FOREWORD INTRODUCTION

PROPYLENE GLYCOL PHENYL ETHER

CAS N°:

770-35-4 (major isomer – Secondary Alcohol)
4169-04-4 (minor isomer – Primary Alcohol)
41593-38-8 (commercial mixed isomer product)

SIDS Initial Assessment Report

For

SIAM 18

Paris, France, 20-23 April 2004

1. Chemical Name:	Propylene Glycol Phenyl Ether
2. CAS Number:	770-35-4 (major isomer – Secondary Alcohol) 4169-04-4 (minor isomer – Primary Alcohol) 41593-38-8 (commercial mixed isomer product)
3. Sponsor Country:	United States U.S. Environmental Protection Agency Mr. Oscar Hernandez, Director Risk Assessment Division (7403M) 1200 Pennsylvania Ave., NW Washington, DC 20460 Phone: 202-564-7641
4. Shared Partnership with:	Industry Consortia
5. Roles/Responsibilities of the Partners:	Environmental and human health testing of propylene glycol ether
• Name of industry sponsor /consortium	Dr. Susan A. Lewis American Chemistry Council 1300 Wilson Boulevard Arlington, VA 22209
• Process used	Regulatory requirements
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme?	Initiative of the industry consortium and the U.S. Environmental Protection Agency.
7. Review Process Prior to the SIAM:	Data gathering, summarization and review by industry consortia and the U.S. Environmental Protection Agency.
8. Quality check process:	The manufacturers of propylene glycol phenyl ether (PPh) keep up to date with the published literature on PPh and periodically conduct literature searches for all important toxicological and environmental endpoints and adds any new studies to its files. All such published studies were provided for compiling the SIDS dossier, as well as pertinent unpublished data from the manufacturer. On completing the literature search and data collection, important and significant studies were identified for all

endpoints. These studies were reviewed and summarized following current guidelines for robust summaries. Reliability ratings were assigned following the Klimisch rating system. Studies assigned ratings of 1 or 2 were considered to be acceptable. The key studies were identified based on completeness, protocol and GLP use and other quality factors. These were flagged as critical studies. The summaries were compiled using the IUCLID program. EPA consultants reviewed the documents and robust study summaries prepared by the industry consortium for adherence to OECD and SIDS Guidance and to determine whether there were any data gaps.

9. Date of Submission: January 2004

10. Comments: In the U.S., PPh has been evaluated under the Premanufacture Notification procedures of the Toxic Substances Control Act (Section 5), in accordance with TSCA Testing Requirements (Section 4). Under this program, PPh was subjected to extensive testing. In addition, PPh has been tested to fulfill the requirements of other governmental regulatory bodies. Consequently, a comprehensive body of knowledge has been developed for both environmental and human health effects. Analysis of this extensive database indicates that PPh is of low priority for further testing.

SIDS INITIAL ASSESSMENT PROFILE

CAS No(s).[1]	770-35-4 (major isomer – Secondary Alcohol) 4169-04-4 (minor isomer – Primary Alcohol) 41593-38-8 (commercial mixed isomer product)
Chemical Name	Propylene Glycol Phenyl Ether (PPh)
Structural Formula	OH | CH_3-CH-CH-O-(C_6H_5) (major isomer) (O-C_6H_5) | CH_3-CH-CH_2- OH (minor isomer)

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Propylene glycol phenyl ether (PPh) is rapidly absorbed, distributed throughout the body, metabolized, and eliminated after oral administration. The major routes of elimination are via the urine and feces. The types of metabolites are parent ether conjugates, hydrolyzed propylene glycol, and hydrolyzed alcohol (phenol) conjugates.

Propylene glycol phenyl ether exhibits low acute toxicity by the oral, and inhalation routes. The oral LD50 in rats exceeds 2000 mg/kg (1 death from 10 subjects occurred at this highest dose tested); and the 4-hour inhalation LC50 in rats was greater than 5400 mg/m^3 (no deaths). PPh was severely irritating to the eyes but non-irritating to skin in rabbits tested and evaluated according to the Draize criteria. PPh did not cause skin sensitization when tested with guinea pigs by the Buehler method.

In repeated dose-studies ranging in duration from 4 to 26 weeks, few adverse effects were found even at high exposure levels and effects that did occur were mild in nature. In one study, PPh was administered to two generations of rats (25/sex/group) in drinking water for 26 weeks at concentrations of 0, 100, 1000, or 5000 ppm (equivalent to doses of 0, 11.3, 113, or 478 mg/kg-d) (this was a 2-generation reproductive toxicity study also discussed below). Effects were seen only at the highest exposure concentration that manifested as reduced body weights and corresponding reduced food and water consumption. No clinical signs were evident during the course of exposure and no gross or histopathological lesions were seen at autopsy. The NOAEL for this drinking water study with rats was 1000 ppm (113 mg/kg-d) and the LOAEL was 5000 ppm (478 mg/kg-day), based on body weight changes. In another repeated dose test, this time by the dermal route of exposure, rabbits (5/sex/group) received daily applications of PPh 5 days/week for four weeks (19 total applications). A slight increase in platelet counts was found that reached statistical significance in males at the high dose level. Platelet counts in females were unaltered at any dose level. No other parameters were affected other than a local thickening of the skin at the site of application. The increased platelet count in males was considered spurious since no other hematological or clinical chemistry (or any other) parameters corroborated this finding. Thus, the systemic toxicity NOAEL for PPh by the dermal route of exposure in rabbits was the highest dose tested of 1000 mg/kg-day.

In the two-generation reproductive toxicity study discussed above (rats 25 pairs/generation) treated orally with 0, 100, 1000, or 5000 ppm PPh in drinking water, no adverse effects were found on fertility, reproductive performance, or on reproductive tissues in parental generations. In offspring, reduced pup weights as well as decreased relative spleen weights and increased relative brain weights and retarded sexual maturation were found at the high dose (but with no effect on reproductive parameters in the F1 generation once they reached sexual

maturity). In a developmental toxicity study, PPh was administered daily by gavage to pregnant rabbits (15 per group) over the period of organogenesis at doses of 0, 60, 180, or 540 mg/kg-day. In the dams, the high dose of PPh caused decreased food consumption, decreased body weights, and prostration. No maternal toxicity was seen at the lower dose levels. .In fetuses, a statistical increase in the rate of total soft tissue variations was detected (septal heart defect) in the medium and high dose groups. It is possible that this may be considered coincidental because of the low incidence (1 fetus in each group), the common spontaneous occurrence of the variation in this strain of rabbit, and because statistical significance was conferred only due to the unusually low level in the concurrent control group (2.2% fetal incidence and 7.1% litter incidence versus 7.7% and 30.2%, respectively, in the laboratory historical controls). With regard to skeletal variations (predominantly an increase in 13^{th} ribs when combined with other skeletal variations), a statistical increase was detected in the high dose group. This increase in skeletal variations was considered treatment related because the incidence (approximately 10%) exceeded historical control levels. The NOAEL for maternal toxicity was 180 mg/kg-day and the LOAEL was 540 mg/kg-day, based on reduced body weight and clinical signs. The NOAEL for fetal toxicity was 180 mg/kg-day and the LOAEL was 540 mg/kg-day based on the increased incidence of 13^{th} rib buds. PPh exhibits toxicity in the developing rabbit conceptus at high doses that produce toxicity in the dam.

PPh tested negative in the Ames Salmonella assay and also was negative in an *in vitro* chromosome aberration study with human lymphocytes. In an *in vivo* mouse bone marrow micronucleus test, mice received two consecutive daily doses of 0, 500, 1000, or 2000 mg/kg-day. The high dose animals had a slightly increased incidence of micronuclei that reached statistical significance in a first assay but did not in a second (although a trend was evident). The study authors attributed this finding to hypothermia, which occurred only in the high dose animals and which has been shown with other chemicals to cause increased micronuclei as a secondary effect from hypothermia. It seems reasonable to conclude that the negative *in vitro* results and the equivocal *in vivo* results at a very high dose level that may be due to physiological stress indicate that propylene glycol phenyl ether does not pose a genotoxicity hazard at doses that would likely be encountered in the environment. PPh has not been tested for carcinogenicity.

Environment

The melting point of PPh is 11.4 ºC and the boiling point is 253 ºC. Vapor pressure is 0.029 hPa at 25 ºC and the log octanol-water partition coefficient is 1.5. Finally, water solubility is 10,000 mg/L.

If released into the environment, PPh will distribute primarily to water and soil. The log octanol-water partition coefficient (log K_{ow}) for PPh is 1.50 and the BCF is 0.776 (log BCF = -0.110). Both parameters indicate that PPh will not tend to bioaccumulate up food chains. The Henry's Law Constant, which indicates propensity to partition from water to air, is low for PPh: 4.36×10^{-7} atm-m^3/mole. Fugacity modeling (Mackay Level III) indicates that PPh is likely to partition roughly equally and predominantly into the soil and water with small to negligible amounts distributing to other environmental compartments (air, sediment, and aquatic biota).

PPh is unlikely to persist in the environment. Once in air, the half-life of PPh due to direct reactions with photochemically generated hydroxyl radicals is estimated to be 3.45 hours. In water, PPh is readily biodegraded under aerobic conditions. In a biodegradation study that measured oxygen depletion, CO_2 production, and organic carbon disappearance (OECD 301F), PPh was "readily biodegradable" by all criteria. In soil, biodegradation also is rapid. When incubated with three soil types for 25 days, PPh degraded rapidly under aerobic conditions and very little under anaerobic conditions. Under aerobic conditions, time to 50% removal usually ranged from 1 to 7 days.

Acute aquatic testing indicates a low order of toxicity for PPh. The acute aquatic toxicity in the Golden Orfe with the 96-hour LC50 was between 215 and 464 mg/L; in the Fathead minnow, the 96-hour LC50 was 280 mg/L (263 mg/L < 95%CL > 297 mg/L). The 48-hour LC50 in daphnia was 370 mg/L (321 mg/L < 95%CL > 431 mg/L). In algae, the 72-hr EC50 was 74.5 mg/L (biomass) and > 100 mg/L (growth rate).

Exposure

In 1999, approximately 16 million pounds (7.3 thousand tonnes) of propylene glycol phenyl ether was produced worldwide and this is projected to increase to 18 million pounds (8.2 thousand tonnes) in 2004. Modern production methods result in major isomer content in excess of 85% and minor isomer content less than 15%.

A major use of PPh is as a solvent that facilitates the mixing of aqueous and organic constituents in paints, coatings, and films. PPh is used as a latex coalescent in water-based architectural and industrial coatings and adhesives, a carrier solvent for textile dyes, a solvent for inks in ball point and felt tip pens, stamp pads, and

textile printing pastes, and paint remover. Due to its antibacterial properties, PPh also is used in cosmetics and soaps.

During manufacture and transport, occupational exposure potential is low due to the enclosed systems employed. For either occupational or consumer exposure, the most significant likelihood of exposure is by dermal contact or inhalation during application of paints and coatings, or application of materials for which PPh is a solvent or carrier. No occupational or other exposure limits have been established for PPh.

Individuals applying paint or other PPh-containing coatings may be exposed to this propylene glycol ether. 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.

Propylene glycol phenyl ether typically enters the environment through slow escape and evaporation from the solvent or coating system 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.

General population exposure also is possible through inhalation of ambient air containing low concentrations of PPh that may be released from industrial processes or through evaporation of coatings or other products containing it.

RECOMMENDATION

Environment: This chemical is currently of low priority for further work.

Human Health: This chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Environment:
This chemical is currently of low priority for further work because of its low hazard profile.

Human Health:
The chemical possesses properties indicating a hazard for human health (eye irritation – which is reversible - and developmental toxicity at high doses associated with maternal toxicity). Based on data presented by the Sponsor country, exposure is controlled in the occupational setting. Due the wide dispersive use, member countries are invited to perform an exposure assessment and if then indicated, a risk assessment, especially for consumers. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Note: PPh may be evaluated further under the EU Biocides Directive. This will include exposure assessment on operators (occupational) and by-standers (consumers).

[1]Note: the commercial product is commonly referred to as CAS# 770-35-4. CAS# 41593-38-8, which is uncommon, also can refer to the commercial mixed isomer product. However, CAS# 41593-38-8 is rarely used, especially in Europe because it is not listed on EINECS. The commercial product is listed under both CAS #s because modern production methods result in the major isomer content being in excess of 85% and the minor isomer content less than 15%. The major isomer is thermodynamically favored during synthesis and consists of a secondary alcohol configuration.

SIDS Initial Assessment Report

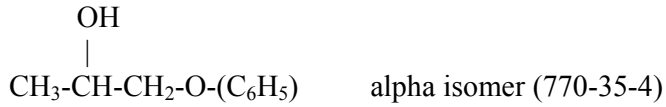
1 IDENTITY

1.1 Identification of the Substance

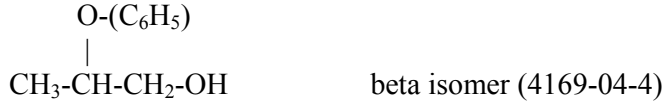
CAS Number:	770-35-4 (alpha isomer) 4169-04-4 (beta isomer) 41593-38-8 (mixture)
IUPAC Name:	1-phenoxy-propan-2-ol
Molecular Formula:	$C_9H_{12}O_2$
Structural Formula:	$(C_6H_5)OCH_2CH(OH)CH_3$
Molecular Weight:	152.19
Synonyms:	Propylene Glycol Phenyl Ether 1-Phenoxy-2-propanol; 1-Phenoxypropan-2-ol; Phenoxyisopropanol; Propylene phenoxetol; 2-Propanol, 1-phenoxy-

Propylene glycol phenyl ether has the following structure.

Molecular structures:



alpha isomer (770-35-4)



beta isomer (4169-04-4)

Note that all monopropylene glycol ethers may exist in two isomeric forms, alpha and beta. The alpha form, which is thermodynamically favored during synthesis, accounts for the majority of the glycol ether mass and is a secondary alcohol. The beta form is an impurity and is a primary alcohol. The two isomeric forms are shown above.

1.2 Purity/Impurities/Additives

Propylene glycol phenyl ether has a minimum purity of 93%. At least 93% of commercial propylene glycol phenyl ether is comprised of a mixture of 1-phenoxy-propan-2-ol and 2-phenoxy-propan-1-ol, with the former isomer as the major constituent. The individual isomers are not separated nor produced as individual chemicals. The remaining 7% consists of up to 7% di-PPh, 0.1% phenol and 0.35% water. Of the 93% that is a mixture of the two isomers, 1-phenoxy-propan-2-ol (CAS No. 770-35-4) constitutes > 85% of the mixture (is the thermodynamically favored isomer) and 2-phenoxy-propan-1-ol (CAS No. 4169-04-4) constitutes < 15%. All testing was conducted on this commercial mixture.

1.3 Physico-Chemical properties

Table 1 Summary of Physico-Chemical Properties

Property	Value	Reference
Physical state	Clear liquid at room temperature	Dow Chemical Company (2002)
Melting point	11.4°C	Boatman (2001), Staples and Davis (2002), Dill and Davis (1997)
Boiling point	242.7, 253°C	ECETOC (1995), Boatman (2001), Dow Chemical Company (2002)
Relative density	1.059	Dow Chemical Company (2002),, Canadian Centre for Occupational Health and Safety (2001)
Vapor pressure	0.029 hPa	Staples and Davis (2002), Boatman (2001)
Water solubility	10,000 mg/liter	ECETOC(1995), Dill and Davis (1997), Dow Chemical Company (2002)
Partition coefficient n-octanol/water (log value)	1.52, 1.50	EPIWIN KowWin (v1.67), Staples and Davis (2002)
Soil/Water or Soil/Sediment Partition Coefficient (Koc)	19	Calculated using EPIWIN/ PCKOC (v1.66)
Henry's law constant	2.05×10^{-8} atm-m^3/mole (Bond estimate)	Calculated using EPIWIN/HENRY (v3.10)

2 GENERAL INFORMATION ON EXPOSURE

The most likely routes of human exposure to PPh 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 liquid products containing PPh are otherwise used. 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 limit exposure potential. Processors use enclosed equipment for the formulation of products containing PPh. Worker exposure is more likely to occur while applying coating products containing PPh to various surfaces. Dermal contact and inhalation exposure are expected exposure routes. Individuals applying paint or other PGE-containing coatings may be exposed to PPh. Dermal contact through minor spills or accidental contact is a source of exposure, as is inhalation from aerosol or vapor generated during application or usage. General population exposure also is possible through inhalation of ambient air containing low concentrations of PPh that may be released from industrial processes or through evaporation of coatings or other products containing them. Ingestion of drinking water containing PPh as a contaminant also is possible.

2.1 Production Volumes and Use Pattern

According to the Chemical Economics Handbook (SRI International, 2000), in 1999, total worldwide production of all of the various propylene glycol ethers was approximately 810 million pounds (368.2 thousand tonnes). The United States accounted for 285 million pounds (129.5 thousand tonnes) of these, Europe 472 million pounds (214.5 thousand tonnes), and Japan 53 million pounds (24 thousand tonnes). In the U.S., a production volume of 340 million pounds

(154.5 thousand tonnes) of all propylene glycol ethers was estimated for 2004 (SRI International, 2000).

PPh is just one of a series of commercial propylene glycol ethers. In 1999, 16 million pounds (7.3 thousand tonnes) of PPh was manufactured in the U.S. by a single producer. Estimated 2004 production in the U.S. for PPh was 18 million pounds (8.2 thousand tonnes) (SRI International, 2000).

Exposure limits have not been established for PPh. Protective gloves will minimize dermal absorption when prolonged skin exposure is anticipated. Proper ventilation or wearing of respiratory protection will minimize inhalation exposures.

The primary use of propylene glycol phenyl ether is as a solvent that facilitates the mixing of aqueous and organic constituents in paints, coatings, and films. PPh is used as a latex coalescent in water-based architectural and industrial coatings and adhesives, a carrier solvent for textile dyes, a solvent for inks in ball point and felt tip pens, stamp pads, and textile printing pastes, and a paint remover. Due to its antibacterial properties, PPh also is used in cosmetics and soaps. The most significant exposure potential is by inhalation and dermal contact during application of paints and coatings, or application of materials for which PPh is a carrier. The types of products in which PPh is used (and their percents of production), and the approximate concentrations of PPh used in products are shown in Table 2 for the year 1993 and are based on unpublished data gathered by the American Chemistry Council and the Consumer Product Safety Commission. Current uses are the same as was the case in 1993 (SRI International, 2000).

Table 2: 1993 PPh Data on Types of Commercial Products, Approximate Percent of Production and Weight Fractions in Products

Types of Commercial End Products	Percent of Production (%)	Approx. Weight Fraction in Product Types
Surface Coatings	75	2 – 10%
Adhesives	5	2 – 10%
Inks	20	2 – 10%
Cosmetics, soaps	4	0.1 – 1%

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

During manufacture emissions to the atmosphere or surface water are minimized by the predominately enclosed nature of the process and equipment. A similar situation exists when processing PPh into product formulations, such as coatings. Manufacturing or processing wastes are typically incinerated or submitted to in-plant wastewater treatment systems. Emissions are much more likely during the end use application of products containing PPh, such as coatings. Propylene glycol phenyl ether typically enters the environment through slow escape and evaporation from the solvent or coating system used. Spills of products containing PPh can also occur during application of coatings, resulting in releases to water or soil. Typically such spills would be a few drops to under a liter of liquid. In PPh's reported use as a solvent carrier for textile dyes, release to wastewater can occur. Also, any PPh present in dyes or soaps or coatings used by the consumer is likely to be released to municipal waste water systems.

Table 3 shows physicochemical characteristics predictive of the environmental fate of PPh. Data for Henry's Law Constant, the photodegradation rate constant, and environmental transport for PPh are available in the manufacturers' technical reports or the IUCLID dossier for PPh. The values in Table 3 below were estimated (calculated) using EPIWIN modeling, including Mackay Level III fugacity modeling or similar approaches. In running the EPIWIN fugacity model Level III program, the following inputs were used: CAS No. 770-35-4, melting point 11.4 degrees C, boiling point 242.7 degrees C, vapor pressure 0.022 mm Hg and water solubility 10,000 mg/l. Default emission rates of 1000 kg/hr to air, water and soil were used.

Table 3. Environmental Fate Parameters for Propylene Glycol Phenyl Ether*

Henry's Law Constant (atm-m^3/ mole) (Bond estimate)[a]	Photodegradation OH radical rate constant [a] (cm^3/mol-sec)	Soil-Water or Sediment Water Partition Coeff. (Koc) [a]	Predicted Environmental Distribution (Mackay III Fugacity Model) [a]			
			Air (%)	Water (%)	Soil (%)	Sed. (%)
2.05 E-08	37 E-12	19	1.03	46.6	52.3	0.104

[a] Calculated using the EPIWIN™ Suite of Programs (v3.10) Program.

PPh's low Henry's Law constant indicates that it will not partition preferentially from water to air. Its photodegradation rate constant suggests moderately rapid atmospheric degradation (i.e., half-life less that a day). Its predicted environmental distribution shows that it will partition predominantly to water and soil. The inherent chemical stability of PPh indicates that it is stable in the presence of acidic or neutral water at ambient temperatures. It should be noted that even though PPh is slow to evaporate and based on the low Henry's Law Constant and fugacity model predictions, it partitions preferentially to water and soil, nearly all use of PPh is in applications (such as in coatings and inks) in which PPh can evaporate from the product.

2.2.2 Photodegradation

The photodegradation constant (37 x 10^{-12} cm^3/mol/sec) was calculated using the EPIWIN (v3.10) program. From this constant, a half-life of 0.3 days (over 12 hours of daylight) or 3.6 daylight hours was calculated, based on an assumed 12 hour day and an assumed hydroxy radical concentration of 1.5 x 10^6 OH/cm^3.

2.2.3 Stability in Water

The ether linkage of PPh is not expected to hydrolyze readily. The EPIWIN program (HYDROWIN module) 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. Material safety data sheets (MSDSs) indicate that PPh is 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).

2.2.4 Transport between Environmental Compartments

The distribution of PPh among various environmental media has been predicted using the Mackay Level III fugacity modelling approach (EPIWIN, version 3). Such models estimate the relative

distribution of chemicals within different environmental compartments, based on key physical and chemical parameters. The Level III estimated mass balances for PPh (at equilibrium), shown in Table 3, reflect the limited volatilization and high water solubility characteristics of PPh, indicating a preference for partitioning to water and soil. Once it enters the aqueous compartment, PPh possesses physical properties that cause it to remain dissolved in water. An organic carbon – water partition coefficient (Koc) of 19 has been estimated for PPh using the PCKOCWIN module of the EPIWIN model (Table 3). These results suggest that PPh has high soil mobility. Thus, although PPh has a slight preference to partition to soil over water, PPh can (because of its high water solubility) leach from soil deposits to groundwater, and be transported to environments where aerobic biodegradation can take place. Based on EPIWIN modelling, PPh has an estimated log bioconcentration factor (log BCF) of –0.110 (BCF = 0.776). Thus, the propensity of PPh to accumulate in biological media is low.

2.2.5 Biodegradation

To test for its biodegradability potential, PPh was tested aerobically by OECD Method 301F (Manometric Respirometry Test) using sediment and activated sludge from a domestic sewage treatment plant (Goodwin and West, 1998). PPh was incubated for 28 days in continuously agitated closed, 1 liter bottles in the dark (in duplicate) at a concentration of 92.4 mg/l ThOD as test material with an activated inoculum originally collected from a local municipal sewage treatment facility. The average mixed liquor suspended solids concentration (MLSS) was 2810 mg/liter. This was diluted to 30 mg/liter for the incubation with a pH of 7.2 to 7.6. The incubation temperature was 22 ± 1°C. PPh degradation was monitored by assessing: 1) the disappearance of O_2, 2) the evolution of CO_2 gas from mineralization of the exogenous organic substrate by the inoculum, and 3) the disappearance of organic carbon. O_2 and CO_2 were measured at 4-hour intervals throughout the 28-day incubation period. Incubation of PPh with inoculum resulted in: 1) 72% degradation after 28 days based on O_2 consumption, 2) 61% degradation after 28 days based on CO_2 evolution, and 3) 72% 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 O_2 consumption, CO_2 production, and DOC removal. By all measures of biodegradation, PPh met the criteria of "readily biodegradable," having achieved a biodegradation level of 60% or more within a 10-day window.

The biodegradation of PPh also was assessed in three soil types under both aerobic and anaerobic conditions (Gonsior and West, 1991). For the aerobic assessment, biodegradation in soil was studied by placing 20 grams of soil (dry weight) and 20 grams of water in a glass container with ^{14}C-radiolabeled PPh (labeled on the phenyl moiety) dissolved in 1,4-dioxane. PPh was added at nominal concentrations of 1, 10, or 100 ppm to the Londo sandy loam and 1 or 100 ppm to the sandy soil and Tappan sandy loam. An excess of oxygen was supplied to ensure aerobic conditions. Duplicate microcosms were incubated in the dark at 25 ± 2°C for 7 days. Radioactivity was recovered by extraction with 20 ml acetonitrile. The extract was separated by HPLC and radioactive fractions were counted by scintillation for characterization and quantification of metabolites and by-products (CO_2 was converted to bicarbonate and carbonate before separation). Sterile controls were used to distinguish biological chemical degradation. For the anaerobic assessment, microcosms were prepared and treated as above but were sealed with an atmosphere of 70% nitrogen, 28% carbon dioxide, and 2% hydrogen. These microcosms were incubated for up to 2 months.

Results of biodegradation under aerobic conditions are shown in Table 4 below. Recovery of radioactivity was close to 100%.

Table 4: Study Design for the Soil Biodegradation Assay

Soil type	Nominal Conc ppm	Actual Conc ppm	Time to 50% removal (days)	Max CO_2 (%)
Londo	1	1.4	<1	31
Londo	10	10	<2	50
Londo	100	107	<5	43
Tappan	1	1.5	<1	38
Tappan	100	104	<7	55
Sand	1	1.5	<5	62
Sand	100	108	<23	66

After 2 months under anaerobic conditions (at a nominal concentration of 10 ppm PPh), a 16% reduction in PPh was observed in sodium acetate supplemented microcosms whereas, in the sterile controls, a 7% reduction was observed. Where sodium acetate was not used as a supplement, a 9% reduction was observed after 2 months compared to 4% in the sterile controls. HPLC revealed no breakdown products.

PPh was quickly biodegradable in all three soil types under aerobic conditions but was not biodegradable under anaerobic conditions. The sandy soil biodegraded PPh somewhat more slowly than the sandy loams probably because of the approximately 10-fold lower microorganism concentration. The biodegradation rate was dependent on the initial concentration of PPh with higher concentrations of PPh taking longer to reach the 50% biodegradation point. CO_2 comprised 31 to 66% of the biodegradation products of PPh. Under anaerobic conditions, only a small portion of PPh was biodegraded and addition of sodium acetate as a supplemental carbons source did not facilitate this process.

2.2.6 Bioaccumulation

PPh has a very limited potential to bioaccumulate based on its low log K_{ow} and bioconcentration factor. The log K_{ow} for PPh is 1.50. As stated above, the predicted log bioconcentration factor (log BCF) for PPh also is low: 0.776 (log BCF = -0.110) (EPIWIN/BCF Program).

2.3 Human Exposure

The most likely routes of human exposure to PPh 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 liquid products containing PPh are otherwise used. Unless an aerosol is formed, the extent of inhalation exposure is limited by the low vapour pressure of PPh (2.9 Pa) in product formulations that typically contain 2-10% PPh. Exposure via the dermal route is therefore likely to be more important.

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 limit exposure potential. Processors use enclosed equipment for the formulation of products containing PPh. Worker exposure is more likely to occur while applying coating products

containing PPh to various surfaces. Dermal contact and inhalation exposure are expected exposure routes.

2.3.2 Consumer Exposure to Commercial Products containing PPh

Individuals applying paint or other PPh-containing coatings may be exposed to this propylene glycol ether. 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.

