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 - Dipropylene Glycol Monomethyl Ether (DPGME), CAS Reg. No. 34590-94-8

FROM: Pauline Wagner, Chief Pauline Wagner 5/10/06
Inert Ingredient Assessment Branch
Registration Division (7505P)

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

FQPA REASSESSMENT ACTION

Action: Reassessment of two exemptions from the requirement of a tolerance for Dipropylene Glycol Monomethyl Ether (DPGME), CAS Reg. No. 34590-94-8. The reassessment decision is to maintain each of the two inert tolerance exemptions "as-is".

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]	Dipropylene glycol monomethyl ether	(none)	Stabilizer	34590-94-8 Propanol, 1(or 2)-(2-methoxymethylethoxy)-
180.930[b]	Dipropylene glycol monomethyl ether	(none)	Surfactants, related adjuvants of surfactants	

[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 stabilizer in pesticide formulations applied to growing crops only; and/or a surfactant 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 dipropylene glycol monomethyl ether (CAS No. 34590-94-8). 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 Dipropylene Glycol Monomethyl Ether (DPGME); CAS Reg. No. 34590-94-8

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

EXECUTIVE SUMMARY

This document evaluates DPGME, 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, DPGME is exempt from the requirement for a tolerance when used: 1) as a stabilizer in pesticide formulations applied to growing

crops only (40 CFR 180.920); and/or 2) as a surfactant in pesticide formulations applied to animals (40 CFR 180.930). DPGME is also used in the manufacture of a wide variety of industrial or commercial products including paints, varnishes, inks and cleaners, and is an intermediate in the manufacture of dipropylene glycol methyl ether acetate (DPGMEA).

DPGME is produced as a four-isomer mixture. The four isomers are not separated nor produced as individual chemicals. The available toxicity database for DPGME consists of acute, subchronic, developmental and mutagenicity data from studies conducted in laboratory animals. No chronic or neurotoxicity studies were identified. Although reproductive and chronic/carcinogenicity studies conducted with DPGME are not available, information collected on the structurally similar PGME is considered adequate to characterize DPGME and is included in this assessment. DPGME exhibits low acute toxicity by the oral, dermal, and inhalation routes. Studies with rats and rabbits showed that DPGME was not a developmental toxicant via the inhalation route. Information collected on the structurally similar PGME suggests that DPGME is not carcinogenic and is not a reproductive toxicant. Correspondingly, no effects on the testes and ovaries were seen in the subchronic inhalation studies conducted with DPGME.

Exposure to DPGME as a result of its use as an inert ingredient in pesticides is possible through dietary (food and/or drinking water) or residential (dermal and inhalation) routes of exposure. However, based on its use patterns, physical-chemical properties, and probable rapid biodegradation in soils and water, these exposures are expected to be below levels associated with adverse health effects.

There is adequate physical-chemical and toxicological data available to characterize DPGME. The toxicity of DPGME is low for both aquatic and mammalian species. The low toxicity combined with the fact that it biodegrades readily under aerobic conditions, does not persist in the environment, and has a low potential for bioaccumulation will limit the potential for risk to human health. Inhalation exposure to concentrations of DPGME greater than 75 ppm would likely be self-limiting due to the irritant effects of the chemical to the eyes, nose, throat, and respiratory tract.

Taking into consideration all available information on DPGME, the Agency has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to DPGME 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 DPGME when used: 1) as a stabilizer in pesticide formulations applied to growing crops only; and/or 2) a surfactant 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).

