

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



OFFICE OF PREVENTION,
 PESTICIDES, AND TOXIC SUBSTANCES

DATE: June 29, 2006

ACTION MEMORANDUM

SUBJECT: Reassessment of 3 Tolerance Exemptions for Ethylene Glycol, Diethylene Glycol, and the Combination of Diethylene Glycol Monomethyl Ether, Diethylene Glycol Monoethyl Ether, and Diethylene Glycol Monobutyl Ether

FROM: Pauline Wagner, Chief *Pauline Wagner 6/30/06*
 Inert Ingredient Assessment Branch
 Registration Division (7505P)

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

I. FQPA REASSESSMENT ACTION

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

Table 1. Tolerance Exemptions Being Reassessed in this Document

Citation as it Appears in the CFR				CAS Registry Number Name
40 CFR 180 ^a	Tolerance Exemption Expression	Limits	Uses	
920	Ethylene glycol	---	Antifreeze, deactivator for all pesticides used before crop emerges from soil and in herbicides before or after crop emerges	107-21-1 1,2-Ethanediol
920	Diethylene glycol	---	Deactivator, adjuvant for formulations used before crop emerges from soil and deactivator for formulations used before crop emerges from soil, stabilizer	111-46-6 Ethanol, 2,2'-oxybis- (9CI)
920	Diethylene glycol monomethyl ether	---	Deactivator for formulations used before crop emerges from soil, stabilizer	111-77-3 Ethanol, 2-(2-methoxyethoxy)-
	Diethylene glycol monoethyl ether			111-90-0 Ethanol, 2-(2-ethoxyethoxy)-
	Diethylene glycol monobutyl ether			112-34-5 Ethanol, 2-(2-butoxyethoxy)-

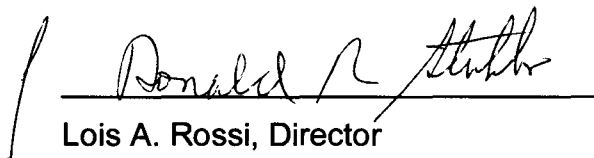
a. Residues listed in 40 CFR 180.920 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.

Use Summary: These chemicals have many uses and are also used as antifreeze and deicers, as solvents, humectants, as chemical intermediates in the synthesis of other chemicals, and as components of many products such as brake fluids, lubricants, inks, lacquers, and cosmetics.

List Reclassification Determination: The current List Classifications for ethylene glycol and diethylene glycol are List 3, and the current List Classifications for diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, and diethylene glycol monobutyl ether are List 2. Because EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to these chemicals when used as inert ingredients in pesticide formulations, the List Classification for these chemicals will change from List 2 and 3 to List 4B.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of one tolerance exemption for ethylene glycol (CAS 107-21-1), one tolerance exemption for diethylene glycol (CAS 111-46-6), and one tolerance exemption for the combination of diethylene glycol monomethyl ether (CAS 111-77-3), diethylene glycol monoethyl ether (CAS 111-90-0), and diethylene glycol monobutyl ether (CAS 112-34-5), and with the List reclassification determinations, as described above. I consider the three exemptions established in 40 CFR part 180.920 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

7/3/06
Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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



OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

June 30, 2006

MEMORANDUM

SUBJECT: Reassessment of Tolerance Exemptions for Ethylene Glycol, Diethylene Glycol, Diethylene Glycol Monomethyl Ether, Diethylene Glycol Monoethyl Ether, and Diethylene Glycol Monobutyl Ether

FROM: Kit Farwell, D.V.M.
Reregistration Branch 1
Health Effects Division (7509P)

Handwritten signature of Kit Farwell in black ink.

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

BACKGROUND

This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, and exposure profile for ethylene glycol, diethylene glycol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, and diethylene glycol monobutyl ether. The purpose of this document is to reassess the exemptions from the requirement of a tolerance for residues of these chemicals when used as inert ingredients in pesticide formulations as required under the Food Quality Protection Act (FQPA).

EXECUTIVE SUMMARY

This document evaluates ethylene glycol (EG), diethylene glycol (DG), diethylene glycol monomethyl ether (DGME), diethylene glycol monoethyl ether (DGEE), and diethylene glycol monobutyl ether (DGBE), pesticide inert ingredients for which an exemption from the requirement of a tolerance exists. There is one tolerance exemption for DG and one tolerance exemption for the combination of DGME, DGEE, and DGBE under 40 CFR 180.920, and both limit use of the chemicals to before the crop emerges from soil. EG has a tolerance exemption in 40 CFR 180.920 that limits use to before the crop emerges from soil and in herbicides before or after crop emerges.

