DATE: October 11, 2005

MEMORANDUM

SUBJECT: ***TRIETHYLENE GLYCOL*:** Revised Toxicology Chapter in Support of Issuance of the Reregistration Eligibility Decision (RED) Document. PC Code: 083501 Reregistration Case Number: 3145. CAS Registry Number: 112-27-6. DP#: 325786

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Attached is the revised **Triethylene Glycol** toxicology chapter for incorporation into the risk assessment document and the Reregistration Eligibility Decision (RED) document.

Supporting documentation used to generate the toxicology chapter are listed below:

1. ***TRIETHYLENE GLYCOL*** - Revised Report of the Antimicrobials Division Toxicology Endpoint Selection Committee (Memorandum: T. McMahon, 11/21/05).

2. EPA ID# 083501: Triethylene glycol. Review of Phase IV Response Submissions in Support of FIFRA 88. (Memorandum: G. Reddy, 12/12/93).

3. ***TRIETHYLENE GLYCOL:*** Antimicrobials Division Review of Toxicity Studies Submitted to the Agency's Office of Pollution, Prevention and Toxics. PC Code: 083501. Reregistration Case Number: 3145. CAS Registry Number: 112-27-6. DP#: 305169 (Memorandum: M. Centra, 10/11/05).

TRIETHYLENE GLYCOL
PC Code: 083501

Revised Toxicology Disciplinary Chapter
for the Reregistration Eligibility Decision (RED) Document

Antimicrobials Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Revised Date: October 11, 2005

INTRODUCTION

The active ingredient, triethylene glycol, was first registered by the FDA for use in hospitals as an air disinfectant on August 3, 1948 (James Varley & Sons' Glyco Mist, EPA Reg. No. 421-21). As an active ingredient, triethylene glycol is formulated primarily as a pressurized liquid and is used in two types of applications: air sanitizers/hospital disinfectants, and pest (mites and red lice) control on caged birds. As an inert ingredient, triethylene glycol facilitates delivery of formulated pesticide chemical products that are used as herbicides, fungicides, insecticides, growth regulators and attractants on a wide variety of agricultural commodities.

The majority of the producers of triethylene glycol formulated pesticide products are represented by a consortium called the CSPA (Consumer Specialty Products Association) Glycols Joint Venture (formerly known as the CMSA Glycol Joint Venture). The member companies currently represented by this consortium are: Amrep, Inc., Medo Industries, Inc., S.C. Johnson & Son, and Waterbury Companies, Incl.

In 1997, the Office of Pesticide Programs, Health Effects Division conducted an evaluation of the toxicity of the active ingredient, triethylene glycol as required by law under FIFRA for the reregistration of pesticidal chemicals.

The triethylene glycol mammalian toxicity database consists of published literature studies and monographs submitted by the Glycols Joint Venture consortium as a result of the Phase IV review of triethylene glycol for reregistration under FIFRA. These submitted data were reviewed by the Agency and classified as acceptable or waived as indicated below in Table 2. At that time, these data were determined to satisfy the Subdivision F guideline test guideline requirements and no additional data requirements were identified for the non-food use of triethylene glycol.[1]

Table 2. Data Requirements for Non-Food Use of Triethylene Glycol (1997)

Guideline Number	Study Type	Required	Satisfied
§ 81-1	Acute Oral - Rat	Yes	Yes
§ 81-2	Acute Dermal - Rabbit	Yes	Waived
§ 81-3	Acute Inhalation - Rat	Yes	Yes
§ 81-4	Primary Eye Irritation	Yes	Yes
§ 81-5	Primary Dermal Irritation	Yes	Yes
§ 81-6	Skin Sensitization	Yes	Yes
§ 82-1a	Subchronic Oral - Rodent	No	No
§ 82-1b	Subchronic Oral - Non Rodent	Yes	Yes

Table 2. Data Requirements for Non-Food Use of Triethylene Glycol (1997)			
§ 82-2	21-Day Dermal	Yes	Yes
§ 82-4	90-Day Inhalation	Yes	Yes
§ 83-3a	Developmental Toxicity - Rodent	Yes	Yes
§ 83-3b	Developmental Toxicity - Non Rodent	Yes	Yes
§ 83-4	Reproductive Toxicity - Rodent	Yes	Yes
§ 83-1b	Chronic Toxicity - Non Rodent	Yes	Yes
§ 83-1a	Carcinogenicity - Rodent	Yes	Yes
§ 84-2	Gene Mutation - Ames	Yes	Waived[a]
§ 84-2	Cytogenetics - Structural Chromosomal Aberration	Yes	Waived[a]
§ 85-1	General Metabolism	Yes	Yes

