally during nursing. At sacrifice, female body weights in the 2% group were lower than controls; absolute testis, and relative epididymis and prostate weights were also reduced. F1 female body-weight-adjusted liver weights were increased. |
| **Conclusions** | : | NOAELs occurred at the 1% level. Effects seen did not include reproductive toxicity related to mating, fertility indices, or offspring viability. The effects on parental organ weights (epididymis and prostate) may have been secondary to body weight decreases which paralleled these decreases in magnitude. |
| **Data Quality** | : | The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1. |
| **Quality Check** | : | This study appeared to follow modern guidance. |
| **Reference** | : | Chapin, R.E., Sloane, R.A., (1997). Reproductive assessment by continuous breeding: Evolving Study Design and Summaries of Ninety Studies; Propylene glycol monomethyl ether. Environ Health Perspect. 105 (Suppl 1), 233-234. |
| **Other** | : | N/A |
| **Source** | : | Dow Chemical Co. |

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Propylene glycol methyl ether (surrogate chemical)

| | | |
|---|---|---|
| **Study Type** | : | 2-Generation Reproduction |
| **Species/strain** | : | Rat/Sprague-Dawley |
| **Sex** | : | Male and Female |
| **Route of Admin.** | : | Inhalation (whole-body) |
| **Exposure Period** | : | Before mating, through gestation, and post-birth. |
| **Treatment Frequency** | : | 6 hr/day |
| **Post-exposure observ.** | : | Not reported. |
| **Premating exposure** | : | 5 days/week prior to mating; 7 days/week post mating |
| **Exposure Levels** | : | 0, 300, 1000, or 3000 ppm (0, 1106, 3686, or 11,058 mg/m3) |
| **Control Group** | : | Yes, air-only. |
| **NOAEL Patenal** | : | 300 ppm |
| **NOAEL F1 Offspring** | : | 1000 ppm |
| **NOAEL F2 Offspring** | : | 1000 ppm |
| **Protocol Guideline** | : | OECD 416. |
| **Year of Study** | : | 1997. |
| **GLP** | : | Yes. |

| | | | |
|---|---|---|---|
| **Test Substance** | : | Identity: | 97.99% - 98.07% 1-methoxy-2-hydroxypropane or propylene glycol methyl ether (alpha isomer). CAS # 107-98-2<br>1.86% –1.90% 2-methoxy-1-hydroxypropane or propylene glycol methyl ether (beta isomer). |
| | | Source: | Dow Chemical Company (Midland, MI) |
| | | Lot No.: | MM950417. |
| | | Purity: | See above. Impurities: none detected at >0.1% |

**Method** : In a 2-generation reproductive toxicity study by Carney et al. (1999) exposed Sprague-Dawley rats (30/sex/exposure level) to 0, 300, 1000, or 3000 ppm PM 6 hr/day, 5 days/wk prior to mating and 7 days/week during mating, gestation and lactation, for two generations.

**Results** : At 3000 ppm, toxicity in the P1 and P2 adults was marked, as evidenced by sedation during and after exposure for several weeks, and mean body weights which were as much as 21% lower than controls. This marked parental toxicity was accompanied by lengthened estrous cycles, decreased fertility, decreased ovary weights, reduced pup survival and litter size, slight delays in puberty onset, and histologic changes in the liver and thymus of the F1 and F2 offspring. At 3000 ppm, there was an increase in histologic ovarian atrophy in P1 and P2 females, and at 1000 ppm, there was a decrease in pre-mating body weight in the P1 and P2 females. No treatment-related differences in sperm counts or motility were observed among the P1 or P2 males.

**Conclusions** : The NOAEL for paternal toxicity is 300 ppm and for offspring toxicity is 1000 ppm. Effects appear secondary to parental weight loss.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : The protocol followed OECD 416.