General population exposure also is possible through inhalation of ambient air containing low concentrations of PPh that may be released from industrial processes or through evaporation of coatings or other products containing it. The rapid photochemical degradation of PPh would suggest that this means of exposure to the general population would be low. Ingestion of drinking water containing PPh as a contaminant (e.g., from a spill) also is possible. The ready biodegradability of PPh, again, would suggest that exposure of the general population to such a source of PPh would be low.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

In a toxicokinetics study conducted by Saghir et al. (2003), three male rats were administered single oral doses via gavage of 10 or 100 mg C^{14}-radiolabelled PPh/kg body weight. The specific activity of original [C^{14}]-PPh was 6.8 mCi/mmole, with a radiochemical purity >95%.The specific activity of both dosing solutions in 0.5% methylcellulose ether was 50 µCi/g. The C^{14} label was on the phenyl ring. Rats were housed in metabolism cages where urine and feces were collected in various time increments over a total period of 48 hours and monitored for radioactivity. Urine was collected after 12, 24, and 48 hours and feces in 24-hour increments. Because urine and feces contained virtually all the administered dose, the expired air, specific tissues and the carcass were not evaluated for radioactivity. Urine samples were split into non-acid hydrolyzed and acid hydrolyzed fractions for analysis of metabolites by HPLC with a C^{14} detector. The structures of metabolites in fractions containing >5% of the dose were identified using HPLC separations equipped with electrospray ionization (ESI) and identified by mass spectrometry. Feces contained less than 5% of the dose and were not subjected to metabolite identification procedures.

Most of the dose, 83-91%, was eliminated in the urine within the first 12 hours. Within the second 12 hours, additional urinary excretion was 3.3-6.8% of the original dose; within the last 24-hour period, an incremental 1.0 to 2.7% was excreted in the urine. A total of 93 ± 5% of the low dose (10 mg/kg) was excreted in the urine within the entire 48 hours collection period and 96 ± 3% of the high dose (100 mg/kg) was excreted in urine within this timeframe. Over the 48-hour collection period, fecal excretion accounted for 7.1 ± 1.3% (low dose) and 5.6 ± 0.13% (high dose) of the administered dose. Urinary and fecal excretion together accounted for virtual total elimination of the administered dose within 48 hours.

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 HPLC/ESI/MS and HPLC/ESI/MS/MS techniques:

LC Peak A (<1%) –	Glucuronide conjugate of hydroquinone
LC Peak B (1-2%) –	Not identified
LC Peak C (1.3-3.8%) –	Not identified
LC Peak D (<1%) –	Not identified
LC Peak E/F (60-63%) –	Sulfate and glutathione conjugates of phenol; Sulfate and glucuronide conjugates of PPh, sulfate conjugates of ring-hydroxylated PPh and 1-phenoxy-2-propanone
LC Peak G (<1%) –	Not identified
LC Peak H (1-2%) –	Not identified
LC Peak I (4-5%) –	Glucuronide conjugate of PPh
LC Peak J (<1%) –	Not identified
LC Peak K (8-9%) –	Glucuronide conjugate of PPh
LC Peak L (9- 10%) –	Sulfate conjugate of PPh

Based on comparisons of chromatographic retention times with authentic materials, acid hydrolysis of urine yielded free phenol (61%), hydroquinone (1.5%), and parent PPh (13%).

In conclusion, PPh is rapidly absorbed, distributed, and quickly metabolized and eliminated in male rats. Virtually all the administered dose is eliminated within 48 hours in the urine and feces. The three major routes of metabolism are 1) cleavage of PPh by O-dealkylation, yielding propylene glycol and phenol, followed by excretion of phenol as a sulfate, or glutathione conjugate in the urine; 2) direct sulfate or glucuronide conjugation of parent PPh and excretion into the urine; and 3) ring hydroxylation of parent PPh or its oxidized propanone metabolite, followed by sulfate conjugation and excretion into the urine. Minor urinary metabolites included the glucuronide conjugate of hydroquinone.

PPh is rapidly absorbed, distributed throughout the body, metabolized, and eliminated. The major routes of elimination are via the urine and feces. The types of metabolites are parent ether conjugates, hydrolyzed propylene glycol, and hydrolyzed alcohol (phenol) conjugates.

3.1.2 Acute Toxicity

For the acute toxicity of PPh, data on all three physiologically realistic routes of exposure are available. Table 5 shows the acute dose mammalian toxicity LD50s via three routes of exposure.

Table 5. Summary Table
Acute Mammalian Toxicity for Propylene Glycol Phenyl Ether *

Acute rat oral LD_{50}	Acute rat inhalation LC_{50} (4 hr) [2]	Acute rabbit dermal LD_{50} (24 hr)
>2,000 mg/kg (1/10 deaths) [1]	>5400 mg/m^3 [3] (No deaths) [1]	2,000 mg/kg (No deaths) [1,4]

* Study details and references are found in the robust summaries
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] Results were from a company summary report (study specifics not provided).

Results from the acute studies indicate low toxicity by the oral, inhalation and dermal routes of exposure for propylene glycol phenyl ether. The individual studies, by route of exposure, are discussed below.

Inhalation

The acute inhalation toxicity of PPh was tested in rats by Gamer et al. (1991). Animals were assigned to the test group noted in the table below. Rats were exposed to PPh by nose-only inhalation exposure for 4 hours using a head-nose inhalation system. The test atmosphere was sampled from the breathing zone of the animals at regular intervals to determine concentration and particle size (see below). Subjects were observed for signs of toxicity during exposure, immediately upon removal from the chambers after exposure, repeatedly on the day of exposure, and daily thereafter for 14 days. After 14 days of observation, all animals were terminated and a necropsy was performed.

Table 6. Acute Inhalation Toxicity:
Concentrations, Exposure Conditions, Mortality/Animals Treated

Nominal Conc.	Analyti-cal Conc.	MMAD* (µm)	GSD* (µm)	Number dead/total (Males)	Number dead/total (Females)	Number dead/total (Combined)
28 mg/l	5.41 ± 0.08 mg/l	1.9	3.5	0/5	0/5	0/10

MMAD = Mass Median Aerodynamic Diameter; GSD = Geometric Standard Deviation

Generation of the test atmosphere and description of the chamber: Aerosols were generated by atomization. Nominal concentrations were calculated by dividing the amount of test material used per unit time by the airflow rate. Actual concentrations were determined by aspirating air samples near the breathing zone of the animals through isopropanol and measuring PPh by gas chromatography. Particle sizes were determined using an Anderson cascade impactor. Some chamber parameters are shown in Table 7, which follows.

Table 7. Acute Inhalation Toxicity
Chamber Environmental Data, Aerosol Concentrations, and Particle Size

EXPOSURE LEVEL = 5.4 mg/l	
Chamber and Exposure Data:	
Chamber volume (L)	55
Mean air flow rate (L/min)	250
Mean air changes per hour	27.27
Equilibration time (min)	not specified
Exposure time (min)	240
De-equilibration time (min)	not specified
Aerosol Concentrations:	
Calculated nominal concentration (mg/l)	28
Time-weighted mean gravimetric concentration (mg/l)	5.4
Aerosol Particle Size Analysis:	
Mass median aerodynamic diameter (:)	1.9
Geometric standard deviation	±3.5
Percentage of particles #5.5:m	91
Chamber Environmental Data:	
Temperature range (ºF)	66-77
Humidity range (%)	not specified
Oxygen content (%)	not specified

No mortalities occurred as a result of exposure to this test material.

The LC50 for males is: >5.4 mg/l (or 5,400 mg/m^3)
for females is > 5.4 mg/l (or 5,400 mg/m^3)
for both sexes combined is >5.4 mg/l (or 5,400 mg/m^3)

Clinical abnormalities were noted in the test subjects on the first day of exposure but not thereafter. These included breathing difficulties during the 4-hour exposure period in all subjects. No changes in either absolute or relative body weights were noted over the course of the study. No adverse findings attributable to PPh were reported when animals were necropsied at the end of the 14-day observation period.

For PPh administered as a liquid aerosol by inhalation to rats by nose-only exposure, the 4-hour inhalation LC50 (combined sexes) is greater than 5.4 mg/l (or 5,400 mg/m^3). No deaths occurred in 5 males or 5 females at this exposure level so the actual LC50 may be considerably higher than this value. Using the formula: ppm = mg/m3 x 24.45/M.W. and a molecular weight of 152.19 for PPh, 5,400 mg/m^3 converts to an LC50 exceeding approximately 870 ppm.

Dermal

In an older study, Norris and Olson (1968) treated rabbits with 0.5, 1.0, or 2.0 ml/kg PPh. Two rabbits were treated per dose level but sex was not specified. PPh was kept in contact with the rabbit's skin for 24 hours but whether the material was kept occluded or open was not specified in the report. No deaths occurred at any dose level. The reliability of this study could not be determined due to insufficient information

Oral

Young adult male and female Wistar rats (5/sex/group) were administered single gavage doses of 1000 or 2000 mg/kg PPh in an olive oil vehicle (Kirsch and Hildebrand, 1987). Rats were observed for mortality and signs of toxicity for 14 days after administration of the test material.

The experimental design is shown in the table below along with mortality results.

Table 8: Acute Oral Toxicity: Study Design with Mortality Results

Group	PPh Dose (mg/kg)	PPh/Olive Oil Ratio (w/v)*	Adminis-tered Volume	#/Sex/ Dose	No. Males Dead	No. Females Dead	Total Dead
Group 1	1000	200 mg/ml	5 ml	5	0/5	0/5	0/10
Group 2	2000	400 mg/ml	5 ml	5	1/5	0/5	1/10

* mg PPh per ml olive oil.

One male rat from the high dose group died on day 1; all remaining rats survived the 14-day observation period. Rats from the high dose group seemed to gain weight less rapidly than rats from the low dose group. Rats from both dose groups exhibited dyspnea, apathy, and poor general state. In the high dose group, additional symptoms included abnormal stance, staggering, atonia, paresis, absence of pain reflex, absence of corneal reflex, piloerection, and dehydration. Generally, these signs disappeared after the first day. At necropsy, the single rat that did not survive showed signs of "general congestion." At autopsy after the 14-day observation period, none of the 19 survivors exhibited any grossly observable lesions.

The oral LD50 exceeds 2000 mg/kg in rats. A single death (among 10 subjects) occurred at this level. These results indicate low acute oral toxicity for PPh.

Conclusion

Acute toxicity studies by all three common routes of exposure show low toxicity for PPh. This is shown by oral and dermal LD50s exceeding 2000 mg/kg, and an inhalation LC50 exceeding 5000 mg/m^3 (870 ppm). Only one death (by inhalation) occurred in any of these studies at the highest levels tested so the actual 50% lethality levels may be considerably higher.

3.1.3 Irritation

PPh has a potential for severe eye irritation but is not significantly irritating to skin after acute exposure, as shown in Table 9.

Table 9. Summary Table
Eye/Skin Irritation and Sensitization Testing

Eye Irritation (Rabbits)	**Skin Irritation (Rabbits)**	**Skin Sensitization (Guinea Pigs)** [1]
Severely irritating	Non-irritating according to OECD criteria	Negative, Buehler Test

Skin Irritation

The dermal irritation potential of PPh was tested in rabbits (Kirsch and Hildebrand, 1991a), according to OECD Guideline 404.

PPh was practically nonirritating as shown by the scores in the table below. When the scores for the 24, 48, and 72 hour observation periods were averaged, the average score was 0, either for erythema or edema. The only irritation score exceeding 0 was observed after 30 – 60 minutes in one of the two male rabbits, which exhibited a score of 1 (very slight) for erythema (and 0 for edema). The remaining two subjects had scores of 0 both for erythema and edema at this time interval. Results from this study indicate that PPh has low potential for acute dermal irritation.

Table 10. Skin Irritation Results in Rabbits

			30-60 Minute Score		24-hr Score		48-hr Score		72-hr Score	
Animal	Sex	Dose (ml)	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
1	M	0.5	0	0	0	0	0	0	0	0
2	M	0.5	1	0	0	0	0	0	0	0
3	F	0.5	0	0	0	0	0	0	0	0

Eye Irritation

In a primary eye irritation test, approximately 0.1 milliliter of undiluted PPh was instilled into the conjunctival sac of the right eye of three Vienna white rabbits (2 males and 1 female) (Kirsch and Hildebrand, 1991b) according to OECD Guideline 405.

PPh produced average scores of 1 for corneal opacity, 0.4 for iritic damage, 2.0 for redness (erythema), and 0.9 for swelling (chemosis). These scores represented averages from the three rabbits from the three time points of 24, 48, and 72 hours. After 23 days, two rabbits (1 male and 1 female) still had scores of 1 for corneal opacity. In addition, redness scores 2 and 3 occurred through day 23 while conjunctival swelling had subsided in all subjects by day 23. These results indicate that PPh has significant potential for eye irritation (i.e., is a severe eye irritant).

3.1.4 Sensitization

The potential of PPh to cause skin sensitization was tested in guinea pigs by Haut and Bell (1998) using a modified Buehler 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. From this pilot study, 100% PPh was selected as an appropriate concentration to use in the main study.

For the induction phase of the main study, 20 male Hartley guinea pigs were treated topically with 0.4 ml of undiluted PPh. At one-week intervals this treatment was repeated twice, completing the induction phase of the study. For the challenge phase, conducted 14 days after the third induction, 0.4 ml of undiluted PPh was applied to a naive site on the flanks of the guinea pigs. A control group of 10 naive males was treated similarly (received PPh during challenge phase only) in order to distinguish potential irritation effects from possible hypersensitization.

After the challenge dose, the site of skin application was scored for irritation at 24 and 48 hours following removal of the test material. Responses were graded by evaluating erythema or 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 in Table 11 below.

Table 11. Study Design
Skin Sensitization in Guinea Pigs (Buehler Method)

Group	Test/Control Material	No. Male Guinea Pigs	Topical Induction Dose	Topical Challenge Dose
1. Test Group	PPh Induction & Challenge	20	3 X 0.4 ml PPh, applied for 6 hr.	0.4 ml PPh, applied for 6 hr.
2. Naive Control	PPh Challenge phase only	10	No treatment	0.4 ml PPh, applied for 6 hr.

All subjects survived treatment with the test compound. Neither clinical signs of toxicity nor skin irritation at the site of application were reported. Body weights were unaffected. At necropsy, no gross lesions were noted. Regarding sensitization, at the 24-hour reading, all scores in treated animals were 0 for erythema or edema. Scores remained 0 at the 48-hour reading. Consequently, PPh did not cause contact hypersensitivity under the conditions of this test.

3.1.5 Repeated Dose Toxicity

Repeated dose toxicity data are available for propylene glycol phenyl ether. Results are summarized in Table 12.

Table 12. Summary Table
Repeated Dose Toxicity of Propylene Glycol Phenyl Ether*

Oral (NOAEL, LOAEL in mg/kg-day)	Inhalation (NOAEL, LOAEL in mg/kg-day)	Dermal (NOAEL, LOAEL in mg/kg-day)
2-Generation Reproductive Toxicity Test NOAEL = 1000 ppm (118 mg/kg-d) LOAEL = 5000 ppm (478 mg/kg-d) [1]	No Studies	(28-day - rabbit) NOAEL = 1,000 mg/kg-day[1]

* Study details and references are discussed below.
NOAEL = no observable adverse effect level; LOAEL = lowest observable adverse effect level.
[1] Highest dose used in study

Table 6 shows that repeated dosing of PPh at high levels is well tolerated by the oral and dermal routes of exposure. Study specifics are described below. Propylene glycol phenyl ether at these high dose levels caused: 1) no testicular damage (e.g., no decreased testicular weight, no damaged sperm or sperm-producing cells, no damage to seminiferous tubules, no damage to the epididymis), 2) no hemolysis or damage to blood forming tissues, and 3) no thymic atrophy (reduced thymus weights, depletion of white cells in thymus). Results from the dermal repeated dose study indicate low toxicity for propylene glycol phenyl ether.

Studies in Animals

Inhalation

No repeated-dose inhalation toxicity studies have been conducted in animals with PPh.

Dermal

Calhoun et al. (1986) applied PPh daily to the clipped dorsal skin of rabbits (5/sex/dose) at doses of 0, 100, 300, or 1000 mg PPh/kg body weight-day, 5 days/week, over a period of 4 weeks (total of 19 applications). The 0 control group was treated with approximately 1 ml/kg-d distilled water. PPh was applied uniformly over a 10 x 15 cm area of the back using a syringe with a blunt needle. The dose was covered with gauze, non-absorbent cotton, then an occlusive bandage, all held in place for 6 hours with a lycra/spandex jacket. After the 6-hour exposure period, the bandage was removed and the area washed clean of PPh with a water-dampened towel. Over the course of the study, rabbits were monitored for clinical signs of toxicity, body weight changes, alterations in hematology, clinical chemistry, or urinalysis, as well as variations in organ weights, and gross and microscopic pathology at autopsy. Specimens were collected from over 40 tissues and preserved from all animals. These tissues were examined microscopically from the high dose and control animals.

All rabbits survived treatment with no changes in body weights and no overt signs of systemic toxicity. All subjects showed some dermal irritation at the site of PPh application, characterized by moderate exfoliation and hyperemia in the high dose group, slight exfoliation and transient hyperemia in the mid-dose group, and very slight exfoliation in the low dose group. No changes were noted in absolute or relative organ weights compared to controls. No consistent changes were noted in clinical laboratory studies other than a slight increase in platelet counts in males, which was statistically significant in high dose group and approached significance in mid-dose males. Females showed no platelet response to PPh exposure. Except for skin at the site of application, neither gross nor histopathological examination revealed any adverse changes related to PPh treatment when high dose subjects were compared to controls. In skin at the site of application, a thickening of the epidermis was detected that was considered to be an adaptive response.

PPh applied dermally to the backs of rabbits for 6 hr/day, 5 days/wk over a 28-day period produced no systemic toxicity at dose levels up to 1000 mg/kg-day. This study established a NOAEL of 1000 mg/kg-day for subchronic dermal toxicity. The same NOAEL was established in a study in which the material was applied to clipped dorsal skin of 10 female rabbits for 14 consecutive days under occlusion for (what appeared to be) 24 hours (Phillips et al., 1985).

Oral

Repeat dose toxicity has not been tested specifically by the oral route for PPh. However, in a two-generation reproductive toxicity study, conducted by BASF (2000), the oral toxicity of PPh was assessed. For a more complete description of this study, see the reproductive toxicity section that follows. Briefly, PPh was administered to adult male and female Wistar rats daily in their drinking water at concentrations of 0, 100, 1000, or 5000 ppm (equal to doses of 0, 11.3, 113.9, or 477.5 mg/kg-d) for a period of 26 weeks following OECD Guideline 416 ("Two-generation Reproduction Toxicity Study").

No effects were seen in adult rats (or their offspring) at the two lower exposure/dose levels. High dose rats of both sexes exhibited reduced body weights or weight gains compared to controls during various phases of the study. Body weight effects were reflected in reduced food and water intake at the high dose level. Histopathological lesions did not accompany these changes when many tissues from the adult animals were examined microscopically. Reproductive parameters were not affected in this study. The oral subchronic toxicity NOAEL for this study is 1000 ppm or (114 mg/kg-d) and the LOAEL, based on body weight reductions, is 5000 ppm (478 mg/kg-d).

3.1.6 Mutagenicity

In vitro Studies

Two Ames tests (Bootman and May, 1985; BASF AG, 1996) and a human lymphocyte chromosome aberration study (Bootman, 1986) have been conducted with PPh. These unpublished study reports could not be retrieved for review due to their submission under the EU Biocides directive. For the BASF Ames study, a robust summary was provided by the study sponsor and followed OECD protocols and EEC directives. Results for the Ames studies are described in the dossier. However, the information reported for the chromosome aberration study is from secondary review sources and is brief (i.e., a robust summary was not generated). The aberration study results were summarized in the ECETOC Monograph on glycol ethers (1995) and the results are reviewed below.

In the first study, an Ames point mutation bioassay was conducted with 4 strains of *Salmonella typhimurium* (TA-98, TA-100, TA-1535 and TA-1537), and with *E. coli* WP2 uvrA, with and without an S-9 metabolic activation system (using Aroclor 1254-induced rat liver) (Bootman and May, 1985). Concentrations of 0, 20, 100, 500, 2500 and 5000 µg/plate were employed. Appropriate positive controls were employed to verify tester strain sensitivity. PPh did not increase mutation rates over negative controls in any strain at any dose level, with or without activation. In the second study, an *in vitro* chromosome aberration assay was conducted with PPh using human lymphocytes (Bootman, 1986). Concentrations of PPh up to 400 µg/ml were incubated with human lymphocytes, with and without metabolic activation. No increases in chromosomal aberrations were detected in this assay.

In vivo Studies

In an *in vivo* mouse bone marrow micronucleus assay, Day (2000) subjected groups of 6 male mice (Outbred CD-1 (1CR)BR) per dose level to doses of 0, 500, 1000, or 2000 mg PPh/kg body weight on 2 consecutive days by oral intubation. Doses were selected from a pilot dose-range finding study. Because hypothermia resulted from treatment in this Phase 1 study in the high dose subjects, the experiment was repeated with both sexes (Phase 2) with 6 additional animals per sex in the high dose group to serve as replacements in the event of mortality. The study designs for the two phases are shown in Table 13.

PPh dosing solution concentrations were diluted in corn oil in order to provide a dosing volume of 2 ml/kg body weight. Cyclophosphamide monohydrate was used as the positive control agent and was administered in distilled water at a dose level of 120 mg/kg body weight. Mice were observed for mortality and clinical signs of toxicity at least once per day following the initial dose. Body temperature was monitored using an implanted transponder; temperatures were recorded immediately prior to dosing, 6-hours post-dosing, and prior to termination.

Table 13. In Vivo Mouse Bone Marrow Micronucleus Assay Study Design

Dose Level (mg/kg-d)	# Consec Daily Doses	# Mice	Post-last-dose termination time (hr)
Phase 1			
0 (corn oil)	2	6 males	24
500	2	6 males	24
1000	2	6 males	24
2000	2	6 males	24
CP* 120	1	6 males	24
Phase 2			
0 (corn oil)	2	6 m & f	24
500	2	6 m & f	24
1000	2	6 m & f	24
2000	2	12 m & f	24
CP* 120	1	6 m & f	24

* CP = Cyclophosphamide monohydrate dissolved in distilled water.

Twenty-four hours after the last dose, mice were euthanized with CO_2 and bone marrow was collected by aspiration from both femurs. Bone marrow was mixed with 0.5 ml serum, and then centrifuged. The resulting pellet was resuspended, smeared onto slides, allowed to dry, and stained with Wright-Giemsa. For each subject, 2000 polychromatic erythrocytes (PCEs) were examined microscopically for the presence of micronuclei (MN-PCE). The number of MN-PCE was expressed as a percentage of total PCE.

In Phase 1, 1 of 6 males died from treatment in the high dose group (2000 mg/kg-d). Autopsy did not reveal a cause for death. Three males from this group (including the one that died) showed clinical signs of shallow breathing, decreased to absent activity, and hypothermia. The two

surviving animals showing hypothermia were placed in a warm environment. No deaths, clinical signs, or hypothermia occurred in the lower dose groups or in the cyclophosphamide control groups. The high dose group showed an increased frequency of micronuclei. The %MN-PCE (% micronuclei) values from two animals with hypothermia accounted for the increased average of this group and the authors of the study attributed the increase to hypothermia. These values were 18.0 % and 11.5% while the values in the three other survivors were 1.0%, 4.5%, and 3.0%, similar to the corn oil control group values. Subjects treated with lower doses of PPh showed no effects on any parameter.

In Phase 2, the effects seen in Phase 1 were observed again in the 2000 mg/kg-day group. Although not statistically significant, the %MN-PCE was elevated once more. Marked hypothermia was observed yet again at this dose level only in both sexes. As in Phase 1, the ratio of polychromatic (PCE) to normo-chromatic erythrocytes (NCE) was decreased in the high dose group. Body weights were unaffected in either Phase. Results are tabulated in Table 14 below.

The authors of this study concluded that, most likely, the increased incidence of micronuclei seen at 2000 mg/kg-day was attributable to the hypothermia induced by PPh and not as a direct clastogenic effect of PPh. The authors cited papers by Asanami and Shimono (1997) and Asanami et al. (1998), showing that agents such as reserpine and chlorpromazine, which induce hypothermia, cause increased micronuclei as an indirect result of this physiological change. Asanami et al. hypothesize that hypothermia may cause clastogenic injury by interfering with microtubule assembly and spindle function.

Since a separate, additional group at the high dose level was not placed in a warmed environment after treatment to directly test the hypothesis of hypothermia causing the increased micronuclei, the possibility that the increased incidence of micronuclei at the high dose was directly attributable to PPh cannot be excluded. On the other hand, it is relevant to note that the next lower dose (still a very large dose of 1000 mg/kg) did not cause hypothermia or an increase in micronuclei. If the increase was directly attributable to PPh and not hypothermia, it is significant that only a marginal effect resulted (not statistically significant when repeated in a second experiment), which required a very large dose of 2000 mg/kg.

Table 14. *In Vivo* Mouse Bone Marrow Micronucleus Assay Results

Dose Level (mg/kg-d)	Mortality	Clinical Signs	Hypo-thermia	% PCE among PCE+NCE (± S.D)	% MN-PCE among PCE (± S.D)
Phase 1					
0	0/6	0/6	N/R**	61.4 (± 9.4)	2.9 (± 2.2)
500	0/6	0/6	N/R**	60.4 (± 6.9)	1.6 (± 0.9)
1000	0/6	0/6	N/R**	60.3 (± 3.0)	2.2 (± 2.1)
2000	1/6	3/6	N/R**	55.7 (± 5.0)	7.6 (± 7.0)
CP* 120	0/6	0/6	N/R**	45.5 (± 9.3)	37.4 (± 17.6)
Phase 2 (males)					
0	0/6	0/6	0/6	56.3 (± 12.3)	0.5 (± 0.4)
500	0/6	0/6	0/6	59.6 (± 8.2)	0.8 (± 0.4)
1000	0/6	2/6	0/6	60.1 (± 11.5)	0.5 (± 0.6)
2000	4/12	10/12	7/7	48.2 (± 9.2)	4.4 (± 4.5)
CP* 120	0/6	0/6	0/6	40.9 (± 8.1)	41.1 (± 13.5)
Phase 2 (females)					
0	0/6	0/6	0/6	64.7 (± 9.0)	0.4 (± 0.5)
500	0/6	1/6	0/6	67.9 (± 5.2)	0.3 (± 0.5)
1000	0/6	5/6	0/6	60.3 (± 5.7)	0.8 (± 0.7)
2000	6/12	12/12	8/8	53.3 (± 3.4)	4.5 (± 4.3)
CP* 120	0/6	0/6	0/6	47.0 (± 5.4)	52.8 (± 17.4)

* CP = Cyclophosphamide monohydrate dissolved in distilled water.
** N/R = Not reported.

Conclusion

It seems reasonable to conclude that the negative *in vitro* results and the equivocal *in vivo* results at a very high dose level that may be due to physiological stress indicate that propylene glycol phenyl ether does not pose a significant genotoxicity hazard.

3.1.7 Carcinogenicity

PPh has not been tested for carcinogenicity.

3.1.8 Toxicity for Reproduction

Effects on Fertility

In a two-generation reproduction toxicity test, BASF Corporation (2000) administered PPh in the drinking water to two parental generations of male and female Wister rats (25/sex/dose level) at

concentrations of 0, 100, 1000, or 5000 ppm. These exposure concentrations corresponded to 11.4, 114, or 478 mg/kg-day and exposure durations averaged 26 weeks in parental generations. First generation (F0) rats received PPh 77 days prior to mating. The second parental generation (F1) received PPh for their lifetimes until termination. Parental animals were evaluated for mortality, clinical signs of toxicity, body weights, behavior (nesting, littering, and lactation), food and water consumption, and reproductive performance. For females, reproductive performance was evaluated by monitoring: estrous cycle length and normality; reproductive organ weights and morphology; and mating, fertility, and gestation indices. Histopathology of major organs was conducted in the high dose and control animals from both the F0 and F1 parental generations. In males, mating and fertility indices, sperm counts, morphology, motility, and gonad weights were evaluated. Parameters monitored in pups (litter data) included: viability and lactation indices, sex ratios, pup weights, time to sexual maturation, developmental abnormalities in soft and skeletal tissues, and organ weights.