These chemicals have many uses and are also used as antifreeze and deicers, as solvents, humectants, as chemical intermediates in the synthesis of other chemicals, and as components of many products such as brake fluids, lubricants, inks, lacquers, and cosmetics.

The acute toxicities of EG, DG, DGME, DGEE, and DGBE are low with oral LD₅₀ values > 5,000 mg/kg for all of the chemicals. Systemic toxicity from longer term oral exposure is also low: kidney toxicity generally occurring in the 1,000 – 6,000 mg/kg/day range, although mild kidney toxicity was reported at 300 mg/kg/day in an older rat study with DG. Microscopic liver lesions were seen with EG, thymus toxicity with DGME, and testicular toxicity was reported with DGME and DGEE, also at higher oral doses. Minor hematological effects were reported in several studies.

No systemic toxicity was noted in inhalation studies with DGME and DGEE. No toxicity after dermal exposure was reported in DGBE reproductive and neurotoxicity studies. Mild liver changes were reported after dermal exposure to DGME in guinea pigs at 200 mg/kg/day.

No treatment related neoplasms were found in a mouse carcinogenicity study with EG. Bladder tumors, mostly benign, occurred at 1,500 and 3,000 mg/kg/day in male rats treated with DG; these tumors were associated with irritation from bladder stones which occurred at those doses. Genetic toxicity studies with these chemicals were negative, except for chromosomal damage which occurred in a bone marrow assay with DG.

EG underwent a comprehensive review by NTP of potential human developmental and reproductive toxicity which concluded that “there is negligible concern of adverse developmental toxicity from EG at exposures below 125 mg/kg”. There was no evidence of reproductive toxicity from EG in lab animals. DG caused developmental toxicity in mice at 10,000 mg/kg/day and caused fetal/pup mortality in a reproductive mouse study 6,125 mg/kg/day. DGME caused decreased ossification at 600 mg/kg/day in a rat oral developmental study (NOAEL = 200 mg/kg/day) and at 250 mg/kg/day in a rabbit dermal developmental study (NOAEL = 50 mg/kg/day). Overall, there are no concerns for potential sensitivity of infants and children to these chemicals because developmental toxicity only occurred at doses much greater than that expected from use as inert ingredient.

Exposure to these chemicals as a result of use as an inert ingredient in pesticidal products is possible through the dietary (food and/or drinking water) or residential (dermal and inhalation) routes of exposure. The tolerance exemptions for DG, DGME, DGEE, and DGBE significantly limit the potential for exposure by only allowing applications before the crop emerges from soil. This typically equates to one application. EG’s tolerance exemption also limits applications to use before the crop emerges from soil, except in herbicides. EG, DG, DGME, DGEE, and DGBE all biodegrade quickly in soil and water, and bioconcentration in aquatic organisms is expected to be low. Considering the ready biodegradation and use limitations of these chemicals, dietary and residential exposures of concern are not anticipated.

The low exposure potential for these chemicals limits the potential for risk to human health. Taking into consideration all available information for these chemicals, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure when considering exposure through dietary exposure and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the exemption from the requirement of a tolerance established for residues of EG, DG, DGME,

DGEE, and DGBE when used as inert ingredients in pesticide formulations applied to growing crops under 40 CFR part 180.920 can be considered reassessed as safe under section 408(q) of the FFDCA.

I. Introduction

This report provides a qualitative assessment for ethylene glycol (EG), diethylene glycol (DG), diethylene glycol monomethyl ether (DGME), diethylene glycol monoethyl ether (DGME), and diethylene glycol monobutyl ether (DGBE) when used as a pesticide inert ingredient with tolerance exemptions under 40 CFR 180.920. There is sufficient information to conduct this assessment.

II. Use Information

A. Pesticides. The tolerance exemptions for EG, DG, DGME, DGME, and DGBE when used as inert ingredients in pesticide formulations are shown in Table 1.