Introduction

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

II. Use Information

A. Pesticides

The tolerance exemptions for DPGME are provided in Table 1

Table 1. Tolerance Exemptions Being Reassessed in this Document

Citation as it Appears in the CFR				CAS Registry Number 9CI Name
40 CFR 180	Tolerance Exemption Expression	Limits	Uses	
.920[a]	Dipropylene glycol monomethyl ether	--	Stabilizer	34590-94-8 Propanol, 1(or 2)-(2-methoxymethylethoxy)-
.930[b]	Dipropylene glycol monomethyl ether	--	Surfactants, related adjuvants of surfactants	

[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

DPGME is used in the manufacture of a wide variety of industrial and commercial products including paints, varnishes, inks and cleaners. DPGME is used as a solvent in the manufacture of water-based coatings and as a coalescing agent for water-based paints and inks. DPGME is also an intermediate in the production of dipropylene glycol methyl ether acetate (DPGMEA). It is widely used in industrial, commercial, automotive and household cleaners. Consumer products containing DPGME include: glass, surface, and all-purpose cleaners; floor polish and carpet cleaners; paints and paintbrush cleaners; inks and dyes; rust remover and aluminum brightener; and cosmetic agents and their residues in packaging. Most products contain levels of DPGME between 1–10%, although some industrial products may have levels as high as 50% (BUA, 1995 as cited in OECD SIDS).

C. Manufacture/Production/Use

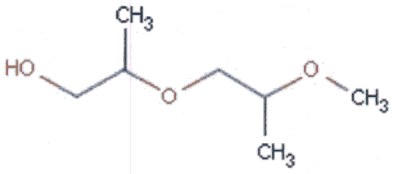
Commercial DPGME is produced as a four-isomer mixture. The four isomers are not separated nor produced as individual chemicals. OECD SIDS (2001) reported that

production of DPGME in the United States was estimated at 35 million pounds (16,000 tons) in 2000. The current production volume is not available.

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of DPGME, along with its structure and nomenclature, are found in Table 3. DPGME is produced as a four-isomer mixture. The respective fractions of the structural isomers are: 40-50% 1-(2-methoxypropoxy)propanol-2 (CAS No. 13429-07-7); 40-45% 1-(2-methoxy-1-methylethoxy)propanol-2 (CAS No. 20324-32-7); 2-5% 2-(2-methoxypropoxy)propanol-1 (CAS No. 13588-28-8); and 3-5% 2-(2-methoxy-1-methylethoxy)propanol-1 (CAS No. 55956-21-3).

Table 3. Physical and Chemical Properties of DPGME

Parameter	Value	Reference
Structure		www.sis.nlm.nih.gov/chemical.html
CAS #	34590-94-8	OECD SIDS, 2001
Empirical Formula	$CH3-(OC_3H_6)_2-OH$	OECD SIDS, 2001
Molecular Weight	148.2 g/mol	OECD SIDS, 2001
Purity	>98%	OECD SIDS, 2001
Impurities	Water (<0.1%)	OECD SIDS, 2001
Common Names	Dipropylene glycol methyl ether, Methoxypropoxypropanol, MDP, Acrosolv DPM, DOWANOL DPM®, Solvenon DPM, Dimethyl Proxitol	OECD SIDS, 2001
Physical State	Liquid	OECD SIDS, 2001
Melting Point	-83°C	OECD SIDS, 2001
Boiling Point	190°C	OECD SIDS, 2001
Water Solubility	Miscible	OECD SIDS, 2001
Relative Density (water=1)	0.948 g/cm^3	OECD SIDS, 2001
Vapor Pressure	0.37 hPa @ 20 °C	OECD SIDS, 2001
log Kow	0.0061	OECD SIDS, 2001
Henry's Law Constant	1.2E-4 Pa/m^3 mol-1	OECD SIDS, 2001

IV. Hazard Assessment

DPGME 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 DPGME, 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 DPGME was held in Paris, France on June 27-29, 2001.

Technical and scientific literature information on DPGME is also available through the American Chemistry Council Ethylene and Propylene Glycol Ethers Panel (ACC EGE/PGEP) which was formed in 1993 to expand the toxicity database on propylene-based glycol ethers (http://www.pgep.org). The members of the Panel include Arch Chemical, The Dow Chemical Company, and Lyondell Chemical Company (Shell Chemical LP is a former Panel member). The 2001 OECD SIDS report and select primary information from the ACC EGE/PGEP were the major sources of the information discussed in this reassessment.