Reproductive performance or fertility was not affected in F0 or F1 parental animals of either dose group. Estrous cycle, mating behavior, conception, gestation, parturition, lactation and weaning as well as sperm parameters, sexual organ weights, and gross and histopathological findings of these organs were similar between control and treated animals.

Signs of general, systemic toxicity were noted in both parental generations (F0 and F1) in groups receiving 5000 ppm, but not at lower exposure levels. Toxicity was characterized by decreased water and food consumption and decreased body weight and body weight gain in parental F0 an F1 males and female. Pathology and histopathology did not reveal substance-related adverse effects in F0 and F1 parental animals. The clinical, gross and histopathological examinations in F0 and F1 parental animals from the low and intermediate dose groups did not indicate systemic toxicity.

Substance-related signs of developmental toxicity were seen in progeny of the high dose (5000 ppm) F0 and F1 parents in terms of reduced pup body weight and body weight gain. Some pup organ weights were also reduced or increased. For example, relative brain weight was increased and relative spleen weight was decreased. Other organ weight changes (i.e. reductions) may have been a consequence of reduced pup body weight, itself caused by parental weight loss during pregnancy. Pups also exhibited delayed sexual maturation. Significantly, reproduction parameters of the F1 animals were not adversely affected after gaining sexual maturity. This supports the view that delayed preputial separation and vaginal opening resulted from a general retardation of physical development. No signs of developmental toxicity were seen in pups from groups receiving medium or low doses (1000 or 100 ppm).

Under the conditions of this study, NOAELs were established as follows: NOAEL for reproductive performance and fertility: 5000 ppm (about 475 mg PPh/kg-d) for the F0 and F1 parents; NOAEL for developmental toxicity: 1000 ppm (about 115 mg PPh/kg-d) for the F1 and F2 progeny; NOAEL for general systemic toxicity: 1000 ppm (about 115 mg PPh/kg-d) for the F0 and F1 parents.

Thus developmental toxicity, manifested as reduced pup body and organ weights and delayed sexual maturation, was seen at a dose that was also toxic to the parent animals. No sign of frank teratogenicity was seen at any dose in this study.

In addition to the test described above, a 28-day repeat dose dermal toxicity study with rabbits also is relevant in regard to the possible reproductive effects of PPh (Calhoun, 1986). This study is relevant to the reproductive toxicity endpoint because it evaluated the effects of PPh on reproductive organs via gross and histopathological examination of these tissues. Rabbits

(5/sex/dose) were treated dermally with 0, 100, 300, or 1000 mg/kg-d, 5 days/week for four consecutive weeks, (19 applications) with PPh (6 hr/day exposures). No toxicity to reproductive organs was evident based on organ weights, gross observation, or microscopic examination.

Developmental Toxicity

Developmental toxicity data are available in rabbits for propylene glycol phenyl ether by the oral route of exposure (Hellwig, 1995). Results are summarized in Table 15 below.

Table 15. Developmental Toxicity of Propylene Glycol Phenyl Ether*

Route of Exposure Species, Doses/Exposure Levels	Results: Maternal Tox. (NOAEL, LOAEL)	Results: Offspring (NOAEL, LOAEL)
Oral (Gavage) Rabbit 0, 60, 180 or 540 mg/kg-d during gestation	No effects at 0, 60, or 180 Decr wt gain, apathy at 540 NOAEL = 180 mg/kg-d LOAEL = 540 mg/kg-d	No effects at 0, 60, or 180 Incr skel var (13^{th} rib) at 540 NOAEL = 180 mg/kg-d LOAEL = 540 mg/kg-d

*Study details and references are found in the robust summaries.
NOAEL = no observable adverse effect level; LOAEL = lowest observable adverse effect level.

PPh was administered daily to pregnant Himalayan rabbits (15 dams/group) by stomach tube over the period of organogenesis (days 7 through 19 of gestation) at doses of 0, 60, 180, or 540 mg/kg-day. At the high dose level, PPh caused a transitory decrease in food consumption, markedly reduced body weight gain, apathy and prostration in the dams. One high dose dam aborted on day 26 and was euthanized on day 28, after showing no food consumption and defecation since days 16 and 19 (respectively), and weight loss throughout the study. No maternal toxicity was seen at lower doses. In fetuses, a statistical increase in the rate of total soft tissue variation was detected (e.g., septal heart defect and agenesis of the gall bladder) in the medium and high dose groups. It is possible that these are coincidental, however, because of their low incidence (1 fetus in each group), the common spontaneous occurrence of these variations in this strain of rabbit, and because statistical significance was conferred only due to the unusually low level of malformations in the concurrent control group (.2.2% fetal incidence and 7.1% litter incidence versus 7.7% and 30.2%, respectively, in the laboratory historical controls). Moreover, the rate of total soft tissue malformations in each group (including PPh treated groups) from this study was within the range of the laboratory historical controls. With regard to skeletal variations (predominantly an increase in 13^{th} ribs when combined with other skeletal variations), a statistical increase was detected in the high dose group. This increase in skeletal variations was considered treatment related because the incidence (approximately 10%) exceeded historical control levels. The authors noted that such skeletal variations are common and can be caused by unspecified stress (e.g., maternal toxicity at a very high dose level exceeding 500 mg/kg-d) that may not be related to toxicity inherent to the chemical's structure.

This study and the reproductive toxicity study discussed above (BASF Corporation, 2000) show that propylene glycol phenyl ether exhibits toxicity in the developing rabbit conceptus at high doses that produce toxicity in the dam.

Conclusion

The results of the oral 2-generation reproductive with rats and the oral developmental toxicity studies with rabbits, along with the histopathological results of reproductive organs from the 30-day repeat-dose dermal study, show that no frank birth defects occur at doses that are very high (i.e. on the order of 500 mg/kg-d orally and over 2000 mg/kg-day dermally). The developmental study found increased incidence of skeletal variations at 540 mg/kg-day, mainly due to increased numbers of 13th ribs. Marginal findings, such as reduced pup body and organ weights and delayed sexual maturation, were found in the 2-generation reproduction study at the highest doses tested where maternal toxicity also is evident. PPh caused no adverse effects on parental reproductive performance at any dose.

3.2 Initial Assessment for Human Health

PPh displays low acute toxicity by the oral, inhalation and dermal routes of exposure. This chemical may be severely irritating to the eyes, but is minimally irritating to skin after acute exposure. The material does not show a potential to cause sensitization. Repeated dosing by the dermal and oral routes of exposure resulted in very little toxicity (other than dermal irritation). The systemic toxicity that was found occurred at high levels and usually consisted of increased organ weights without accompanying histopathology. Regarding reproductive toxicity, no gonadal toxicity was found for either sex in repeated-dose toxicity tests. A two-generation test with rats at concentrations up to 5000 ppm in drinking water indicated no effects on reproductive performance. Developmental tests in rabbits with PPh administered orally showed excess skeletal variations (consisting predominantly of extra 13th ribs) in pups from the highest dose group of 540 mg/kg bw/day (which also was associated with maternal toxicity). PPh tested negative in the Ames Salmonella assay and also was negative in an *in vitro* chromosome aberration study with human lymphocytes. It is possible that the equivocal *in vivo* genotoxicity results at a high dose level (2000 mg/kg bw/day) may be due to physiological stress, although a direct effect of PPh cannot be excluded.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

Acute Toxicity to Fish: Adult Golden Orfe fish (*Leuciscus idus, l.*) were exposed under static (slightly aerated) conditions to PPh to nominal concentrations of 0, 100, 215, 464, or 1000 mg/liter for a period of 96 hours, at 20 ± 1°C (Munk and Kirsch, 1988). Actual concentrations were not determined, however, the high water solubility and low vapor pressure of PPh suggest that nominal concentrations would approximate actual concentrations. The content of each vessel was renewed midway through the exposure period. Each exposure group was comprised of 10 fish (sex unspecified). Fish were observed for mortality and signs of toxicity at 1, 4, 24, 48, 72, and 96 hours after exposure to the test material. The study design is shown with the results in Table 16.

Table 16. Acute Fish Toxicity (Golden Orfe)
Study Design and Results

Group	PPh Conc.* (mg/l)	No./Conc.**	No. Dead	Symptoms
1	0	10	0/10	None
2	100	10	0/10	None
3	215	10	0/10	Narcosis & Tumbling at 1 hr; Narcosis only at 4 hr.; No symptoms thereafter
4	464	10	10/10	100% mortality by 1 hr
5	1000	10	10/10	100% mortality by 1 hr

* Nominal concentration (actual concentration not determined).
** Sex not specified.

The 96-hr LC50 fell within 215 and 464 mg/l. At the two highest concentrations (464 or 1000 mg/liter), all fish died during the first hour. The mortality NOEC is 215 mg/l and the NOEC for clinical signs is 100 mg/l. In the 215 mg/liter exposure group, while no mortalities occurred, symptoms of tumbling swimming and a narcotic-like state were reported at 1 hour and narcosis only at 4 hours. No symptoms were noted in this group after 4 hours. In the control and lowest exposure groups (0 or 100 mg/liter), no deaths or signs of toxicity were observed over the 96-hour exposure period. The rapid onset of mortality from PPh indicates that the LC50 for shorter time periods is the same. The approximate 2-fold difference in the concentration causing no mortality and that causing 100% mortality indicates a steep dose-response curve. The magnitude of these lethality levels show that PPh is not highly toxic to freshwater aquatic species.

In a second acute fish toxicity test, fathead minnows (*Pimephales promelas*) were exposed under static (slightly aerated) conditions to PPh to nominal concentrations of 0, 240, 280, 320, or 420 mg/liter for a period of 96 hours (Dill, 1978). Actual concentrations were not determined and water hardness, acidity, etc. were not reported. Each exposure group was comprised of 10 fish (sex unspecified). Fish were observed for mortality and signs of toxicity over the course of the study. The design is shown with some results in Table 17, which follows.

Table 17. Acute Fish Toxicity (Fathead Minnow)
Study Design and Results

Group	PPh Conc.* (mg/l)	No./Conc.**	No. Dead
1	240	10	0/10
2	280	10	6/10
3	320	10	9/10
4	420	10	10/10

* Nominal concentration (actual concentration not determined).
** Sex not specified.

None of the subjects died that were exposed to the lowest concentration of 240 mg/liter. Six of 10 died at 280 mg/l, 9 of 10 died at 320 mg/l, and 10 of 10 died at 420 mg/l. The 96-hr LC50 of PPh was calculated to be 280 mg/liter with 95% confidence limits ranging from 263 to 297 mg/liter. The slope of the dose-response curve was 27.2 (95% CL: 11.7 – 43).

The mortality NOEC is 240 mg/l. The dose-response curve is steep, indicating an abrupt transition from no effect to lethality. The magnitude of LC50 itself indicates that PPh is not highly toxic to freshwater aquatic species.

Acute Toxicity to Daphnia:

In a 48-hour LC50 test, thirty *Daphnia magna* per level were exposed for 48 hours to nominal concentrations of 100, 180, 320, 560, or 1000 mg PPh/liter water (Dill, 1978). Daphnia were observed for immobilization and mortality at 24 and 48 hours. At these time points, the LC50 but not the EC50 was determined (with confidence limits). Actual concentrations were not determined and water hardness, acidity, etc. were not reported. The high water solubility and low vapor pressure of PPh suggest that nominal concentrations would be close to actual concentrations.

Zero of 30 daphnia exposed to the lowest concentration of 100 mg PPh/liter died after 24 hours. After 48 hours, mortality in this group had increased to 7 of 30. At the highest concentration of 1000 mg/liter, mortality was 100% by 24 hours. Mortality for these and the intermediate exposure groups are shown in the following table.

Table 18. Acute Toxicity to Daphnia
Study Design and Results

Concen.*	# Exposed**	# Dead - 24 hr	# Dead - 48 hr
100 mg/l	30	0	7
180 mg/l	30	1	9
320 mg/l	30	10	10
560 mg/l	30	11	12
1000 mg/l	30	30	30

* Nominal concentration (actual concentration not determined).
** Sex not specified.

The 24-hour LC50 was 471 mg/liter with 95% confidence limits ranging from 439 to 505 mg/liter. The 48-hour LC50 was 370 mg/liter with 95% confidence limits ranging from 321 to 431 mg/liter. The NOEC is less than 100 mg/liter for mortality. The EC50 (for immobilization) was not determined. These results indicate that PPh is moderately to slightly toxic to daphnia under the conditions of this test.

Acute Toxicity to Algae: In a study by BASF (1992), algae (*Scenedesmus subspicatus*) were exposed to PPh. Algae growth rate was tested by measuring chlorophyll fluorescence in vivo as an indicator of cell density, followed by cell counting at the end of the test. Algae (initial concentration: 10,000 cells/ml test solution) were exposed for 72 hrs at 23±2°C in a 250 ml Erlenmeyer vessel. PPh concentrations were 0; 6.25; 25; 100 and 125 mg/l. Three replicates were incorporated per concentration. Fluorescence was measured after 0, 24, 48 and 72 hrs. pH was measured at the start and the end of the exposure period.

The NOEC and concentrations of PPh that effectively reduced the growth rate by 10%, 50%, and 90% were: NOEC = 12.5 mg/l, EbC10 = 55.5 mg/l, EbC50 > 100 mg/l, and EbC90 > 100 mg/l. The NOEC and concentrations of PPh that effectively reduced biomass growth by 10%, 50%, and

90% were: EbC10 = 37.2 mg/l, EbC50 = 74.5 mg/l, and EbC90 > 100 mg/l. These results indicate that PPh is slightly toxic to algae under the conditions of this test.

The EPIWIN suite of environmental models is capable of predicting algae toxicity for chemicals based on their physicochemical characteristics of Kow, molecular weight, molecular structure, etc. The ECOSAR program module of EPIWIN (v0.99) predicted a Green Algae 96-hour EC50 of 201 mg/l and a ChV of 15.23 mg/l.

Acute Toxicity to Bacteria: Studies performed by Clausen and Hegna (Hegna and Clausen, 1988; Clausen and Hegna, 1977) indicate that at concentrations ≤ 1%, PPh is not a particularly effective antimicrobial agent against *S. aureus*, *S. faecalis*, *P. aeruginosa*, *E. coli*, *C. albicans* and *A. fumigatus*. Growth of *S. aureus* and S. *faecalis* bacteria was not inhibited by incubation with 1% PPh for up to 15 minutes, and growth of *P. aeruginosa* and *E. coli* was inhibited by 1% PPh only if incubation times were ≥ 10 minutes. PPh also was ineffective in inhibiting growth of *C. albicans* and *A. fumigatus* fungi at a concentration of 1% and exposure time of 2 hours. By contrast, a combination of 0.1% benzalkonium chloride and 1% PPh inhibited growth of all the aforementioned organisms after an incubation time of 1 minute.

4.2 Terrestrial Effects

No studies were located that investigated the potential adverse effects of PPh on terrestrial organisms.

4.3 Other Environmental Effects

No information about other environmental effects was located

4.4 Initial Assessment for the Environment

Environmental fate parameters, such as the Log K_{ow}, photodegradation rate, Henry's Law constant, used with MacKay Level III fugacity modelling, predict percentages of PPh in air, water, soil and sediment that show a limited tendency to volatilize, partitioning instead to water and soil. PPh is resistant to water hydrolysis under neutral ambient conditions, but is readily biodegradable and has a low bioaccumulation potential. Aquatic toxicity data indicate that PPh is of low toxicity to aquatic species.

5 RECOMMENDATIONS

Environment: The chemical is currently of low priority for further work because of its low hazard profile.

Human health: This chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (eye irritation - which is reversible – and developmental toxicity at high doses associated with maternal toxicity). Based on data presented by the Sponsor country, exposure is controlled in the occupational setting. Due to the wide dispersive use, member countries are invited to perform an exposure assessment and if then indicated, a risk assessment, especially for consumers. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Note: PPh may be evaluated further under the EU Biocides Directive. This will include exposure assessment on operators (occupational) and bystanders (consumers).

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Propylene Glycol Phenyl Ether
CAS No. 770-35-4

S I D S

Dossier

Existing Chemical	:	ID: 770-35-4
CAS No.	:	770-35-4
EINECS Name	:	1-phenylpropan-2-ol
EINECS No.	:	212-222-7
Molecular Weight	:	152.21
Structural Formula	:	C6H5OCH2CHOHCH3
Molecular Formula	:	C9H12O2

Producer Related Part

Company	:	American Chemistry Council
Creation date	:	14.01.2004

Substance Related Part

Company	:	American Chemistry Council
Creation date	:	14.01.2004
Memo	:	
Printing date	:	26.01.2004
Revision date	:	23.01.2004
Date of last Update	:	26.01.2004
Number of Pages	:	109
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, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	2-Propanol, 1-phenoxy-
Smiles Code	:	O(c(cccc1)c1)CC(O)C
Molecular formula	:	C9 H12 O2
Molecular weight	:	152.19
Petrol class	:	

09.03.2005

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	> 93 % w/w
Colour	:	Clear
Odour	:	

Remark : Propylene glycol phenyl ether has a minimum purity of 93%. At least 93% of commercial propylene glycol phenyl ether is comprised of a mixture of 1-phenoxy-propan-2-ol (CAS No.770-35-4) and 2-phenoxy-propan-1-ol (CAS No. 4169-04-4), with the former isomer as the major constituent. The individual isomers are not separated nor produced as individual chemicals. The remaining 7% consists of up to 7% dipropylene glycol phenyl ether, 0.1% phenol and 0.35% water. Of the 93% that is a mixture of the two isomers, 1-phenoxy-propan-2-ol (CAS No. 770-35-4) constitutes > 85% of the mixture (is the thermodynamically favored isomer) and 2-phenoxy-propan-1-ol (CAS No. 4169-04-4) constitutes <15%. Another CAS Number (CAS No. 41593-38-8) has been assigned to the generic isomeric mixture of CAS Nos. 770-35-4 and4169-04-4, without indicating any ratio of these isomers. CAS No. 770-35-4 is the CAS No. normally used for the commercial product, since the commercial product is predominately this isomer.

15.03.2005

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

2-Propanol, 1-phenoxy
Source : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND
Dow Deutschland Inc Stade 5

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

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

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

1.3 IMPURITIES

Purity :
CAS-No :
EC-No :
EINECS-Name : Dipropylene glycol phenyl ether
Molecular formula : C12H183
Value : <= 7 % w/w

Source : The Dow Chemical Company
09.03.2005

Purity :
CAS-No : 108-95-2
EC-No : 203-632-7
EINECS-Name : phenol
Molecular formula : C6H6O
Value : <= .1 % w/w

Source : The Dow Chemical Company
09.03.2005

Purity :
CAS-No : 7732-18-5
EC-No : 231-791-2
EINECS-Name : water
Molecular formula :
Value : <= .35 % w/w

Source : The Dow Chemical Company
09.03.2005

1.4 ADDITIVES

1.5 QUANTITY

Quantity : ca. 7300 - tonnes produced in 1999

Result : According to the Chemical Economics Handbook (SRI International, 2000), in 1999, total worldwide production of all of the various propylene glycol ethers was approximately 810 million pounds (368.2 thousand tonnes). The United States accounted for 285 million pounds (129.5 thousand tonnes) of these, Europe 472 million pounds (214.5 thousand tonnes), and Japan 53 million pounds (24 thousand tonnes). According to the Chemical Economics Handbook, in the U.S., a production volume of 340 million pounds (154.5 thousand tonnes) of all propylene glycol ethers is estimated for 2004. PPh is just one of a series of commercial propylene glycol ethers. In 1999, 16 million pounds (7.3 thousand tonnes) of PPh was manufactured in the U.S. by a single producer. Estimated 2004 production in the U.S. for PPh is 18 million pounds (8.2 thousand tonnes).
Reliability : (2) valid with restrictions
Reference : (SRI International (2000). Chemical Economics Handbook).
15.03.2005

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

Type of use : industrial
Category : Paints, lacquers and varnishes industry

Reliability : (2) valid with restrictions
Data obtained from a published industry survey.

Reference : SRI International (2000). Chemical Economics Handbook.
15.03.2005

Type of use : industrial
Category : Textile processing industry

Reliability : (2) valid with restrictions
Data obtained from a published industry survey.
Reference : SRI International (2000). Chemical Economics Handbook.
15.03.2005

Type of use : industrial
Category : other: inks

Reliability : (2) valid with restrictions
Data obtained from a published industry survey.
Reference : SRI International (2000). Chemical Economics Handbook.
15.03.2005

Type of use : industrial
Category : other: adhesives

Reliability : (2) valid with restrictions
Data obtained from a published industry survey.
Reference : SRI International (2000). Chemical Economics Handbook.
15.03.2005

Type of use : industrial
Category : other: paint remover

Reliability : (2) valid with restrictions
Data obtained from a published industry survey.
Reference : SRI International (2000). Chemical Economics Handbook.
15.03.2005

Type of use : type
Category : Wide dispersive use

Result : Used in cosmetics and soaps, which may be consumer products.
Reliability : (2) valid with restrictions
Data obtained from a published industry survey.
Reference : SRI International (2000). Chemical Economics Handbook.
15.03.2005

Type of use : type
Category : Wide dispersive use

Result : Predominate uses in coatings, inks, adhesives and as a carrier for dyes are dispersive uses.
Reliability : (2) valid with restrictions
Data obtained from a published industry survey.
Reference : SRI International (2000). Chemical Economics Handbook.
15.03.2005

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

Remark : None established.
Source : CHEMOXY INTERNATIONAL PLC MIDDLESBROUGH, CLEVELAND
Source : Dow Deutschland Inc Stade 5

1.9 SOURCE OF EXPOSURE

Remark : no data available
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

Remark : May 23, 2002

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value : = 11.4 °C
Sublimation :
Method : other
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
The melting point was taken from a peer reviewed reference.
Flag : Critical study for SIDS endpoint
Reference : Boatman RJ (2001). Glycol ethers: Ethers of propylene, butylenes glycols, and other glycol derivatives. Chapter 87. In: Bingham E, Cohrssen B, Powell CH (Eds). Patty's Toxicology (Fifth Ed.). New York : John Wiley & Sons, Inc. Staples CA and Davis JW (2002). An examination of the physical properties, fate, ecotoxicity and potential environmental risks for a series of propylene glycol ethers. Chemosphere 49:61-73.

09.03.2005

Value : = 11.4 °C
Sublimation :
Method : other
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
The melting point was obtained from the manufacturer's internal report. Although there is lack of detail about the method of determination, this value is a supporting data point, because it came from the manufacturer and the test substance was typical commercial material from that manufacturer.
Reference : Dill DC, Davis JW (1997). Environmental assessment of the Dowanol glycol ethers P-series product family. Dow Chemical Company Study ID ES-3186. August 12, 1997. Unpublished Report.

09.03.2005

Value : ca. 13 °C
Sublimation :
Method : other
Year :
GLP : no data
Test substance : no data

Reliability : (4) not assignable
Although the result was published in a peer reviewed source, the composition of the test substance was not specified.
Reference : ECETOC Monograph (1995). The toxicology of glycol ethers and its relevance to man. Technical Report No. 64. European Centre for Ecotoxicology and Toxicology of Chemicals. Brussels, Belgium.

09.03.2005

2.2 BOILING POINT

Value	:	= 242.7 °C at 1013 hPa
Decomposition	:	
Method	:	other
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions The boiling point was obtained from a peer reviewed reference.
Flag	:	Critical study for SIDS endpoint
Reference	:	Boatman RJ (2001). Glycol ethers: Ethers of propylene, butylenes glycols, and other glycol derivatives. Chapter 87. In: Bingham E, Cohrssen B, Powell CH (Eds). Patty's Toxicology (Fifth Ed.). New York : John Wiley & Sons, Inc. ECETOC Monograph (1995). The toxicology of glycol ethers and its relevance to man. Technical Report No. 64. European Centre for Ecotoxicology and Toxicology of Chemicals. Brussels, Belgium.
14.03.2005		

Value	:	= 253 °C at 1013 hPa
Decomposition	:	no
Method	:	other
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions The value was obtained from a peer published reviewed source (ChemInfo Report).
Reference	:	Canadian Centre for Occupational Health and Safety (2001). ChemInfo report for propylene glycol phenyl ether. Record number 197. May 2001. Dow Chemical Company (1999). Dowanol PPH Glycol Ether MSDS (Material Safety Data Sheet).
14.03.2005		

2.3 DENSITY

Type	:	density
Value	:	= 1.059 g/cm³ at °C
Method	:	other
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions
	:	The value was obtained from two sources, one published, and the other the manufacturer's MSDS for typical commercial product.

Reference	:	Boatman RJ (2001). Glycol ethers: Ethers of propylene, butylenes glycols, and other glycol derivatives. Chapter 87. In: Bingham E, Cohrssen B, Powell CH (Eds). Patty's Toxicology (Fifth Ed.). New York : John Wiley & Sons, Inc. Canadian Centre for Occupational Health and Safety (2001). ChemInfo report for propylene glycol phenyl ether. Record number 197. May 2001. (Dow Chemical Company (1999). Dowanol PPH Glycol Ether MSDS
09.03.2005		(Material Safety Data Sheet).

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .029 hPa at 25 °C
Decomposition	:	
Method	:	other (measured)
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions The value was obtained from a peer reviewed study.
Flag	:	Critical study for SIDS endpoint
Reference	:	Boatman RJ (2001). Glycol ethers: Ethers of propylene, butylenes glycols, and other glycol derivatives. Chapter 87. In: Bingham E, Cohrssen B, Powell CH (Eds). Patty's Toxicology (Fifth Ed.). New York: John Wiley & Sons, Inc. Staples CA and Davis JW (2002). An examination of the physical properties, fate, ecotoxicity and potential environmental risks for a series of propylene glycol ethers. Chemosphere 49:61-73.
09.03.2005		

Value	:	< .05 hPa at 25 °C
Decomposition	:	
Method	:	other (measured)
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions Data came from a peer reviewed publication.
Reference	:	ECETOC Monograph (1995). The toxicology of glycol ethers and its relevance to man. Technical Report No. 64. European Centre for Ecotoxicology and Toxicology of Chemicals. Brussels, Belgium.
09.03.2005		

Value	:	< .13 hPa at 25 °C
Decomposition	:	
Method	:	other (measured)
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions Data came from a peer reviewed reference publication.

Reference : Canadian Centre for Occupational Health and Safety (2001). ChemInfo report for propylene glycol phenyl ether. Record number 197. May 2001.

09.03.2005

Value : < .13 hPa at 20 °C
Decomposition :
Method : other (measured)
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
Data came from the manufacturer's MSDS.
Reference : Dow Chemical Company (1999). Dowanol PPH Glycol Ether MSDS (Material Safety Data Sheet).

09.03.2005

Value : = 2.97 hPa at 25 °C
Decomposition :
Method : other (measured)
Year : 1997
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Test substance : Purity of test substance was not specified, but is probably typical Dow Chemical Company commercial product as described in Sections 1.1 -1.4.
Reliability : (4) not assignable
Purity of test material was not specified, and this value is not in close agreement with all other values given.
Reference : Dill DC, Davis JW (1997). Environmental assessment of the Dowanol glycol ethers P-series product family. Dow Chemical Company Study ID ES-3186. August 12, 1997. Unpublished Report.

09.03.2005

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = 1.52 at °C
pH value : = 7 -
Method : other (calculated)
Year : 2005
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Test condition : The input to the model was CAS No. 770-35-4.
Reliability : (2) valid with restrictions
The value was estimated using the EPIWIN model program.
Flag : Critical study for SIDS endpoint
Reference : EPIWIN KOWWIN (v1.67).
09.03.2005

Partition coefficient : octanol-water
Log pow : = 1.497 at °C
pH value :
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability	:	(2) valid with restrictions The partition coefficient was obtained from a peer reviewed reference.
Reference	:	Dill DC, Davis JW (1997). Environmental assessment of the Dowanol glycol ethers P-series product family. Dow Chemical Company Study ID ES-3186. August 12, 1997. Unpublished Report. Staples CA and Davis JW (2002). An examination of the physical properties, fate, ecotoxicity and potential environmental risks for a series of propylene glycol ethers. Chemosphere 49:61-73.