Table 1. Tolerance Exemptions Being Reassessed in this Document

Citation as it Appears in the CFR				
40 CFR 180 ^a	Tolerance Exemption Expression	Units	Uses	CAS Registry Number Name
920	Ethylene glycol	---	Antifreeze, deactivator for all pesticides used before crop emerges from soil and in herbicides before or after crop emerges	107-21-1 1,2-Ethanediol
920	Diethylene glycol	---	Deactivator, adjuvant for formulations used before crop emerges from soil and deactivator for formulations used before crop emerges from soil, stabilizer	111-46-6 Ethanol, 2,2'-oxybis- (9CI)
920	Diethylene glycol monomethyl ether	---	Deactivator for formulations used before crop emerges from soil, stabilizer	111-77-3 Ethanol, 2-(2-methoxyethoxy)-
	Diethylene glycol monoethyl ether			111-90-0 Ethanol, 2-(2-ethoxyethoxy)-
	Diethylene glycol monobutyl ether			112-34-5 Ethanol, 2-(2-butoxyethoxy)-

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. Other Uses

EG is used as a de-icer and anti-icer, is a component in hydraulic brake fluid and inks, and is used as a solvent.

DG is used as a solvent and as a humectant in many products. It is used in brake fluids, lubricants, mold release agents and inks. It is used in the lacquer industry, in cosmetics, as an antifreeze solution for sprinkler systems; and as a lubricating and finishing agent for wool, worsted cotton, rayon, and silk. DG is an intermediate in the production of explosive diethylene glycol dinitrate.

DGME is used as a solvent; in varnish removers, cleaning solution, dye baths; brake fluid component; aviation fuel antiicing additive; solvent in paints, printing inks resins, waxes and dyes. DGME is used as a coupling agent for preparing miscible aqueous systems.

DGBE is used as a solvent and is used as a coupling solvent (in liquid cleaners, cutting fluids, textile auxiliaries). It is also used as a chemical intermediate in the synthesis of diethylene glycol dibutyl ether, diethylene glycol monobutyl ether acetate, and piperonyl butoxide.

DGEE is used as a solvent for dyes, nitrocellulose, and resins; mutual solvent for mineral-oil-soap and mineral-oil-sulfonated-oil mixtures; non-aqueous stains for wood, for setting the twist and conditioning yarns and cloth; textile printing, textile soaps, lacquers, organic synthesis; brake fluid diluent. It is also used as a chemical intermediate for the synthesis of 2-(2-ethoxyethoxy) ethyl acrylate.

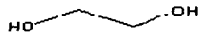
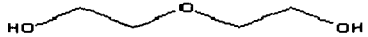
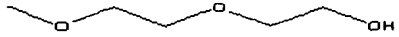
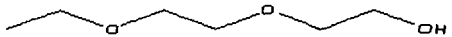
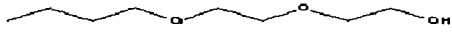
III. Physical and Chemical Properties

EG, DG, and the DG ethers are all colorless liquids. Physical and chemical characteristics and structure and nomenclature are found in Tables 2 and 3.

TABLE 2. The physical and chemical properties (Toxnet SIS, 2005; BIBRA, 1993; ECETOC, 1995; Gingell et al. 1996; Boatman, 2005, ATSDR Medical Management Guideline; Calif. Air Resources Board).

Name/CAS #	EG/107-21-1	DG/111-46-6	DGME/111-77-3	DGEE/111-90-0	DGBE/112-34-5
Synonyms:	Ethylene glycol; 1,2-dihydroxyethane; 1,2-ethanediol; monoethylene glycol	Diethylene glycol, Bis(2-hydroxyethyl) ether, Glycol ethyl ether, Diglycol, Digol, Dissolvent APV	Diethylene glycol (mono) methyl ether, Methyl carbitol, 2,(2-Methoxyethoxy)ethanol, Dowanol DM	Diethylene glycol (mono) ethyl ether, Ethyl carbitol, 2,(2-Ethoxyethoxy)ethanol, Dowanol DE, Poly-solve DE	Diethylene glycol (mono) butyl ether, Butyl carbitol, 2,(2-Butoxyethoxy)ethanol, Dowanol DB
Structure:	HO-CH ₂ -CH ₂ -OH	HO-CH ₂ -CH ₂ -O-CH ₂ -CH ₂ -OH	CH ₃ -(O-CH ₂ -CH ₂) ₂ -OH	C ₂ H ₅ -(O-CH ₂ -CH ₂) ₂ -OH	C ₄ H ₉ -(O-CH ₂ -CH ₂) ₂ -OH
Molecular formula:	C ₂ H ₆ O ₂	C ₄ H ₁₀ O ₃	C ₅ H ₁₂ O ₃	C ₆ H ₁₄ O ₂	C ₈ H ₁₈ O ₃
Molecular weight	62.7	106.12	120.17	134.17	162.23
Color/form	colorless viscous liquid	colorless syrupy liquid	Colorless liquid	Colorless liquid	Colorless liquid
Odor/Taste	odorless, sweet	Odorless/ sweet	ether-like odor/bitter	Mild, pleasant odor/bitter	Faint, butyl odor
Boiling point	198 ⁰ C	244-245E C	193E C	196E C	230.4E C
Melting point	-13 ⁰ C	-6.5 ⁰ C	-85 ⁰ C	-76 ⁰ C	-68 ⁰ C
Specific gravity	1.11	1.18	1.035	0.985	0.935
Vapor pressure	0.06 mm Hg at 20 ⁰ C 0.092 mm Hg at 25 ⁰ C	0.006 mm Hg at 25 ⁰ C	0.256 mm Hg at 25 ⁰ C	0.13 mm Hg at 25 ⁰ C	0.002 mm Hg at 25 ⁰ C
Solubility	6.0x10 ⁻⁸ atm-m ³ /mole	miscible with water, alcohol, ether, acetone	miscible with water, alcohol, ether, acetone	miscible with water, alcohol, ether, acetone	miscible with water, alcohol, ether, acetone
Log Kow	1	N/A	N/A	-0.54	0.56
	None				
	miscible with water, hygroscopic				
	10				
	50 hours				
	-1.36 / 0.04				