A. Hazard Profile

The available toxicity database for DPGME consists of acute, subchronic, developmental, and mutagenicity data from studies conducted in laboratory animals. No chronic or neurotoxicity studies were identified. Although reproductive and chronic/carcinogenicity studies conducted with DPGME are not available, information collected on the structurally similar compound, PGME, is available and included in this assessment.

According to OECD SIDS (2001) review, DPGME exhibits low acute toxicity by the oral, dermal, and inhalation routes. In rabbits, DPGME was not a skin irritant and was only slightly irritating to the eye. In repeat dose inhalation studies ranging from 2 to 31 weeks in duration, No Observed Adverse Effect Levels (NOAELs) of 50-200 ppm were seen in rats, mice, rabbits, guinea pigs and monkeys. Effects observed at higher dose

levels (300-400 ppm) showed signs of central nervous system depression and adaptive liver changes. In a rat study lasting 4 weeks, an oral NOAEL of 200 mg/kg/day was established based on observations of tentative salivation (immediately following dosing) and adaptive liver changes at the limit dose (1000 mg/kg/day). Studies with rats and rabbits showed that DPGME was not a developmental toxicant (two inhalation studies, both with NOELs of 300 ppm). The available data indicate that DPGME is not genotoxic. Information collected on the structurally similar PGME suggests that DPGME is not carcinogenic and is not a reproductive toxicant. Correspondingly, no effects on the testes and ovaries were seen in the subchronic inhalation studies conducted with DPGME.

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

B. Toxicological Data

The toxicity information for DPGME presented in this section is from OECD SIDS (2001) publication. This report has undergone several levels of technical review and therefore, the toxicity data should be sufficiently reliable for use in this reassessment.

Acute Toxicity

Acute toxicity of DPGME by the oral, dermal and inhalation route is low. Data on acute toxicity studies are presented in Table 4.

Table 4. Summary of Acute Toxicity Data for DPGME

Parameter	Toxicity Value	Reference[a]
Oral LD_{50}, rat	5180-5400 mg/kg	Rowe et al., 1954; Smyth et al., 1962
Dermal LD_{50}, rabbit	9500 mg/kg	Smyth et al., 1962; Browning, 1965; Clayton and Clayton, 1982
Acute Inhalation, rat	LOAEL = 500 ppm	Rowe et al., 1954
Eye Irritation, rabbit	Slightly Irritating	OECD SIDS, 2001
Skin Irritation, rabbit	Non-irritating	OECD SIDS, 2001

[a] All references provided from OECD SIDS.

Eye Irritation:
Studies on the effects of DPGME on the eyes of rabbits resulted in non-irritating and slightly irritating results (Ballantyne, 1984a; Prehled Prumyslove Toxikol Org Latky, 1986; Union Carbide, 1971; Rowe *et al.*, 1954., all cited in OECD SIDS).

Skin Irritation:
In rabbits, DPGME was classified as non-irritating to the skin (Ballantyne, 1983; Rowe *et al.,* 1954; Smyth et al., 1962; Union Carbide, 1971., all cited in OECD SIDS).

Subchronic Toxicity

Laboratory animals (rats, mice, rabbits, guinea pigs and monkeys) exposed to DPGME via inhalation have reportedly developed mild symptoms of toxicity, including central nervous system effects (sedation), adaptive hepatic changes, and decreases in body weight gain at concentrations of 140-400 ppm. NOELs ranged from >50 to 400 ppm in experiments in rats lasting 2 to 28 weeks (Landry *et al.*, 1981; Landry and Yano, 1984; Rowe *et al.*, 1954, all cited in OECD SIDS). For mice, a NOEL of >50 ppm and a LOEL of 140 ppm in an experiment lasting 2 weeks were reported (Landry *et al.*, 1981, as cited in OECD SIDS). In experiments in rabbits lasting 13 and 31 weeks, NOELs of > 200 ppm and 300-400 ppm were observed, respectively (Landry *et al.*, 1983; Rowe *et al.*, 1954, both cited in OECD SIDS). In other inhalation studies lasting 6 months, NOELs of 300 ppm and > 300 ppm were observed for monkeys and guinea pigs, respectively (Rowe *et al.*, 1954, as cited in OECD SIDS).