12.03.2005

2.6.1 WATER SOLUBILITY

Solubility in	:	Water
Value	:	= 10000 mg/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Reliability	:	(2) valid with restrictions Solubility data taken from published peer reviewed monograph.
Flag	:	Critical study for SIDS endpoint
Reference	:	Dill DC, Davis JW (1997). Environmental assessment of the Dowanol glycol ethers P-series product family. Dow Chemical Company Study ID ES-3186. August 12, 1997. Unpublished Report. ECETOC Monograph (1995). The toxicology of glycol ethers and its relevance to man. Technical Report No. 64. European Centre for Ecotoxicology and Toxicology of Chemicals. Brussels, Belgium.

12.03.2005

Solubility in	:	Water
Value	:	= 11000 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other
Year	:	1999
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Reliability	:	(2) valid with restrictions Solubility data were obtained from a published peer reviewed monograph.
Reference	:	Canadian Centre for Occupational Health and Safety (2001). ChemInfo report for propylene glycol phenyl ether. Record number 197. May 2001.

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Solubility in	:	Water
Value	:	= 10630 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
Data obtained from the manufacturer's MSDS for manufacturer's typical commercial product.

Reference : Dow Chemical Company (1999). Dowanol PPH Glycol Ether MSDS (Material Safety Data Sheet).

12.03.2005

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	= 129 °C
Type	:	open cup

Reliability : (2) valid with restrictions
Measured value from a peer reviewed reference source.

Reference : Canadian Centre for Occupational Health and Safety (2001). ChemInfo report for propylene glycol phenyl ether. Record number 197. May 2001.

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Value	:	= 116 °C
Type	:	open cup

Reliability : (2) valid with restrictions
Measured value from a peer reviewed reference source.

Reference : Canadian Centre for Occupational Health and Safety (2001). ChemInfo report for propylene glycol phenyl ether. Record number 197. May 2001.

15.03.2005

Value	:	= 120 °C
Type	:	closed cup

Reliability : (2) valid with restrictions
Measured value from manufacturer on manufacturer's commercial product.

Reference : Dow Chemical Company (1999). Dowanol PPH Glycol Ether MSDS (Material Safety Data Sheet).

15.03.2005

2.8 AUTO FLAMMABILITY

Value	:	= 490°C (autoignition temperature)
Method	:	other
Year	:	2000
GLP	:	no
Test substance	:	other TS: Commercial material, n.o.s.
Reliability	:	(4) not assignable
	:	Methodology not described
Reference	:	Dow Chemical Company (1999). Dowanol PPH Glycol Ether MSDS (Material Safety Data Sheet).

2.9 FLAMMABILITY

Remark	:	The lower flammability limit of Dowanol PPh is 0.8 %vol/vol (calculated). Upper flammability limit not available.
Test Substance	:	other TS: Commercial material, n.o.s.
Reliability	:	(4) not assignable Methodology not described
Reference	:	Dow Chemical Company (1999). Dowanol PPH Glycol Ether MSDS (Material Safety Data Sheet).

2.10 EXPLOSIVE PROPERTIES

Result	:	not explosive
Method	:	other
Year	:	
GLP	:	No
Test substance	:	other TS: Commercial material, n.o.s.
Remark	:	Dowanol PPh is stable under normal storage conditions.
Reliability	:	(4) not assignable Methodology not described
Reference	:	Canadian Centre for Occupational Health and Safety (2001). ChemInfo report for propylene glycol phenyl ether.Record number 197. May 2001

2.11 OXIDIZING PROPERTIES

Result	:	no oxidizing properties
Method	:	other
Year	:	
GLP	:	No
Test substance	:	other TS: Commercial material, n.o.s.
Reliability	:	(4) not assignable Methodology not described

2.12 ADDITIONAL REMARKS

Remark	:	Disposal considerations ---------- Incinerate under controlled conditions according to local and national regulations.
Source	:	Dow Chemical Company

(3)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	Sun light
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000 molecule/cm³
Rate constant	:	= .000000000037 cm³/(molecule*sec)
Degradation	:	= 50 % after .3 day(s)
Deg. product	:	
Method	:	other (calculated)
Year	:	2005
GLP	:	
Test substance	:	other TS
Test condition	:	The input to the EPIWIN AOP program was CAS No. 770-35-4.
Test substance	:	The test substance for the program was theoretically pure CAS No. 770-35-4.
Reliability	:	(2) valid with restrictions Data estimated using a modeling program.
Flag	:	Critical study for SIDS endpoint
Reference	:	EPIWIN AOP (v1.91).

14.03.2005

3.1.2 STABILITY IN WATER

Deg. product	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Ether functions are generally stable in water under neutral, abiotic conditions at ambient temperatures. Ether functions can be hydrolyzed in the presence of boiling aqueous hydriodic acid. PPh is chemically stable in water under a variety of conditions.
Reliability	:	(2) valid with restrictions The stability of the ether functions in water under neutral conditions at ambient temperatures is well documented in organic chemistry textbooks.
Flag	:	Critical study for SIDS endpoint
Reference	:	Dow Chemical Company (1999). Dowanol PPH Glycol Ether MSDS (Material Safety Data Sheet). Fieser LF and Fieser M (1960). Organic Chemistry. D.C. Heath and Company, Boston. p.137.

15.03.2005

3.1.3 STABILITY IN SOIL

Remark	:	See section 3.5
Type	:	Soil biodegradation (aerobic and anaerobic conditions)
Soil types	:	Sandy soil (Bay County MI - 9.3 x 10^5 bacteria/gr soil) Sandy loam 1 (Tappan series) (Midland, MI - 9.9 x 10^6 bacteria/gr soil)

Sandy loam 2 (Londo series) (Bay County, MI - 9.9 x 10^6 bacteria/gr soil)

Test Concentrations : Sandy soil: 1 or 100 ppm PPh nominal (1.5 or 108 ppm actual)
Tappan sandy loam: 1 or 100 ppm PPh nominal (1.5 or 104 actual)
Londo sandy loam: 1, 10, or 100 PPh nominal (1.4, 10, or 107 actual)

Contact time : Up to 2 months

Degradation : See results below

Deg. Product : Metabolism and mineralization to CO_2.

Protocol Guideline : None cited.

Year of Study : 1991

GLP : Yes

Test substance : Propylene glycol phenyl ether

Method : For the aerobic assessment, biodegradation in soil was studied by placing 20 grams of soil (dry weight) and 20 grams of water in a glass container with ^{14}C-radiolabeled PPh (labeled in the phenyl moiety) dissolved in 1,4-dioxane. PPh was added at nominal concentrations of 1, 10, or 100 ppm to the Londo sandy loam, and 1 or 100 ppm to the sandy soil and Tappan sandy loam. Whether ppm meant vol/vol, wt/wt, etc., dry wt soil or wet weight soil, was not defined in the report. The three soils used are described above. An excess of oxygen was supplied to ensure aerobic conditions. Duplicate microcosms were incubated in the dark at 25±2°C for 7 days. Radioactivity was recovered by extraction with 20 ml acetonitrile. The extract was separated by HPLC and radioactive fractions were counted by scintillation for characterization and quantification of metabolites and by-products (CO_2 was converted to bicarbonate and carbonate before separation). Sterile controls were used to distinguish biological chemical degradation.

For the anaerobic assessment, microcosms were prepared and treated as above but were sealed with an atmosphere of 70% nitrogen, 28% carbon dioxide, and 2% hydrogen. These microcosms were incubated for up to 2 months.

Results : Results of biodegradation under aerobic conditions are shown in the table below. Recovery of radioactivity was close to 100%.

Soil type	Nominal Conc ppm	Actual Conc ppm	Time to 50% removal (days)	Max CO_2 (%)
Londo	1	1.4	<1	31
Londo	10	10	<2	50
Londo	100	107	<5	43
Tappan	1	1.5	<1	38
Tappan	100	104	<7	55
Sand	1	1.5	<5	62
Sand	100	108	<23	66

After 2 months under anaerobic conditions (at a nominal concentration of 10 ppm PPh), a 16% reduction in PPh was observed in sodium acetate supplemented microcosms whereas, in the sterile controls, a 7% reduction was observed. Where sodium acetate was not used as a supplement, a 9% reduction was observed after 2 months compared to 4% in the sterile controls. HPLC revealed no breakdown products.

Conclusions : PPh was quickly biodegradable in all three soil types under aerobic conditions but not biodegradable under anaerobic conditions. The sandy soil biodegraded PPh somewhat more slowly than the sandy loams probably because of the approximately 10-fold lower microorganism concentration. The biodegradation rate was dependent on the initial concentration of PPh with higher concentrations of PPh taking longer to reach the 50% biodegradation point. CO_2 comprised 31 to 66% of the biodegradation products of PPh.

Under anaerobic conditions, only a small portion of PPh was biodegraded and addition of sodium acetate as a supplemental carbons source did not facilitate this process.

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 (that 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 no OECD or EPA protocol guidelines were referenced, the report provided documentation that the study was conducted to standards provided in OECD Protocol 304 "Inherent Biodegradability in Soil." Specifically, the incubation conditions and the inoculum used were mostly as prescribed in the aforementioned guidance. Test material characterization was adequate. The concentrations tested, the length of the monitoring period, and method for measuring test compound degradation were typical for this type assay and adequately recorded.

Reference : Gonsior, S.J., West, R.J., (1991). Biodegradation of Dowanol PM, Dowanol PPH, and Dowanol PMA glycol ethers in soil. Dow Chemical Company Study No. ES-2232. November 8, 1991. Unpublished study.

Other : PPh is quickly degraded in soils.

Source : Dow Chemical Company

(6)

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
Media : other: air, water, soil and sediment
Air : 1.03 % (Fugacity Model Level I)
Water : 46.6 % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : .104 % (Fugacity Model Level II/III)
Soil : 52.3 % (Fugacity Model Level II/III)
Method : other: calculated
Year : 2005

Result : The Fugacity model level III program estimates the following half-lives: air = 6.907 hours, water = 360 hours, soil = 360 hours and sediment = 1440 hours. The EPIWIN HENRY program (v3.10) provides a bond estimate of the Henry's Law Constant of 2.05E-008 atm-m3/mole. The EPIWIN PCKOC program (v1.66) calculates a Koc (soil/sediment partition constant) of 18.7.

Test condition : Inputs to the model program were CAS No. 770-35-4, melting point 11.4 degrees C, boiling point 214.7 degrees C, vapor pressure 0.022 mm Hg and water solubility 10,000 mg/l. Default emission rates of 1000 kg/hr to air, water and soil were used.

Test substance : The test substance inputted into the model was theoretically 100% pure CAS No. 770-35-4.
Reliability : (2) valid with restrictions
The data were estimated using a model program.
Flag : Critical study for SIDS endpoint
Reference : EPIWIN Level III Fugacity program
14.03.2005

Type : fugacity Model Level III
Media :
Air : 1.03 % (Fugacity Model Level I)
Water : 46.6 % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : .104 % (Fugacity Model Level II/III)
Soil : 52.2 % (Fugacity Model Level II/III)
Method : other : Mackay Level III and EPIWIN/AOP (v3.10) Program
Year : 2002
Results : CHEMICAL PROPERTIES

Chemical Type: 1
Molecular Mass (g/mol): 152.21
Data Temperature (Degrees Celsius): 25
Log Kow: 1.5
Water Solubility (g/m3): 10000
Water Solubility (mol/m3): 65.6987
Henry's Law Constant (Pa.m3/mol): 4.414091E-02 (4.47E-07 atm-m^3/mol)
Vapour Pressure (Pa): 2.90
Melting Point (Degrees Celsius): 11.4
Half-Life in Air (h): 22
Half-Life in Water (h): 216
Half-Life in Soil (h): 168
Half-Life in Sediment (h): 168
Half-Life in Suspended Sediment (h): 168
Half-Life in Fish (h): 168
Half-Life in Aerosol (h): 216

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

Log Octanol-Water Partition Coefficient: 1.5
Octanol-Water Partition Coefficient: 31.62278
Organic Carbon-Water Partition Coefficient (L/kg): 12.96534
Air-Water Partition Coefficient: 1.78072313961456E-05
Soil-Water Partition Coefficient: 0.622336204283694
Soil-Water Partition Coefficient (L/kg): 0.259306751784872
Sediment-Water Partition Coefficient: 1.24467240856739
Sediment-Water Partition Coefficient (L/kg): 0.518613503569745
Suspended Sediment-Water Partition Coefficient: 6.22336229541321
Suspended Sediment-Water Partition Coefficient (L/kg): 2.59306762308884
Fish-Water Partition Coefficient: 1.517893
Fish-Water Partition Coefficient (L/kg):1.51789331436157
Aerosol-Water Partition Coefficient: 0
Aerosol-Air Partition Coefficient: 2068965.4191194

Reliability : (2) Valid with restrictions
The data were estimated using a model program.
Dill DC, Davis JW (1997). Environmental assessment of the Dowanol glycol ethers P-series product family. Dow Chemical Company Study ID ES-3186. August 12, 1997. Unpublished Report

Staples CA and Davis JW (2002). An examination of the physical properties, fate, ecotoxicity and potential environmental risks for a series of propylene glycol ethers. Chemosphere 49:61-73)

3.3.2 DISTRIBUTION

Remark	:	See section 3.3.1 above note: this information was moved to section 3.1. Data appears in Second summary
Distribution at Equilibrium	:	See EPIWIN modeling results below
Air	:	1.03%
Water	:	46.6%
Soil	:	52.2%
Sediment	:	0.104%
Source	:	EPIWIN/AOP (v3.10) Program
Remark	:	Henry's Law Constant = 4.47E-07 atm-m^3/mol (or 4.47E-02 Pa-m^3/mol).
Source	:	Dow Chemical Company

(1,5)

3.4 MODE OF DEGRADATION IN ACTUAL USE

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

3.5 BIODEGRADATION

Type	:	Aerobic
Inoculum	:	other bacteria: Sediment and activated sludge from a domestic sewage treatment plant.
Concentration	:	
Contact time	:	28 days
Degradation	:	= 72% after 28 days
Result	:	readily biodegradable
Kinetics of test substance	:	Day 5.1 = 10% Day 9.8 = 60% Day 28 = 72%
Control substance	:	Benzoic acid, sodium salt
Kinetic	:	3 day(s) = 60 % 28 day(s) > 100 %
Deg. Product	:	Yes
Method	:	OECD Guideline 301F "Manometric Respirometry Test"
Year	:	1998
GLP	:	Yes
Test substance	:	as prescribed by 1.1 -1.4 Identity: Propylene glycol phenyl ether, PPh, (1-phenoxy-2-hydroxypropane or propylene glycol normal-butyl ether). CAS # 770-35-4 (also 41593-38-8) Batch No.: MA30011T02 Purity: 95%
Remark	:	Degradation and kinetics results listed above are based on O2 consumption

Test condition : To test for its biodegradability potential, PPh was incubated for 28 days in continuously agitated closed, 1 liter bottles in the dark (in duplicate) at a concentration of 92.4 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 a pH of 7.2 to 7.6. The incubation temperature was 22±1°C. Controls were: 1) sodium benzoate at 198.1 mg/liter with inoculum (positive or reference control), 2) inoculum alone (to determine O_2 depletion, CO_2 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 PPh to determine and correct for non-biological degradation. Degradation of PPh was monitored by assessing 1) the disappearance of O_2, 2) the evolution of CO_2 gas from mineralization of the exogenous organic substrate by the inoculum, and 3) the disappearance of organic carbon. O_2 and CO_2 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 O_2 uptake by PPh minus O_2 uptake by blank) divided by the theoretical oxygen demand (ThOD), times 100. For CO_2 evolution, biodegradation was measured by first subtracting the CO_2 evolved by the blanks from the CO_2 evolved by the PPh sample and dividing the result by the theoretical CO_2 (Th CO_2). The resulting mineralization yield was divided by the theoretical maximum CO_2 that could be evolved from PPh (i.e., ThCO_2), to give the biodegradation based on CO_2 evolution. A similar calculation was used to express biodegradation based on the disappearance of dissolved organic carbon.

Results :

Incubation of PPh with inoculum resulted in: 1) 72% degradation after 10 or 28 days based on O2 consumption, 2) 61% degradation after 28 days based on CO2 evolution, and 3) 72% based on DOC removal. The sodium benzoate reference compound showed 60% biodegradation after 2.6 days (based on O2 consumption) and 107%, 82%, and 96% degradation after 28 days (based on O2 consumption, CO2 evolution and DOC removal, respectively). The negative control blanks showed appropriate levels of O2 consumption, CO2 production, and DOC removal.
The pH remained within the required range of 6.0 -8.5 over the course of the study.

Conclusions : By all measures of biodegradation, PPh 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).

Reliability : (1) valid without restriction
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 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.

Reference : 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.

Flag : Critical study for SIDS endpoint

(7)

Method : other: OECD protocol not referenced, but the report provided documentation that the study was conducted to standards provided in OECD Protocol 304 "Inherent Biodegradability in Soil."

Year : 1991

GLP : Yes

Test substance : as prescribed by 1.1 - 1.4

Test condition : The study was soil biodegradation (aerobic and anaerobic conditions). The soil types were: Sandy soil (Bay County MI - 9.3 x 10E5 bacteria/gr soil), Sandy loam 1 (Tappan series) (Midland, MI - 9.9 x 10E6 bacteria/gr soil), Sandy loam 2 (Londo series) (Bay County, MI - 9.9 x 10E6 bacteria/gr soil). The test concentrations were: Sandy soil: 1 or 100 ppm PPh nominal (1.5 or 108 ppm actual), Tappan sandy loam: 1 or 100 ppm PPh nominal (1.5 or 104 actual) and Londo sandy loam: 1, 10, or 100 PPh nominal (1.4, 10, or 107 actual).

For the aerobic assessment, biodegradation in soil was studied by placing 20 grams of soil (dry weight) and 20 grams of water in a glass container with ^{14}C-radiolabeled PPh (labeled in the phenyl moiety) dissolved in 1,4-dioxane. PPh was added at nominal concentrations of 1, 10, or 100 ppm to the Londo sandy loam, and 1 or 100 ppm to the sandy soil and Tappan sandy loam. Whether ppm meant vol/vol, wt/wt, etc., dry wt soil or wet weight soil, was not defined in the report. The three soils used are described above. An excess of oxygen was supplied to ensure aerobic conditions.

Duplicate microcosms were incubated in the dark at 25±2°C for 7 days. Radioactivity was recovered by extraction with 20 ml acetonitrile. The extract was separated by HPLC and radioactive fractions were counted by scintillation for characterization and quantification of metabolites and by-products (CO_2 was converted to bicarbonate and carbonate before separation). Sterile controls were used to distinguish biological chemical degradation.

For the anaerobic assessment, microcosms were prepared and treated as above but were sealed with an atmosphere of 70% nitrogen, 28% carbon dioxide, and 2% hydrogen. These microcosms were incubated for up to 2 months.

Results : Results of biodegradation under aerobic conditions are shown in the table below. Recovery of radioactivity was close to 100%.

Soil type	Nominal Conc (ppm)	Actual Conc (ppm)	Time to 50% removal (days)	Max CO_2 (%)
Londo	1	1.4	<1	31
Londo	10	10	<2	50
Londo	100	107	<5	43
Tappan	1	1.5	<1	38
Tappan	100	104	<7	55
Sand	1	1.5	<5	62
Sand	100	108	<23	66

After 2 months under anaerobic conditions (at a nominal concentration of 10 ppm PPh), a 16% reduction in PPh was observed in sodium acetate supplemented microcosms whereas, in the sterile controls, a 7% reduction was observed. Where sodium acetate was not used as a supplement, a 9% reduction was observed after 2 months compared to 4% in the sterile controls. HPLC revealed no breakdown products.

Conclusions : PPh was quickly biodegradable in all three soil types under aerobic conditions but not biodegradable under anaerobic conditions. The sandy soil biodegraded PPh somewhat more slowly than the sandy loams probably because of the approximately 10-fold lower microorganism concentration. The biodegradation rate was dependent on the initial concentration of PPh with higher concentrations of PPh taking longer to reach the 50% biodegradation point. CO_2 comprised 31 to 66% of the biodegradation products of PPh.

Under anaerobic conditions, only a small portion of PPh was biodegraded and addition of sodium acetate as a supplemental carbons source did not facilitate this process.

Reliability : (1) valid without restriction
The data quality from this study is considered good. The report included documentation for methods and results. The report included GLP and Quality Assurance statements, signed by the Study Director and Head of the QA Unit, respectively. Although no OECD or EPA protocol guidelines were referenced, the report provided documentation that the study was conducted to standards provided in OECD Protocol 304 "Inherent Biodegradability in Soil." Specifically, the incubation conditions and the inoculum used were mostly as prescribed in the aforementioned guidance. Test material characterization was adequate. The concentrations tested, the length of the monitoring period, and method for measuring test compound degradation were typical for this type assay and adequately recorded.

Reference : Gonsior, S.J., West, R.J., (1991). Biodegradation of Dowanol PM, Dowanol PPH, and Dowanol PMA glycol ethers in soil. Dow Chemical Company Study No. ES-2232. November 8, 1991. Unpublished study.

3.6 BOD5, COD OR BOD5/COD RATIO

Remark : BOD5 = 3% of TOD
BOD20 = 42% for municipal seed
BOD20 = 50% for industrial seed
Source : Dow Chemical Company
Reliability : (4) not assignable. Documentation insufficient for assessment.

(8)

3.7 BIOACCUMULATION

BCF : .776
Method: : other: estimated using EPIWIN BCF Program (v2.15)
Year : 2005
GLP : no
Test substance : as prescribed by 1.1 – 1.4
Remark : Low potential for bioaccumulation based on high water solubility.

Result	:	estimated log BCF = -0.110
Test condition	:	The input to the program was CAS No. 770-35-4.
Reliability	:	(2) valid with restrictions The data were estimated using a model program

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	Static
Species	:	*Leuciscus idus*
Exposure period	:	96 hour(s)
Unit	:	mg /liter
Analytical monitoring	:	no
NOEC	:	= 215
LC50	:	215 …464
Limit test	:	no
Protocol Guideline	:	Other: Specific guidance not referenced. However, OECD Guideline 203 "Fish, Acute Toxicity Test" followed.
Year of Study	:	1988
GLP	:	Yes
Test substance	:	As prescribed by 1.1 – 1.4 Identity: Solvenon PP (1-phenoxy-2-hydroxypropane or propylene glycol phenyl ether, commercial mixture). Purity: 100% CAS # 770-35-4
Test conditions	:	Adult Golden Orfe fish (*Leuciscus idus, l.*) were exposed under static (slightly aerated) conditions to Solvenon PP (propylene glycol phenyl ether. PPh) to nominal concentrations of 0, 100, 215, 464, or 1000 mg/liter for a period of 96 hours. Actual concentrations were not determined. These exposure concentrations were selected from a pilot study. Each exposure group was comprised of 10 fish (sex unspecified). Fish were observed for mortality and signs of toxicity at 1, 4, 24, 48, 72, and 96 hours after exposure to the test material. Clinical signs observed for included: narcosis, tumbling swim, gasping, etc. The design is shown with some results in the table below. Exposures were conducted in 10 liter glass vessels maintained at a temperature of 20±1°C. Ten fish of 6.6-9.1 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. The content of each vessel was renewed midway through the exposure period. Water: Temperature: 20 +/- 1°C Total Hardness: ~ 2.5 mmole/liter Acid Capacity: ~5.5 mmole/liter Oxygen Content: > 60% of maximum saturation pH: ~ 8.0

Results : An overview of the results is shown in the following table.

Group	PPh Conc.* (mg/L)	No./Conc.**	No. Dead	Symptoms
1	0	10	0/10	None
2	100	10	0/10	None
3	215	10	0/10	Narcosis & Tumbling at 1 hr; Narcosis only at 4 hr.; No symptoms thereafter
4	464	10	10/10	100% mortality by 1 hr
5	1000	10	10/10	100% mortality by 1 hr

* Nominal concentration (actual concentration not determined).
** Sex not specified.

The LC50 falls within 215 and 464 mg/l. At the two highest concentrations (464 or 1000 mg/liter), all fish died during the first hour. In the 215 mg/liter exposure group, while no mortalities occurred, symptoms of tumbling swimming and a narcotic-like state were reported at 1 hour and narcosis only at 4 hours. No symptoms were noted in this group after 4 hours. In the control and lowest exposure groups (0 or 100 mg/liter), no deaths or signs of toxicity were observed over the 96 hour exposure period.

Conclusions : The 96-hr LC50 of Solvenon PP (PPh or propylene glycol phenyl ether, CAS# 770-35-4) lies between 215 and 464 mg/liter. The mortality NOEC is 215 mg/l and the NOEC for clinical signs is 100 mg/l. The rapid onset of mortality from PPh indicates that the LC50 for shorter time periods is the same. 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 PPh is not highly toxic to freshwater aquatic species.

Reliability : (2) valid with restrictions
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, the study was comprehensively documented. The study report did not specifically reference OECD Protocol 203 "Fish, Acute Toxicity Test." However, 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.

Reference : Munk, R., Kirsch, P, (1988). Report on the Study of the Acute Toxicity (in the Golden Orfe, *Leuciscus idus l*. of Solvenon PP). BASF Aktiengesellschaft. Study No. 10F0406/875079, August 23, 1988. Unpublished report.

Remark : 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 PPh is ~11,000 mg/liter (CHEMINFO, 2001), the test material is theoretically soluble at the highest concentration tested. Moreover, because of its low Henry's Law Constant of 4.47E-07 atm-m^3/mol (reflecting its low vapor pressure and relatively high hydrophilicity), PPh will not have a propensity to evaporate from the water. Finally, the chemical stability of PPh suggests that this chemical will not break down spontaneously over the 4 day exposure period. The mortality observed in the two highest exposure groups indicates that the test material had not degraded chemically and was soluble and stable enough to exert toxic effects. Although Finney is referenced as the method by which the

LC50 was calculated, no LC50 was calculated. Manual observation of the data was used to bracket the LC50 between the 215 and 464 mg/l groups. The loading factor of 4.7 grams fish to 1 liter water exceeds the recommended value in the OECD guidance of 1.0 gram/liter (Protocol 203).

Flag : Critical study for SIDS endpoint

(9)

Type : Static
Species : *Pimephales promelas*
Exposure period : 96 hours
Unit : mg/l
Limit test : no
Analytical monitoring : no data
LC50 : 280
Method : other
Year of Study : 1978
GLP : no data
Test substance : as prescribed by 1.1 -1.4

Dowanol PPH; 1-phenoxy-2-hydroxypropane or propylene glycol phenyl ether commercial mixture. The sample contained 95% propylene glycol phenyl ether, 5% dipropylene glycol phenyl ether and 0.05 - 0.07% phenol.

Test condition :

Fathead minnows (Pimephales promelas) were exposed under static (slightly aerated) conditions to Dowanol PPH (propylene glycol phenyl ether) in dechlorinated Lake Huron water for a period of 96 hours at 12 degrees C. Nominal concentrations were 0, 240, 280, 320, or 420 mg/liter Actual concentrations were not analytically determined. Each exposure group was comprised of 10 fish (sex unspecified). Fish were observed for mortality over the course of the study. Water condition data were not provided.

The concentrations that caused 10%, 50% or 90% mortality (LC10, LC50, LC90) over 96 hours and their 95 % confidence intervals were calculated using Finney's method of probit analysis.

Results : The results are shown in the table below:

Group	PPh Conc.* (mg/L)	No./Conc.**	No. Dead
1	240	10	0/10
2	280	10	6/10
3	320	10	9/10
4	420	10	10/10

* Nominal concentration (actual concentration not determined).
** Sex not specified.

None of the subjects died that were exposed to the lowest concentration of 240 mg/liter. Six of 10 died at 280 mg/l, 9 of 10 died at 320 mg/l, and 10 of 10 died at 420 mg/l. The 96-hr LC50 of PPh was calculated to be 280 mg/liter with 95% confidence limits ranging from 262.6 to 297.5 mg/liter. The slope of the dose-response curve was 27.2 (95% CL: 11.7 - 42.8).

Conclusions : The mortality NOEC is 240 mg/l. The dose-response curve is steep, indicating an abrupt transition from no effect to lethality. The magnitude of LC50 itself indicates that PPh is not highly toxic to freshwater aquatic species.