Table 3. Chemical Structures

<p>Ethylene glycol 107-21-1</p> <p>EG</p>	
<p>Diethylene glycol 111-46-6</p> <p>DG</p>	
<p>Diethylene glycol monomethyl ether 111-77-3</p> <p>DGME</p>	
<p>Diethylene glycol monoethyl ether 107-21</p> <p>DGEE</p>	
<p>Diethylene glycol monobutyl ether 112-34-5</p> <p>DGBE</p>	

IV. Hazard Assessment

A. Hazard Profile

There is an extensive toxicological database for EG, DG and the DG ethers. In some of the older studies with DG and its ethers, the test material was contaminated with ethylene glycol. This assessment places the most reliance upon the more recent higher quality studies, although some older studies are cited. Particular emphasis was placed upon studies and a monograph by the National Toxicology Program (NTP). Other references included reviews by the World Health Organization (WHO) and the Agency for Toxic Substances and Disease Registry (ATSDR). Summaries from representative studies are reported here with citations listed in the References section.

B. Toxicological Data

Acute toxicity: The acute toxicity values are provided in the Appendix at the end of this report. EG, DG and the three ethers have low acute toxicity in lab animals. Oral LD₅₀ values are all greater than 5,000 mg/kg. Dermal and inhalation lethal concentrations are also high for the available studies. Clinical signs of acute toxicity are non-specific depression of the central nervous system commonly seen with solvents.

The acute toxicity of EG is well described because of many poisoning incidents from its use in antifreeze. Following an initial CNS depression similar to drunkenness, metabolic acidosis develops and calcium oxalate crystals are formed which can result in kidney damage and eventual death. There are fewer clinical reports for DG and its ethers.

Subchronic and chronic toxicity

Ethylene glycol: In a subchronic mouse study conducted by NTP, the NOAEL = 3,000 mg/kg/day based upon kidney toxicity and microscopic liver changes seen at 6,000 mg/kg/day. No tumors were reported in rats and mice after treatment for two years at 1,000 mg/kg/day (DePass; Woodside; cited by ATSDR). No treatment-related neoplasms were seen in a 2-year mouse carcinogenicity study conducted by NTP at 6,000 mg/kg/day in males and 12,000 mg/kg/day in females. Microscopic liver changes occurred at 3,000 mg/kg/day and higher. Kidney toxicity was not noted though there were small numbers of oxalate-like crystals and calculi seen in the urinary tract.

Diethylene glycol: In a 1976 99-day rat study cited by BIBRA, there were urinary crystals and a mild effect on kidney function at 300 mg/kg/day; more severe effects at 1500 mg/kg/day; and mortality from kidney damage at 3300 mg/kg/day.

In an NTP developmental study in mice, maternal toxicity included increased kidney weights and microscopic changes in the kidneys at 5,000 mg/kg/day; the dose of 10,000 mg/kg/day caused maternal mortality.

In a 2-year rat study, bladder tumors, mostly benign developed at 1,500 and 3,000 mg/kg/day in males (Fitzhugh, cited in BIBRA). Tumors may have been due to chronic irritation from treatment-related bladder stones which developed in those dose groups.