In rats exposed to either 0, 40, 200, or 1000 mg/kg-day DPGME via gavage for 4 weeks, tentative salivation (immediately after dosing) and liver effects (increased relative liver weight, centrilobular hypertrophy) were observed in animals exposed to the highest dose (Dow Chemical Japan, 2000, as cited in OECD SIDS). No effects were observed in rats exposed to 200 mg/kg/day. Additionally, laboratory animals exposed to PGME (a compound similar to DPGME) via ingestion have reportedly developed central nervous system effects (mild to severe depression), enlarged livers, and weight loss. Minor kidney damage was reported following large oral doses. However, the renal effects in rats appear to be due to α2-microglobulin-mediated mechanism of action which is species specific to rats and is not applicable to humans. NOELs of < 459.5 and 919 mg/kg were observed in subchronic experiments lasting 13 and 5 weeks, respectively, in which PGME was administered orally to rats (Rowe *et al.*, 1954; Stenger *et al.*, 1972, both cited in OECD SIDS).

Laboratory animals dermally exposed to DPGME have reportedly developed dermal effects (skin irritation, scaling, minimal inflammation, and skin thickening). Large dermal doses (10 mg/ml) can produce kidney effects (hydropic degeneration), narcosis and death. In a subchronic study in which DPGME was dermally applied to rabbits, a NOEL of 2,850 mg/kg and a LOEL of 4,750 mg/kg were observed (Rowe *et al.*, 1954, as cited in OECD SIDS). A NOEL of 1,000 mg/kg was reported for rats exposed to DPGME for 4 weeks (Fairhurst *et al.*, 1989, as cited in OECD SIDS).

Neurotoxicity

Neurotoxicity studies were not available. However, OECD SIDS reports that rats, mice, rabbits, guinea pigs and monkeys were observed to have central nervous system (CNS) depression when exposed by inhalation to 300-400 ppm DPGME.

Mutagenicity

DPGME was not mutagenic in *in vitro* tests on mammalian cells. No evidence of genotoxicity was reported in *Salmonella typhimurium* or *Escherichia coli,* with or without

metabolic activation, using concentrations ranging from 313 to 5000 ug/plate (Dow Chemical Japan, 2000, as cited in OECD SIDS). Similarly, no evidence of chromosomal aberrations was noted in Chinese hamster lung cells exposed to 0.371-1.482 mg/L for 6 or 25 hours (Dow Chemical Japan, 2000, as cited in OECD SIDS). DPGME was not toxic to Chinese hamster ovary (CHO) cells up to 5 mg/L, but reduced survival to approximately 50% at 10 mg/L. Since metaphase analysis showed no differences between DPGME-treated and untreated cells, with or without metabolic activation, DPGME is considered not to be a chromosome mutagen for CHO cells (Kirkland, 1983, as cited in OECD SIDS). In a rat hepatocyte unscheduled DNA synthesis (UDS) assay, DPGME failed to elicit significant UDS at any concentration tested (0-0.0000316 M without metabolic activation). This result suggests an apparent lack of genotoxic activity under the test conditions (Mandrala, 1983). In a study by Kirkland and Varley (1983, as cited in OECD SIDS), DPGME was tested in a bacterial reverse mutation assay (Ames Test) on *Salmonella typhimurium* with and without metabolic activation. DPGME tested negative for genotoxic effects.

No *in vivo* data are available for DPGME. However, concentrations up to 6,000 mg/kg PGME (a structurally similar chemical) administered to mice did not increase the frequency of micronuclei in polychromatic erythrocytes harvested from bone marrow (Elias *et al.*, 1996, as cited in OECD SIDS).

Carcinogenicity

While DPGME has not been evaluated in a chronic toxicity/oncogenicity bioassay to date, its low toxicologic potential in subacute and subchronic studies, lack of genotoxic activity, and biotransformation via the same general routes and types of metabolites as the noncarcinogen PGME, indicate that DPGME is unlikely to be carcinogenic in man or animals.