Reliability : (2) valid with restrictions
This study was conducted in 1978, prior to the introduction of published GLP and protocol guidelines. As such, the report does not contain as much documentation as a more modern report. The report does reference standard laboratory procedures for conducting a 96-hour toxicity test with fish but much of the methodology is not described in the report itself.

Reference : Dill, D.C., (1978). Evaluation of Dowanol PPH (propylene glycol phenyl ether) in the aquatic environment. Dow Report No. ES-259. November 7, 1978. Unpublished report.

Remark : These results corroborate those of the BASF study (immediately previous) with a similar LC50 in a second freshwater fish species. The arguments cited in this segment for the previous study indicate that nominal concentrations reflect actuals despite the latter not having been measured.

(8)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : Static
Species : *Daphnia magna* (Crustacea)
Exposure period : 48 hours
Unit : mg/l
Limit test : no
Analytical monitoring : no
NOEC : < 100
Protocol Guideline : other
Year of Study : 1978
GLP : No
Test substance : as prescribed by 1.1 – 1.4
Dowanol PPH; 1-phenoxy-2-hydroxypropane or propylene glycol phenyl ether, commercial mixture. The sample contained 95% propylene glycol phenyl ether, 5% dipropylene glycol phenyl ether and 0.05 - 0.07% phenol.

Test condition :

Thirty Daphnia magna per level were exposed for 48 hours to nominal concentrations of 100, 180, 320, 560, or 1000 mg PPh/liter dechlorinated Lake Huron water (at 17 degrees C). Daphnia were observed for mortality at 24 and 48 hours. At these time points, the LC50 was determined (with confidence limits) using Thompson's method of moving averages. Water conditions were not provided.

Results : Zero of 30 daphnia exposed to the lowest concentration of 100 mg PPh/liter had died after 24 hours. After 48 hours, mortality in this group had increased to 7 of 30. At the highest concentration of 1000 mg/liter, mortality was 100% by 24 hours. Mortality for these and the intermediate exposure groups are shown in the table below.

Concen.*	# Exposed**	# Dead - 24 hr	# Dead - 48 hr
100 mg/l	30	0	7
180 mg/l	30	1	9
320 mg/l	30	10	10
560 mg/l	30	11	12
1000 mg/l	30	30	30

* Nominal concentration (actual concentration not determined).
** Sex not specified.

The 24-hour LC50 was 471 mg/liter with 95% confidence limits ranging from 439 to 506 mg/liter. The 48-hour LC50 was 370 mg/liter with 95% confidence limits ranging from 321 to 431 mg/liter. The NOEC is less than 100 mg/liter for mortality.

Conclusions : These results indicate that PPh is moderately to slightly toxic to daphnia under the conditions of this test.

Reliability : (2) valid with restrictions
This study was conducted in 1978, prior to the introduction of published GLP and protocol guidelines. As such, the report does not contain as much documentation as a more modern report. The report does reference standard laboratory procedures for conducting a 96-hour toxicity test with fish but much of the methodology is not described in the report itself.

Reference : Dill, D.C., (1978). Evaluation of Dowanol PPH (propylene glycol phenyl ether) in the aquatic environment. Dow Report No. ES-259. November 7, 1978. Unpublished report.

Remark : The arguments cited in this segment for the previous BASF fish studies (2 previous) indicate that nominal concentrations reflect actuals despite the latter not having been measured.

Flag : Critical study for SIDS endpoint

(8)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : *Scenedesmus subspicatus*
Exposure period : 72 hours
Unit : mg/l
Limit test : no
Analytical monitoring : Yes
NOEC : NOEC: = 12.5
LOEC: = 25
EC10: = 55.5
EC 50: > 100
EC 90: > 100
Method : Directive 92/69/EEC, C.3
Year of Study : 1992
GLP : Yes
Test substance : other TS

Identity: Protectol PP
Synonyms: Propylene Glycol Phenyl Ether, PPh

Purity: Isomeric mixture (86/14). Presumably, this means 86% 1-phenoxy-2-propanol (*secondary alcohol*, CAS No. 770-35-4) and 14% 2-phenoxy-1-propanol (primary alcohol, CAS No. 41593-38-8).

Test condition : Algae: 10000 cells / ml test volume

Water conditions: not provided

Test system:
Algae growth rate was tested by measurement of chlorophyll fluorescence in vivo as an indicator of cell density, followed by cell counting at the end of the test. Algae were exposed for 72 hrs at 23 +/- 2 centigrade in a 250 ml Erlenmeyer vessel. PPh concentrations were 6.25; 25; 100 and 125 mg/l. Blank control were included. Three replicates were incorporated per concentration.

Monitoring:
Fluoroscence measurements after 0, 24, 48 and 72 hrs. pH was measured at the start and the end of the exposure period. The concentration of the test substance was analytically monitored by a HPLC method with UV detection. The recovery rate was greater than 80%.

Results : Effect on growth rate is listed above under the NOEC, EC10, EC50 and EC90 headings.

Effect on the development of biomass (72 hrs)
EbC10 = 37.2 mg/l
EbC50 = 74.5 mg/l
EbC90 > 100 mg/l

Conclusions : These results indicate that PPh is slightly toxic to algae under the conditions of this test.

Reliability : (1) Valid without restriction, GLP guideline study.

Flag : Critical study for SIDS endpoint.
Reference : BASF Corporation. (1992). Toxicity of Protectol PP to Algae. Unpublished report.

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : other
Species : other bacteria: Pseudomonas aeruginosa , Escherichia coli, Staphylococcus aureus, Streptococcus faecalis, Bacillus subtilis
Exposure period :
Unit :
Analytical monitoring : no
Method : other
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : The results with Propylene glycol phenyl ether (PPh) are shown in the following table:

Microbe	Exposure Time (min)	1/100 dil. PPh	1/200 dil. PPh
P.aeruginosa	1	G	G
	5	G	G
	10	NG	G
	15	NG	G
E. coli	1	G	G
	5	G	G
	10	G	G
	15	NG	G
S. aureus	1	G	G
	5	G	G

	10	G	G
	15	G	G
S. faecal	1	G	G
	5	G	G
	10	G	G
	15	G	G

G = growth, NG = no growth

In the presence of 20% or 50% horse serum all strains incubated with a 1/100 dilution of PPh exhibited growth. The material did not have an effect on B. subtilis spores, even with an exposure time of 1 day at 22 degrees C.

No growth was observed in any cultures exposed to 1/1000 or 1/2000 dilutions of benzalkonium chloride (BCl). Growth of all cultures was observed in those exposed to a 1/32000 dilution of this material. The results with dilutions of benzalkonium chloride in between these concentrations are shown in the following table:

Microbe	Exposure Time (min)	1/4000	1/8000	1/16000
P.aeruginosa	1	G	G	G
	5	NG	NG	G
	10	NG	NG	G
	15	NG	NG	NG
E. coli	1	G	G	G
	5	NG	G,NG	G
	10	NG	G,NG	G
	15	NG	NG	NG
S. aureus	1	NG	G	G
	5	NG	NG	G
	10	NG	NG	G
	15	NG	NG	NG
S. faecalis	1	NG	NG	G
	5	NG	NG	NG
	10	NG	NG	NG
	15	NG	NG	NG

G = growth, NG = no growth

In cultures containing 20% horse serum, all strains except S. faecalis grew after exposure to a 1/1000 dilution of benzalkonium chloride for 1 minute. Longer exposures resulted in no growth. With 50% serum, a 1/1000 dilution of benzalkonium chloride was only effective in inhibiting growth of S. faecalis and S. aureus. The material did not have an effect on B. subtilis spores, even with an exposure time of 1 day at 22 degrees C.

When used in combination (at 1/1000 BCl plus 1/100 PPh, 1/2000 B plus 1/200 PPh and 1/4000 BCl plus 1/400 PPh, no growth was observed for any of the test conditions in any of the strains. A dilution of 1/16000 BCl plus 1/1600 PPh was only effective in inhibiting growth of S. faecalis (after 5, 10 or 15 min of exposure). Higher dilutions of the mixture were not effective in any strain. The combination of a 1/1000 dilution of BCl plus 1/100 dilution of PPh also was effective against all strains in the presence of 20% or 50% horse serum. The combination of a 1/2000 dilution of BCl plus 1/200 dilution of PPh also was effective against S. aureus and S. faecalis in the presence of 20% or 50% horse serum. The combination did not have an effect on B. subtilis spores, even with an exposure time of 1 day at 22 degrees C.

Test condition : Test materials:
Propylene glycol phenyl ether (PPh, Nipa Laboratories Ltd., Pontypridd, Glam., Great Britain) was tested in an initial sterile aqueous dilution of

1/100 (w/v) at pH = 5.6, and at lower geometrical dilutions.

Benzalkonium chloride (BCl, Norsk Medisinaldepot, Danochemo A/S, Copenhagen) was used at an initial sterile, aqueous dilution of 1/1000 (w/v) at pH = 5.6, and at lower geometrical dilutions.

Benzalkonium chloride (1/1000 w/v) + propylene glycol phenyl ether (1/100, w/v) and also were tested in combination (Ph = 5.2). Geometrical dilutions of the mixture also were tested.

The lowest dilution of each single compound as well as the lowest 2 dilutions of the mixture were also tested in the presence of 20% (pH = 7.3 - 7.7) and 50% w/v (pH = 7.5 - 7.7) normal horse serum.

Control medium: Modified HS medium plus 10% w/v normal horse serum

Bacteria: Twenty-hour (37 degrees C), beef-infusion peptone phosphate broth cultures were used as inocula. The cultures were well shaken and stored for approximately 30 minutes at 22 degrees C prior to being transferred to the disinfectant solutions. Counts revealed the following numbers of live bacteria in 1 ml inoculum: Pseudomonas aeruginosa = 7E8, Escherichia coli = 1.5E9, Staphylococcus aureus = 5E8, Streptococcus faecalis = 1E9. The spore inoculum of B. subtilits was prepared as a suspension in beef-infusion peptone phosphate broth of a 4-week agar slant culture (37 degrees C) and heated at 80 degrees C for 20 min. After cooling, counts revealed a content of 1E9 living spores per ml.

Study conduct: To one ml of each disinfectant solution was added 0.1 ml (3 drops form a Pasteur pipette) of one of the aforementioned inocula. Only suspensions free from visible lumps were transferred. The tubes were immediately sealed with sterile rubber stoppers and shaken. One standard platinum loopful (4 mm int. diam.) of each sample was transferred to the control medium (10 ml) after 1, 2, 5, 10 and 15 minutes. Controls without test materials were run for each test series. The test temperature was 22 degrees C. Tests were run in duplicate. The bacterial samples were incubated for 4 days at 37 degrees C before growth (or no growth) was recorded.

Conclusion : A combination of propylene glycol phenyl ether and benzalkonium chloride was more effective than benzalkonium chloride alone in inhibiting growth of bacteria. Propylene glycol phenyl ether was not very effective by itself.

Reliability : (1) valid without restriction
Meets generally accepted scientific standards and is described in sufficient detail.

Reference : Clausen OG and Hegna IK (1977). Determination of the bactericidal and fungicidal effects of alklydimethylbenzylammonium chloride and propyleneglycol-b-phenylether, singly and in combinations. Medd. Nor. Farm. Selsk. 39, 197-204.

15.03.2005

Type : other
Species : other bacteria: Pseudomonas aeruginosa SIFF 627, Escherichia coli Sc, Klebsiella sp. SIFF 7550, Proteus mirabilis (API) Sr, Staphylococcus aureus SIFF 1085, Streptococcus faecalis Sc
Exposure period :
Unit :
Analytical monitoring : no
Method : other
Year : 1988
GLP : no data

Test substance : other TS

Result : The results are shown in the following table:

Bacteria:	Stage 1	Stage 2	Stage 3
Pseudomonas aeruginosa:			
clean:	NG	NG	G
dirty:	NG	G	G
Escherichia coli:			
clean:	NG	NG	NG
dirty:	NG	NG	NG,G
Klebsiella sp. SIFF 7550:			
clean:	NG	NG	NG,G
dirty:	NG	G	G
Proteus mirabilis (API) Sr:			
clean:	NG	NG,G	G
dirty:	NG	G	G
Staphylococcus aureus SIFF 1085:			
clean:	NG	NG	NG
dirty:	NG	NG	NG
Streptococcus faecalis Sc:			
clean:	NG	NG	NG
dirty:	NG	NG	G

NG = no growth, G = growth. Results for both replicates are shown if different.

Test condition : Test material: The propylene glycol phenyl ether was diluted 1/200 (w/w) and mixed with a 1/1000 (w/w) solution of benzalkonium chloride. The pH of the mixture was 7.8.

Test microbes: All microbes were originally provided by Statens Institut for Folkehelse (SIFF), Oslo and were preserved at the Department of Microbiology, Institute of Pharmacy, University of Oslo. Strains labeled as Sc were test strains selected and used in the laboratory and strains labeled SR were resistant strains (especially against quaternaries). The bacterial strains were cultivated on 5% (v/v) blood agar (SIFF) for 20 hr at 37 degrees C. The test strains were taken from freeze-dried samples and all strains were cultivated 3 times on their respective media until used as inocula.

Inocula: The bacterial cultures were suspended in sterile saline (0.9%) to a fixed optical density (EEL colorimeter) corresponding to approximately 10E9 living bacteria/ml. The inocula were prepared by diluting 10 ml of this solution with 6.7 ml sterile distilled water (clean conditions) or 6.7 ml of sterilized 5% yeast suspension (dirty conditions).

Recovery medium: Dithionite-thioglycollate (HS-T) broth (Clausen medium, Oxoid Ltd., London) was used as recovery medium.

Study design: The test temperature was approximately 22 degrees C. Stage 1: Test material solution (1.5 ml) was mixed with 0.5 ml inoculum in a small glass flask. After 8 min, 0.03 ml of the mixture was transferred to and mixed in 160 ml of HS-T broth (in a 100 ml flask), with two (or more) parallels in each test. Stage 2: Ten minutes later a new dose of the 0.5 ml of the same inoculum was added to the same solution. After 18 min, new

		0.03 ml samples (at least 2) were transferred to and mixed well with the recovery medium. Stage 3: Twenty minutes from the start of the test, another 0.5 ml inoculate was added to the solution, which was now at half of its original strength. The last samples (0.03 ml), which were transferred to and mixed well with 60 ml of recovery medium, were taken 28 min after the beginning of the experiment. Each condition was tested in duplicate. The bacterial samples were incubated in recovery broth for 6 days at 37 degrees C and checked daily for growth.
Test substance	:	The test material was propylene glycol phenyl ether (Nipa Laboratories Ltd) combined with 6' benzalkonium chloride (NMD).
Conclusion	:	The combination of propylene glycol phenyl ether (1/200) and benzalkonium chloride (1/1000) was moderately effective as an antibacterial agent.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards. The effect of the material without benzalkonium chloride was not tested.
Reference	:	Hegna IK and Clausen OG (1988). An investigation of the bactericidal and fungicidal effects of certain disinfectants by use of a capacity test. Ann. Inst. Pasteur/Microbiol. 139: 473 - 483.
15.03.2005		
Type	:	other
Species	:	other fungi: Candida albicans and Aspergillus fumigatus
Exposure period	:	
Unit	:	
Analytical monitoring	:	no
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The effects of propylene glycol phenyl ether (PPh) and benzalkonium chloride (BCl) (used singly or in combination) are as follows: PPh was ineffective in both fungi at a dilution of 1/100 and exposure time of 2 hours. This dilution also was ineffective in the presence of 20% or 50% horse serum. BCl displayed a fungicidal effect on C. albicans after 2 minutes' exposure at a dilution of 1/1000. This same dilution was effective in the presence of 20% horse serum after 5 minutes of exposure. No effects of BCl were noted in the presence of 50% horse serum (even after 2 hours of incubation). The same dilution was not effective on A. fumigatus (either in the absence or presence of horse serum). The combination of 1/1000 BCl and 1/100 PPh was effective on C. albicans after 2 minutes of exposure and on A. fumigatus after 30 minutes' exposure. With 20% horse serum, the fungicidal effect on C. albicans and A. fumigatus was demonstrated after 2 minutes' and 1 hours' exposure (respectively). With 50% horse serum, the corresponding results were 5 min for C. albicans and 2-5 hours for A. fumigatus.
Test condition	:	Test materials: Propylene glycol phenyl ether (PPh, Nipa Laboratories Ltd., Pontypridd, Glam., Great Britain) was tested in an initial sterile aqueous dilution of 1/100 (w/v) at pH = 5.6, and at lower geometrical dilutions. Benzalkonium chloride (BCl, Norsk Medisinaldepot, Danochemo A/S, Copenhagen) was used at an initial sterile, aqueous dilution of 1/1000 (w/v) at pH = 5.6, and at lower geometrical dilutions. Benzalkonium chloride (1/1000 w/v) + propylene glycol phenyl ether

(1/100, w/v) and also were tested in combination (Ph = 5.2). Geometrical dilutions of the mixture also were tested.

The lowest dilution of each single compound as well as the lowest 2 dilutions of the mixture were also tested in the presence of 20% (pH = 7.3 - 7.7) and 50% w/v (pH = 7.5 - 7.7) normal horse serum.

Control medium: Modified HS medium plus 10% w/v normal horse serum

Fungi: The inoculi were prepared from solid cultures (grown on Sabouraud agar for 10 days at 25 degrees C) in beef-infusion peptone phosphate broth in mortars. The numbers of organisms per ml were as follows: C. albicans: 5 E7 and A. fumigatus 1-2E7. The inoculum of A. fumigatus consisted mainly of spores.

Study conduct: To one ml of each disinfectant solution was added 0.1 ml (3 drops form a Pasteur pipette) of one of the aforementioned inocula. Only suspensions free from visible lumps were transferred. The tubes were immediately sealed with sterile rubber stoppers and shaken. One standard platinum loopful (4 mm int. diam.) of each sample was transferred to the control medium (10 ml) after 1, 2, 5, 10, 15, and 30 minutes and 1 and 2 hours. Controls without test materials were run for each test series. The test temperature was 22 degrees C. Tests were run in duplicate. The fungal samples were incubated for 3 weeks at 25 degrees C before growth (or no growth) was recorded.

Conclusion : A combination of propylene glycol phenyl ether and benzalkonium chloride was more effective than benzalkonium chloride alone in inhibiting growth of fungi. Propylene glycol phenyl ether was not effective by itself.

Reliability : (1) valid without restriction
Meets generally accepted scientific standards and is described in sufficient detail.

Reference : Clausen OG and Hegna IK (1977). Determination of the bactericidal and fungicidal effects of alklydimethylbenzylammonium chloride and propyleneglycol-b-phenylether, singly and in combinations. Medd. Nor. Farm. Selsk. 39, 197-204.

15.03.2005

Type : other
Species : other fungi: Candida albicans Sc and Aspergillus fumigatus Sc
Exposure period :
Unit :
Analytical monitoring : no
Method : other
Year : 1988
GLP : no data
Test substance : other TS

Result : The results are shown in the following table:

Fungus:	Stage 1	Stage 2	Stage 3
C. albicans:			
clean:	NG	NG	NG
dirty:	G	G	G
A. fumigatus			
clean:	G	G	G
dirty:	G	G	G

NG = no growth

G = growth

Test condition : Test material: The propylene glycol phenyl ether was diluted 1/200 (w/w) and mixed with a 1/1000 (w/w) solution of benzalkonium chloride. The pH of the mixture was 7.8.

Test microbes: All microbes were originally provided by Statens Institut for Folkehelse (SIFF), Oslo and were preserved at the Department of Microbiology, Institute of Pharmacy, University of Oslo. Strains labeled as Sc were test strains selected and used in the laboratory and strains labeled SR were resistant strains (especially against quaternaries). The c. albicans strain was cultivated on 5% (v/v) blood agar (SIFF) for 3 days at 37 degrees C. The A. fumigatus strain was cultivated on Sabouraud agar (SIFF) at 25 degrees C before use. The test strains were taken from freeze-dried samples and all strains were cultivated 3 times on their respective media until used as inocula.

Inocula: The C. albicans bacteria were suspended in sterile saline (0.9%) to a fixed optical density (EEL colorimeter) corresponding to approximately 8E7 colony forming units/ml. The A. fumigatus inoculum was prepared in a small amount (to 2 ml) of beef extract peptone phosphate broth (SIFF), homogenized and brought to the same OD as the C. albicans inoculum with sterile saline. The inocula were prepared by diluting 10 ml of these solutions with 6.7 ml sterile distilled water (clean conditions) or 6.7 ml of sterilized 5% yeast suspension (dirty conditions).

Recovery medium: Dithionite-thioglycollate (HS-T) broth (Clausen medium, Oxoid Ltd., London) was used as recovery medium.

Study design: The test temperature was approximately 22 degrees C. Stage 1: Test material solution (1.5 ml) was mixed with 0.5 ml inoculum in a small glass flask. After 8 min, 0.03 ml of the mixture was transferred to and mixed in 160 ml of HS-T broth (in a 100 ml flask), with two (or more) parallels in each test. Stage 2: Ten minutes later a new dose of the 0.5 ml of the same inoculum was added to the same solution. After 18 min, new 0.03 ml samples (at least 2) were transferred to and mixed well with the recovery medium. Stage 3: Twenty minutes from the start of the test, another 0.5 ml inoculate was added to the solution, which was now at half of its original strength. The last samples (0.03 ml), which were transferred to and mixed well with 60 ml of recovery medium, were taken 28 min after the beginning of the experiment. Each condition was tested in duplicate. The fungal samples were incubated in recovery broth for 14 days at 25 degrees C and checked daily for growth.

Test substance : The test material was propylene glycol phenyl ether (Nipa Laboratories Ltd) combined with 6' benzalkonium chloride (NMD).

Conclusion : At the concentration tested, the material was not effective against A. fumigatus, and was effective against C. albicans only under "clean" conditions.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards. The effect of the material without benzalkonium chloride was not tested.

Reference : Hegna IK and Clausen OG (1988). An investigation of the bactericidal and fungicidal effects of certain disinfectants by use of a capacity test. Ann. Inst. Pasteur/Microbiol. 139: 473 - 483

15.03.2005

4.5.1 CHRONIC TOXICITY TO FISH

Remark : no studies
Source :

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Remark : No studies
Source :

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

Remark : No studies
Source :

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Remark : No studies
Source :

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

Remark : No studies
Source :

4.7 BIOLOGICAL EFFECTS MONITORING

Source : No studies

4.8 BIOTRANSFORMATION AND KINETICS

Source : No studies

4.9 ADDITIONAL REMARKS

Remark : no remarks

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	In vivo
Type	:	toxicokinetics
Species	:	rat
Number of animals		
Males	:	6
Females	:	
Doses		
Males	:	10 or 100 mg/kg
Females	:	
Vehicle	:	other: methyl cellulose ether
Route of admin.	:	gavage
Exposure time	:	48 hours
Method	:	Other: None specified although complies with OECD 417 "Toxicokinetics" and OPPTS 870.7485 "Metabolism and Pharmacokinetics"
Year of Study	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 – 1.4 The test material was derived from a commercial product. The specific activity of original [14C]-PPh was 6.8 mCi/mmole, with a radiochemical purity >95% (Sigma Chemical Co, Milwaukee, WI). Specific activity of both dosing solutions in 0.5% methylcellulose ether was 50 µCi/g. The C^{14} label was on the phenyl ring. Identity Propylene glycol phenyl ether (PPh). CAS # 770-35-4. Appearance: Clear, colorless liquid. Batch No.: Not specified. Source: Dow Chemical Company (Midland, MI). Expiration Date: None specified. Purity: >93% (non-labeled). Specific Gravity: 1.06 kg/liter (from other reports). Solubility in water: 10,000 mg/l (from other reports). Stability: Stable up to 200°C (from other reports). Boiling point: 253°C at 760 mmHg (from other reports). Vapor pressure: 0.029 hPa at 25°C (from other reports). Storage: Not specified.
Test condition	:	Three male rats were administered single oral doses via gavage of 10 or 100 mg C^{14}-radiolabelled PPh/kg body weight. Rats were housed in metabolism cages where urine and feces were collected in varying time increments over a total period of 48 hours and monitored for radioactivity. Urine was collected after 12, 24, and 48 hours and feces in 24-hour increments. Because urine and feces contained virtually all the administered dose, the expired air, specific tissues and the carcass were not evaluated for radioactivity. Urine samples were split into non-acid hydrolyzed and acid hydrolyzed fractions for analysis of metabolites by HPLC with a C^{14} detector. The structures of metabolites in fractions containing >5% of the dose were identified using HPLC separations equipped with electrospray ionization (ESI) and detection by mass spectrometry. Feces contained less than 5% of the dose and were not subjected to metabolite identification procedures.
Results	:	Most of the dose, 83-91%, was eliminated in the urine within the first 12 hours. Within the second 12 hours, additional urinary excretion was 3.3-6.8% of the original dose; within the last 24-hour period, an incremental 1.0 to 2.7% was excreted in the urine. A total of 93 ± 5% of the low dose (10 mg/kg) was excreted in the urine within the entire 48 hours collection

period and 96 ± 3% of the high dose (100 mg/kg) was excreted in urine within this timeframe. Over the 48-hour collection period, fecal excretion accounted for 7.1 ± 1.3% (low dose) and 5.6 ± 0.13% (high dose) of the administered dose. Urinary and fecal excretion together accounted for virtual total elimination of the administered dose within 48 hours.

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 HPLC/ESI/MS and HPLC/ESI/MS/MS techniques:

LC Peak A (<1%) – Glucuronide conjugate of hydroquinone
LC Peak B (1-2%) – Not identified
LC Peak C (1.3-3.8%) – Not identified
LC Peak D (<1%) – Not identified
LC Peak E/F (60-63%) – Sulfate and glutathione conjugates of phenol; Sulfate and glucuronide conjugates of PPh, sulfate conjugates of ring-hydroxylated PPh and 1-phenoxy-2-propanone
LC Peak G (<1%) – Not identified
LC Peak H (1-2%) – Not identified
LC Peak I (4-5%) – Glucuronide conjugate of PPh
LC Peak J (<1%) – Not identified
LC Peak K (8-9%) – Glucuronide conjugate of PPh
LC Peak L (9- 10%) – Sulfate conjugate of PPh

Based on comparisons of chromatographic retention times with authentic materials, acid hydrolysis of urine yielded free phenol (61%), hydroquinone (1.5%), and parent PPh (13%).

Conclusions : In male rats, PPh is rapidly absorbed, distributed, and quickly metabolized and eliminated. Virtually all the administered dose is eliminated within 48 hours in the urine and feces. The three major routes of metabolism are 1) cleavage of PPh by O-dealkylation, yielding propylene glycol and phenol, followed by excretion of phenol as a sulfate, or glutathione conjugate in the urine; 2) direct sulfate or glucuronide conjugation of parent PPh and excretion into the urine; and 3) ring hydroxylation of parent PPh or its oxidized propanone metabolite, followed by sulfate conjugation and excretion into the urine. Minor urinary metabolites included the glucuronide conjugate of hydroquinone.

PPh is rapidly absorbed, distributed throughout the body, and eliminated, similar to other propylene glycol ethers (PGEs). The major routes of elimination, urine and feces, also are similar to other PGEs. The types of metabolites, parent ether conjugates, hydrolyzed propylene glycol, and hydrolyzed alcohol (phenol) conjugates, also are similar.

Reliability : (1) valid without restriction
The methods followed were comprehensively documented in the report. The report consisted of a manuscript submitted for publication. The original 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 collection period was sufficient, and evaluation criteria and statistical methods were typical for this type assay and adequately recorded.

References : Saghir, S.A., Brzak, K.A., Bartels, M.J., (2003). Oral absorption, metabolism, elimination of 1-phenoxy-2-propanol in rats. Manuscript submitted for publication. Report of the Dow Chemical Company, 2003.