Diethylene glycol monomethyl ether: Testicular and thymus toxicity were reported in an oral study in rats at doses of 500 mg/kg/day and greater (Kawamoto, 1990, cited in ECETOC). The maternal NOAEL in a rat oral developmental study with DGME (Yamano, 1990), was 600 mg/kg/day based on decreased thymus weight and slightly decreased body weight at 1800 mg/kg/day.

The NOAEL in a dermal toxicity study in guinea pigs was 40 mg/kg/day based on microscopic liver changes (mild fatty change) and decreased splenic weight at 200 mg/kg/day; no testicular changes were noted. The maternal NOAEL in a rabbit dermal developmental study was 250 mg/kg/day based on decreased weight gain and a slight decrease in red blood cell count at 750 mg/kg/day (Scortochini).

No toxicity was reported in a rat inhalation study at the high dose of 1.06 mg/L, which was reportedly the “maximum attainable vapor concentration” (Miller, 1985).

Diethylene glycol monoethyl ether: In a 28-day inhalation study, the NOAEL for systemic toxicity was 1.1 mg/L, reportedly in “excess of the saturated vapor pressure concentrations”.

In a 90 day feeding study in rats with DGEE (Hall, 1966, cited by FAO/WHO), the NOAEL was 800 mg/kg/day and the LOAEL was 4,000 mg/kg/day based on increased testes weight and microscopic changes in the kidneys. Test material contained 0.64% ethylene glycol. In another 90-day feeding study in rats with DGEE (Gaunt, 1966, cited by FAO/WHO), the NOAEL was 250 mg/kg/day and the LOAEL was 2500 mg/kg/day based on slight anemia, increased relative kidney weight, and microscopic changes in the kidneys. Test material contained <0.4% ethylene glycol.

Diethylene glycol monobutyl ether: A 13-week drinking water study in rats reported increased kidney weights and slight decreases in hematological parameters at 1,000 mg/kg/day; the NOAEL was 250 mg/kg/day (Johnson, 2005). In two separate dermal studies in rats, no FOB changes, clinical signs, reproductive toxicity, or systemic toxicity were seen at the high dose of 2,000 mg/kg/day (Beyrouy, 1993; Auletta, 1993).

Metabolism and pharmacokinetics

The diethylene glycol ethers are rapidly absorbed by the oral route and are eliminated in the urine. Dermal absorption of the ethers decreases with increasing molecular weight of the compounds, which correlates with decreased toxicity seen with increasing molecular weight. Dermal absorption of DG and for DGEE was < 10% (Matthews, BIBRA; WHO). Dermal absorption for DGBE was 34 - 65% although this study used prolonged exposure.

DGME is an inducer of the mixed function oxidase enzyme system. Ethylene glycol is metabolized to glycolic acid, which is responsible for developmental toxicity, and ultimately to

oxalic acid which will form crystals in kidney tubules at high doses. Glycolic and oxalic acid are not significant metabolites of the diethylene glycol ethers.

Genetic toxicology

EG, DG, DGME, DGEE, and DGBE were all negative in Ames assays and in a number of *in vivo* and *in vitro* tests although DG did cause chromosomal damage in bone marrow cells.

Cancer

Ethylene glycol was tested in a rat carcinogenic study (Woodside, cited by ATSDR) at 1,000 mg/kg/day and in mouse carcinogenic studies (NTP; DePass, cited by ATSDR) at doses as high as 12,000 mg/kg/day; there was no evidence of carcinogenicity in any of the studies.

DG treatment at high doses (1,500 mg/kg/day) caused bladder stones in male rats but not in females. The bladder stones were associated with bladder tumors in males (Fitzhugh, 1946; Weil, 1965; cited in BIBRA). The bladder tumors may be due to irritation from bladder stones and thus would not occur at doses below that causing bladder stones. Carcinogenicity studies were not available for the other chemicals.

Developmental and Reproductive Toxicity

Ethylene glycol (EG): The potential human reproductive and developmental effects of ethylene glycol underwent a comprehensive review by the National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction and an expert panel. The NTP monograph reported that EG caused increased fetal deaths, skeletal and external malformations, and reduced body weight in offspring in lab animals; fetal effects occurred at doses below those causing maternal toxicity. A metabolite of EG, glycolic acid, is believed to be responsible for the developmental toxicity. As long as EG exposure does not reach a level that saturates the EG-metabolizing enzymes, then developmental toxicity is not expected. The NTP expert panel concluded that “there is negligible concern of adverse developmental toxicity from EG at exposures below 125 mg/kg”.