In a 2-year inhalation carcinogenicity study sponsored by the CMA PGE Panel (Cieszlak *et al.,* 1998, as cited in OECD SIDS) with the structurally similar chemical propylene glycol monomethyl ether (PGME) no evidence of carcinogenicity has been found in either rats or mice. The highest dose tested in both sexes of both species was 300 ppm. Major metabolic pathways for DPGME include conjugation with glucuronic acid and sulfate; hydrolysis of the methoxy group to form dipropylene glycol; and hydrolysis of the dipropylene glycol backbone of DPGME to form PGME and propylene glycol (Miller *et al* 1985, as cited in OECD SIDS). The glucuronide and sulfate conjugates of DPGME are essentially non-toxic and rapidly eliminated from the body. DPGME is less volatile and has been shown in comparable studies to be similar to, or less toxic than dipropylene glycol, PGME and propylene glycol, each of which are of low toxicity, themselves. Therefore, no major differences in the systemic toxicological properties of DPGME and PGME would be anticipated, including carcinogenic potential. Consistent with this view is the fact that DPGME has been shown not to be genotoxic in several *in vitro* assay systems; DPGME was negative in an Ames bacterial gene mutation assay, did not induce unscheduled DNA synthesis (DNA damaged-induced repair) in rat hepatocytes, and was not clastogenic in CHO cells (ECETOC, 1995, as cited in OECD SIDS).

Developmental and Reproductive Toxicity

Developmental:
Studies in laboratory animals indicate that DPGME is not a developmental toxicant when administered via inhalation. In a study of rats exposed to DPGME via inhalation, NOELs of 300 ppm (maternal) and 300 ppm (teratogenic) were observed. NOELs of 300 ppm were also reported for both maternal and teratogenic effects in rabbits (Breslin *et al.*, 1990, as cited in OECD SIDS). No teratogenic effects were observed in rabbits up to the highest concentration attainable (300 ppm) at room temperature and normal pressure.

No oral developmental toxicity data is available for DPGME, however, no maternal toxicity, fetotoxicity, or teratogenicity was observed in rats, mice, and rabbits administered PGME (a compound similar to DPGME) via oral gavage. NOELs of 0.8 mL/kg, 2 mL/kg, and 1 mL/kg were observed for rats, mice, and rabbits, respectively (Stenger *et al.,* 1972, as cited in OECD SIDS).

Although tests on commercial DPGME and PGME have been negative in developmental studies, the pure β-isomer of PGME (present at levels less than or equal to 0.5% in commercial PGME) has produced developmental effects in animals (BASF, 1988; Hellwig et al., 1994, as cited in OECD SIDS). Unlike the α-isomer of PGME, the β-isomer is an excellent substrate for alcohol/aldehyde dehydrogenases and is oxidized primarily to 2-methoxypropionic acid (2-MPA) (Miller et al., 1986, as cited in OECD SIDS). It is this alkoxyacid metabolite that is the likely mediator of developmental toxicity (Carney et al., 2000, as cited in OECD SIDS). DPGME differs from PGME in that it does not contain the β-isomer thus the formation of the primary alcohol from DPGME is dependent upon the potential to hydrolyze the central ether linkage in certain isomers of DPGME. Only two of the four DPGME isomers have the potential to be hydrolyzed to the β-isomer. *In vivo* and *in vitro* studies provide support that significant cleavage of the dipropylene glycol backbone does not occur (Mendrala et al., 1993; Pottenger et al., 1995, as cited in OECD SIDS) precluding the formation of levels of the β-isomer capable of producing toxicologically significant effects even at very high doses of DPGME. The low potential to generate the β-isomer of PGME, taken together with negative results in developmental toxicity studies in multiple species conducted with PGME and DPGME, indicate it is unlikely that DPGME would be a developmental toxicant by oral ingestion or inhalation.