Remark : Because the radiolabel was on the phenol moiety of PPh, it was not possible to follow the disposition of propylene glycol after cleavage from phenol. Other studies have shown that propylene glycol is consumed in intermediary metabolism and/or exhaled as propylene glycol or CO_2. Some metabolites found in the urine from this study reflect those found when free phenol is administered to rats (i.e., sulfate and glucuronide conjugates of phenol, glucuronide conjugate of hydroquinone). The administered high dose in this study, 100 mg/kg, is approximately 1/3 to 1/5 the oral LD50 in rats published in Patty's Toxicology; 340 to 530 mg/kg (5th Ed., Vol 4, pp. 386). Frank symptoms of neurotoxicity (e.g., tremors, convulsions) have been reported in rats receiving a single phenol dose of 224 mg/kg (ibid). The rat oral LD50 of PPh is <2,000 mg/kg (1 death in 10 - highest dose tested). The much higher LD50 of PPh compared to phenol without similar symptoms would suggest that the production of phenol from O-dealkylation of PPh does not occur at a rate or to an extent to cause similar acute toxicity.

(23)

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	20
Vehicle	:	other: olive oil.
Doses	:	1000 and 2000 mg/kg bw
Value	:	> 2000 mg/kg bw
Method	:	other: Not specifically referenced. Generally follows OECD Guideline 401 "Acute Oral Toxicity"
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4

Identity:	Solvenon PP (only a separate page in a large BASF submission identifies Solvenon PP as Propylene glycol phenyl ether by the CAS# 770-3549)
Purity:	Not characterized; the report is a "sanitized" version indicating only that: "A detailed product characterization is include in the raw data."
Supplied as:	Not reported.
Administered as:	Solution in olive oil vehicle.

Test condition : Young adult male and female Wistar rats (5/sex/group) were administered single gavage doses of 1000 or 2000 mg/kg Solvenon PP (propylene glycol phenyl ether, PPh) in an olive oil vehicle. Rats were observed for mortality and signs of toxicity for 14 days after administration of the test material.

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 euthanization with CO_2 on day 14 and were subjected to gross necropsy.

Results) : The results are shown in the following table:

Group	PPh Dose (mg/kg)	PPh/- Olive Oil Ratio (mg/ml)*	Volume	#/Sex/ Dose	No. Dead (M)	No. Dead (F)	Total Dead
Group 1	1000	200 mg/ml	5 ml	5	0/5	0/5	0/10
Group 2	2000	400 mg/ml	5 ml	5	1/5	0/5	1/10

M = male
F = female
* Mg PPh per ml olive oil.

One male rat from the high dose group died on day 1; all remaining rats survived the 14-day observation period. Rats from both dose groups exhibited dyspnea, apathy, and poor general state. In the high dose group, additional symptoms included apathy, abnormal stance, staggering, atonia, paresis, absence of pain reflex, absence of corneal reflex, piloerection, and dehydration. Generally, these signs disappeared after the first day. At necropsy, the single rat that did not survive showed signs of "general congestion." No grossly observable lesions were reported in the remaining subjects that survived until study termination.

Weight gain in high dose males and females was lower than that of low dose males and females. Males in the low and high dose groups gained 64 and 51 g by 7 days (respectively) and 100 and 78 g 13 days (respectively). Females in the low and high dose groups gained 31 and 18 g by 7 days (respectively) and 43 and 24 g by 13 days (respectively). It is not known if the differences in weight gain between groups are significant since statistical analyses were not performed.

Conclusions : The oral LD50 exceeds 2000 mg/kg in rats. A single death (of 10 subjects) occurred at this level. The mortality NOAEL is 1000 mg/kg and the NOAEL for clinical signs is less than 1000 mg/kg. These results indicate low acute oral toxicity for PPh.

Reliability : (2) valid with restrictions
This study was identified as key for this toxicity endpoint because of the methods followed (which were comprehensively documented in the study 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 were as prescribed in the aforementioned guidance. 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 : Kirsch, Hildebrand, 1987. Report on the Study of Acute Oral Toxicity (for Solvenon PP). Unpublished report from BASF Aktiengesellschaft, Department of Toxicology, Project No. 10A0406/871172. November 24, 1987.

Remark : There was no control group and statistical analyses were not performed.

The oral LD50 found in this study is consistent with other published values for this chemical (see below).

Flag : Critical study for SIDS endpoint.

(10)

Type : LD50
Species : Rat

Strain	:	no data
Sex	:	Male/ female
Number of animals	:	60
Vehicle	:	
Doses	:	0.25, 0.50, 1.0, 2.0, 4.0, or 8.0 grams/kg.
Value	:	
Method	:	other
Test condition	:	Males and females (5/sex) were administered single doses of PPh at levels of 0.25, 0.50, 1.0, 2.0, 4.0, or 8.0 grams/kg.
Results	:	Male LD50: 2.83 g/kg (95% upper & lower conf. limits: 1.77 to 4.53 g/kg Female LD50: 3.73 g/kg (95% upper & lower conf. Limits: 2.42 to 4.74 g/kg
Year	:	1968
GLP	:	No
Test substance	:	As prescribed by 1.1 -1.4
Test substance	:	Propylene glycol phenyl ether, commercial, n.o.s. (not otherwise specified)
Reliability	:	(4) not assignable
Reference	:	Norris, J.M., Olson, K.J., (1968). Toxicological properties and industrial handling hazards of Dowanol PPh (1-phenoxy-2-propanol), Toxicology research laboratory report. Unpublished data, Summary Report from the Dow Chemical Company, 1968.
Reliability	:	(4) not assignable Documentation insufficient for assessment

(3, 11)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Species	:	Rat
Strain	:	Wistar
Sex	:	Male/ female
Number of animals	:	10
Vehicle	:	
Exposure time	:	4 hours
Value	:	> 5.4 mg/l
Protocol Guideline	:	OECD 403 “Acute Inhalation Toxicity.“
Year of Study	:	1991
GLP	:	Yes
Test substance	:	other TS

Identity:	Protectol PP
Synonyms:	Propylene Glycol Phenyl Ether, PPh
Purity:	Isomeric mixture (86/14). Presumably, this means 86% 1-phenoxy-2-propanol (*secondary alcohol, CAS No. 770-35-4*,) and 14% 2-phenoxy-1-propanol (primary alcohol, CAS No. 4169-04-4).
Description:	Colorless liquid.
Lot/Batch #:	P. 70-1840 (manufactured July 14, 1990).
Quantity Received:	Not specified.
Source of material:	BASF AG
Storage conditions:	Room temperature.
Stability:	Not specified.
Administered as:	Airborne aerosol.

Test condition	:	Animals (5/sex) were assigned to the test group noted in Table 1 below. Rats were exposed to Protectol PP (PPh) by nose-only inhalation exposure for 4 hours using a head-nose inhalation system INA 20 (glass-steel construction) with their snouts projected into the inhalation chamber. The test atmosphere was sampled from the breathing zone of the animals at

regular intervals to determine concentration and particle size (see below). Subjects were observed for signs of toxicity during exposure, immediately upon removal from the chambers after exposure, repeatedly on the day of exposure, and daily thereafter for 14 days. After 14 days of observation, all animals were terminated and a necropsy was performed.

Table 1. Concentrations and exposure conditions

Nominal Conc.	Analytical Conc.	MMAD (:m)	GSD (:m)
28 mg/L	5.41 ± 0.08 mg/L	1.9	3.5

Generation of the test atmosphere and description of the chamber:

Aerosol Generation: Aerosols were generated using a two-component Schlick Model 970 atomizer by mixing pure Protectol PP with air. This test material was aspirated into the atomizer using a motorized continuous infusion pump INFU 362 (INDIGEL/Switzerland) and the resulting aerosol was injected into a mixing vessel. Air-conditioned external air (1,500 liter/hr) was mixed with the aerosol inside the chamber to achieve the desired concentration. Chamber airflow was monitored at the beginning of exposures and at approximately 60-minute intervals after equilibration over the 4-hour aerosol exposure. The chamber to which the nose-only tubes attached had a volume of 55 liters. Venting and disposal of the aerosol atmosphere was not described. The airflow rate, measured at ~60 minute intervals, was 25 liters/minute, resulting in ~27 air changes per hour and sufficient to provide adequate oxygen. The time to t_{99} (equilibration time to reach 99% of target concentration) was not specified. The percent of particles that were respirable is reported below.

Test atmosphere measurement: The nominal concentration was calculated by dividing the amount of test material used per unit time, by the airflow rate. To determine actual concentrations, the test atmosphere was sampled near the breathing zone of the subjects using a sampling probe connected to a flask containing a sorption solvent (isopropanol). Five liters of test atmosphere was drawn through the sampling probe (7 mm diameter) at a sampling velocity of 1.25 m/s at approximately 1-hour intervals. The sorption solvent was analyzed for the test substance using a Hewlett Packard gas chromatograph (Model GC HP 5840 A) equipped with a flame ionization detector. GC parameters are listed in the report. Results of the analysis are given in Table 1 above.

Method : Particle size determination: To measure particle size, a sample of the chamber atmosphere (taken once during the exposure period at least 30 minutes after commencement of exposure) was drawn through an Anderson Mark III stack cascade impactor. This cascade impactor was comprised of seven stages with each stage holding a glass fiber filter of progressively smaller pore size, each designed to collect particles of a specific range of aerodynamic diameter (up to 9 micrometers). Rather than measure the net weight increase of each filter, test material was eluted from each filter stage using isopropanol as a sorption solvent. The solvent was measured for test material content using a gas chromatograph (see description above). Results of the analysis are given in Table 1 and Table 2.

Table 2: Chamber & Exposure Atmosphere Characteristics

EXPOSURE LEVEL = 5.4 MG/L	
Chamber and Exposure Data:	
Chamber volume (L)	55
Mean air flow rate (L/min)	250
Mean air changes per hour	27.27
Equilibration time (min)	not specified
Exposure time (min)	240
De-equilibration time (min)	not specified
Aerosol Concentrations:	
Calculated nominal concentration (mg/L)	28
Time-weighted mean gravimetric concentration (mg/L)	5.4
Aerosol Particle Size Analysis:	
Mass median aerodynamic diameter (:)	1.9
Geometric standard deviation	±3.5
Percentage of particles #5.5:m	91
Chamber Environmental Data:	
Temperature range (ºF)	66-77
Humidity range (%)	not specified
Oxygen content (%)	not specified

Results : No mortalities occurred as a result of exposure to this test material.

The LC50 for males is › 5.4 mg/L (or 5,400 mg/m3)
females is › 5.4 mg/L (or 5,400 mg/m3)
combined is › 5.4 mg/L (or 5,400 mg/m3)

Clinical abnormalities were noted in the test subjects on the first day of exposure but not thereafter. These included breathing difficulties during the 4-hour exposure period in all subjects. Body weight gains were not affected by exposure. No adverse findings attributable to Protectol PP were reported when animals were necropsied at the end of the 14-day observation period.

Conclusions : For “Protectol PP” (i.e. 86% CAS# 770-35-4, , 14% CAS No. 4169-04-4), administered as a liquid aerosol by inhalation to rats, the 4-hour inhalation LC50 (combined sexes) is greater than 5.4 mg/l (or 5,400 mg/m^3). No deaths occurred in 5 males or 5 females at this exposure level so the actual LC50 may be considerably higher than this value.

Reliability : (1) valid without restriction
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 specified that OECD Protocol 403: “Acute Inhalation Toxicity” was followed. Specifically, the number and type of test animal used and husbandry conditions were as recommended in this 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 : Gamer, A.O., Kirsch, P., Freisberg, K.O., (1991). Study on the Acute Inhalation Toxicity LC50 of Protectol PP as a Liquid Aerosol in rats, 4-hour exposure. BASF Akteingesellschaft. Study No. I3I0634/907055, August 30,

1991. Unpublished.

Remark : The low acute inhalation toxicity found in this study for PPh is consistent with other propylene glycol ethers.

Flag : Critical study for SIDS endpoint.

(12)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	l LD50
Value	:	> 2000 mg/kg bw
Species	:	Rabbit
Strain	:	No data
Sex	:	No data
Number of animals	:	6
Vehicle	:	
Doses		0.5, 1.0, or 2.0 g/kg bw
Value	:	>2000 mg/kg bw
Method	:	other
Year	:	1968
GLP	:	No
Test substance	:	as prescribed by 1.1 -1.4
Remark	:	The ability to draw conclusions from this study is limited due to the use of only 2 animals per dose.
RTest condition	:	Rabbits (2 per dose level –sex not specified) received single applications of 0.5, 1.0, or 2.0 grams PPh per kilogram body weight. PPh was held in contact with skin for a period of 24 hours.
Result	:	No deaths resulted from this treatment at any dose level.
Reliability	:	(4) not assignable. Documentation insufficient for assessment.
References	:	Norris, J.M., Olson, K.J., (1968). Toxicological properties and industrial handling hazards of Dowanol PPh (1-phenoxy-2-propanol), Toxicology research laboratory report. Unpublished data; Summary report from the Dow Chemical Company, 1968.

(3, 11)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Remark : no data

5.2.1 SKIN IRRITATION

Species	:	Rabbit
Concentration	:	Undiluted
Exposure	:	semi-occlusive
Exposure time	:	4 hours
Number of animals	:	3
PDII	:	
Result	:	Not irritating
EC classification	:	Not irritating
Protocol Guideline	:	OECD Guideline 404 "Acute Dermal Irritation/Corrosion"
Year of Study	:	1991
GLP	:	Yes
Test substance	:	Other TS

Identity: Protectol PP

Synonyms:	Propylene Glycol Phenyl Ether, PPh
Purity:	Isomeric mixture (84.8/15.2). Presumably, this means 84.8% 1-phenoxy-2-propanol (*secondary alcohol, CAS No. 770-35-4*) and 15.2% 2-phenoxy-1-propanol (*primary alcohol, CAS No. 4169-04-4*).
Description:	Colorless liquid.
Lot/Batch #:	P. 70-1840 (manufactured July 14, 1990).
Quantity Received:	Not specified.
Source of material:	BASF AG
Storage conditions:	Room temperature.
Stability:	Not specified.
Administered as:	Neat liquid.

Test condition : The dorso-lumbar region of three White Vienna rabbits (2 males and 1 female) was clipped free of hair at least 15 hours prior to application of the test material. On the day of treatment, gauze patches with dimensions of 2.5 x 2.5 cm were treated with 0.5 ml of the undiluted test material. One of these patches was applied to one of the sides of the rabbits. The opposite side served as the negative control. The site of application was wrapped with a semi-occlusive bandage to hold the test material in place for a period of 4 hours. At the end of the exposure period, the wrapping and gauze patches were removed and the test material was washed off using a 1:1 mixture of lutrol and water. 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. The sites were scored 30-60 minutes after removal of the test material and also at 24, 48, and 72 hours after removal. The overall irritation score was an average of the scores from the 24, 48, and 72-hour observation intervals for all three test subjects.

Results : Protectol PP was practically nonirritating as shown by the scores in the table below. When the scores for the 24, 48, and 72 hour observation periods were averaged, the average score was 0, either for erythema or edema. The only irritation score exceeding 0 was observed after 30 – 60 minutes in one of the two male rabbits, which exhibited a score of 1 (very slight) for erythema (and 0 for edema). The remaining two subjects had scores of 0 both for erythema and edema at this time interval.

			30-60 Minute Score		24-hr Score (ER, ED)		48-hr Score (ER, ED)		72-hr Score (ER, ED)	
Animal	Sex	Dose (ml)	ER	ED						
1	M	0.5	0	0	0,0		0,0		0,0	
2	M	0.5	1	0	0,0		0,0		0,0	
3	F	0.5	0	0	0,0		0,0		0,0	

ER = erythema, ED = edema

Conclusions : Results from this study indicate that Protectol PP (85% CAS# 770-35-4, 15% CAS No. 4169-04-4),) has low potential for dermal irritation.

Reliability : (1) valid without restriction.
The methods followed 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 : Kirsch, P., Hildebrand, (1991). Report on the Acute Dermal Irritation/Corrosivity to the Intact Dorsal Skin of Protectol PP in White Rabbits. BASF Akteingesellschaft. Study No. 18H0634/902206, February 21, 1991. Unpublished.

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5.2.2 EYE IRRITATION

Species	:	Rabbit
Concentration	:	Undiluted
Dose	:	0.1 ml
Comment	:	not rinsed
Number of animals	:	3
PDII	:	
Result	:	Highly irritating
EC classification	:	
Protocol Guideline	:	OECD Guideline 405 "Acute Eye Irritation/Corrosion"
Year of Study	:	1991
GLP	:	Yes
Test substance	:	Other TS

Identity:	Protectol PP
Synonyms:	Propylene Glycol Phenyl Ether, PPh
Purity:	Isomeric mixture (84.8/15.2). Presumably, this means 84.8% 1-phenoxy-2-propanol (secondary alcohol, CAS No. 770-35-4) and 15.2% 2-phenoxy-1-propanol (*primary alcohol, CAS No. 4169-04-4*).
Description:	Colorless liquid.
Lot/Batch #:	P. 70-1840 (manufactured July 14, 1990).
Quantity Received:	Not specified.
Source of material:	BASF AG
Storage conditions:	Room temperature.
Stability:	Not specified.
Administered as:	Neat liquid.

Test condition : In a primary eye irritation test, approximately 0.1 milliliter of undiluted Protectol PP (propylene glycol phenyl ether) was instilled into the conjunctival sac of the right eye of three Vienna white rabbits (2 males and 1 female). The test material was not washed out. Eyes were read for irritation at various time intervals over a period of 23 days. Readings were made at 1 hour, 24 hours, 48 hours, 72 hours, 8 days, 17 days, and 23 days. 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]). Overall scores were based on observations averaged from the 24, 48, and 72 hour observation intervals.

Results	:	Protectol PP produced average scores of 1 for corneal opacity, 0.4 for iritic damage, 2.0 for redness (erythema), and 0.9 for swelling (chemosis). These scores represented averages from the three rabbits from the three time points of 24, 48, and 72 hours. After 23 days, two rabbits (1 male and 1 female) still had scores of 1 for corneal opacity. In addition, redness scores 2 and 3 occurred through day 23 while conjunctival swelling had subsided in all subjects by day 23. These results indicate that Protectol PP has significant potential for eye irritation.
Conclusions	:	Results indicate that Protectol PP (85% CAS# 770-35-4, 15% CAS No. 4169-04-4) has a significant potential for eye irritation (i.e., severe eye irritant).
Reliability	:	(1) valid without restriction The methods followed 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 number and type of test animal used and husbandry conditions were as recommended in this guidance. Test material characterization was adequate. The amount of test material applied complied with guidance, the length of the observation period (23 days) exceeded guidance, and scoring criteria and averaging methods were typical for this type assay and adequately recorded.
Reference	:	Kirsch, P., Hildebrand, (1991). Report on the Acute Eye Irritation to the Eye of Protectol PP in White Rabbits. BASF Akteingesellschaft. Study No. 18H0634/902207, February 21, 1991. Unpublished.

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Species	:	Rabbit
Concentration	:	
Dose	:	2 drops
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	slightly irritating
EC classification	:	
Method	:	Draize Test
Year	:	1968
GLP	:	No
Test substance	:	Propylene glycol phenyl ether.
Remark	:	Study not suitable for EC classification purpose. This study does not lead to any EU classification.
Result	:	PPh produced initial conjunctival pain, slight irritation, and slight corneal injury that cleared within several days to one week.
Reliability	:	(4) not assignable. Documentation insufficient for assessment.
Reference	:	Norris, J.M., Olson, K.J., (1968). Toxicological properties and industrial handling hazards of Dowanol PPh (1-phenoxy-2-propanol), Toxicology research laboratory report. Unpublished data, the Dow Chemical Company, 1968.

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5.3 SENSITIZATION

Type	:	Buehler Test
Species	:	guinea pig
Number of animals	:	30

Result : not sensitizing
Classification : not sensitizing
Protocol Guideline : OECD Guideline 406 "Skin Sensitization"
Year of Study : 1998
GLP : Yes
Test substance : as prescribed by 1.1 -1.4

Identity: Dowanol-PPh (1-phenoxy-2-hydroxypropane or propylene glycol phenyl ether). CAS # 770-35-4 (also 41593-38-8)
Batch No.: LE08011T01
Purity: 93.7%
Supplied as: Not reported.
Appearance: Liquid.
Administered as: Undiluted

Remark : 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. Nine dilutions, as well as undiluted PPh were tested (using Methocel/water 1:20 as a diluent) including, 0.1%, 0.5%, 1%, 5%, 10%, 25%, 50%, 75%, and 100% PPh. A volume of 0.4 ml was applied in each case. No irritation occurred with undiluted PPh or lower concentrations. Consequently, 100% PPh was selected as an appropriate concentration to use in the main study.

Test condition : For the induction phase of the main study, the backs of 20 male Hartley guinea pigs were clipped free of hair and 0.4 ml of undiluted PPh 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. For the challenge phase, conducted 14 days after the third induction, 0.4 ml of undiluted PPh 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 naïve 10 males was treated similarly (received PPh during challenge phase only) in order to distinguish potential irritation effects from hypersensitization.

After the challenge dose, the site of skin application was depilitated six hours prior to the initial scoring 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. Male Guinea Pigs	Topical Induction Dose	Topical Challenge Dose
Test	PPh I, C	20	3 X 0.4 ml PPh, (6 hr)	0.4 ml PPh (6 hr)
Control	PPh C	10	None	0.4 ml PPh (6 hr)

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 : PPh did not cause contact hypersensitivity under the conditions of this test.

Reliabilty : (1) valid without restriction. The methods followed 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 specifically cited OECD Protocol 406: "Skin Sensitization." The number and type of test animal and husbandry conditions were as recommended in this guidance. Test material application, scoring intervals, and other study parameters followed guidance. The amount of test material applied complied with guidance, as did other procedures reflecting a modified Buehler assay, and findings were adequately recorded. All scoring criteria recommended in the guidance were evaluated. The data quality from this study is considered acceptable. .

References : Haut, K.T., Bell, T.J., (1998). Dowanol-PPh glycol ether: Dermal sensitization potential in Hartley albino guinea pigs. Dow Chemical Report No. HET K-005220-009, Laboratory Study ID No. 971184, 7 January 1998. Unpublished.

Remark : The findings are consistent with propylene glycol ethers in general. [moved up to other remarks section]

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5.4 REPEATED DOSE TOXICITY

Type : Sub-chronic
Species : Rabbit
Strain : New Zealand White
Sex : male/female

Test condition : Husbandry Conditions:
Age at dosing: Approximately 5 months of age.
Source: Hazleton-Dutchland, Inc., Denver, PA.
Acclimation period: At least 14 days.
Average weight at start of study: 3-4 kilograms.
Assignment to groups: Computer generated random number tables.
Diet: Certified Rabbit Chow #5322 (Ralston Purina Company, St. Louis, MO).
Access to food: Restricted to 8 ounces per day.
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 (for non-exposure periods):
Temperature: ~20°C. Recording frequency not reported.
Humidity: ~50%. Recording frequency not reported.
Air changes: Not specified.
Photoperiod: 12 hr light/12 hr dark.

Route of admin. : dermal
Exposure period : 28 days
Frequency of treatment : once daily, 5 days/week (19 applications total)
Post obs. period : none
Doses : 0, 100, 300, 1000 mg/kg bw/day
Control group : Other: distilled water (~1 ml/kg)
NOAEL : = 1000 mg/kg bw
Method : other: While a specific OECD or EPA Protocol guideline was not referenced, this study followed the requirements of EPA Protocol Guideline 870.3200 "21/28-Day dermal toxicity" and OECD 410: “Repeated Dose Dermal Toxicity: 21/28 day.”
Year of Study : 1986
GLP : Yes
Test substance : as prescribed by 1.1 – 1.4
Test substance :
Identity: Dowanol-PPh (1-phenoxy-2-hydroxypropane or propylene glycol phenyl ether). CAS # 770-35-4 (also 41593-38-8)
Batch No.: LE08011T01
Purity: 95.55% (4.37% dipropylene glycol phenyl ether (DiPPh) 0.08% Phenol)
Supplied as: Not reported.
Vapor Pressure: <1.0 mmHg.
Specific Gravity: 1.059.
Appearance: Liquid.

Remark : The NOAEL listed above is for systemic toxicity. The NOAEL for local effects on the skin is < 100 mg/kg.

Test condition : Study Design: PPh was applied daily to the clipped dorsal skin of rabbits (5/sex/dose) at doses of 0, 100, 300, or 1000 mg PPh/kg body weight-day, 5 days/week, over a period of 4 weeks (total of 19 applications). The 0 control group was treated with approximately 1 ml/kg-d distilled water. PPh was applied uniformly over a 10 x 15 cm area of the back using a syringe with a blunt needle. The dose was covered with gauze, non-absorbent cotton, then an occlusive bandage, all held in place for 6 hours with a lycra/spandex jacket. After the 6 hour exposure period, the bandage was removed and the area washed clean of PPh with a water-dampened towel. Over the course of the study, rabbits were monitored for clinical signs of toxicity, body weight changes, hematological, clinical chemistry, and urinalysis changes, as well as organ weights, gross and microscopic pathology at autopsy. Tissues were collected and preserved from all animals. Tissues examined microscopically from the high dose and control animals included: heart, liver, gall bladder, spleen, pancreas, brain, pituitary, spinal cord, peripheral nerve, adrenals, kidneys, esophagus, stomach, small intestine, sacculus rotundus, appendix, cecum, large intestine, uterus, cervix, vagina, ovaries, oviducts, testes, epididymides, prostate, urinary bladder, trachea, lungs, thymus, aorta, skeletal muscle, mediastinal lymph node, mesenteric lymph node, skin (treated and untreated), thyroid gland, parathyroid glands, nasal tissues, salivary glands, tongue, bone, mammary gland, eyes, larynx, bone marrow, mediastinal tissue, oral tissues, mesenteric tissues.

Results : All rabbits survived treatment with no changes in body weights and no overt signs of systemic toxicity. All subjects showed some dermal irritation at the site of PPh application, characterized by moderate exfoliation and hyperemia in the high dose group, slight exfoliation and transient hyperemia in the mid-dose group, and very slight exfoliation in the low dose group. No changes were noted in absolute or relative organ weights compared to controls. No consistent changes were noted in clinical laboratory studies other than a slight increase in platelet counts in males, which was statistically significant in high dose group and approached significance in mid-dose males. Females showed no platelet response to PPh exposure. Except for skin at the site of application, histopathological examination revealed no adverse changes related to PPh treatment when high dose subjects were compared to controls. In skin at the site of application, a thickening of the epidermis was detected that was considered to be an adaptive response.

Conclusions : PPh applied dermally to the backs of rabbits for 6 hr/day, 5 days/wk over a 28 day period produced no systemic toxicity at dose levels up to 1000 mg/kg-day. This study established a NOAEL of 1000 mg/kg-day.

Reliability : (1) valid without restriction
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 870.3200 "21/28-Day dermal toxicity" and OECD 410: “Repeated Dose Dermal Toxicity: 21/28 day.” 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 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	:	Calhoun, L.L., Zimmer, M.A., Schuetz, D.J., Miller, R.R., (1986). Propylene glycol phenyl ether: 28-day dermal toxicity study in rabbits. Dow Report No. HET K-005220-006. July 16, 1986. Unpublished report.
Remark	:	Note that the treatment regimen in this study differs from that of the following 14 day study in that, in this study, dosing was not performed on weekends. In addition, the daily dose was held in place for 6 hour/day in this study while the exposure period appeared to be 24 hours as described in the 14-day study.
Flag	:	Critical study for SIDS endpoint. (16)
Type	:	Sub-acute
Species	:	rabbit
Sex	:	female
Strain	:	New Zealand white
Route of admin.	:	dermal
Exposure period	:	14 days
Frequency of treatment	:	24 hr/day 7 days/week
Post obs. period	:	no data
Doses	:	1000 mg kg bw/day
Control group	:	other:distilled water
NOAEL	:	= 1000 mg/kg bw
Method	:	other : Not specified. Generally follows EPA Protocol Guideline 870.3200 "21/28-Day dermal toxicity"
Year of Study	:	1985
GLP	:	Yes
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	The NOAEL listed above is for systemic toxicity. The NOAEL for dermal irritation is < 1000 mg/kg bw.
Test substance	:	as prescribed by 1.1 – 1.4 PPh 93.4%, DPPh (dipropylene glycol phenyl ether), 5.7%, phenol 0.06%, EGPh (ethylene glycol phenyl ether) 0.3%
Test condition	:	1000 mg PPh/kg body weight was applied to the clipped dorsal skin of 10 female rabbits for 14 consecutive days under occlusion for (what appeared to be) 24 hours. Rabbits were observed for mortality and clinical signs at least once daily and were weighed immediately prior to treatment, on day 7 and on day 14. Hematology was evaluated prior to the 5^{th} and 12^{th} exposures. Urinalysis was performed at necropsy.
Results	:	Direct dermal effects included erythema and exfoliation in all rabbits. No effects on survival, body weights, urinalysis, organ weights, or gross pathology were noted. Other than incidental findings not considered related to treatment, hematological evaluation did not reveal the potential for hemolysis by PPh.
Conclusions	:	At dermal dose of 1000 mg PPh/kg body weight, applied daily for 24 hours for 14 consecutive days did not result in significant systemic toxicity.
Data Quality	:	(1) valid without restriction
Reliability	:	Meets generally accepted scientific standards and is described in sufficient detail. The methods followed 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 870.3200 "21/28-Day dermal toxicity." Specifically, the numbers and type of test animals used and their husbandry conditions followed guidance (however, only females were used). Test material characterization was adequate. The amount of test material applied

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 : Phillips, J.E., Quast, J.F., Miller, R.R., Calhoun, L.L., Dittenber, D.A., (1985) Ethylene glycol phenyl ether and propylene glycol phenyl ether: Comparative 2-week dermal toxicity study in female rabbits. Dow Study No. HET-T2.2-192-(5)P & K-5220-(5)PV. December 19, 1985. Unpublished.