Reproductive toxicity studies with EG found no evidence of reproductive toxicity at high doses (2826 mg/kg/day in mice and 1000 mg/kg/day in rats. The NTP monograph concluded that there was “negligible concern of adverse reproductive toxicity from EG”.

Diethylene glycol (DG): In an NTP developmental study in mice, the dose of 5,000 mg/kg/day caused maternal toxicity (increased kidney weight), but no developmental toxicity. The dose of 10,000 mg/kg/day caused maternal mortality and decreased fetal body weight.

In an NTP mouse reproduction study, the dose of 6,125 mg/kg/day caused fetal/pup mortality in the absence of parental toxicity in the first generation. The next lower dose, 3,062 mg/kg/day was the NOAEL. No reproductive toxicity was noted in the second generation although parental body weights were decreased.

Diethylene glycol monomethyl ether (DGME): In a rat oral developmental study with DGME (Yamano, 1993), the developmental/offspring NOAEL was 200 mg/kg/day based on decreased body weight, decreased ossification, and effects on the thymus at 600 mg/kg/day. The maternal NOAEL was 600 mg/kg/day based on decreased thymus weight and slightly decreased body weight at 1800 mg/kg/day.

A reproduction study with DGME was not available.

Diethylene glycol monoethyl ether (DGEE): No developmental toxicity was reported at 6,000 mg/kg/day in a dermal developmental study in rats (Hardin, 1984). Maternal weight gain was decreased at the same dose.

Decreased pup body weight and decreased sperm motility were noted at 4400 mg/kg/day; the NOAEL was 2200 mg/kg/day. There was no effect upon reproductive parameters.

Diethylene glycol monobutyl ether (DGBE): No maternal or developmental toxicity was noted in an oral developmental study with rats at 1000 mg/kg/day or in a dermal developmental study in rabbits at 1000 mg/kg/day (Nolen, 1985).

No parental or offspring toxicity was noted in a 1-generation dermal reproduction study with DGBE (Auletta) at the high dose of 2,000 mg/kg/day.

C. Special Considerations for Infants and Children

As reported by the NTP, there is negligible concern of developmental toxicity from EG at exposures below 125 mg/kg. This dose is much greater than exposures expected from use as an inert ingredient.

DG caused fetal/pup mortality in a reproduction study at a dose causing minimal maternal toxicity, however, this occurred above the limit dose at 6,125 mg/kg/day, well above exposures expected from use as an inert ingredient in pesticides used pre-emergent. No developmental toxicity was noted in the NTP mouse study.

Developmental toxicity was noted for DGME at levels below maternal toxicity (offspring NOAEL was 200 mg/kg/day with decreased body weight, decreased ossification, and effects on the thymus observed at 600 mg/kg/day; maternal NOAEL was 600 mg/kg/day with decreased thymus weight and slightly decreased body weight observed at 1800 mg/kg/day). This dose is much greater than exposures expected from use of DGME as an inert ingredient limited to applications before crop emerges from soil.

Developmental toxicity with DGEE occurred at high doses (6000 mg/kg/day) and was accompanied by maternal toxicity. No developmental or reproductive toxicity was noted in an oral study in rats or in dermal studies in rats and rabbits.

There are no concerns from developmental or reproductive toxicity from DGBE.

Overall, there are no concerns for potential sensitivity of infants and children to these chemicals because developmental toxicity only occurred at doses much greater than that expected from use of these chemicals as inert ingredients. For this reason, a safety factor analysis has not been used to assess risk and the 10-fold safety factor for protection of infants and children is not needed.

V. Environmental Fate Characterization/Drinking Water Considerations

Most of the following information was obtained from HSDB Toxnet Database, as of 6/17/2006. Table 2 contains the relevant environmental fate and physicochemical characteristics of EG, DG, DGME, DGEE, and DGBE. There are common environmental fate characteristics to the ethylene glycols. For example, the characteristics of these chemicals suggest that they tend to remain dissolved in water and may be transported in the water column due to their high solubility in water and low organic carbon partition coefficient. They have a relatively low Henry's Law constant, indicating that they tend to remain in moist surfaces such as moist soils, or bodies of water (Henry's Law Constant $<5.3 \times 10^{-6}$ atm-m³/mole). They may volatilize from dry surfaces (Vapor Pressure >0.002 mmHg). Calculated soil and sediment organic carbon partition coefficients indicate that the glycol ethers would be highly mobile in soil and would easily move through a soil via erosion dissolved in the water column or to the subsurfaces to ground water ($K_{OC} < 50$). Soil binding is expected to be minimal. If the chemical reaches bodies of water, it will remain in the water column, as opposed to bound to sediment particles or to organic matter or to living organisms (bioconcentrated). However, these compounds appear to biodegrade relatively quickly in soil and water. Considering the ready biodegradation and use limitations of these chemicals, contributions to drinking water are anticipated to be very low.

