UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: May 9, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessment - Propylene Glycol Monomethyl Ether (PGME), CAS Reg. No. 107-98-2

FROM: Pauline Wagner, Chief Pauline Wagner S 10/06
Inert Ingredient Assessment Branch
Registration Division (7505P)

TO: Lois A. Rossi, Director
Registration Division (7505P)

I. FQPA REASSESSMENT ACTION

Action: Reassessment of two exemptions from the requirement of a tolerance. The reassessment decision is to maintain both of the exemptions "as-is".

Chemical: Propylene Glycol Monomethyl Ether

Table 1. Tolerance Exemptions Being Reassessed in this Document

CFR Citation				CAS Reg. No. 9CI Name
40 CFR §	Inert Ingredients	Limits	Uses	
180.920[a]	Propylene glycol monomethyl ether	(none)	Solvent	
	Propylene glycol monomethyl ether	(none)	Deactivator, emolient	

[a]Residues listed in 40 CFR 180.920 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.

[b]Residues listed in 40 CFR 180.930 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals.

Use Summary: The predominant use of this chemical is in consumer products, including paints, varnishes, inks and cleaning products. It is also has limited use as an inert ingredient in pesticide products as a solvent in pesticide formulations applied to growing crops only; and/or a deactivator, emollient in pesticide formulations applied to animals.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the two exemptions from the requirement of a tolerance for the inert ingredient propylene glycol monomethyl ether (CAS Reg. No. 107-98-2). I consider the two exemptions established in 40 CFR parts 180.920 and 180.930 to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois A. Rossi, Director
Registration Division

5/10/06
Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

May 9, 2006

MEMORANDUM

SUBJECT Reassessment of the Two Exemptions from the Requirement of a Tolerance for Propylene Glycol Monomethyl Ether (PGME; CAS Reg. No. 107-98-2)

FROM: Keri Grinstead
Inert Ingredient Assessment Branch
Registration Division (7505P)

And

Brenda S. May
Science Information Management Branch (SIMB)
Health Effects Division (7509P)

TO: Pauline Wagner, Chief
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505P)

BACKGROUND

Attached is the science assessment for propylene glycol monomethyl ether (PGME). This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of PGME. The purpose of this document is to reassess the existing exemptions from the requirement of a tolerance for residues of PGME as required under the Food Quality Protection Act (FQPA).

EXECUTIVE SUMMARY

This document evaluates PGME, a pesticide inert ingredient for which two exemptions from the requirement for a tolerance exist. An inert ingredient is defined by the U.S. Environmental Protection Agency (USEPA) as any ingredient in a pesticide product that is not intended to affect a target pest.

As an inert ingredient in pesticide products, PGME is exempt from the requirement for a

tolerance when used: 1) as a solvent in pesticide formulations applied to growing crops only (40 CFR 180.920); and/or 2) as a deactivator, emollient in pesticide formulations applied to animals (40 CFR 180.930). PGME is also used as a solvent in other industrial or commercial products including paints, varnishes, inks and cleaners and is an intermediate in the manufacture of propylene glycol methyl ether acetate (PMA).

PGME is a mixture of two isomers (α and β) and contains less than 0.5% of the β-isomer. The available toxicity database for PGME consists of acute, subchronic, developmental and reproduction, mutagenicity, and carcinogenicity data from studies conducted in laboratory animals. No chronic or neurotoxicity studies were identified. PGME exhibits low toxicity by the oral, dermal and inhalation routes of exposure. Studies in laboratory animals indicate that PGME is not a developmental toxicant when administered via inhalation or ingestion. There is no evidence that the chemical is mutagenic or carcinogenic.

Exposure to PGME as a result of its use as an inert ingredient in pesticides products is possible through dietary (food and/or drinking water) or residential (dermal and inhalation) routes of exposure. Although exposures to PGME are possible from its use as an inert ingredient in pesticide products, these exposures are expected to be below levels associated with adverse health effects.

There is adequate physical-chemical and toxicological data available to characterize PGME. The toxicity of PGME is low for both aquatic and mammalian species. The low toxicity combined with the fact that it biodegrades rapidly and has a low potential for bioaccumulation in the environment will limit the potential for risk to human health. Inhalation of relatively high concentrations of PGME would likely be self-limiting due to the irritant effects of the chemical.

Taking into consideration all available information on PGME, the Agency has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to PGME when considering exposure through food commodities and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the two exemptions from the requirement of a tolerance established for residues of PGME when used: 1) as a solvent in pesticide formulations applied to growing crops only; and/or 2) a deactivator, emollient in pesticide formulations applied to animals can be considered reassessed as safe under section 408(q) of the Federal Food, Drug and Cosmetic Act (FFDCA).

I. Introduction

This report provides a qualitative assessment for Propylene glycol monomethyl ether (PGME), a pesticide inert ingredient with two tolerance exemptions under: 40 CFR 180 180.920 and 180.930.

II. Use Information

A. Pesticides

The tolerance exemptions for PGME are provided in Table 1.

Table 1.

CFR Citation				CAS Reg. No. 9CI Name
40 CFR §	Inert Ingredients	Limits	Uses	
180.920[a]	Propylene glycol monomethyl ether	(none)	Solvent	107-98-2 2-Propanol, 1-methoxy-
180.930[b]	Propylene glycol monomethyl ether	(none)	Deactivator, emolient	

[a]Residues listed in 40 CFR 180.920 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.

[b]Residues listed in 40 CFR 180.930 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals.

B. Other Uses

PGME is primarily used in the chemical, agricultural (pesticides), automotive, paint and varnish industries. Commercial PGME is a mixture of two isomers (α and β) and contains less than 0.5% of the β-isomer. The predominant use of PGME is as a solvent in various manufacturing processes, but it is also used as an intermediate in the manufacture of propylene glycol methyl ether acetate (PMA).

C. Manufacture/Production/Use

The U.S. manufacturers of PGME are Dow Chemical USA, Atlantic Richfield Co., and Olin Corporation (Toxnet SIS, 2005a). OECD SIDS (2001) reported that approximately 100,000 to 500,000 tons of PGME are produced worldwide each year. In 2000, an estimated 165 million tons of PGME were produced in the United States. The current production volume is not available. U.S. production and use information for 1999 are summarized in Table 2.