**Reference** : Liberacki AB et al. (1997) Propylene glycol monomethyl ether: Two-generation inhalation reproduction study in Sprague-Dawley rats. Dow Chemical Company. Unpublished report

Carney, E.W., Crissman, J.W., Liberacki, A.B., Clements, C.M., Breslin, W.J., (1999). Assessment of adult and neonatal reproductive parameters in Sprague-Dawley rats exposed to propylene glycol monomethyl ether vapors for two generations. Toxicol. Sci. 50:249-258.

**Other** : The nature of the reproductive/neonatal effects and their close individual correlation with decreased paternal body weights suggest that these effects were secondary to general toxicity and/or nutritional stress. No such effects were observed at 1000 ppm, a concentration that caused less marked, but significant, body weights effects without sedation.

**Source** : Dow Chemical Company.

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## 5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

**Type** : Aerosol Inhalation Teratology with Rat
**Species** : Rat

**Sex** : Female
**Strain** : Sprague-Dawley
**Route of admin.** : Inhalation
**Exposure period** : Day 6 through 15 of gestation
**Frequency of treatment** : Daily
**Duration of test** : 20 days
**Doses** : 0, 0.1, 0.3, 1.0 mg/liter (0, 100, 300, 1000 mg/m3) (0, 27, 81, 271 ppm)
**Control group** : Yes, air control
**NOAEL Maternalt.** : = 0.3. mg/liter
**NOAEL Teratogen** : > 1. mg/liter
**Protocol Guideline** : Although not specifically referenced in the report, this study satisfies the criteria specified in OECD Guideline 414 "Teratogenicity"
**Year of Study** : 1985
**GLP** : Yes
**Test substance** :

| | |
|---|---|
| Identity: | DOWANOL TPM, Tripropylene glycol methyl ether (TPM). CAS # 25498-49-1 or 20324-33-8 |
| Appearance: | Translucent liquid. |
| Batch No.: | 18-8876. |
| Shipping container: | 45 gallon drum containing 125 kg TPM. |
| Source: | Dow Chemical Canada via Van Waters Rodgers. |
| Expiration Date: | Not specified. |
| Purity: | 98.5% TPM isomers. |
| Specific Gravity: | 0.965 |
| Solubility in water: | Miscible (from other reports). |
| Stability: | Stable up to 200°C (from other reports). |
| Boiling point: | 242.8°C at 760 mmHg (from other reports). |
| Vapor pressure: | 0.017 mmHg at 25°C (from other reports). |
| Storage: | Room temperature in shipping container. |

**Method** : Mated female Sprague-Dawley rats (25/group) were exposed to aerosol atmospheres of tripropylene glycol methyl ether (TPM) at concentrations of 0, 0.1, 0.3, or 1.0 mg TPM per liter of air, 6 hours per day on gestation days 6 through 15. Rats were exposed in 600-liter whole-body inhalation chambers (glass and steel “Rochester” type). The flow rate was 60 liters/min resulting in 6 air changes per hour and test subjects comprised less than 5% of the total chamber volume. During exposures, rats were individually housed in wire mesh cages (7” x 4” x 3”) and did not have access to food or water during the 6-hour exposure period. The experimental design is shown below.

| Group | Nominal (Actual) Exposure (mg TPM/liter) | No. Mated Females Treated | No. Pregnant Females Treated | Treatment Period (days) |
|---|---|---|---|---|
| Group 1 | 0 (0) | 25 | 22 | 6 thru 15 gest. |
| Group 2 | 0.1 (0.1) | 25 | 20 | 6 thru 15 gest. |
| Group 3 | 0.3 (0.29) | 25 | 21 | 6 thru 15 gest. |
| Group 4 | 1.0 (1.02) | 25 | 23 | 6 thru 16 gest. |