These molecules are not susceptible to hydrolysis or direct photolysis at the environmentally relevant spectrum (>290 nm). If these compounds reach the ambient, they will exist as vapor phase only. They may undergo indirect photodegradation via formation of hydroxyl radicals in the atmosphere with varying half-lives (10-50 hrs). The bioconcentration in aquatic organisms is expected to be very low ($BCF < 10$; $K_{OW} < 30$).

VI. Exposure Assessment

EG, DG and the DG ethers are as used inert ingredients in pesticide formulations, as antifreeze, as solvents, and as ingredients in a number of industrial products. Human exposure to these chemicals may occur via dietary (food and drinking water) and/or residential pathways of exposure. Dietary exposure to residues of these chemicals would be via the oral route, by consumption of raw agricultural commodities to which pesticide products containing these chemicals have been applied, and/or by consumption of drinking water.

The tolerance exemptions for EG, DG, DGME, DGEE, and DGBE significantly limit the potential for exposure by only allowing applications before the crop emerges from soil. This typically equates to one application. EG's tolerance exemption also limits applications to use before the crop emerges from soil, except in herbicides. EG, DG, DGME, DGEE, and DGBE all biodegrade quickly in soil and water, and bioconcentration in aquatic organisms is expected to be low. Considering the ready biodegradation and use limitations of these chemicals, dietary and residential exposures of concern are not anticipated.

VII. Aggregate Exposures

For 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 non-occupational 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 EG, DG, DEME, DGEE, and DGBE, 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 these chemicals as inert ingredients 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 EG, DG, DGME, DGEE, DGBE and any other substances, and this material does not appear to produce toxic metabolites produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that these chemicals have 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/>.

IV. Human Health Risk Characterization

Few studies had side-by-side comparisons of the chemicals so direct comparisons cannot be made, however, it can be generalized that for the DG ethers, increasing molecular weight resulted in decreased toxicity by the oral or dermal route and decreased dermal absorption.

The acute toxicities of EG, DG, DGME, DGEE, and DGBE are low with oral LD₅₀ values > 5,000 mg/kg for all of the chemicals. Toxicity from longer term oral exposure is generally low. EG caused kidney and liver toxicity at 3,000 mg/kg/day in a chronic mouse study. DG caused kidney toxicity in rats at 300-1500 mg/kg/day after subchronic oral exposure. DGME caused testicular and thymus toxicity in rats at 500 mg/kg/day. DGEE caused slight anemia and kidney toxicity at 1,250 mg/kg/day in rats and mortality and increased testes weight at 4,000 mg/kg/day. DGBE caused slight anemia and increased kidney weight at 1,000 mg/kg/day.

No systemic toxicity resulted from inhalation studies with DGEE and DGBE at doses that were reportedly the maximum attainable vapor pressure or in dermal studies with DGBE at 2,000 mg/kg/day.

All chemicals were negative in the Ames assay and in a number of other genetic toxicity tests, although DG did cause chromosomal damage in bone marrow cells. There was no evidence of carcinogenicity in rats and mice treated with EG. DG treatment resulted in bladder tumors which were believed to be caused by irritation from bladder stones. Because of the negative results from genetic toxicity studies, there are no carcinogenicity concerns for these chemicals.

EG underwent a comprehensive review by NTP of potential human developmental and reproductive toxicity which concluded that “there is negligible concern of adverse developmental toxicity from EG at exposures below 125 mg/kg”. There was no evidence of reproductive toxicity from EG in lab animals. DG caused developmental toxicity in mice at 10,000 mg/kg/day and caused fetal/pup mortality in a reproductive mouse study 6,125 mg/kg/day. DGME caused decreased ossification at 600 mg/kg/day in a rat oral developmental study (NOAEL = 200 mg/kg/day). Overall, there are no concerns for potential sensitivity of infants and children to these chemicals because developmental toxicity only occurred at doses much greater than that expected from use as inert ingredient in pesticide products.