[a]The data waivers granted by the Agency in 1997 for the triethylene glycol mutagenicity assays are no longer applicable to this chemical. Several mutagenicity assays submitted to the Agency's Office of Toxic Substances were reviewed by OPP's Antimicrobials Division and determined to be acceptable/non-guideline studies. These four mutagenicity studies have been incorporated into the toxicity data base for triethylene glycol.

HAZARD PROFILE

Acute Toxicity

Published literature studies submitted by the Glycols Joint Venture consortium show low toxicity (Toxicity Categories III and IV) following acute exposures (Table 3). The acute oral and dermal toxicity of the chemical appears to be low, with reported oral LD_{50} values ranging from 15-22 g/kg compiled from monographs and review articles. The data available on acute dermal toxicity were insufficient to establish a dermal LD_{50}, but the data requirement was waived based on the low order of toxicity observed in other studies with triethylene glycol. Data on inhalation toxicity showed a maximum tolerated level of 800 mg/m^3 in rats, but intratracheal instillation of 0.25 cc undiluted chemical caused marked pulmonary irritation, edema, and later, fibrosis and abcess formation in these animals (intratracheal instillation is not an accepted route of administration for the Agency's toxicity testing guidelines). Published literature data on the skin and eye irritation as well as skin sensitization showed triethylene glycol to be non-irritating to the skin and eye (when tested at the limit doses established by the Agency for acute toxicity testing) and not a dermal sensitizer. [2-5]

Triethylene glycol was evaluated for acute inhalation toxicity in male and female Sprague-Dawley albino rats in a study submitted to the Agency's Office of Toxic Substances. A review of this study by the Antimicrobials Division established a four hour LC_{50} greater than 5.2 mg/L, and

places acute inhalation in Toxicity Category IV. Based on these results, this study was determined to be adequate for regulatory purposes and it now replaces the earlier submitted acute inhalation information.[6]

Table 3. Acute Toxicity Profile of Triethylene Glycol				
Guideline	**Study Type**	**MRID No.**	**Results**	**Toxicity Category**
870.1100	Acute Oral - Rat	42814404	LD_{50} = 15-22 g/kg	IV
870.1200	Acute Dermal - Rabbit	42814404	LD_{50} not determined	Study requirement waived
870.1300	Acute Inhalation - Rat	OTS0527779-2	LC_{50} > 5.2 mg/L	IV
870.2400	Acute Eye Irritation - Rat	42814404	mild irritant	III
870.2500	Acute Skin Irritation - Rabbit	42814404	slight irritant	IV
870.2600	Skin Sensitization	42814404	non- sensitizer	N/A

N/A = Not applicable

Subchronic Toxicity

Repeat oral dosing studies conducted in rats to determine triethylene glycol toxicity showed in general, that the chemical was either without any adverse effects or produced toxicities only at doses at or greater than the limit doses established for EPA guideline test requirements. Triethylene glycol administered in the drinking water to rats at concentrations of 3% and 5% by volume for 30 days showed signs of toxicity (weight loss, alopecia and poor grooming) at the lower concentration with one animal dying on day 25 of the study. All rats in the 3% test group survived to study completion with no signs of toxicities.[7] In a 14-day oral toxicity study, Fischer 344 rats receiving triethylene glycol in the feed (doses equivalent to 1132, 2311, or 3916 mg/kg/day for males and 1177, 2411, or 6209 mg/kg/day for females) showed only changes in urinalysis (increased urine volume, decreased urine pH, and decreased urine triple phosphate crystals) at the highest respective doses tested in male and female rats.[8] In a third oral toxicity study conducted for 90-days in rats, triethylene glycol was administered in the diet at doses of 748, 1522, or 3849 mg/kg/day (males), and 848, 1699, or 4360 mg/kg (females). Although toxicities were noted at the high dose in male and female rats (decreases in body weight, slight decreases in hemoglobin and hematocrit, slight increases in mean corpuscular volume, and increased relative kidney and brain weights), these effects were noted at dose levels that exceed the established limit dose of 1000 mg/kg/day for such studies.[9]