**Method continued** : At least once each day, rats were observed for clinical signs of toxicity, abortion, and delivery over the exposure and post-exposure periods. Individual body weights were recorded on days 0, 6, 9, 12, 15, 18, 20 of gestation. At sacrifice (day 20 of pregnancy), all animals were subjected to necropsy and examined for gross abnormalities. The ovaries, uterus, kidneys, and livers were removed and weighed. The number of corpora lutea was counted in each ovary. Early and late resorptions and live and dead fetuses were counted. Implantation sites in both uterine horns were counted and the empty uterus weighed. Fetuses were removed from the uterus, weighed, lengths recorded, and examined for gender and external and internal gross abnormalities. Heads were removed from 2/3 of the fetuses and examined after the method of Wilson. The bodies of these fetuses, as well as the remaining 1/3, were stained with Alizarin Red S and skeletons were examined. Percentages of pre- and post-implantation loss were calculated, as was the degree of ossification for each fetus. Soft tissue and skeletal anomalies or abnormalities were recorded. Findings were categorized into major malformation, minor anomalies, and common variants.

**Results** : Nominal concentrations were calculated daily. Aerosol atmospheres of TPM were generated using a Thermo Systems Incorporated (TSI) 6-jet atomizer. Actual concentrations were measured gravimetrically using an open-face filter oriented vertically at the animal breathing zone. Aerosol particle size was analyzed daily for each TPM treatment chamber using an Anderson 1ACFM Ambient Particle Size Sampler. Chamber temperature and relative humidity were measured on an hourly basis during exposures; airflow rates were monitored continuously and recorded hourly. Chamber concentrations of TPM were stable at all exposure levels. Nominal concentrations were 0, 0.39, 0.62, and 2.18 mg/liter. The average mass median particle diameter (MMAD) ranged from 2.47 to 3.75 micrometers for the three TPM exposure groups; the geometric standard deviation ranged from 0.12 to 0.66. These particle size parameters indicate that the aerosol was deep-lung respirable.

No maternal deaths occurred in any of the groups. Fifteen of 25 dams in the high exposure group exhibited red staining around the muzzle, compared to 0/25, 1/25, and 0/25 in the control, low, and mid-exposure groups, respectively. No other clinical signs of toxicity were noted. No effect upon body or organ weights was noted in the dams. Pregnancy and abortion rates were comparable among all groups. The pregnancy rate was comparable among groups.

No effects were noted from TPM exposure on the number of live fetuses, fetal weights, sex ratio, or early or late resorptions. No fetal variation or abnormalities were found to occur at a greater incidence in TPM-treated subjects than in air-only controls.

**Conclusions** : TPM did not cause embryo-, fetal, or developmental toxicity in fetuses at any exposure level. Maternal toxicity was evident in the high exposure level only, based on an increased incidence of red staining of the muzzle compared to controls. The NOAEL for maternal toxicity is 0.29 mg/liter and the LOAEL is 1.02 mg/liter, based on stained muzzles. The NOAEL for developmental effects is 1.02 mg/liter and the LOAEL is > 1.02 mg/liter.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

| | | |
|---|---|---|
| **Quality Check** | : | This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report contained signed GLP and Quality Assurance statements. The report adequately described the various study parameters, satisfying OECD Protocol 414: "Teratogenicity" (12 May 1981), including the numbers and type of test animals used and their husbandry conditions. Test material characterization was adequate. The amount of test material to which test subjects were exposed complied with guidance, the length of the treatment period (organogenesis) was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded. |
| **References** | : | Breckenridge, C., Collins, C., Robinson, K., Lulham, G., Hamelin, N., Osborne, B., Procter, B.G., (1985). A teratological study of inhaled Dowanol TPM in the albino rat. Bio-Research Laboratories Ltd. Confidential report of the Dow Chemical Company, August 2, 1985. |
| **Other** | : | The lack of developmental effects with TPM is consistent with other propylene glycol ethers. |
| **Source** | : | Dow Chemical Canada |