Reproductive:
No effects were observed on the testes and ovaries in a 28-day repeat dose oral toxicity study on DPGME (as cited in OECD SIDS). Additionally, in a 2-generation inhalation reproduction study sponsored by the CMA Propylene Glycol Ethers Panel with the structurally similar chemical propylene glycol monomethyl ether (PGME) no adverse fertility or reproductive effects were observed (at 1,000 ppm PGME). Levels of α-isomer (1-methoxy-2-propanol) ranged from 97.99-98.07%, while the β-isomer (2-methoxy-1-propanol) ranged from 1.86-1.90% (commercially available PGME contains <0.5% of the β-isomer as an impurity.

C. Metabolism and Pharmacokinetics

In a study by Miller et al., male Fischer 344 rats were given a single oral dose of carbon-14 labeled DPGME. Approximately 60% of the administered ^{14}C activity was excreted in the urine, while 27% was eliminated as $^{14}CO_2$ within 48 hours after dosing. DPGME, PGME, as well as sulfate and glucuronide conjugates of DPGME were identified in urine of animals given (^{14}C) DPGME. Major metabolic pathways for DPGME include conjugation with glucuronic acid and sulfate and hydrolysis of the methoxy group to form dipropylene glycol. Hydrolysis of the dipropylene glycol backbone of DPGME to form PGME (propylene glycol monomethyl ether) and propylene glycol is considered a minor metabolic pathway as indicated by the fact that conjugates of DPGME, dipropylene glycol and the parent compound accounted for more than half of the total radiolabel in the urine (Miller et al, 1985, as cited in OECD SIDS). Like PGME and other propylene based glycol ethers, microsomal O-demethylation is a significant route of biotransformation of DPGME. The glucuronide and sulfate conjugates of DPGME are essentially non-toxic and rapidly eliminated from the body. DPGME is less volatile and has been shown in comparable studies to be similar to, or less toxic than dipropylene glycol, PGME and propylene glycol, each of which are of low toxicity.

Although tests the pure β-isomer of PGME (present as an impurity at levels no greater than 0.5% in commercial PGME) has been shown to produce developmental effects in animals (BASF, 1988; Hellwig et al., 1994, as cited in OECD SIDS), studies of commercial PGME have indicated a low potential for toxicity. Unlike the α-isomer, the β-isomer is an excellent substrate for alcohol/aldehyde dehydrogenases and is oxidized primarily to 2-methoxypropionic acid (2- MPA) (Miller et al., 1986, as cited in OECD SIDS). It is this alkoxyacid metabolite that is the likely mediator of developmental toxicity (Carney et al., 2000, as cited in OECD SIDS). DPGME differs from PGME in that it does not contain the β-isomer so that formation of the primary alcohol from DPGME is dependent upon the potential to hydrolyze the central ether linkage in certain isomers of DPGME. Only two of the four DPGME isomers have the potential to be hydrolyzed to the β-isomer. Assuming that 100% cleavage of the ether bridge occurs, only 0.6 mmol of 2-MPA can be theoretically produced for every mmol of DPGME. A pharmacokinetic study with a structurally similar dipropylene glycol ether, dipropylene glycol dimethyl ether (DPGDME) showed a very low potential for cleavage of the glycol ether backbone with only 4.3% of the theoretical maximum of 2-MPA recovered at low doses and 13% of the theoretical maximum at higher doses (Mendrala et al., 1993, as cited in OECD SIDS). In an *in vitro* liver slice metabolism assay used to investigate the formation of 2-MPA from six propylene glycol ethers including the β-isomer of PGME and DPGDME, none of the di- or triether substrates evaluated were metabolized to 2-MPA as effectively as the β-isomer of PGME. The *in vitro* formation of 2-MPA from the β-isomer ranged from 3-170 fold higher than from any of the diethers tested (Pottenger et al., 1995, as cited in OECD SIDS). The *in vivo* metabolism study with DPGME taken together with the *in vivo* and *in vitro* studies with structurally analogous diglycol ethers indicate that hydrolysis of the central ether linkage to form the primary alcohol and subsequent hydrolysis to the alkoxyacid metabolite is a minor metabolic pathway for DPGME. This minor pathway is likely to result in levels of MPA that are well below the levels that produce toxicologically significant effects even at high doses of DPGME.