Table 2. Production and Use Information for PGME[a]

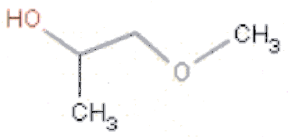
Type of End Product	Percent Production
PMA Production	34%
Surface Coatings	30%
Cleaners	23%
Inks	6%
Miscellaneous (adhesives, etc.)	7%

[a]Based on 1999 production volume of 145 million pounds; Information provided by the American Chemistry Council Propylene Glycol Ethers Panel.

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of PGME, along with its structure and nomenclature, are found in Table 3. Commercially available PGME exists primarily as the α-isomer and less than 0.5% of the β-isomer as an impurity.

Table 3. Physical and Chemical Properties of PGME

Parameter	Value	Reference
Structure		http://www.sis.nlm.nih.gov/chemical.html
CAS Reg. No.	107-98-2	
Chemical Formula	$CH_3OCH_2CHOCH_3$	OECD SIDS, 2001
Molecular Weight	90.1 g/mol	OECD SIDS, 2001
Purity	>99%	OECD SIDS, 2001
Impurities	β-isomer (<0.5%)	OECD SIDS, 2001
Synonyms	1-methoxypropanol-2ol, 1-methoxy-2-propanol, DOWNOL®, Poly-Solve MPM Solvent	OECD SIDS, 2001
Physical State	Clear, colorless, liquid with a sweet ether-like odor	OECD SIDS, 2001
Melting Point	-95° to -97°C	OECD SIDS, 2001
Boiling Point	120 °C	OECD SIDS, 2001
Water Solubility	200 g/L @ 20 °C (miscible)	OECD SIDS, 2001
Relative Density (water=1)	0.92 g/cm^3	OECD SIDS, 2001
Vapor Pressure	11.5 hPa @ 20 °C	OECD SIDS, 2001
log Kow	-0.437	OECD SIDS, 2001
Henry's Law Constant	6.76E-6 to1.35E-5 atm-m^3/mol	OECD SIDS, 2001

IV. Hazard Assessment

PGME is sponsored under EPA's High Production Volume (HPV) Challenge Program (http://www.epa.gov/chemrtk/volchall.htm). The goal of the HPV program is to collect and make publicly available a complete set of baseline health and environmental effects data on those chemicals that are manufactured in or imported into the United States in amounts equal to or exceeding one million pounds per year. Industry sponsors volunteer to evaluate the adequacy of existing data and to conduct tests where needed to fill the gaps in the data, and EPA (and the public) has an opportunity to review and comment on the sponsors' robust summary report. The industry sponsor has not submitted a robust summary for PGME, however, the chemical is being handled under the Organization for Economic Cooperation and Development (OECD) HPV SIDS Program and a company or consortium has had their sponsorship of this chemical confirmed by the International Council of Chemical Associations (ICCA) through the HPV Initiative of ICCA.

The OECD Screening Information Data Set (SIDS) Program is a voluntary cooperative international testing program that began in 1989. It is focused on developing base level test information on approximately 600 poorly characterized international HPV chemicals. The SIDS data are used to "screen" the chemicals and set priorities for further testing or risk assessment/management activities. The priorities are set at the SIDS Meeting (SIAM). The SIAM for PGME was held in the U.S. on January 23-26, 2001.

Technical and scientific literature information on PGME is also available through the American Chemistry Council Propylene Glycol Ethers Panel which was formed in 1993 to expand the toxicity database on propylene-based glycol ethers (http://www.pgep.org).

PGME is being evaluated as part of EPA's tolerance reassessment of inert ingredients. This chemical was the subject of a previous hazard and risk assessment by the EPA (Toxnet SIS, 2005b) in addition to the literature reviews conducted by OECD SIDS (2001) and McGregor (1984). A literature summary report has also been prepared for PGME wherein numerous databases and EPA sources were searched for toxicity data on PGME (see Appendix A for listing of sources searched). These reviews, as well as select primary literature were the major sources of the information discussed in this reassessment.

A. Hazard Profile

The available toxicity database for PGME consists of acute, subchronic, developmental and reproduction, mutagenicity, and carcinogenicity data from studies conducted in laboratory animals. No chronic or neurotoxicity studies were identified.

According to OECD SIDS (2001) review, PGME exhibits low acute toxicity by the oral, dermal, and inhalation routes. PGME is not a skin sensitizer or skin irritant and was only slightly irritating to the eye. In repeat dose inhalation studies ranging from 11 days

to six months in duration, No Observed Adverse Effect Levels (NOAELs) of 300 ppm and higher were seen in rats, mice, rabbits, guinea pigs and monkeys. Effects observed included sedation, hepatic changes and a decrease in body weight gain. Oral NOAELs of 459.5 mg/kg and 919 mg/kg/day were observed in rat studies lasting 13 and 5 weeks, respectively. Observations included central nervous system effects, enlarged livers and weight loss. In a reproduction study conducted via the inhalation route, offspring effects seen at 3000 ppm appear to be related to decreased maternal body weight and secondary to general toxicity and nutritional stress. Decreased maternal body weight was also noted at the next lower dose. NOAELs in this study were 300 ppm for adults and 1000ppm for offspring. Studies with rats, mice, and rabbits showed that PGME was not a developmental toxicant (two inhalation and three gavage studies). Weight-of-evidence indicates that PGME is not genotoxic or carcinogenic. In a 2-year bioassay, there were no statistically significant increases in any tumor type in rats and mice.

The available toxicity information is summarized in more detail in the following section.

B. Toxicological Data

Much of the toxicity information for PGME presented in this section is from OECD SIDS (2001) publication and Toxnet SIS (2005b). These reports have undergone several levels of technical review and therefore, the toxicity data should be sufficiently reliable for use in this reassessment.

Acute Toxicity

The acute toxicity of PGME is low. Data on acute toxicity studies are presented in Table 4.