Remark : In this study, ethylene glycol phenyl ether (EPh) was also tested at the same dose. EPh caused hemolysis while PPh did not.

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5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537
Concentration : up to 5000 micrograms per plate
Cytotoxic conc. : not reported
Metabolic activation : with and without
Result : negative
Method : other: Test Guidelines OECD TG 471 and TG 472 and EEC Directives 96/69 B14 and B13
Year of study : 1985
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Test condition : Test substances:

test material: Propylene glycol phenyl ether
standard plate test : 0, 20, 100, 500, 2500 & 5000 µg/plate +/- S9 mix from Arochlor-induced rat liver
preincubation test : 0, 20, 100, 500, 2500 & 5000 µg/plate +/- S9

positive controls :

with S9 :
2.5 µg 2-Aminoanthracene (2-AA)
with Salm. typh. strains TA 100, TA 98, TA 1537 & TA 1535
60 µg 2-Aminoanthracene (2-AA)
with E. coli WP2 uvrA

without S9:
5 µg N-methyl-N'-nitro-N-nitroso guanidine (MNNG)
with Salm. typh. strains TA 100 & TA 1535

10 µg 4-nitro-o-phenylenediamine (NOPD)
with Salm. typh. strain TA 98

100 µg 9-amino acridine (AAC)
with Salm. typh. strain TA 1537

10 µg N-ethyl-N'-nitro-N-nitroso guanidine (ENNG)
with E. coli WP2 uvrA

Results : No increase in number of his+ and trp+ revertants in either standard plate or preincubation test.

Result Positive controls:

Protocol	Strain	Subst.	Ind.Fact. w/o S9	Ind.Fact. w S9
Standard plate assay	TA 1535	MNNG	54	
		2-AA		6.9
	TA 100	MNNG	7.9	
		2-AA		8.5
	TA 1537	AAC	63.7	
		2-AA		10.5
	TA 98	NOPD	36.3	
		2-AA		24.7
	E. coli	ENNG	48.0	
		2-AA		5.1
Preincubation test	TA1535	MNNG	62.1	
		2-AA		6.7
	TA 100	MNNG	9.8	
		2-AA		5.3
	TA 1537	AAC	56.9	
		2-AA		10.3
	TA 98	NOPD	27.5	
		2-AA		18.2
	E. coli	ENNG	16.9	
		2-AA		5.4

Conclusions : Not mutagenic in the Ames test.
References : BASF Corporation. (1996). Ames-Test, performed in 1996 by BASF AG; Project No. 40M0344/964214; unpublished results.
Reliability : (2) valid with restrictions. This study could not be retrieved for review due to its submission under the EU Biocides directive. Only a robust summary was available from the sponsoring entity. Dose ranges were adequate. Data quality appears to be acceptable with appropriate strains tested showing verifiable sensitivity through use of standard positive controls. Postive control values were in acceptable ranges.
Flag : Critical study for SIDS endpoint.

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Type : Ames test
System of testing : *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537
Concentration : up to 5000 micrograms per plate
Cytotoxic conc. : not reported
Metabolic activation : With and without
Result : Negative
Year of study : 1985
GLP : no data
Test substance : as prescribed by 1.1 -1.4
Method : other: Not specified; description is from a ECETOC monograph review. Tests were repeated twice with each *Salmonella* strain.
Remark : S9 mix was prepared from Aroclor-induced rat liver
Results : Negative
Conclusions : Not mutagenic in the Ames test.
Reference : Bootman, J., May,K., (1985). Mutagenicity studies. Ames test. Report, December 1985. Life Science Res.Ltd. UK.
Reliability : (4) not assignable. This study could not be retrieved for review due to its submission under the EU Biocides directive. The information reported is from secondary review sources and is brief.

Reference	:	ECETOC Monograph. (1995). Technical Report No. 64. The toxicology of glycol ethers and its relevance to man. August 1995. European Centre for Ecotoxicology and Toxicology of Chemicals. Brussels, Belgium (18) (4)
Type	:	chromosome aberration test
System of testing	:	peripheral human lymphocytes
Concentration	:	up to 400 micrograms per milliliter culture medium
Cytotoxic conc.	:	not reported.
Metabolic activation	:	With and without
Result	:	Negative
Year of Study	:	1986
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Method	:	.other
Results	:	No increase in aberration frequency found, either with or without metabolic activation.
Conclusions	:	Not claustogenic in peripheral human lymphocytes
Reference	:	Bootman, J., (1986). Mutagenicity test. Metaphas analysis. Human peripheral lymphocytes. Chromosome aberration. Confid. Report NIPA Lab. Ltd. Life Science Res. Mid Clamorgen, GB-CF-38-25N, UK.
Test condition	:	S9 mix was prepared from Aroclor-induced rat liver. Ethyl methanesulfonate (400 µg/ml) and cyclophosphamide (6 µg/ml) served as positive controls for non-activation and activation systems, respectively.
Reliability	:	(4) not assignable. This study could not be retrieved for review due to its submission under the EU Biocides directive. The information reported is from secondary review sources and is brief.
Reference	:	ECETOC Monograph. (1995). Technical Report No. 64. The toxicology of glycol ethers and its relevance to man. August 1995. European Centre for Ecotoxicology and Toxicology of Chemicals. Brussels, Belgium (19) (4)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	micronucleus assay
Species	:	mouse
Strain	:	CD-1
Sex	:	male
Route of Administration	:	gavage
Exposure period	:	2 days
Concentration	:	0, 500, 1000, or 2000 mg /kg bw
Result	:	positive
Remark	:	The authors of this study concluded that, most likely, the increased incidence of micronuclei seen at 2000 mg/kg-day was attributable to the hypothermia induced by PPh and not as a direct claustogenic effect from PPh. The authors cited papers by Asanami et al. showing that agents such as reserpine and chlorpromazine, which induce hypothermia, cause increased micronuclei as an indirect result of this physiological change. Asanami et al. hypothesize that hypothermia may cause claustogenic injury by interfering with microtubule assembly and spindle function.
Method	:	Although the report indicates that EPA and OECD protocol guidelines were followed, no specific protocol guidelines were mentioned in the report. However, OECD Guideline 474 " Mammalian Erythrocyte Micronucleus Test" and EPA 870.5395 were followed.
Year of Study	:	2000
GLP	:	yes

Test substance : Identity: Dowanol-PPh (1-phenoxy-2-hydroxypropane or propylene glycol phenyl ether). CAS # 770-35-4 (also 41593-38-8)
Batch No.: 04114EU
Purity: 93.35%
Appearance: Colorless liquid.
Source: Aldrich Chemical Company.
Administered as: Dilution in corn oil.

Test condition : Groups of 6 male mice (outbred CD-1 (1CR)BR, 8-12 weeks old) per dose level from Charles River Laboratories, Portage, MI were administered 0, 500, 1000, or 2000 mg PPh/kg body weight by gavage on 2 consecutive days by oral intubation. PPh was mixed in corn oil to achieve a constant dosing volume among groups. These doses were selected from a pilot dose-range finding study. Because hypothermia resulted from treatment in this Phase 1 study, particularly in the high dose subjects, the experiment was repeated with both sexes (Phase 2) with 6 additional animals in the high dose group to serve as replacements in the event of mortality. The study design is shown below:

Dose Level (mg/kg-d)	# Consec Daily Doses	# Mice	Post-last-dose termination time (hr)
Phase 1			
0 (corn oil)	2	6 males	24
500	2	6 males	24
1000	2	6 males	24
2000	2	6 males	24
CP* 120	1	6 males	24
Phase 2			
0 (corn oil)	2	6 m & f	24
500	2	6 m & f	24
1000	2	6 m & f	24
2000	2	12 m & f	24
CP* 120	1	6 m & f	24

* CP = Cyclophosphamide monohydrate dissolved in distilled water.

For PPh, dosing solution concentrations were adjusted (diluted in corn oil) in order to provide a dosing volume of 2 ml/kg body weight. Cyclophosphamide monohydrate was used as the positive control agent and was administered in distilled water at a dose level of 120 mg/kg body weight. Mice were observed for mortality and clinical signs of toxicity at least once/day following the initial dose. Body temperature was collected using an implanted transponder; temperatures were recorded immediately prior to dosing, 6-hours post-dosing, and prior to termination.

24-Hours after the last dose, mice were euthanizedd with CO_2 and bone marrow was collected by aspiration from both femurs. Bone marrow was mixed with 0.5 ml serum, then centrifuged. The resulting pellet was resuspended, smeared onto slides, allowed to dry, and stained with Wright-Giemsa. For each subject, 2000 polychromatic erythrocytes (PCEs) were examined microscopically for the presence of micronuclei (MN-PCE). The number of MN-PCE was expressed as a percentage of total PCE.

Results : In Phase 1, 1 of 6 males died from treatment in the high dose group (2000 mg/kg-d). Autopsy did not reveal a cause for death. Three males from this group (including the one that died) showed clinical signs of shallow breathing, decreased to absent activity, and hypothermia. The two surviving animals showing hypothermia were placed in a warm environment. No deaths, clinical signs, or hypothermia occurred in the lower dose groups or in the cyclophosphamide control groups. The high dose group showed an average increased frequency of micronuclei. The %MN-PCE (% micronuclei) values from two animals with hypothermia accounted for the increased average of this group and the authors of the study attributed the increase to hypothermia. These values were 18.0 %

and 11.5% while the values in the three other survivors were 1.0%, 4.5%, and 3.0%, similar to the corn oil control group values. For more perspective on the effects of hypothermia upon micronuclei frequency, see "Remarks". Subjects treated with lower doses of PPh showed no effects on any parameter.

In Phase 2, the effects seen in Phase 1 were observed again in the 2000 mg/kg-day group. Although not statistically significant, the %MN-PCE was elevated once more. Marked hypothermia was observed yet again at this dose level only in both sexes. As in Phase 1, the ratio of polychromatic (PCE) to normo-chromatic erythrocytes (NCE) was decreased in the high dose group. Body weights were unaffected in either Phase.

Results are tabulated in the table below:

Dose Level (mg/kg/d)	Deaths	Clin. Signs	Hypot her.	% PCE (± S.D)	% MN-PCE (± S.D)
Phase 1					
0	0/6	0/6	N/R**	61.4 (± 9.4)	2.9 (± 2.2)
500	0/6	0/6	N/R**	60.4 (± 6.9)	1.6 (± 0.9)
1000	0/6	0/6	N/R**	60.3 (± 3.0)	2.2 (± 2.1)
2000	1/6	3/6	N/R**	55.7 (± 5.0)	7.6 (± 7.0)
CP* 120	0/6	0/6	N/R**	45.5 (± 9.3)	37.4 (± 17.6)
Phase 2 (males)					
0	0/6	0/6	0/6	56.3 (± 12.3)	0.5 (± 0.4)
500	0/6	0/6	0/6	59.6 (± 8.2)	0.8 (± 0.4)
1000	0/6	2/6	0/6	60.1 (± 11.5)	0.5 (± 0.6)
2000	4/12	10/12	7/7	48.2 (± 9.2)	4.4 (± 4.5)
CP* 120	0/6	0/6	0/6	40.9 (± 8.1)	41.1 (± 13.5)
Phase 2 (females)					
0	0/6	0/6	0/6	64.7 (± 9.0)	0.4 (± 0.5)
500	0/6	1/6	0/6	67.9 (± 5.2)	0.3 (± 0.5)
1000	0/6	5/6	0/6	60.3 (± 5.7)	0.8 (± 0.7)
2000	6/12	12/12	8/8	53.3 (± 3.4)	4.5 (± 4.3)
CP* 120	0/6	0/6	0/6	47.0 (± 5.4)	52.8 (± 17.4)

% PCE = among PCE+NCE
% MN-PCE = among PCE
SD= standard deviation
Clin signs = clinical signs
Hpyother = hypothermia
* CP = Cyclophosphamide monohydrate dissolved in distilled water.
** N/R = Not reported.

Remark : Only males (6/dose level) were used in phase 1 while male and females (6/sex/dose level) were used in phase two.

The authors of this study concluded that, most likely, the increased incidence of micronuclei seen at 2000 mg/kg-day was attributable to the hypothermia induced by PPh and not as a direct claustogenic effect from PPh. The authors cited papers by Asanami et al. (Asanami, S., Shimono, K., (1997). High body temperature induces micronuclei in mouse bone marrow. Mutation Research, 390:70-83 and Asanami, S., Shimono, K., Kaneda, S., (1998). Transient hypothermia induces micronuclei in mice. Mutation Research, 413:7-14) showing that agents such as reserpine and chlorpromazine, which induce hypothermia, cause increased micronuclei as an indirect result of this physiological change. Asanami et al. hypothesize that hypothermia may cause claustogenic injury by interfering with microtubule assembly and spindle function.

Since a separate, additional group at the high dose level was not placed in a warmed environment after treatment to directly test the hypothesis of hypothermia causing the increased micronuclei, the possibility that the increased incidence of micronuclei at the high dose was directly attributable to PPh cannot be excluded. On the other hand, it is relevant to note that the next lower dose (still a very large dose of 1000 mg/kg) did not cause hypothermia or an increase in micronuclei. If the increase was

directly attributable to PPh and not hypothermia, it is significant that only a marginal effect resulted (not statistically significant when repeated in a second experiment), which required a very large dose of 2000 mg/kg.

Reliability : (1) valid without restriction
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 subjects and numbers per dose level employed, test substance concentrations and dose spacing (4 dose levels including negative control, with highest being 2000 mg/kg), number of doses, positive control agent used, and scoring criteria all followed or exceeded guidance as specified in OECD Guideline 474 and EPA Guideline 870.5395 " Mammalian Erythrocyte Micronucleus Test". The positive control agents gave the expected results showing that the test system was responsive to this type of toxic insult.

Flag : Critical study for SIDS endpoint.
Reference : Day, J.S., (2000). Evaluation of Dowanol PPh in the mouse bone marrow micronucleus test. Dow Chemical Company Study ID Number 991204 (File # HET K-005220-010). 7 April 2000. Unpublished report.

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5.7 CARCINOGENICITY

Remark : No studies

5.8.1 TOXICITY TO FERTILITY

Type of Study	:	Two Generation Study
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	drinking water
Exposure period	:	26 weeks
Frequency of treatment	:	7 days/week
Premating Exposure Period	:	Males: 77 days Females: 77 days
Duration of test	:	40 weeks
Doses	:	0, 100, 1000, 5000 ppm (11.3, 113.9, 477.5 mg/kg bw/day)
Control group	:	yes
NOAEL Parental	:	=5000 ppm
NOAEL F1 Offspring	:	=1000 ppm
NOAEL F2 Offspring	:	=1000 ppm
NOAEL Parental (systemic toxicity)	:	=1000 ppm
Result	:	Developmental toxicity occurred only at a dose that was toxic to the parental generation.
Method	:	OECD Guideline 416 "Two-generation Reproduction Toxicity Study"
Year of Study	:	1996
GLP	:	Yes
Test substance	:	Other TS Identity: Protectol PP Synonyms: Propylene Glycol Phenyl Ether, PPh Purity: Isomeric mixture (85/15). Presumably, this means 85% 1-phenoxy-

2-propanol (secondary alcohol, CAS No. 770-35-4) and 15% 2-phenoxy-1-propanol (primary alcohol, CAS No. 41593-38-8).

The stability of the test material in drinking water was established over a period of 96 hrs at room temperature and dose concentrations.

Remark : The relationship to treatment of reduced relative spleen weights to body weights in the progeny of high dose animals is unclear, since a similar effect was not noted in the parental animals.

Test condition : TEST ORGANISMS

F0 generation: a total of 200 rats; 25 rats per sex and dose, age 34 days at the beginning of the treatment; mean bw 120.5 g (range 102-140) for males and 106.0 g (90-122) for females.
F1 generation: a total of 200 rats, 25 rats per sex and dose of the F1 pups. The F1 animals received the same concentration in drinking water as their respective F0 parent animals.

ADMINISTRATION

PPh was continuously administered to male & female F0 and F1 animals with drinking water at concentrations of 0, 100, 1000, 5000 ppm, respectively, until animals were terminated. Solutions were prepared once or twice a week. PPh concentrations were checked at start and at 3-monthly intervals during the administration period, and at its end.

EXPERIMENTAL PROCEDURE

Animals were housed individually during the study period. F0 parental animals received PPh continuously until they were terminated. After at least 77 d, male and female animals from the same dose were paired 1:1. Females were allowed to litter and rear their pups until day 4 (standardization) or 21 after parturition (pp). F0 parental animals were euthanized after weaning of F1 pups.

After weaning, 25 males and females of the F1 pups were taken per group as the basis for the F1 parental generation. Each litter was taken into account. All animals were exposed continuously to the same PPh dose level as their parents from their growth into adulthood until they were euthanized. F1 animals were randomly paired 1:1 at least 75 days after assignment; however, pairing of siblings was avoided. Females were allowed to litter and rear their pups (F2) until day 4 (standardization) or 21 after parturition (pp). F1 parental animals and F2 animals were terminated after weaning of F2 pups.

MATING PROCEDURE

Male and female animals were generally paired overnight at a 1:1 ratio for a maximum of 3 weeks by placing the females in the cage of the male partner over night. The day on which sperm was detected was denoted day 0 and the following day "day 1 pc" (post coitum).

LITTER STANDARDIZATION

Where possible litters were standardized on day 4 pp such that each litter contained 4 male and 4 female pups; otherwise the study proceeded with 8 pups per litter (e.g. 5m, 3f). Litters with <8 pups were not standardized.

PARAMETERS ASSESSED

(1) Parental animals
Mortality and signs of toxicity were checked daily, along with nesting, littering and lactation behaviour.
Water consumption of F0 and F1 parental animals was determined once a week during the premating periods. After premating (10th wk), water consumption of females during gestation was determined for days 0-1, 6-7, 13-14 and 19-20 pc, and during lactation period for days 1-2, 4-5, 7-8 and 14-15 pp (post parturition). After day 15 pp water consumption of the F0 and F1 dams was not determined since from then onwards the pups begin to consume considerable amounts of water. Water consumption was not determined for F0 and F1 males after the premating phase and for females without evidence of sperm or without litters in the lactation phase.

Food consumption was determined once a week during the premating phase of both F0 and F1, and weekly during gestation. During lactation it was determined weekly on days 1, 4, 7 and 14, but not during 14-21 as required by the guideline since the pups start to consume considerable amounts of solid food. Food consumption was not determined for F0 and F1 males after the premating phase and for females without evidence of sperm or without litters in the lactation phase.
Intake of PPh was calculated from the daily water consumption.
Body weights of parental animals were recorded weekly with the following exceptions for females:
-during mating periods females were weighed on day 0 and on days 7, 14, 20 pc
-females without evidence of sperm were not weighed during the mating period
-females with litters were weighed on days 1,4,7,14 and 21 post partum
-females without litters were not weighed during lactation period
-F0 and F1 females were weighed after weaning of the last F1 or F2 pups, parallel to the F0 and F1 males, once weekly until termination.

Estrous cycle length and normality were evaluated for all F0 and F1 females for a minimum of 3 weeks prior to mating; this was continued throughout the mating period. Vaginal smear was examined at necropsy to determine the stage of the estrous cycle for each F0 and F1 female.
Male reproduction indices (mating and fertility index) were calculated. Sperm parameters were determined (sperm motility, morphology, sperm head count in testis and in cauda epididymis) immediately after necropsy and weighing the right testis and cauda epididymis. Sperm motility examinations were randomized; sperm morphology and sperm head count were evaluated in control and highest dose animals only.

For females, indices pertaining to mating, fertility, gestation were calculated. For F1 and F2 litters, live birth index was calculated (percentage of liveborn pups). Postimplantation loss was calculated after termination of females from the number of implantations and pups delivered.

(2) Litter data
On the day of birth all live and dead pups were examined and

sexed. Viability index and lactation index were calculated which give the percentage of surviving pups on day 4 and day 21, respectively. Sex ratios were calculated for live pups on day 4 and 21.
Pups were examined each day for clinical symptoms. Pups' body weight changes were calculated from body weight data collected on days 1, 4, 7, 14 and 21 after birth. Sexual maturation was evaluated in all pups to become the F1 parental generation, examinations initiating for females on day 27 pp, and on day 40 for males.
Pup necropsy: all pups with scheduled termination, i.e. those culled on day 4 pp, and those terminated at day 21, were examined externally and eviscerated; organs were assessed macroscopically, and additionally, if this was deemed necessary due to notable findings and abnormalities. The same procedure was applied to all stillborn pups and all pups that died up to weaning. After scheduled termination, of the pups' organs brain, spleen and thymus were weighed of one pup/sex and litter from F1 and F2 pups.
Extensive statistical evaluation of the clinical data included the use of the Dunnett-test for comparison with the control group, Fisher's exact test, Wilcoxon-test and Kruskal-Wallis-test.

(3) Pathology
Organ weights of all F0 and F1 parental animals terminated at schedule were determined: body weight, liver, kidneys, adrenals, testes, epididymides (total, cauda), prostate gland, seminal vesicles with coagulation glands, ovaries, uterus (with cervix and oviducts), thymus, spleen, brain, pituitary gland.
The following organs were fixed or embedded for histopathology: vagina, cervix uteri, uterus, ovaries, oviducts, left testicle and epididymides, seminal vesicles, coagulating glands, prostate gland, pituitary gland, liver, kidneys, urinary bladder, thymus, spleen, brain, adrenal glands, and all gross lesions. In ovaries, a Differential Ovarian Follicle Count (DOFC) was also included.
Statistical evaluation of the organ weight parameters involved Kruskal-Wallis test and Wilcoxon test, if p was equal to or < 0.05. Follicle data from DOFC were evaluated using a Wilcoxon test.

Results :

Dose: Administered mean doses in the low, intermediate and high dose group were 11.3, 113.9, and 477.5 mg/kg bw/d, respectively. PPh intake by premating F0 and F1 females was slightly enhanced compared with values for males (total treatment period) in all dose groups. PPh intake was markedly enhanced during gestation and lactation when compared with premating animals (up to ca. 1.5 fold in F0 females). Intake of PPh was also enhanced in F1 parental animals compared with F0 parents.

Low dose group at 100 ppm (ca. 11.3 mg/kg bw/d):
F0 and F1 parental animals: No substance-related adverse effects seen with respect to clinical examination, reproductive performance, organ weights, pathology and histopathology.
F1 and F2 pups: no substance-related adverse effects seen with respect to clinical examination, sexual maturation (F1 pups only), pup organ weights, pathology.

Intermediate dose group at 1000 ppm (ca. 113.9 mg/kg bw/d)

F0 and F1 parental animals: No substance-related adverse effects seen with respect to clinical examination, reproductive performance, organ weights, pathology and histopathology.
F1 and F2 pups: no substance-related adverse effects seen with respect to clinical examination, sexual maturation (F1 pups only), pup organ weights, pathology.

High dose group at 5000 ppm (ca. 477.5 mg/kg bw/d)
F0 parental animals: No mortalities were seen. Compared with controls significant reductions in consumption of water during premating (-20% males, -22% females), gestation (-21%) and lactation (-19%) and in food consumption (signifcant on some days) during premating (-6% males, -5% females), gestation (-5%) and lactation (-8%). This was paralleled by a clearly decreased body weight (bw) and body weight change (bwc) in males (-10% each). In females, reduced values were also seen during premating, gestation and lactation (bw: -6, -7, -11%; bwc: -8, -14, -8%). No adverse effects were seen with respect to reproductive performance, organ weights and pathology.
F1 pups: Significantly lower bw at weaning on d 21 (-11%, both sexes combined) and lower bwc (-13%). Concomitantly a retardation in sexual maturation as evidenced by delayed preputial separation and vaginal opening in the selected F1 male and female animals.
F1 parental animals: Significantly decreased water consumption during premating (up to -20% males, -29% females), gestation (-25%) and lactation (-33%). Mainly significantly reduced food consumption during premating (-8% males and females), gestation (-12%) and lactation (-18%). Clearly decreased bw and bwc in males (bw -19%, bwc ca. -10%). In females, reduced values were seen during premating, gestation and lactation (bw: -22, -15, -16%; bwc: +/-0, -25, -31%). Though clear effects on body weight were seen in both, males and females, level of significance was achieved only for single periods. No adverse effects were seen with respect to reproductive performance, organ weights and pathology.
F2 pups: Significantly lower mean bw in male pups from day 4 pp (post parturition) onwards. During d 7-21 pp lowered by 23% (both sexes combined). Significantly impaired bwc in male and female pups (-26%; d 4-21pp). During pathological examinations, organ weight changes (both sexes combined) were seen as follows: significantly lower mean absolute weights of brain (-6%), thymus (-23%) and spleen (-34%) compared to controls. Significant relative organ weight changes were noted for brain (+30%) and spleen (-18%).

Conclusions : PPh was continuously administered with drinking water to rats over two parental generations at concentrations of 0, 100, 1000 and 5000 ppm.

Reproductive performance or fertility was not affected in F0 or F1 parental animals of either dose group. Estrous cycle, mating behavior, conception, gestation, parturition, lactation and weaning as well as sperm parameters, sexual organ weights, and gross and histopathological findings of these organs were similar between control and treated animals.

Signs of general, systemic toxicity were noted in both parental generations (F0 and F1) in groups receiving 5000 ppm, but not in others. Toxicity was characterized by decreased water and food consumption, decreased body weight and body weight gain in parental F0 an F1 males and females. Pathology and histopathology did not reveal substance-related adverse effects in F0 and F1 parental animals.

The clinical, gross and histopathological examinations in F0 and F1 parental animals from the low and intermediate dose groups did not yield any indication of systemic toxicity.

Substance-related signs of developmental toxicity were seen in progeny of the high dose (5000 ppm) F0 and F1 parents in terms of reduced pup body weight and body weight gain. This is directly related to lower absolute weights of the thymus, spleen and brain in pups and delayed sexual maturation. The increase in relative brain weights and decrease in relative spleen weights of progeny of the 5000 ppm group are of potential concern. Moreover, reproduction parameters of these animals were not adversely affected after gaining sexual maturity. This supports the view that delayed preputial separation and vaginal opening resulted from a general retardation of physical development. No signs of developmental toxicity were seen in pups from groups receiving medium or low doses (1000 or 100 ppm, resp.).

Under the conditions of this study, NOAELs were established as follows:
NOAEL for reproductive performance and fertility: 5000 ppm (about 477.5 mg PPh/kg bw/d) for the F0 and F1 parents
NOAEL for developmental toxicity: 1000 ppm (about 113.9 mg PPh/kg bw/d) for the F1 and F2 progeny
NOAEL for general systemic toxicity: 1000 ppm (about 113.9 mg PPh/kg bw/d) for the F0 and F1 parents

Thus, developmental toxicity was seen only at a dose which was also toxic to the parent animals. No sign of teratogenicity was seen at either dose in this study.