The American Chemistry Council's Ethylene and Propylene Glycol Ethers Panel (ACC EGE/PGE) has recently submitted draft results of a metabolism study conducted with DPGME (CAS. Reg. No. 34590-94-8) to the Agency under Section 8(e) of the Toxic Substances Control Act (TSCA; Submission # 8EHQ-05-16297). The objective of the study was to evaluate metabolism of DPGME and its metabolite, methoxyacetic acid (MPA) in rats and rabbits. The draft results indicate that 5.8-12.3% and 1.5-2.4% of MPA is recovered in the urine of rats and rabbits, respectively, after 72 hours (ACC EGE/PGEP, 2006). These draft results are consistent with predicted theoretical values.

OECD SIDS reports that the database on the metabolites of DPGME also includes studies that have not been conducted with DPGME such as reproductive and chronic toxicity/oncogenicity studies. Based upon the low probability to form the β-isomer of PGME, similarities in metabolism and modes of action of DPGME and its metabolites, it is highly probable that DPGME will be similar to or less toxic than its metabolites in reproductive, chronic toxicity, and carcinogenicity studies.

D. Special Considerations for Infants and Children

It is concluded that DPGME is not a developmental toxicant when administered via inhalation or ingestion (by the surrogate chemical PGME). Developmental studies conducted in rats and rabbits with DPGME administered via inhalation showed no developmental or maternal toxicity at the highest dose tested (300 ppm). Although no oral developmental study is available for DPGME, in studies conducted with a related compound, PGME, no developmental toxicity was observed in rats, mice or rabbits via oral gavage (Stenger at al., 1972, as cited in OECD SIDS).

Although studies on animals using the pure β-isomer of PGME have shown developmental effects (BASF, 1988; Hellwig et al., 1994, as cited in OECD SIDS), studies using commercial PGME (which contains < 0.5% of the β-isomer as an impurity) have indicated a low potential for toxicity. In addition, it has been shown that DPGME has a low potential to generate the PGME β-isomer. This low potential to generate the β-isomer, in addition to the negative results in developmental toxicity studies in multiple species, indicate it is unlikely that DPGME would be a developmental toxicant by oral ingestion or inhalation.

Information on reproductive toxicity collected on the structurally similar PGME suggests that DPGME is not a reproductive toxicant. OECD SIDS reports that no adverse fertility or reproductive effects were observed at 1,000 ppm in a 2-generation inhalation reproduction study conducted with the structurally similar chemical PGME. Correspondingly, there were no effects on the testes and ovaries in the subchronic inhalation studies conducted with DPGME. OECD SIDS further concludes that based upon the similarities in metabolism and modes of action of DPGME and its metabolites, it is highly probable that DPGME will be similar to or less toxic than its metabolites in reproductive toxicity studies.

Based on this information there is no concern, at this time, for increased sensitivity to infants and children to DPGME 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 dipropylene glycol monomethyl ether (DPGME) is relatively well known based on information submitted in support of the OECD's Screening Information Data Set, Initial Assessment Profile (SIAP). Dipropylene glycol monomethyl ether is a mixture of four isomers, which as a whole are unlikely to persist in the environment and expected to be mobile based on the low measured octanol-water partition coefficient and estimated soil-water partition coefficient. DPGME is miscible in water, likely resistant to hydrolysis due to a lack of active hydrolysable functional groups and photolysis is not likely to be a significant degradation pathway in natural waters or on soils. Based on measured data in studies using water and sewage inoculums, biodegradation is likely the major dissipation pathway with more than 50 percent degradation under aerobic conditions in 14 to 21 days. Anaerobic degradation is a minor dissipation pathway. Aerobic degradation in soils is expected to occur rapidly. DPGME 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. DPGME 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 probable rapid biodegradation in soils and water. Based on a projected half-life in soil and water of less than 21 days and other physical-chemical properties, application rates of 1 pound per acre will likely result in concentrations in the low parts per billion in untreated water. The effect of common drinking water treatment processes is largely unknown, but coagulation, flocculation, and sedimentation are not expected to be very effective. In addition, because DPGME was found in both sewage effluent and in water from a landfill recovery well, oxidation (e.g., chlorination) may not be very effective in transforming the compound. No ambient monitoring data are available for this compound.