Table 4. Summary of Acute Toxicity Data for PGME

Species	Route	Toxicity Value	Reference[a]
Rat	Oral	LD_{50}=6100 mg/kg	Rowe et al.
	Oral	LD_{50}=5710 mg/kg	Smyth et al., 1941
	Oral	LD_{50}= 5200 mg/kg	Smyth et al., 1962
	Oral	LD_{50} >5000 mg/kg	BASF AG, 1979
	Oral	LD_{50}= 5900 mg/kg	BASF AG, 1964
	Oral	LD_{50}=10,800 mg/kg	Stenger et al.
	Oral	LD_{50}= 5300 mg/kg	Stenger et al.
	Oral	LD_{50} >1840 mg/kg	BASF AG, 1965
	Oral	LD_{50} = 9000 mg/kg	Shideman and Puscita
	Oral	LD_{50}= 4600-5500 mg/kg	Stenger et al.
	Oral	LD_{50} >1840 mg/kg	BASF AG, 1965
	Inhalation	LC_0 >7559 ppm	Cieszlak and Crissman
	Inhalation	LC_0= 18,200 mg/m^3	Rowe et al.
	Inhalation	LC_0= 36,400 mg/m^3	Smyth et al., 1962
	Inhalation	LC_0= 1000 ppm	Smyth et al., 1962
	Inhalation	LC_{50}= 54,600 mg/m^3	Rowe et al.
	Inhalation	LC_{50} >6000 mg/m^3	Gelbke

Table 4. Summary of Acute Toxicity Data for PGME

Species	Route	Toxicity Value	Reference[a]
Rat	Inhalation	LCL_0= 25,500 mg/m^3	Gelbke
Rat	Inhalation	LC_{50} >24,000 mg/m^3	Gelbke
Rat	Inhalation	LC_{50}= 36,400 mg/m^3	Rowe et al.
Mouse	Inhalation	LC_{50} <6038 ppm	Cieszlak and Crissman
Rabbit	Inhalation	LCL_0= 54,600 mg/m^3	Rowe et al.
Guinea Pig	Inhalation	LC_0= 18,750 mg/m^3	Rowe et al.
Guinea Pig	Inhalation	LC_{50}= 54,600 mg/m^3	Rowe et al.
Guinea Pig	Inhalation	LC_0= 36,400 mg/m^3	Rowe et al.
Rabbit	Dermal	LD_{50}= 13,000 mg/kg	Rowe et al.
Rabbit	Dermal	LD_{50}= 14,100 mg/kg	Smyth et al., 1962

[a] All references provided from OECD SIDS, 2001.

Eye Irritation:

Exposure of PGME to the eyes of rabbits was non-irritating (Rowe et al.; Smyth et al, 1962; BASF AG, 1979, all cited in OECD SIDS).

Skin Irritation:

In rabbits, PGME was found to be non-irritating to the skin (BASF AG, 1979; Smyth et al., 1962, both cited in OECD SIDS).

Sensitization:

PGME was non-sensitizing in guinea pigs (Carreon and Wall, as cited in OECD SIDS).

Subchronic Toxicity

Inhalation exposure of rats to PGME resulted in central nervous system (CNS) effects (sedation), adaptive hepatic changes, and decreases in body weight gain. NOAELs ranged from 300 to 5,000 ppm in experiments lasting 11 days to 6 months (Cieszlak et al.; Goldberg et al.; Landry et al.; Miller et al., 1981; and Rowe et al., all cited in OECD SIDS). In rabbit experiments lasting 6 months and 13 weeks, NOELs of >800 ppm and 1,000 ppm were observed, respectively (Landry et al.; Rowe et al., both as cited in OECD SIDS).

Rats (5/sex/group) and mice (5/sex/group) were exposed to 0, 300, 1000 or 3000 ppm PGME 6 hours/day for 9 days over an 11-day period (Miller et al., 1981, as cited in Toxnet SIS, 2005b). Increased liver weight was observed in male rats at the highest dose tested. The LOAEL for neurotoxicity (CNS depression) in rats and mice was 3000 ppm.

In a study by Landry et al. (OECD SIDS), Fischer 344 rats (10/sex/group) and New Zealand White rabbits (7/sex/group) were exposed via inhalation to 0, 300, 1000 or 3000 ppm PGME 6 hours/day, 5 days/week for 13 weeks. The parameters examined included daily observations for signs of toxicity, changes in body and organ weight, hematology, clinical chemistry, urinalyses (rats), and gross and histopathological

examinations (nasal turbinates, trachea, lungs, liver, kidneys, brain etc). There were no treatment-related mortalities. During the first two weeks of exposure, rats and rabbits exposed to 3000 ppm appeared sedated during the first several days of exposure. These effects were no longer apparent after 2 weeks. In the rabbits, no other effects were observed. The additional effects seen in female rats at 3000 ppm included a small but significant increase in liver weight (6-8%), increased hepatocyte size and cytoplasmic eosinophilia indicating hepatocellular hypertrophy; however, there was no evidence of degenerative changes in the liver. These liver changes were considered to be an adaptive response. The NOAEL in rats and rabbits was 1000 ppm. The LOAEL for neurotoxicity (mild reversible sedation) for rats and rabbits was 3000 ppm.

In another study by Cieszlak et al.(OECD SIDS), rats were exposed to 0, 300 or 3000 ppm PGME, 6 hours/day for 13 weeks. The 3000 ppm concentration caused sedation during the first week of exposure but declined in subsequent weeks. Hepatic mixed function oxidase activity and hepatocellular proliferation were increased also at 3000 ppm in these studies with mild degenerative changes in the liver. A male rat specific α2-microglobulin- mediated nephropathy was seen in the 3000 ppm animals and at a slight extent in the 300 ppm group. However, the α2-microglobulin-mediated nephropathy is species specific to rats and is not applicable to humans. Therefore, the LOAEL was 3000 ppm in females and 300 ppm in male rats and the NOAELs were 300 ppm for females and not determined for males. Male and female $B6C3F_1$ mice when exposed to 0, 300, 1000 or 3000 ppm PGME by inhalation by the same lab for 13 weeks also displayed a similar hepatic cellular proliferation and hepatic enzyme induction at 3000 ppm as well as sedation in males and females at 3000 ppm for the first exposures and an increased liver weight in females at 3000 ppm. The NOAEL in male and female mice was set at 1000 ppm and the LOAEL at 3000 ppm. In other inhalation studies lasting 6 months, NOELS of 800 ppm and >3000 ppm were observed for monkeys and guinea pigs, respectively. The LOEL in the guinea pig could not be determined and was 1500 ppm for the monkey (Rowe et al., as cited in OECD SIDS).