Reliability : (1) valid without restriction
Guideline study.
Flag : Critical study for SIDS endpoint.
References : BASF (2000). Report No. 71R0109/97119, 08 Sep. 2000.

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Type of Study : other: 28-Day Repeat Dose
In vitro/In vivo In vivo
Species : rabbit
Sex : male/female
Strain : New Zealand White
Test condition : Age at dosing: Approximately 5 months of age.
Source: Hazleton-Dutchland, Inc., Denver, PA.
Acclimation period: At least 14 days.
Average weight at start of study: 3-4 kilograms.
Assignment to groups: Computer generated, random number tables.
Diet: Certified Rabbit Chow #5322 (Ralston Purina Company, St. Louis, MO).
Access to food: Restricted to 8 ounces per day.

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 (for non-exposure periods):
Temperature: ~20°C. Recording frequency not reported.
Humidity: ~50%. Recording frequency not reported.
Air changes: Not specified.
Photoperiod: 12 hr light/12 hr dark.

Route of admin. : Dermal
Exposure period : 28 days
Frequency of treatment : Once daily, 5 days/week (19 applications total)
Doses : 0, 100, 300, 1000 mg/kg bw/d
Control group : yes, distilled water (~1 ml/kg)
Method : other: While a specific OECD or EPA Protocol guideline was not referenced, this study followed the requirements of EPA Protocol Guideline 870.3200 "21/28-Day dermal toxicity" and OECD 410: "Repeated Dose Dermal Toxicity: 21/28 day."
Year of Study : 1986
GLP : Yes
Test substance : As prescribed by 1.1 – 1.4

Identity: Dowanol-PPh (1-phenoxy-2-hydroxypropane or propylene glycol phenyl ether). CAS # 770-35-4 (also 41593-38-8)
Batch No.: LE08011T01
Purity: 95.55% (4.37% DiPPh, 0.08% Phenol)
Supplied as: Not reported.
Vapor Pressure: <1.0 mmHg.
Specific Gravity: 1.059.
Appearance: Liquid.

Test condition : Husbandry Conditions:
Age at dosing: Approximately 5 months of age.
Source: Hazleton-Dutchland, Inc., Denver, PA.
Acclimation period: At least 14 days.
Average weight at start of study: 3-4 kilograms.
Assignment to groups: Computer generated, random number tables.
Diet: Certified Rabbit Chow #5322 (Ralston Purina Company, St. Louis MO).
Access to food: Restricted to 8 ounces per day.
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 (for non-exposure periods):
Temperature: ~20°C. Recording frequency not reported.
Humidity: ~50%. Recording frequency not reported.
Air changes: Not specified.
Photoperiod: 12 hr light/12 hr dark.

PPh was applied daily to the clipped dorsal skin of rabbits (5/sex/dose) at doses of 0, 100, 300, or 1000 mg PPh/kg body weight-day, 5 days/week, over a period of 4 weeks (total of 19 applications). The 0 control group was treated with approximately 1 ml/kg-d distilled water. PPh was applied uniformly over a 10 x 15 cm area of the back using a syringe with a blunt needle. The dose was covered with gauze, non-absorbent cotton, then an occlusive bandage, all held in place for 6 hours with a lycra/spandex jacket. After the 6 hour exposure period, the bandage was removed and the area washed clean of PPh with a water-dampened towel. Over the course of the study, rabbits were monitored for clinical signs of toxicity, body weight

changes, hematological, clinical chemistry, and urinalysis changes, as well as gross and microscopic pathology.

Procedures Relevent to the Evaluation of Reproductive Organ Toxicity: Reproductive organs were weighed and subjected to gross and histopathological evaluation. Testis of the males were weighted but female reproductive organs were not. In control and high dose males, the following reproductive tissues were examined microscopically: testis, epididymides, seminal vesicles, and prostate. In control and high dose females, the following reproductive tissues were examined: mammary glands, ovaries, oviducts, uterus, cervix, and vagina.

Results : All rabbits survived treatment with no changes in body weights and no overt signs of systemic toxicity. All subjects showed some dermal irritation at the site of PPh application, characterized by moderate exfoliation and hyperemia in the high dose group, slight exfoliation and transient hyperemia in the mid-dose group, and very slight exfoliation in the low dose group. No changes were noted in absolute or relative organ weights compared to controls. No consistent changes were noted in clinical laboratory studies other than a slight increase in platelet counts in males, which was statistically significant in high dose group and approached significance in mid-dose males. Females showed no platelet response to PPh exposure. No histopathological changes were noted upon examination of tissues from the high-dose subjects.

Reproductive Organs: No significant differences in testes weights were evident among PPh-treated males. Female reproductive organs were not weighed. In males, gross examination revealed no unusual lesions of testes, epididymides, seminal vesicles, or prostate. In females, gross examination revealed no abnormalities of mammary glands, ovaries, oviducts, uterus, cervix, or vigina. The testis of control and high dose males were normal. Epididymides of all of the high dose males were normal but one of the controls had very slight chronic interstitial unilateral inflammation and a second control had slight granulomatous, unilateral inflammation of the musculature. Seminal vesicles of all control and treated males were normal. The prostates of all control and treated males were normal. In females, ovaries, oviducts, uteri, cervix, and vagina all were normal. Mammary glands of two of the control females exhibited galactocels but all PPh-treated females were normal. To summarize, no reproductive toxicity was evident from treatment with PPh.

Conclusions : PPh applied dermally to the backs of rabbits for 6 hr/day, 5 days/wk over a 28 day period produced no toxicity at dose levels up to 1000 mg/kg-day. This study established a NOAEL of 1000 mg/kg-day. No toxicity to reproductive organs was evident based on organ weights, gross observation, or microscopic examination.

Reliability : (1) valid without restriction
The methods followed 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 870.3200 "21/28-Day dermal toxicity" and OECD 410: “Repeated Dose Dermal Toxicity: 21/28 day.” 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 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 : Calhoun, L.L., Zimmer, M.A., Schuetz, D.J., Miller, R.R., (1986). Propylene glycol phenyl ether: 28-day dermal toxicity study in rabbits. Dow Report No. HET K-005220-006. July 16, 1986. Unpublished report.

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5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rabbit
Sex : female
Strain : Himalayan
Route of admin. : gavage
Exposure period : Days 7 through 19 of gestation.
Frequency of treatment : Daily
Duration of test : Until day 29 post insemination
Doses : 60, 180, 540 mg/kg bw/day
Control group : yes, concurrent vehicle
NOAEL Maternal Tox : = 180 mg/kg bw
NOAEL Teratogen : >540 mg/kg bw
NOAEL Embryotoxicity : = 180 mg/kg bw
Protocol Guideline : OECD Guideline 414 "Teratogenicity"
Year of Study : 1995
GLP : Yes
Test substance : Identity: Protectol PP
Synonyms: Propylene Glycol Phenyl Ether, PPh
Purity: Isomeric mixture (85/15). Presumably, this means 85% 1-phenoxy-2-propanol (secondary alcohol, CAS No. 770-35-4) and 15% 2-phenoxy-1-propanol (primary alcohol, CAS No. 41593-38-8).
Stability of Protectol PP was proven before the study and thereafter. Stability of Protectol PP in emulsion over a period of 3 hrs was proven before the study was started. Emulsions were always stirred during administration in order to prevent separation into two phases.

Test conditions : TEST ANIMALS
15 female rabbits per dose were used, age between 25 and 32 weeks at beginning of the study (day 0, day of insemination). Mean body weight (bw) was 2,727 g.

ADMINISTRATION/EXPOSURE
During a 5 d acclimatization period singly housed animals were weighed and randomly distributed to test groups. Then they were fertilized by means of artificial insemination (day 0; the following day was designated day 1 post
insemination, pi). Protectol PP was administered once daily as an emulsion in distilled water orally by gavage during days 7-19 pi. Based on the results of a preceding range finding study the selected doses were 60, 180, and 540 mg/kg body weight-day. Dose volume was 10 ml/kg bw. On day 29 pi, all animals were terminated and examined.

Study Design:

Group	PPh Dose (mg/kg-d)	Initial No. per Group	Treatment Period (days)
Group 1	0	15	7 thru 19 gest.
Group 2	60	15	7 thru 19 gest.
Group 3	180	15	7 thru 19 gest.
Group 4	540	15	7 thru 19 gest.

EXAMINATIONS
TS stability was analyzed. Emulsions were tested for stability over a 3 hrs period, homogeneity, and twice for nominal concentrations. Examinations of does included food consumption and body weights on days 0, 2, 4, 7, 9, 11, 14, 16, 19, 21, 23, 25, 29 pi. Body weight gain (BWG) was calculated from these data; corrected BWG was calculated as (terminal bw on d 29 pi) - (bw day 7 + uterus weight). The animals were checked at least once per day for signs of toxicity and mortalities.

Terminal examinations:
Dams: Surviving dams were terminated on day 29 pi; dams showing signs of abortion were also terminated and examined as at terminal examination. Terminal examination included necropsy and gross pathology assessment, removal of liver, kidneys, ovaries and uterus. Data pertaining to absolute and relative organ weights, no. of corpora lutea, no. and classification of implantation sites (live/dead fetuses, early/late resorptions) were recorded and used for calculation of conception rates, pre- and post-implantation losses, and corrected BWG.

Fetuses: Fetuses were weighed, macroscopically examined (viability, condition and weight of placenta, fetal membranes and fluids, umbilical cords), and terminated. Abdomen and thorax were opened for internal organ inspection during which heart and kidneys were sectioned. Fetuses were sexed by gonad inspection. Fetuses were preserved in EtOH for 1-5 days. They were removed and a cross section of the head was made for inspection of the brain, then fetuses were placed back into the fixative. If heads revealed severe findings, heads were removed and fixed in BOUIN's solution. Later 10 sections were made for further examinations according to WILSON. Skeletal examination of fetuses was performed on an illuminated plate after staining according to DAWSON.

Evaluation criteria for assessing the fetuses:
-malformations (concerning external, soft tissue and skeleton) permanent structural changes that may adversely affect survival, development or functions.
- variations (concerning external, soft tissue and skeleton) divergency of morphogenetic/organogenetic process, also seen in controls in high frequency that may not adversely affect survival, development or functions
- retardations (concerning skeletal observations only), delays in skeletal development; also seen in controls in high frequency that may not adversely affect survival, development or functions and soft malformations.

Unclassified observations (concerning external tissue only):
Observations other than variations: Percentages of pre- and post-implantation loss were calculated as was the degree of ossification for each fetus. Soft tissue and skeletal or anomalies or abnormalities were recorded.

Statistical evaluation of data included Dunnett's Test for simultaneous comparison of several dose groups with the control for the parameters: food consumption, BW, BWG, corrected BWG; weights of liver, kidney, unopened uterus; nos. of corpora lutea, implantations, resorptions, live fetuses; pre- and post-implantation loss, resorptions and live fetuses in each litter; litter mean fetal BW and litter mean placental weight. Fisher's Exact test was used for female mortality, females pregnant and litters with fetal findings. One-sided Wilcoxon test was used for analysis of the proportion of fetuses with malformations, variations, retardations or unclassified observations in each litter.

Results : MATERNAL DATA
Only pregnant dams were used for calculations of mean food consumption,

BW (body weight) and BWG (body weight gain), and only pregnant dams terminatedas scheduled were included in calculations of pertaining to liver, kidney, and gravid uterine weight, to corrected BWG, and summary of reproductive data. Two animals were excluded from calculations, one each from the control (not pregnant) and the high dose group (terminated after abortion on d 28).

Clinical data
(1) Food intake, body weights

Food intake of the high dose animals (at 540 mg/kg-d) was reduced up to 17% at beginning of the treatment (d 7-11), but reached or even exceeded that of controls thereafter (d 12-29). Food intake of animals receiving 60 or 180 mg/mg-d was not influenced.

With regard to mean BW, no statistically significant differences were seen between controls and treated animals. In contrast, BWG of the high dose animals was significantly (d 7-9) or markedly reduced during days 9-14 pi (post-insemination). During the entire treatment period (d 7-19 pi) these animals gained ca. 79% less than control animals.

No such effect was seen in the groups receiving 60 or 180 mg/kg-d. No differences between test groups were seen with respect to corrected body weight gain, and no clear relation to dosing was observed.

(2) Mortalities, signs of toxicity

No mortalities occurred. One high dose dam (No. 53) which aborted 6 fetuses on d 26 was euthanized on d 28. This same animal showed no defecation from d 19-28. Food consumption in this animal was 31-47% lower than average from d 7-12, and decreased to virtually zero after d 16. Body weight gain of this animal was less than average after approximately d 11. While average wait gain of animals in the group decreased from approximately d 0-11 and then increased, the animal that aborted continued to lose weight until abortion and subsequent euthanization. The necropsy of this animal was normal, with the exception of the finding of 6 abortion sites.

From d 9-19 an increasing number of high dose animals showed apathy shortly after daily dosing (including the animal that aborted). 14/15 animals were affected on d 16-19. Lateral position was seen in 6/15 animals (including the animal that aborted) on some days. These signs appeared shortly after dosing and persisted for several hours (until termination of working hours). The symptoms subsided overnight and animals were free of symptoms the next morning. None of the symptoms were seen after cessation of the treatment (d 20-29). There were no clinical signs in the other does of the study.

(3) Terminal necropsy findings, organ weights, reproductive data

The mean gravid uterus weights did not differ between test groups. Test animals liver and kidney weights (relative and absolute) were not influenced by treatment. At necropsy, only spontaneous findings were noted; i.e. ulceration of the stomach (one control), small necrotic area in liver (one high dose), blind ending uterine horn (in 2 low dose animals).

Conception rate was 93% in the control and 100% in the test groups. No substance-related biological relevant differences between groups were seen with respect to conception rate, mean number of corpora lutea and implantation sites or in the calculated values for pre- and post-implantation losses, the number of resorptions and viable fetuses. No dead fetuses were seen.

FETAL DATA
No differences of biological relevance were seen between test groups with respect to fetal sex distribution, weight of fetuses or placentae weight. Any differences seen were within the range of biological variation of the historical data.

External examination
External malformations were only seen in one high dose fetus (doe No. 47-fetus No 5). Beside numerous external malformations (absence of the head; midline fissure of chest and abdominal wall; reduced number of digits on both forelimbs; shortened toes on both forelimbs and right hind limb) this fetus also showed soft tissue and skeletal malformations. The majority of the above mentioned malformations was already seen sporadically in this rabbit strain. External variations were seen in the high dose fetus mentioned above and in another medium dose fetus. These were (1) a flexure of the forelimb in the carpal joint and (2) rotation of one or two hindlimbs.

Soft tissue examination
In the high dose fetus No.5, malformations of heart, thymus, lung, the great vessels and the gallbladder were seen. A septal defect of the heart was also seen in a medium dose fetus; a low dose fetus showed malformation of the gallbladder. Soft tissue variations were detected in each group including the control . Most frequently it occurred in the medium dose group. Variations included separated origin of the carotids, heart with traces of interventricular foramen, and hypoplasia of the gallbladder. As an unclassified observation, one focal liver necrosis was seen in a low dose fetus.

Skeletal malformations and/or variations
No malformation was seen in the control fetuses (0/90); in the treated groups, 2/91 low dose fetuses (=2.2%), 2/100 medium dose (=2.0%) and 3/82 high dose fetuses (=3.7%) showed skeletal malformations. In the already mentioned fetus No. 5 these were correlates of the external findings (e.g. cleft sternum; digits absent). The other malformations were related to vertebral column and occurred in single fetuses without a clear relation to dosing. Almost all skeletal variations were observed in all groups without a clear relation to dosing, without biological relevant differences between the groups, and/or can be found at a comparable frequency in the historical control data. Combined skeletal variations showed a statistically increased incidence (predominantely accessory 13th rib buds) in high dose fetuses and this was regarded as being treatment-related since the mean percentage of affected fetuses/litter (10.2%) is outside the historical control range (2.0%). Skeletal retardations were observed in all test groups in comparable frequencies.

Conclusions : Oral administration of Protectol PP to pregnant Himalayan rabbits during organogenesis by stomach tube on day 7 to 19 pi led to the following findings:

Test group receiving 540 mg/kg-d:

Decreased food consumption at the beginning of the treatment compared with controls (- 17%) between days 7-11 pi.
Impaired body weight gain between days 7-14. During the total treatment period (d 7-19 pi) the weight gain was ca. 79% less than that of control animals.
Apathy and/or lateral position in an increasing number of rabbits during the treatment period. Symptoms were not seen after cessation of treatment.

One doe aborted on day 26.
Statistically significantly increased rate of skeletal variations in fetuses; predominantly 13th rib.

Test groups receiving 60 or 180 mg/kg-d:

No substance-related effects on does, gestational parameters or fetuses.

Thus, overt maternal toxicity was seen at 540 mg Protectol PP/kg-d, but not at 60 or 180 mg/kg-d. Maternal toxicity was substantiated by reduced food consumption, reduced body weight gain and adverse clinical symptoms. The NOAEL for maternal toxicity is 180 mg/kg-d and the LOAEL is 540 mg/kg-d.

Developmental toxicity was also seen at 540 mg Protectol PP/kg-d, but not at 180 or 60 mg/kg-d. The only indication for developmental toxicity was an increased rate of fetal skeletal variations, predominantly with an extra 13th rib. This is related with unspecific maternal stress. There were no indications for teratogenic effects. The NOAEL for developmental effects is 180 mg/kg-d for variations and anomalies and 540 mg/kg-day for frank teratogenic effects. The LOAEL for variations and anomalies is 540 mg/kg-d.

60 and 180 mg Protectol PP/kg-d had no influence on gestational parameters and induced no signs of developmental toxicity or teratogenicity.

Based on these results, the NOAEL for both maternal toxicity and developmental toxicity (of variations and anomalies) is 180 mg Protectol PP/kg body weight day and the LOAEL is 540 mg/kg-d. For frank teratogenic effects, the highest dose did not cause any effects. The NOAEL for frank teratogenic effects is 540 mg/kg-d.

Remark : The fetal findings were summarized and assessed as follows:

I MALFORMATIONS
(1) The morphological examinations did not reveal dose-related, statistically significant increases in fetal external, soft tissue or skeletal malformations. (2) However, various malformations in the substance-treated groups occurred; fetus No. 5 showed a large variety of external, soft tissue and skeletal malformations. Even though most of these malformations occur in historical control fetuses of this rabbit strain and occurred in this study at a low frequency, a relation to treatment cannot be excluded,

(3) If fetus No. 5 (high dose group) is excluded, only one low and one medium dose fetus showed soft tissue malformations (septal heart defect and agenesia of the gall bladder). Both malformations are considered spontaneous, since they are also present in historical control data even at a higher incidence.

(4) If fetus No. 5 is excluded, skeletal malformations occurred in 6 treated fetuses, 2 in each treatment group. These were vertebral column defects which are also present at even higher rates in the historical control data. Therefore, these findings are considered to be coincidental.

(5) The overall malformation rate was not increased in a dose-related manner.

(6) It was, however, significantly increased in the medium dose group receiving 180 mg/kg-d. Comparison with historical control data from

previous studies with the same strain reveals (Fig. 4.3.4.1 of the report) that the mean percentage of affected fetuses/litter is in the same range as historical control animals (180 mg/kg-d: 3.4%; historical controls: 2.1-5.3%). Statistical significance in the present study resulted from an unexpectedly low incidence of malformations in control animals (0%) in the present study.

II VARIATIONS
Statistically significant increases were seen for (1) one soft tissue variation (heart with interventricular foramen) at the intermediate and high dose levels, (2) for the overall rate of skeletal variations at the high dose, and (3) the overall rate of external, soft tissue and skeletal variations at medium and high dose.

(1) The mentioned soft tissue variation is not regarded as being substance-related. Statistical significance is due to an unexpectedly low incidence in the control group, as evidenced by comparison with historical control data (Fig. 4.3.2.1 of the report).

(2) The increase of skeletal variations in high dose fetuses is mainly caused by an increased occurrence of a 13th rib. Numerous publications dealing with this phenomenon, e.g. KEHRA; KIMMEL&WILSON; WICKRAMARATNE, consider this as manifestation of an unspecific stress, rather than as a teratogenic effect. In this study, maternal toxicity was observed in the high dose group (reduced food intake, reduced body weight gain, adverse clinical symptoms). Therefore, the increased occurrence of accessory 13th rib at 540 mg/kg-d is considered an embryotoxic effect representing a manifestation of a non-specific stress on the does. It is not interpreted as a teratogenic effect of the test substance.

(3) The significantly increased rates of total variations in medium and high dose fetuses are misleading. The facts discussed above, i.e. unexpectedly low incidence in controls and interpretation of 13th rib, need instead to be taken into account.

III SKELETAL RETARDATIONS
No substance-related, biologically relevant difference between the groups occurred. The statistically significant increase in total retardations at 60 mg/kg-d is considered random since it is not dose-related and this degree of variability has been observed in previous studies using this strain of rabbits.

The one soft tissue variation, which occurred at statistically significantly increased rates at 180 and 540 mg/kg-day was
“Heart: Traces of interventricular foramen/septum membranaceum”. This finding and its toxicological relevance are discussed in detail in the report on page 33 (Vol. I) quoted below with data:

” The statistically significant, but not clearly dose-related increase of one soft tissue variation (heart with traces of interventricular foramen/septum membranaceum) at the intermediate and high dose group is not assessed as substance-related, but is due to an unexpected low occurrence of this finding in the concurrent control group. This becomes obvious, if the relevant values are compared with the historical control range (see also Fig. 4.3.2.1.).

Fig. 4.3.2.1.: Fetal and litter incidences and mean percentage of affected fetus/litter for one soft tissue variation (heart with traces of interventricular foramen/septum membranaceum)

Soft tissue variation	Fetal Incidence %	Litter Incidence %	Affected Fetuses/Litter Mean%
Heart with traces of inter-ventricular foramen/septum membranaceum			
0 mg/kg bw/d	2.2	7.1	2.0
60 mg/kg bw/d	5.5	27.0	8.0
180 mg/kg bw/d	10.0	**47.0***	**10.1***
540 mg/kg bw/d	7.3	**43.0***	**7.6***
Historical control range	7.7 (0.0 - 21.3)	30.2 (0.0 - **80.0**)	7.9 (0.0 - **24.0**)

*: $p \leq 0.05$; mg/kg bw/day = milligram per kilogram body weight per day"

These values do not show a clear relation to dosing and are all fully within the historical control range (see also Vol. III of the report, Tab. HCD 009). Therefore, the statistically significantly increased occurrence of the soft tissue variation "Heart: Traces of interventricular foramen/septum membranaceum" at the mid and high dose is still not considered to have any toxicological relevance, but is assessed to be a chance finding.
As already discussed in paragraph 4.3.4., page 38, of the original report, the statistically significantly increased rates of mid and high dose fetuses with total variations (see Tab. 044 of the original report (Vol. I) were assessed differently.

The increase of total variations at 180 mg/kg-day was considered a spurious finding due to the fact, that this increase has to be seen in conjunction with the incidental increase in soft tissue variations at this dose level, particularly of one finding, i.e. "Heart: Traces of interventricular foramen/septum membranaceum". It has been explained above why this increase has no biological relevance.

: The respective increase of total variations at 540 mg/kg-day, however, was assessed to be treatment-related. The main reason for this increase was the higher rate of high dose fetuses with accessory 13th rib(s) at an incidence (10.2% affected fetuses/litter), which was above (even though not statistically significantly increased!) the historical control range (2.0 [0.0 – 7.0]% affected fetuses/litter). This has been also discussed in the original report in paragraph 4.3.3.; the respective summary table is Tab. 038 (Vol. I), associated historical control data are listed in Tab. HCD 013 (Vol. III).

Please note the requested table with the incidences of each developmental endpoint that is statistically significant below. Moreover, appropriate summary tables with total external, soft tissue, skeletal and overall malformations, variations, and/or retardations can be found in Vol. I of the original report (Tabs: 020, 025, 031, and 044).

Table: Occurrence of statistically significantly increased individual and total fetal findings (expressed as mean percentage of affected fetuses/litter) and one important finding without statistical significance (i.e. accessory 13th rib(s)).

Finding	Test group 0 0 mg/kg bw/d	Test group 1 60 mg/kg bw/d	Test group 2 180 mg/kg bw/d	Test group 3 540 mg/kg bw/d	HCD Mean % (range)
Heart: Traces of interventricular foramen/septum membranaceum (see also Tab. 028)	2.0	8.0	10.1*	7.6*	7.9 (0.0 – 24.0)
Accessory 13th rib(s) (see also Tab. 038)	0.8	0.0	1.6	10.2	2.0 (0.0 – 7.0)
Skull incompletely ossified (see also Tab. 039)	0.0	3.0	7.1*	3.5*	1.7 (0.0 – 4.4)
Total skeletal variations (see also Tab. 031)	7.0	11.3	12.2	23.4**	13.1 (4.1 – 24.9)
Total fetal skeletal retardations (see also Tab. 031)	41.6	59.9*	51.7	43.7	55.6 (31.8 – 74.6)
Summary of all fetal external, soft tissue, and skeletal observations (see also Tab. 044)					Not applicable
Total Malformations	0.0	2.4	3.4*	3.2	
Total Variations	18.0	27.2	30.7*	31.2*	
Total Retardations	41.6	59.9*	51.7	43.7	

***: p ≤ 0.05; **: p ≤ 0.01; mg/kg bw/day = milligram per kilogram body weight per day**

: The first two findings in the table above (i.e. Heart: Traces of interventricular foramen/septum membranaceum and accessory 13th rib(s)) have been already discussed before in detail. The incomplete ossification of the skull represents a slight, reversible delay in the ossification process of the fetal skeletons. The statistically significantly increased occurrence of this finding at 180 and 540 mg/kg-day does not reflect a substance-induced finding for the following reasons:

- no dose-response is given
- the rate of total skeletal retardations is devoid of any relation to dosing as indicated in the table (41.6/ 59.9*/ 51.7/ 43.7 % affected fetuses/litter at 0, 60, 180 and 540 mg/kg body weight/day).

The statistical tests used in this study are described in detail on page 18 of the original report. None of the reported external, soft tissue, skeletal, or overall malformations achieved statistical significance as can be seen from Tabs. 020-022, 025-027, 031-035, and 044.
According to the discussion in the finalized study report and the explanations given in this statement 540 mg/kg-day is still considered to represent the LOAEL and 180 mg/kg-day to represent the NOAEL for developmental toxicity. The animal that aborted appeared normal at the beginning of the study and the necropsy did not uncover any abnormalities. Therefore, the reason for the abortion is not clear. The abortion is likely related to lack of food consumption and subsequent loss of weight.

Reliability : (1) Valid without restriction.
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 followed 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 : Hellwig, J., Hildebrand, B., (1995). Study of the prenatal toxicity of Protectol PP in Himalayan rabbits after oral administration (gavage). BASF Project No. 40R0057/93055. 18 December 1995.

Remark : Protectol PP was also tested in a range finding study for maternal toxicity at 200, 400 and 800 mg/kg-d under conditions similar to those of the main study. 4-5 pregnant rabbits were dosed during days 7-19 post insemination (pi) and terminated on day 20 pi.

Results were as follows: Animals at 800 mg/kg-d: Reduced food intake; 58% less than controls over the total treatment period. Body weight loss over the total treatment period. One doe found dead on day 15 pi. All animals with unsteady gait, some with lateral, squatting or abdominal position and/or piloerection during treatment period. Multiple ulcerations in stomach mucosa of two animals (including the one that died). Increased post-implantation loss in at least two does. Animals at 400 mg/kg-d: Some body weight loss at the beginning of treatment phase and marginally reduced body weight gain (BWG) between days 7-19. All animals with unsteady gait on most days during the treatment period. Animals at 200 mg/kg-d: No effects on the animals, the gestational parameters and the uterine contents that could be clearly related to the test substance administration. Marginally reduced BWG and slightly increased post-implantation loss was within the biological variation of the rabbit strain.

Other relevant citations:
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Flag : Critical study for SIDS endpoint.

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5.11 EXPERIENCE WITH HUMAN EXPOSURE

Remark : No relevant information

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