In a 21-day dermal toxicity study, there was no evidence of dermal or systemic toxicity from repeated dermal applications of 2ml (approximately 600 mg/kg) triethylene glycol applied to the skin of rabbits. These results are supported by triethylene glycols' low dermal irritancy a negative response as a skin sensitizer. [10-11]

Sprague-Dawley rats exposed (whole body) to triethylene glycol in an aerosol inhalation study at concentrations of 494, 2011, or 4842 mg/m^3 (0.5, 2.0, or 5.0 mg/L/day), for six hours a day, nine times over a two-week period showed the following toxicities at the highest concentration level tested: ataxia, prostration, unkept fur, labored respiration (males only), ocular discharge, swollen periocular tissue, perinasal and perioral encrustation, blepharospasm and reduced body weight Necropies revealed hyperinflation of the lungs, ocular opacity, congestion and hemorrhage in many organs and tissues (pituitary gland, brain, nasal mucosa, kidney, thymus and lungs). All of the rats in the high dose group died or were sacrificed moribund by day 5 of the study. Clinical signs of toxicity observed at the low- and mid-dose of 0.5 and 2.0 mg/L/day, respectively, were limited to swollen periocular tissues and perinasal encrustations. Treatment-related changes in organ weights in mid-dose males included an increase in liver and kidney weights relative to body weight; mid-dose females showed increases in absolute and relative (to body and brain weights) liver and kidney weights. Statistically significant clinical chemistry findings for males treated with 2.0 mg/L/day triethylene glycol included an increase in ALT activity and a decrease in serum creatinine levels. Mid-dose females showed increases in urea nitrogen, inorganic phosphorus, ALT and ALK activity, and decreases in glucose, creatinine, and chloride. However, the changes in organ weights and clinical chemistry findings were not correlated with any histopathological observations. [13]

Rats exposed to the test material via a whole-body inhalation protocol are also receiving the chemical via the oral and dermal routes. These additional routes of exposure may have increased the total dose received and contributed to the toxicities observed in the whole-body exposure inhalation study. Therefore, a second study was conducted using a nose-only exposure for 6 hours a day, 9 consecutive days. In this second inhalation toxicity study, mean exposure concentrations of 102, 517, or 1036 mg/m^3 (approximately 0.1, 0.5, 1.0 mg/L/day) triethylene glycol produced no treatment-related toxicities at any dose tested. [12]

Monkeys exposed by inhalation to approximately 1 ppm vapor from two weeks to 13 months and human volunteers exposed to air saturated with vapor (approximately 0.5 to 1 ppm) showed no adverse reactions or histopathological changes suggestive of toxicity from prolonged exposure to triethylene glycol.[14]

Dogs given daily intravenous injections (0.1 or 0.5 ml/kg) of triethylene glycol for four weeks showed no mortality or toxicity with the exception of flattened epithelial cells in the urine and phlebitis at the site of injection.[15]

Chronic Toxicity and Carcinogenicity

Published literature sources examining the chronic toxicity and carcinogenic potential of triethylene glycol have shown the chemical to be non toxic/negative in rodent species.

In a 12 month study, monkeys receiving triethylene glycol (0.25 mL to 0.5 mL) orally in egg nog (approximately 50 to 100 times the quantity an animal could absorb by breathing air saturated

with glycol) were without any adverse effects in physiological functions or organ histopathology.[14]

Triethylene glycol administered in feed at levels of 0, 1, 2 or 4% to Osborn-Mendel rats for 2 years showed that the body weight gains, hematological parameters and clinical chemistries were not affected by treatment. Under the conditions of this study, triethylene glycol was not carcinogenic in rats. The dosages tested in rats are equivalent to as much as 3 to 4 g/kg/day which are well above the upper limit dose of 1 g/kg/day (1000 mg/kg/day) for testing pesticides via the oral route in subchronic and chronic toxicity studies. [16]

Mutagenicity

Triethylene glycol was tested for mutagenic or genotoxic potential and found to be negative in a battery of studies: a bacterial gene mutation assay using *Salmonela typhimurium,* an *in vitro* Chinese hamster ovary (CHO) mutation assay, an *in vitro* Chinese hamster ovary (CHO) chromosomal aberration assay and an *in vitro* sister chromatid exchange assay.[17-20]