Oral gavage administration of PGME to rats and dogs for 13 and 14 weeks, respectively, caused mild to severe, dose-dependent CNS depression. Daily doses of 1 mL/kg (919 mg/kg), administered to rats caused enlarged liver swelling accompanied by cell necrosis. Mortality in rats was appreciable at 4 mL/kg (Stenger et al., as cited in OECD SIDS). Rats receiving 26 doses of 1 mL/kg or less PGME over 35-day period showed no adverse effects (Rowe et al., as cited in OECD SIDS). In the same study, only minor liver and kidney effects were seen at 3 g/kg/day (LOAEL). However, these renal effects were caused by an α2-microglobulin-mediated mechanism of action and not relevant to humans.

Dermal exposure of rats to PGME caused scaling, minimal inflammation and skin thickening. Large dermal doses can produce narcosis and death. In two subchronic dermal toxicity studies, PGME was applied dermally to rabbits. NOELs of < 1,000 mg/kg (3 weeks) and 2 mL/kg (90 days) were established (Calhoun and Johnson; Rowe et al., as cited in OECD SIDS). A NOEL of 1000 mg/kg was reported for systemic effects and dermal effects at the 1000 mg/kg were slight scaling, minimal inflammation

with a protective thickening response of the skin. Doses of 1 to 5 mL/kg in male rabbits were generally without effects. The LOEL of 4 mL/kg caused slight narcosis.

Neurotoxicity

Neurotoxicity studies were not available.

Neurotoxic signs (CNS depression) were observed in toxicity studies conducted in rats, mice and rabbits exposed by inhalation to 3000 ppm PGME. In a study by Rowe et al. (OECD SIDS), rats (10 or 20/sex) and guinea pigs (5 or 8/sex) were exposed to 0, 1500, 3000 or 6000 ppm PGME (0, 5530, 11,060 or 22,120 mg/m^3, respectively). Rabbits (1or 2/sex) and monkeys (1 or 2 /group; a total of four females and one male) were exposed to 0, 800, 1500 or 3000 ppm PGME (0, 2949, 5530 or 11,060 mg/m^3). In addition, one female rabbit was exposed to 6000 ppm (22,120 mg/m^3). All animals were exposed for 7 hours/day, 5 days/week for 80-147 exposures. At 6000 ppm, narcosis was observed in rats, guinea pigs and the rabbit, and 4/10 male and 7/10 female rats died. At 3000 ppm, rats exhibited mild CNS depression at the end of each exposure. Increased liver and kidney weight were also observed. The LOAEL for guinea pigs was 6000 ppm based on CNS depression, growth depression, increases in liver and kidney weight and slight typical microscopic changes in the liver. Slightly increased liver weight and slight microscopic changes in the lungs and liver of female rabbits, but not in male, were observed. Slight microscopic changes in the lungs were observed for monkeys at 1500 ppm. The study was limited by the small number of rabbits and monkeys included, lack of statistical analysis of the data, the use of limited control data for rats and guinea pigs, and a limited discussion of observed microscopic changes.

Mutagenicity

As reported in OECD SIDS, PGME is not mutagenic in Salmonella strains TA98, TA100, TA1535, TA1537, and TA1538 at concentrations of 20, 100, 500, 2500 or 5000 ug/plate in the presence or absence of rat S9 mix (BASF AG, 1983). PGME did not induce unscheduled DNA synthesis in primary rat hepatocytes at concentrations of 0.1, 0.0316, 0.01, 0.00316, 0.001, 0.000316, 0.0001 or 0.0000316 M when cultured *in vitro* (Dow Chemical Co, unpublished as cited in McGregor and OECD SIDS).

In an *in vitro* test, cytotoxicity was observed in liver cells of rats by a detachment of cells and/or a granular appearance at 0.0316 and 0.1 M (Mandrala, as cited in OECD SIDS). In a study by Dow Chemical Co. (unpublished as cited in McGregor and OECD SIDS), PGME did not induce chromosomal aberrations in Chinese hamster ovary (CHO) cells at concentrations ranging from >10 to >100 mM. No morphological transformation was observed in Syrian hamster embryo cells treated with PGME *in vitro* (Elias at al., as cited in OECD SIDS). However, cell growth inhibition, a slight increase in SCEs (at a concentration range of >10 to 100mM) and dose-dependent inhibition of intercellular communication (at non-cytotoxic levels) was observed in Chinese hamster lung (V79) cells treated with PGME at concentrations of 14-55 mM (Elias et al., as cited in OECD

SIDS). In this study, SCEs were only noted at very high concentrations, and the resulting dose-response correlation was weak. PGME was not toxic to CHO cells at concentrations of up to 5 mg/mL (Dow Europe SA, as cited in OECD SIDS); however, survival was decreased to 50% at 10 mg/mL.

In an *in vivo* study, PGME administered at concentrations of up to 6,000 mg/kg to mice did not increase the frequency of micronuclei in polychromatic erythrocytes harvested from bone marrow (Elias et al., as cited in OECD SIDS).

The weight of evidence indicates that PGME is not genotoxic. However, PGME did appear to enhance genetic damage induced by methylmethane sulfonate in Chinese hamster lung (V79) cells. The potentiation was dose-dependent at concentrations up to 200 mM PGME (Elias et al., as cited in OECD SIDS).

Carcinogenicity

Studies in laboratory animals indicate that PGME is not carcinogenic. Dose levels of 0, 300, 1000 or 3000 ppm were administered in a 2-year chronic toxicity and carcinogenicity study in both rats and mice. In both species, the highest exposure concentration was chosen based on the results of previous subchronic toxicity studies in which sedation, hepatic enzyme induction, and increased hepatic cellular proliferation were seen. In a 2-year bioassay, no statistically significant increase in tumors in any tissue were observed in male and female rats and mice exposed to PGME via inhalation (Cieszlak et al., 1998 a and b, as cited in OECD SIDS). No histopathological changes of toxicological significance were noted in any tissue in mice.