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## 5.10 OTHER RELEVANT INFORMATION

| | | |
|---|---|---|
| **Type** | : | Biochemical or cellular interactions |
| **Remark** | : | In a 90-day oral toxicity study in rats with the cholinesterase inhibitor fenitrothion, the cosolvent, TPM, given orally daily at a maximum concentration of 0.3 mg/kg/day had no influence on the activity of the enzyme cholinesterase.<br><br>Ref.: H.D. Durham, A.M. Comeau, P.H. Cameron and D.J. Ecobichon Subacute toxicity in rats of orally administered fenitrothion alone and in a selected formulation. Toxicology and Applied Pharmacology 62, 455-464, 1982 |
| **Source** | : | Dow Deutschland Inc Stade 5 |

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| | | |
|---|---|---|
| **Type** | : | Other: Disposition and Metabolism |
| **Species** | : | Rat |
| **Strain** | : | Fischer-344 |
| **Sex** | : | Males (3 per dose level) |
| **Route of admin.** | : | Oral (via gavage) |
| **Frequency of treatment** | : | Single dose |
| **Duration of test** | : | 48 hours |
| **Doses** | : | 1 or 4 mmol TPM/kg body weight (approximately 206 or 825 mg/kg) |
| **Control group** | : | None |
| **Protocol guideline** | : | None specified although complies with OECD 417 "Toxicokinetics" and OPPTS 870.7485 "Metabolism and Pharmacokinetics" |
| **Year of Study** | : | 1986 |

**Test substance** : The specific activity of original [14C]-TPM was 10.2 mCi/mmole, with a radiochemical purity of 98.7% (Wizard Laboratories, Davis, CA). Specific activity of dosing solutions (1 mmole/kg = 41.3 µCi/mmole; 4 mmole/kg = 11.1 µCi/mmole). Location of radiolabel(s) was not reported.

| | |
|---|---|
| Identity: | Tripropylene glycol methyl ether (TPM). CAS # 25498-49-1 or 20324-33-8 |
| Appearance: | Clear, colorless liquid. |
| Batch No.: | Not specified. |
| Source: | Louisiana Dow Division (Tank #56). |
| Expiration Date: | None specified. |
| Purity: | 99.4% TPM isomers (non-labeled). |
| Specific Gravity: | 0.961 kg/liter. |
| Solubility in water: | Miscible (from other reports). |
| Stability: | Stable up to 200°C (from other reports). |
| Boiling point: | 242.8°C at 760 mmHg. |
| Vapor pressure: | 0.017 mmHg at 25°C. |
| Storage: | Ambient temperature in dark. |

**Method** : After an initial pilot study to select doses, 3 male rats were administered oral doses via gavage of 1 or 4 mmole of C14-radiolabelled TPM/kg body weight. These doses correspond to approximately 206 or 825 mg TPM/kg body weight. Rats were housed in metabolism cages where urine, feces, and expired air were collected in varying time increments over a total period of 48 hours and monitored for radioactivity. Urine was collected in 12 hour increments, feces in 24 hour increments, and expired air was collected at 4 hour intervals for the first 12 hours and at 12 hour intervals thereafter. In addition, at the end of 48 hours, brain, muscle, peri-renal fat, skin, kidneys, liver and the remaining carcass were analyzed for total radioactivity. Urine samples were fractionated using liquid chromatography and fractions containing radioactivity were analyzed using GC/MS to identify the structures of the metabolites.

**Results** : After 48 hrs, 75% of the dose was excreted in urine and 16% as C14-CO2 at 1 mmol/kg BW; while the high dose rats excreted 69% in urine and 16% as C14-CO2. Fecal excretion accounted for approximately 5% of the dose at both dose levels. Less than 1% of the dose was eliminated as expired volatile organics at both dose levels. The carcass retained between 1 and 2% of either dose. The distribution of C14-activity in tissues was similar between dose groups with liver, kidneys, and skin containing the highest percentage after 48 hours (all less than 0.5% of the total dose). Metabolite profiles of urinary C14-activity were qualitatively and, to some extent, quantitatively similar between dose levels. After 48 hours, radioactivity in all measured tissues was less than 1% of the original dose (for either the low or high dose). These tissues included blood, bone carcass, skin, liver, kidney, brain, testes, blood, and fat. An exception was the carcass, which contained 1.18% of the dose after 48 hours in the 1 m mmole/kg dose group.