VI. Exposure Assessment

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

Human exposures to residues of DPGME may occur in residential environments via the dermal and inhalation routes. The highest residential exposures are likely associated with the use of cleaning products, paints and cosmetic agents that contain DPGME. However, dietary (oral) exposure is also possible through consumption of agricultural commodities treated with pesticides containing DPGME or drinking water contaminated with DPGME. Based on the environmental fate properties of DPGME, it is not persistent in the environment and not expected to bioaccumulate. As such, DPGME

would likely 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 DPGME, 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 DPGME as an inert ingredient in pesticide formulations.

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 DPGME 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 DPGME 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

DPGME is produced as a four-isomer mixture. The four isomers are not separated nor produced as individual chemicals. DPGME exhibits low acute toxicity by the oral, dermal, and inhalation routes. DPGME is not a skin irritant and was only slightly irritating to the eye. Primary effects in repeat dose inhalation studies in rats, mice, rabbits, guinea pigs and monkeys included sedation, adaptive hepatic changes, and decreases in body weight gain (NOAELs ranged from 50-200 ppm). Effects observed at higher dose levels (300-400 ppm) included signs of central nervous system depression and adaptive liver changes. Primary effects in the repeat dose oral study in rats occurred at the limit dose (1000 mg/kg/day) and included salivation (immediately following dosing) and adaptive liver changes. Studies with rats and rabbits showed that DPGME was not a developmental toxicant. DPGME is structurally related to PGME and

although the β-isomer of PGME is a known teratogen, this isomer is unlikely to be a metabolite of DPGME. The available data indicate that DPGME is not genotoxic. Information collected on the structurally similar PGME suggests that DPGME is not carcinogenic and is not a reproductive toxicant. Correspondingly, no effects on the testes and ovaries were seen in the subchronic inhalation studies conducted with DPGME.

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

There is adequate physical-chemical and toxicological data available to characterize DPGME. The toxicity of DPGME is low for both aquatic and mammalian species. The low toxicity combined with the fact that it biodegrades readily under aerobic conditions, does not persist in the environment and has a low potential for bioaccumulation will limit the potential for risk to human health. Inhalation exposure to concentrations of DPGME greater than 75 ppm would likely be self-limiting due to the irritant effects of the chemical to the eyes, nose, throat and respiratory tract.

Taking into consideration all available information on DPGME, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to DPGME 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 DPGME when used: 1) as a stabilizer in pesticide formulations applied to growing crops only; and/or 2) a surfactant 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 DPGME is practically non-toxic to fish and aquatic invertebrates based on static and flow-through tests conducted for 48h to 96h. LC_{50}'s for fish were all greater than 150 to 10,000 mg/L and >1000 mg/L for aquatic invertebrates. An aquatic plant NOEC was 969 mg/L and an EC_{10} of 133 mg/L was reported for the same study. There were no reported chronic effects studies in fish and an aquatic invertebrate flow-through chronic study on *Daphnia magna* provided a 22-day no observed adverse effects on survival and reproduction at 500 mg/L. Other than mammalian effects data, no terrestrial organism effects data were reported. Terrestrial plant effects data were available for a number of crop and non-crop species. No observed effects levels, using a growth endpoint, ranged from 250 g/L to >1000 g/L. There were no effects data located in the Agency's Ecotox Database (http://www.epa.gov/ecotox).

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 1000 pounds per acre. Likewise, chronic effects are not expected unless application rates well exceed 1000 pounds per acre. Effects due to DPGME degradates are unknown. Terrestrial risks are likely to be low unless application rates exceed 10 pounds per acre based on the available mammalian data used as a surrogate for other terrestrial phase animals. DPGME is not expected to adversely affect plants (listed and non-listed) unless application rates exceed 1000 pounds per acre.

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