Dermal Absorption

No studies have been reported dealing with the skin absorption of triethylene glycol. Although it is possible that, under conditions of very severe prolonged exposures to this chemical, absorption through the skin, it is doubtful any appreciable systemic/dermal injury would occur because triethylene glycol has (1) a low order of dermal irritancy, (2) is not a skin sensitizer, and (3) showed no evidence of dermal or systemic toxicity following repeated dermal applications of 2ml (approximately 600 mg/kg) triethylene glycol applied to the skin of rabbits in a 21-day dermal toxicity study.

Metabolism and Excretion

The fate of ^{14}C-labeled triethylene glycol in rats and of unlabeled material in rabbits was recently studied. Following oral dosing, the rat and rabbit excreted most of the triethylene glycol in both unchanged and/or oxidized forms (mono- and dicarboxylic acid derivatives of triethylene glycol). In rabbits dosed with 200 or 2000 mg/kg triethylene glycol respectively excreted 34.3% or 28%, of the administered dose in the urine as unchanged triethylene glycol and 35.2% as a hydroxyacid form of this chemical. In the studies with rats, little if any C^{14}-oxalate or C^{14}-triethylene glycol in conjugated form was found in the urine. Trace amounts of orally administered ^{14}C triethylene glycol were excreted in expired air as carbon dioxide (<1%) and in detectable amounts in feces (2 to 5 %). The total elimination of radioactivity (urine, feces and CO_2) during the five day period following an oral dose of labeled compound (22.5 mg) ranged from 91 to 98%. The majority of the radioactivity appeared in the urine.[21]

Developmental and Reproductive Toxicity

Triethylene glycol was administered orally at doses of 0, 0.5, 5.6, and 11.27 g/kg/day in timed pregnant CD-1 mice from gestation Days 6 through 15. There were no treatment related maternal deaths and no abortions. Hyperactivity and rapid respiration were observed at the highest dose level. No effects were observed on maternal weight gain or food consumption at any dose level. Pregnancy outcome was unaffected at any dose level tested. There were no treatment-related effects on external or visceral malformations in offspring. Some evidence of delayed ossification was observed at the high dose level.[22]

In a second study, pregnant Sprague-Dawley rats were administered triethylene glycol by gavage on gestation days 6 through 15 at dose levels of 0, 1.0, 5.6, and 11.27 g/kg/day. There were no effects on maternal mortality and there were no abortions. Clinical toxicity was observed in maternal rats at the high dose and consisted of audible respiration, periocular encrustation, and perioral wetness. Decreased body weight and food consumption was observed in maternal rats at the 5.6 g/kg/day dose. No effects were observed at the 1.0 g/kg/day dose. In offspring, mean fetal body weight was decreased at the 11.27 g/kg/day dose level, but there were no treatment-related increases in external, visceral, or skeletal malformations.[23]

Published literature examined the effect of triethylene glycol on reproduction in Swiss CD-1 mice. Doses of 0, 0.3, 1.5, and 3% were administered in drinking water using a continuous breeding protocol. No effects on reproductive function were observed at any dose level tested (up to the high dose of 6.78 g/kg) including sperm concentration, morphology, and motility. Reduced pup weight was observed at the 1.5 and 3% doses of triethylene glycol.[24-25]

In a study submitted to the Agency, rats were exposed to an atmosphere saturated with triethylene glycol (approx. 1 ppm) for 12-18 months with no adverse reproductive effects noted.[14,26]

The available developmental and reproductive studies conducted with triethylene glycol are from published sources or from studies submitted to the Office of Toxic Substances and do not report all the data that are normally reported under the OPPTS 870 toxicity test guidelines. However, it is apparent that the toxicities observed in these studies are consistently manifested only at doses of triethylene glycol that exceed the established limit doses for animal studies and are of a non-specific nature. Therefore, there is no concern for the developmental or reproductive toxicity of triethylene glycol.

Neurotoxicity

From the available repeat dose toxicity studies, there was no evidence of neurotoxicity of triethylene glycol, however, the toxicology data are inadequate to characterize repeated dose toxicity. Therefore, neurotoxicity testing could be required if additional data are needed for future uses of triethylene glycol.

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