Developmental and Reproductive Toxicity

PGME is structurally related to a large group of chemicals collectively known as glycol ethers, some of which have been shown to cause developmental and reproductive effects (especially testicular changes), however, these effects are not expected to be seen in PGME because the metabolism is substantially different.

Developmental:
Pregnant F344 rats and New Zealand rabbits (29-32/group) were exposed to 0, 500, 1500 or 3000 ppm PGME 6 hours/day on Gestation Day (GD) 6-15 (rats) and 6-18 (rabbits) (Hanley et al., as cited in both OECD SIDS and Toxnet SIS, 2005b). The rabbit LOAEL for maternal toxicity was 3000 ppm based on reduction in maternal weight gain and mild transient CNS depression and the NOAEL was 1500 ppm. No significant developmental toxicity was observed in rabbits; therefore, the NOAEL for developmental toxicity was 3000 ppm and the LOAEL was undetermined. The rat LOAEL for maternal toxicity was 3000 ppm based on decreased food intake, decreased body weight gain and transient CNS depression with a NOAEL of 1500 ppm. The LOAEL for rat developmental toxicity was 3000 ppm with slight fetal toxicity observed based on delayed ossification of sternebrae and the NOAEL was 1500 ppm.

Pregnant Wistar rats (20/group) were exposed to PGME at 0, 200 or 600 ppm during GD 6-17 for 6 hours/day (Doe et al., as cited in Toxnet SIS, 2005b). Upon parturition, the litters were observed for 3 days. In a second study, male rats (10/group) were exposed for 10 days, sacrificed, and examined for testicular and hematological effects. No effects were observed in either study. The NOAEL was 600 ppm.

2-Methoxypropanol-1 (2-MP-1), the β-isomer of PGME, was investigated for prenatal toxicity in Himalayan rabbits following inhalation exposure at 0, 145, 225, 350 or 545 ppm for 6 h/day from GD 6-18 (Hellwig et al., 1994; additional details provided in Appendix B, Robust Study Summary). At 350 and 545 ppm, decreased maternal body weight was noted from GD 6-18. There was a dose-dependent statistically significant decrease in uterine weight as well at all doses starting at 225 ppm. The NOAEL for maternal toxicity was set at 145 ppm and the LOAEL at 225 ppm based on this effect. For the fetuses, a dose-dependent increase in resorptions, fetal malformations, and/or variations was observed at 225, 350 and 545 ppm, while no adverse effects were noted at 145 ppm. At the highest exposure level, the incidence of skeletal malformations was 100%. The malformations consisted of absent phalanges, absent or shortened metatarsal bones, malformed ribs and a unique enlargement of sternebrae. Therefore, the developmental NOAEL was set as 145 ppm and the LOAEL at 225 ppm.

Reproductive:
In an inhalation reproductive toxicity study exposing rats to 0, 300, 1000 or 3000 PGME, NOELs observed were 300 ppm for adult rats and 1,000 ppm for offspring (Liberacki et al.; Carney et al., both cited in OECD SIDS). The treatment-related effects seen included sedation, decreased body weight in adults accompanied by lengthened estrous cycles, decreased fertility, decreased ovarian weight accompanied by ovarian atrophy, reduced pup survival, and litter size, slight delays in pubertal indices, and histopathological changes in the liver and thymus in offspring at the highest exposure level (3000 ppm). However, the nature of these effects as well as the observation of decreased maternal body weight suggests that they were secondary to general toxicity and stress. In another study by Doe et al. (as cited in OECD SIDS), male rats exposed to 200 or 600 ppm PGME via inhalation for 6 hrs/day for 10 days showed no adverse effects on the testes.

In a drinking water reproductive toxicity study using the RACB protocol (Chapin and Sloane, as cited in OECD SIDS and Toxnet SIS, 2005a), Swiss CD-1 mice received PGME at concentrations of 0, 0.05%, 1% or 2% in drinking water for two generations. The calculated estimated test material consumption was equal to 0, 950, 1900, or 3300 mg/kg/day, respectively. Task One was conducted to establish doses for the main study. Task Two found no changes in body weight or water consumption in any exposure group. There was no decrease in number of litters/pair, number of live pups/litter or viability of the pups. Mean pup weight was adjusted for litter size and was decreased by 4% compared to controls at the highest dose, with no adverse effects found on fertility, Task Three was not done. Task Four, the evaluation of the 2nd generation, was conducted with the control and high-dose only. The reduced pup weight continued postnatally with males and females weighing $\leq$ 14% of controls during

nursing. Only high-dose male body weight was affected during mating; however, with a decrease of 8% compared to controls. Mating and fertility indices as well as the number and viability of the offspring were again not affected by treatment. After the F_2 pups were delivered, evaluated and sacrificed, the adult F_1 mice in the control and high-dose group were sacrificed. Although females in the high-dose group did not have any effect on body weight, body weight-adjusted liver weight was increased by 7.5%. Male body weights in the high-dose group were 8% lower than controls, with absolute testis, relative epididymis and prostate weights decreased by 7, 7, and 15%, respectively. The NOAEL for oral exposure was 1900 mg/kg/day. The LOAEL was 3300 mg/kg/day which was the highest dose tested and resulted in reduced pup weight and in the second generation reduced adult male body weight. Corresponding decreases in epidydimal and prostate weights were also observed.

C. Metabolism and Pharmacokinetics

When rats were administered a single oral dose of radiolabeled PGME, 50-60% of the label was excreted as CO_2 in expired air and 20% was excreted as the glucuronide conjugate, sulfate conjugate, and propylene glycol within 48 hours (Miller et al.,1983, as cited in OECD SIDS). Following 10 six-hour inhalation exposures at 3,000 ppm, PGME was completely eliminated in rats 24 hours after the last exposure (Margot and Nolan, as cited in OECD SIDS). In mice, PGME was readily absorbed and metabolized to propylene glycol following oral gavage with maximum concentrations of PGME and propylene glycol in plasma attained in 20 and 30 minutes following dosing, respectively (Ferrala et al., as cited in OECD SIDS).