The tolerance exemptions for DGME, DGEE, and DGBE significantly limit the potential for exposure by only allowing applications before the crop emerges from soil. This typically equates to one application. EG’s tolerance exemptions also limit applications to use before the crop emerges from soil, except in herbicides. EG, DG, DGME, DGEE, and DGBE all biodegrade quickly in soil and water, and bioconcentration in aquatic organisms is expected to be low. Considering the ready biodegradation and use limitations of these chemicals, dietary and residential exposures of concern are not anticipated.

Taking into consideration all available information on EG, DG, DGME, DGEE, and DGBE, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to these chemicals when considering exposure through food commodities and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the three exemptions from the requirement of a tolerance established for residues of EG, DG, DGME, DGEE, and DGBE when used on growing crops under 40 CFR part 180.920 can be considered reassessed as safe under section 408(q) of the FFDCA.

V. Ecotoxicity and Ecological Risk Characterization

Studies in the Agency’s Ecotox Database (<http://www.epa.gov/ecotox>) for DG, DGME, DGEE, and DGBE chemicals contained acute fish and invertebrate studies. No terrestrial or aquatic plant studies were available in Ecotox appropriate for guideline studies. There was only one chronic study on fish for EG.

Ecotox studies indicate that EG, DG, DGME, DGEE, and DGBE are practically non-toxic to fish on an acute basis. Ecotox studies also indicate that EG and DGEE are practically non-toxic to invertebrates on an acute basis. LC50's for fish for all chemicals ranged from >2700 mg/L to 81950 mg/L. LC50's for invertebrates for EG and DGEE ranged from 3340 mg/L to 55000 mg/L. Invertebrate studies were not available in Ecotox for DG, DGME, and DGBE. There was one chronic effect study on fish for EG, 15380 mg/L (growth) for a 7 day renewal fathead minnow.

Mammalian data will be used as a surrogate for other terrestrial phase animals. The acute toxicities of EG, DG, DGME, DGEE, and DGBE are low with oral LD₅₀ values of > 5,000 mg/kg for these chemicals. Therefore, EG, DG, DGME, DGEE, and DGBE are classified as practically non-toxic to mammals on an acute basis.

For chronic effects in mammals, there was no evidence of reproductive toxicity from EG in lab animals. DG caused developmental toxicity in mice at 10,000 mg/kg/day and caused fetal/pup mortality in a reproductive mouse study 6,125 mg/kg/day. DGME caused decreased ossification at 600 mg/kg/day in a rat oral developmental study (NOAEL = 200 mg/kg/day). These effects may or may not be important ecologically.

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APPENDIX A

Acute Toxicity

Acute toxicity values of EG

Species	Test	Reference
Rat	Oral LD ₅₀ : 5.89 g/kg	Hazardous Substances Databank
Rabbit	Dermal LD ₅₀ : 9530 mg/kg	Hazardous Substances Databank

Acute toxicity values of DG

Species	Test	Reference
Rat	Oral LD ₅₀ : 13-32 g/kg	Bibra
Mouse	Oral LD ₅₀ : 13.3 g/kg	Patty's Toxicology
Rabbit	Dermal LD ₅₀ : 13.1 g/kg bw (24-hr exposure)	BIBRA

Acute toxicity values of DGME

Species	Test	Reference
Rat	Oral LD ₅₀ : 6.70 mL/kg	Toxnet SIS
Rabbit	Dermal LD ₅₀ : no deaths at 2 g/kg.	Toxnet SIS
Rat	LC ₅₀ : no mortalities at 20 mg/L for 1 h.	Toxnet SIS

Acute toxicity values of DGEE

Species	Test	Reference
Rat	Oral LD ₅₀ : 8.69 g/kg, 5.54 g/kg	Patty's Toxicology
Mouse	Oral LD ₅₀ : 6.58 g/kg	Patty's Toxicology
Rabbit	Eye irritation: moderate	FAO/WHO

Acute toxicity values of DGBE

Species	Test	Reference
Rat	Oral LD ₅₀ : 6.53 g/kg males; 5.08 g/kg females	Toxnet SIS
Mouse	Oral LD ₅₀ : 2406 mg/kg fasted; 5526 mg/kg non-fasted	Toxnet SIS
Rabbit	Oral LD ₅₀ : 2.2 g/kg	Patty's Toxicology
Guinea pig	Dermal sensitization for formulation: positive	ATOFINA Chemicals