The following urinary metabolites were tentatively identified within Liquid Chromatography (LC) peaks using GC/MS techniques:

LC Peak A (11-18%) - sulfate conjugate of TPM
LC Peak B (12-25%) – 4 isomers of dipropylene glycol methyl ether and 6 isomers of TPM
LC Peak C (1.3-3.8%) - propylene glycol
LC Peak D (54-56%) – 3 isomers (50%) of dipropylene glycol and 2 isomers (50%) of 2-(1-hydroxy-2-propoxy) propanoic acid, described as "isomers of a cyclic dehydration product".
LC Peak E (6-12%) – Isomers of tripropylene glycol

**Conclusions** : TPM was rapidly distributed and quickly metabolized and eliminated from the test subjects. Greater than 94% was eliminated within 48 hours. TPM shows similar absorption, distribution, metabolism and elimination patterns as other propylene glycol ethers.

**Data Quality** : The data quality from this study is considered acceptable. The report included documentation for methods and results. This study reaches Klimisch level 1.

**Quality Check** : This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the report). The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although not explicitly identified in the report, this study followed guidance provided in OECD Protocol 417: "Toxicokinetics." The numbers and type of test animals used and their husbandry conditions were as recommended in the guidance. Test material characterization was adequate. The amount of test material administered complied with guidance, the length of the treatment period was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

**References** : Cahoun, L.L., Kastl, P.E., Hannah, M.A., Putzig, C.L., Miller, R.R., Schumann, A.M., (1986). Metabolism and disposition of tripropylene glycol monomethylether (TPGME) in male rats. Confidential Report of the Dow Chemical Company, July 1986.

Miller, R.R., (1987). Metabolism and disposition of glycol ethers. Drug Metab. Reviews 18(1):1-22.

**Other** : The propionic acid isomers described as “cyclic dehydration products” in fraction D do not appear to be of the linear alkoxy-type that has caused toxicity seen with the ethylene glycol ethers or the “beta” isomers of the propylene series.

**Source** : Dow Chemical Company

(22, 23)

**Type** : Other
**Remark** : In dogs the substance was a cardiac (auricular arrhythmia) and central nervous system depressant at near lethal doses. In intact dogs following intravenous administration objective responses follows almost immediately: aimless wandering occurs and shortly thereafter the animal becomes ataxic. Eventually there is complete loss of positional and righting reflexes followed by marked depression with respiration becoming slow and deep. The effects are clearly dose dependent. With higher doses anesthesia follows.

F.E. Shideman and L. Procita The pharmacology of the mono methyl ethers of mono-, di-, and tripropylene glycol in the dog with observations on the auricular fibrillation produced by these compounds. J. Pharmacol. Exp. Therap. 102(2), 79-87, 1951

**Source** : Dow Deutschland Inc Stade 5

(14)

## 5.11 EXPERIENCE WITH HUMAN EXPOSURE

**Remark** : In 1983, a TSCA Section 8(e) report was filed by a company in Arizona. A woman was submitted to a hospital complaining of disorientation in coordination and other unspecified nervous system effects. She had been working 6-8 hours the day before with a floor-care product containing 2.432% of TPM. The other ingredients with the exception of water and ammonia have low or no volatility. It is not known whether the woman in question was wearing gloves. The reporting officer, being aware of the anesthetic effect in rats and in rabbits at levels orally or dermally exceeding 10 ml/kg made therefore the association to TPM as a potential cause of the complaint.

Ref.: 8EHQ-0592-4474 S INIT

**Source** : Dow Deutschland Inc Stade 5

(23)

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