The pharmacokinetics of PGME and propylene glycol monomethyl ether acetate (PGMEAc) in the upper respiratory tract (URT) of rats was studied by Stott and McKenna (as cited in Toxnet SIS, 2005b), as part of a comparative study. Both glycol ethers were found to be completely absorbed (near 100%) by the URT in isolated, ventilated anesthetized F344 rats with a ventilation rate of one or two times the respiratory minute volume. Given the route and extent of absorption in the URT of PGME and PGMEAc, morphologic changes in the URT would be expected once effects were identified. Such effects were not reported in any of the studies reviewed at exposures of PGME up to 3000 ppm. However, exposure to 3000 ppm of PGMEAc, which has similar systemic toxicity as PGME, showed morphologic changes in the olfactory nasal mucosa (Miller et al., 1984b as cited in Toxnet SIS, 2005b). Since PGME and PGMEAc are metabolized in a similar fashion, the histopathological changes were attributed to hydrolysis to acetic acid in the nasal epithelium.

D. Special Considerations for Infants and Children

Studies in laboratory animals indicate that PGME is not a developmental toxicant when administered via inhalation or ingestion.

Developmental studies conducted in rats and rabbits with PGME administered via inhalation showed no developmental toxicity in the rabbit and developmental delays

(delayed sternebral ossification) in the rat but only in the presence of maternal toxicity. In oral developmental studies in rats, mice, and rabbits, developmental delays were seen only in the rat fetuses at the highest dose tested (3000 ppm).

In the oral (drinking water) reproductive study in mice, effects on reproductive organs (decreased absolute testis, relative epididymis and prostate weights) at the highest dose tested may be attributed to the corresponding decreases in adult male body weight. In the reproduction study with PGME administered via inhalation, effects on pup survival and litter size, slight delays in pubertal indices and histological changes (liver and thymus) at the highest dose tested (3000 ppm) were determined by the OECD SIDS to be secondary to the parental toxicity observed and/or general stress. It was also noted that this study was conducted with PGME containing 2% of the β-isomer impurity, a level which is not available commercially. Commercially available PGME contains less than 0.5% of the β-isomer as an impurity. Another inhalation reproduction study conducted in rats by Doe et al. (as cited in OECD SIDS) showed no reproductive effects.

PGME is structurally related to a large group of chemicals collectively known as glycol ethers, some of which have been shown to cause developmental and reproductive effects, especially testicular changes. However, Toxnet SIS (2005b) stated that testicular degeneration, the reproductive effect typically seen in structurally similar chemicals, is not expected to be seen in PGME because the metabolism of PGME is substantially different. PGME is metabolized to innocuous conjugates and not to active testicular degenerative metabolites.

Based on this information there is no concern, at this time, for increased sensitivity to infants and children to PGME when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

V. Environmental Fate Characterization and Drinking Water Considerations

The environmental fate of propylene glycol monomethyl ether (PGME) is relatively well known based on information submitted in support of the OECD's Screening Information Data Set, Initial Assessment Profile (SIAP). Propylene glycol monomethyl ether is unlikely to persist in the environment and is expected to be mobile based on the low measured octanol-water partition coefficient and estimated soil-water partition coefficient. PGME is miscible in water, likely resistant to hydrolysis due to a lack of active hydrolysable functional groups, and photoylsis is not likely to be a significant degradation pathway in natural waters or on soils. Soil dissipation times at which 50 percent of the material is degraded (DT_{50}) on several soils under several test concentrations ranged from less than 1 day to <7 days. In one study at the highest test concentration of 100 ppm, the DT_{50} was >56 days. In this study the low organic carbon content and low nutrient levels appeared to explain the difference in DT_{50} results based on a decrease in the DT_{50} after additional nutrients were added to the soil; DT_{50} <23

days. Based on measured data in studies using sewage inoculums, biodegradation was rapid, consistent with the results in the soil studies. The compound is classified as readily biodegradable, 90% or more of the material degraded in 28 days. Anaerobic degradation is a less important dissipation pathway, 38% degradation after 81 days following a 30-day lag period. PGME is relatively non-volatile from soil and/or water and will undergo rapid photolytic degradation in air should volatilization occur. Leaching to ground water may occur in most soils. PGME is not expected to bioaccumulate in the environment.

Concern for exposures via drinking water is likely to be low. This conclusion is based on its rapid biodegradation in soils and water. Based on a projected half-life in soil and water of less than several days and other physical-chemical properties, application rates of 1 pound per acre will likely result in concentrations in the low parts per trillion in untreated waters. The effect of common drinking water treatment processes is largely unknown, but coagulation, flocculation, and sedimentation are not expected to be very effective. No ambient monitoring data are available for this compound.

Exposure Assessment

PGME is used as an intermediate in the production of propylene glycol monomethyl ether acetate (PMA) and as a solvent in the agricultural (pesticides) and paint, lacquer and varnish industries. It is widely used in industrial, commercial, automotive and household cleaners. Consumer products containing PGME include: floor cleaners and polish; paints, lacquers, and varnishes; caulking compounds and sealants; pesticides; automotive cleaners; dyes and inks; glass window, hard surface and oven cleaners; rug and upholstery cleaners; and laundry aids.

As an inert ingredient in pesticides for agricultural use, PGME is limited to those formulations applied pre-harvest (i.e., to growing crops only) and for animal applications.

Human exposures to residues of PGME may occur in residential environments via the dermal and inhalation routes. The highest residential exposures are likely associated with the use of paints and varnishes that contain PGME. However, dietary (oral) exposure is also possible through consumption of agricultural commodities treated with pesticides containing PGME or drinking water contaminated with PGME. Based on the environmental fate properties of PGME, it is expected to biodegrade rapidly and does not bioaccumulate in the environment. As such, PGME would be present at only low levels in the environment and would not be expected to constitute a significant risk.

Aggregate Exposures

In examining aggregate exposure, the Federal Food, Drug, and Cosmetic Act (FFDCA) section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other nonoccupational exposures, including drinking

water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For PGME, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the lack of human health concerns associated with exposure to PGME as an inert ingredient in pesticide formulations.

VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to PGME and any other substances and, this material does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that PGME has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

IX. Human Health Risk Characterization

PGME is a mixture of two isomers (α and β) and contains less than 0.5% of the β-isomer. PGME exhibits low toxicity by the oral, dermal and inhalation routes of exposure. PGME is neither a skin irritant nor a skin sensitizer and was only slightly irritating to the eye. Primary effects seen in repeated dose inhalation studies in rats, mice, rabbits, guinea pigs and monkeys occurred at relatively high doses (300 ppm or greater) and included sedation, hepatic changes and decreased body weight gain. Primary effects seen in repeated dose oral studies in rats also occurred at high doses and included central nervous system effects, enlarged livers and weight loss. Studies in laboratory animals indicate that PGME is not a developmental toxicant when administered via inhalation or ingestion. There is no evidence that the chemical is mutagenic or carcinogenic. It is also noted that an Agency reference concentration (RfC) is established for PGME of 2 mg/m^3 based on mild reversible sedation in rats and rabbits.

Exposure to PGME as a result of its use as an inert ingredient in pesticides products is possible through dietary (food and/or drinking water) or residential (dermal and inhalation) routes of exposure. Although exposures to PGME are likely to occur, these exposures are expected to be below levels associated with adverse health effects.

There is adequate physical-chemical and toxicological data available to characterize PGME. The toxicity of PGME is low for both aquatic and mammalian species. The low toxicity combined with the fact that it biodegrades rapidly and has a low potential for bioaccumulation in the environment will limit the potential for risk to human health. Inhalation to relatively high concentrations of PGME would likely be self-limiting due to the irritant effects of the chemical.

Taking into consideration all available information on PGME, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to PGME when considering exposure through food commodities and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the two exemptions from the requirement of a tolerance established for residues of PGME when used: 1) as a solvent in pesticide formulations applied to growing crops only; and/or 2.) a deactivator, emollient in pesticide formulations applied to animals can be considered reassessed as safe under section 408(q) of the FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

Available data from the SIAP indicate PGME is practically non-toxic to fish and aquatic invertebrates based on static tests conducted for 48h to 96h. LC_{50}'s for fish were from 4600 mg/L to 20800 mg/L. A single invertebrate LC_{50} was 23300 mg/L. An aquatic plant EC_{50} for growth was >1000 mg/L. There were no reported chronic effects studies in fish and invertebrates. Other than mammalian effects data, no terrestrial organism effects data, including plants, were reported. There were several studies identified in the Agency's Ecotox Database (http://www.epa.gov/ecotox). Three fish 24h effects studies under static conditions looking at behavior indicated an effects concentration of 5 mg/L for observed stress.

Considering the physical properties of the compound, aquatic exposures are possible. Acute effects to aquatic species (listed and non-listed) are unlikely unless application rates exceed thousands of pounds per acre. Likewise chronic effects are not expected unless application rates well exceed 1000 pounds per acre. Effects due to PGME degradates are unknown. Terrestrial risks are likely to be low unless application rates exceed 100 pounds per acre based on the available mammalian data used as a surrogate for other terrestrial phase animals. PGME is not expected to adversely affect plants (listed and non-listed) unless application rates exceed 1000 pounds per acre.

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APPENDIX A
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APPENDIX B

ROBUST STUDY SUMMARY

DEVELOPMENTAL TOXICITY

TEST SUBSTANCE

Identity: 2-Methoxypropanol-1 (α-isomer of 1-methoxypropanol-2 or alpha-PGME)
Description/Lot/Batch #/CAS #: Not provided
‡ **Remarks:** **Purity**: 98.05%

METHOD

Method/guideline followed: OECD #414
GLP (Y/N): Y
Year (study published): 1994
Species: Rabbit
Strain: ChbbHM:Thom
Route of administration: Inhalation-presumably whole body
Doses/concentration levels: 0, 145, 225, 350 or 545 ppm
Sex: Female (artificially inseminated)
Exposure period: GD 6-18
Frequency of treatment: 6 hr daily
Control group and treatment: Air
Duration of test: 30 days
Statistical methods: Williams test:- maternal body weight, body weight changes and uterine and placental weight. Krauth test: conception rates, mortality, and the percentage of litters with fetuses showing anomalies, variations, and/or retardations. Fisher test: corpora lutea, implantations, percentage of viable or dead implantations per dam, and percentage of viable fetuses with anomalies, variations, and/or retardations per litter.
Age at study initiation: 27-33 weeks old
No. of animals per sex per dose: 12 does/group
Vehicle: None
Mating procedures: Artificial insemination
Parameters assessed during study (maternal and fetal)**:** Maternal body weight, clinical symptoms, gross pathological examination of does, uterine weight, number of corpora lutea, live and resorbed implantations, pre-and post implantations losses, conception rate, placental weight, and fetal findings. The heads of fetuses were fixed according to method of Wilson, and fetal skeletons were examined by x- rays; in the case of unclear skeletal findings these skeletons were stained according to the method of Kimmel et al. (1981).
Organs examined at necropsy (macroscopic and microscopic)**:** Animals were sacrificed on GD 30. The uterus was removed, weighed and examined.
‡ **Remarks:** Rabbits were exposed in 1.1m^3 glass/steel chambers. Suitable amounts of 2-MP-1 were supplied by a piston pump to a glass evaporator which was heated to a maximum of 50EC. The vapors were diluted with conditioned air to obtain the

desired concentration and continuously supplied to the steel/glass chamber at a dynamic flow of 15 air exchanges per hour.

RESULTS

NOAEL (NOEL) and LOAEL (LOEL) maternal toxicity: 145 ppm and 225 ppm, respectively
NOAEL (NOEL) and LOAEL (LOEL) developmental toxicity: 145 ppm and 225 ppm, respectively
Measured concentrations/Actual dose received by dose level: 0, 143±3, 220±20 to 223±16, 356±24 to 357± 25, or 539±15 to 540±14 (Concentrations were measured three times during exposures)
Maternal data with dose level (with NOAEL value): Data are presented in Table 1. A statistically significant decreased in maternal body weight compared to controls was observed at 545 ppm during GD 12, 18 and 29 (6%, 10% and 8%, respectively). Throughout the course of the study (GD 0-29), there was a dose-related decrease in maternal body weight gain at 350 and 545 ppm (28% and 41%, respectively), compared to controls. Decreased maternal body weight gain from GD 6-18 was also noted at 350 ppm (85% lower than controls) and 545 ppm (72 g vs. 104 g in controls) indicating a moderate to marked toxicity in the does. Uterine weight was also lower compared to controls at 225, 350 and 545 ppm (21%, 21% and 35%, respectively). However, fetal weight was lower compared to controls only at 350 and 545 ppm. Therefore, the reduced uterus weight at 225 ppm was considered to be treatment-related. NOAEL for maternal toxicity was 145 ppm.
Fetal data with dose level (with NOAEL value): Data are presented in Table 2 and 3. At 350 and 545 ppm, there was a statistically significant decrease in the percentage of live fetuses, and increased percentage of dead implantations/doe, increased incidence of percentage of litters and fetuses/litter with external variations, skeletal anomalies and percentage of fetuses per litter with external and visceral anomalies, and visceral and skeletal variations. The skeletal malformation rate at 545 ppm was 100%. The types of malformations mainly consisted of absent phalanges, absent or shortened metatarsal bones, malformed ribs, and a unique enlargement of sternebrae. The external and visceral anomalies consisted of cleft palate, fetus with multiple anomalies, and truncus arteriosus communis. Fetuses were observed to have a trend of increased anomalies starting at the 225 ppm dose group. The NOAEL for developmental toxicity was 145 ppm.
Statistical results, as appropriate: Refer to maternal and fetal findings discussed above.

‡ **Remarks:** None

TABLE 1. Intergroup comparison of maternal data					
	Exposure Concentration (ppm)				
Observation	Control	145	225	350	545
No. 0f pregnant animals (conception rate)	11 (92)	10 (83)	11 (92)	11 (92)	10 (83)
Body weight change: GD 6-18 GD 0-29	 104 ±53[a] 372± 91	 84 ± 34 354 ±86	 93± 54 328± 78	 16± 82* 268± 102	 -72± 97** 220 ±50**
Gravid uterine wt. (g) Placental weight (g)	346±881 4.82±0.6	332±661 4.62±0.5	275±71* 5.30±0.6	272± 87* 5.39±0.7	226±85** 5.69±09**
Mean corpora lutea/Dam	6.82	6.90	6.55	6.91	6.38
Mean implantations/Dam	6.27	6.40	5.18	5.64	5.75
Mean live fetuses/Dam	6.00	5.90	4.64	4.73	3.75
Mean dead implants/doe	0.27	0.50	0.55	0.91	2.00

[a] Means ± SD
* Statistically different from controls (p= 0.05)
** Statistically different from controls (p= 0.01)

TABLE 2. Developmental findings - external, visceral and skeletal anomalies and variations					
	Exposure concentrations (ppm)				
Observation	Control	145	225	350	545
Total No. of live fetuses (No. litters examined)	66(11)	59 (11)	51 (11)	52 (11)	30 (8)
Mean fetal wt. (g)	41.7	39.5	41.2	38.9	37.0**
Fetal External Findings: Anomalies: No. of litters % of litters No. of fetuses % fetuses/litter	 1 9.09 1 1.30	 0 0.0 0 0.0	 0 0.0 0 0.0	 2 18.18 2 3.12	 4 50.00 6 28.75
Variations: No. of litters % of litters No. of fetuses % Fetuses/litter	 0 0.0 0 0.0	 0 0.0 0 0.0	 0 0.0 0 0.0	 4 36.36 (*) 6 15.45	 6 75.00** 15 47.92

Fetal Visceral Findings:					
Anomalies:					
No. of litters	2	0	0	2	4
% of litters	18.18	0.0	0.0	18.18	50.00
No. of fetuses	2	0	0	3	8
% Fetuses/litter	2.81	0.0	0.0	5.30	18.75
Variations:					
No. of litters	8	10	11	11	8
% of litters	72.73	100.0	100.00	100.00	100.0
No. of fetuses	22	24	35	30	23
% Fetuses/litter	36.36 33.33 ± 33.33[a]	40.33 38.10 ± 12.68	68.86 66.67 ± 25.00**	65.35 60.00 ± 25.00 (*)	84.17 100.00 ± 17.50**
Fetal Skeletal Findings:					
Anomalies:					
No. of litters	0	1	3	10	8
% of litters	0.0	10.00	27.27	90.91**	100**
No. of fetuses	0	1	9	39.21	30
% fetuses/litter	0.0	2.50	16.67	45.75.8338	100.00
Variations:					
No. of litters	3	6	8	8	6
% of litters	27.27	60.00	72.73 (*)	72.73	75.00
No. of fetuses	3	11	10	21	11
% Fetuses/litter	3.95 0.0 ± 6.25	20.79 16.67 ± 20.36(*)	21.44 20.00 ± 12.50*	45.38 50.00 ± 33.33**	39.17 33.33 ± 30.00**

[a] Mean ± quartile deviations
*p<0.05, ** p<0.0, (*) p<0.1

Observation	Control	145	225	350	545
No. of fetuses (litters) examined	66 (11)	59 (10)	51 (11)	52 (11)	30 (8)
External:					
Cleft palate	–	–	–	–	4 (3)
Fetus with multiple anomalies	–	–	–	–	2 (2)
Malposition of toes				2 (2)	2 (2)
Visceral:					
Gall bladder absent	–	–	–	–	3 (1)
Hypoplasia of spleen	1 (1)	–	–	2 (1)	2 (1)
Truncus arteriosus communis	–	–	–	–	2 (2)
Skeletal:					
Fused ribs	–	–	–	5 (4)	4 (2)
Sternebare fused to form a bony	–	1 (1)	4 (2)	29 (10)	28 (7)
plate	–	–	6 (2)	28 (9)	26 (7)
Enlarged rib cartilage	–	–	–	–	1
Absent phalanges	–	–	–	3 (2)	4 (3)
shortened metatarsalia	–	–	–	1 (1)	1 (1)
Absent metatarsalia					

CONCLUSIONS:

Gestational exposure to 2-MP-1 produced maternal and developmental toxicity in rabbits.

‡ **Results:** None

DATA QUALITY:

Reliability: 2, with restrictions

‡ **Remarks:** Rationale for dose-selection was not reported.

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