DATE: November 21, 2005

MEMORANDUM

SUBJECT: ***TRIETHYLENE GLYCOL*** - Revised Report of the Antimicrobials Division Toxicology Endpoint Selection Committee.

FROM: Timothy F. McMahon, Ph.D., Chair, ADTC
Michelle Centra, Pharmacologist, Executive Secretary, ADTC
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TO: Heather Garvie, Chemical Review Manager
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PC Codes: 083501

On February 25, 2003, the Antimicrobials Division Toxicology Endpoint Selection Committee (ADTC) reviewed the available toxicology data for triethylene glycol and discussed endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to triethylene glycol was also evaluated by the committee in order to meet the statutory requirements of the Food Quality Protection Act (FQPA) of 1996.

In November of 2005, the ADTC met to discuss the impact of the human studies rule on the hazard characterization of triethylene glycol. This toxicity endpoint document supercedes the ADTC report for triethylene glycol dated May 6, 2003.

Committee Members in Attendance

Members present: Timothy F. McMahon, Ph.D. Stephen Dapson, Ph.D.; Jonathan Chen, Ph.D.; Timothy Leighton; John Redden; Karen Hamernik, Ph.D., Michelle Centra.

Member(s) in absentia: Roger Gardner, Ph.D.; Sanyvette Williams, D.V.M.; Melba Morrow, D.V.M., Najm Shamim, Ph.D.

DATA PRESENTATION: _____
Timothy F. McMahon, Ph.D., Chair

DRAFT DOCUMENT PREPARATION: _____
Timothy F. McMahon, Ph.D., Chair

FINAL DOCUMENT PREPARATION: _____
Michelle Centra, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence unless otherwise stated)

Stephen Dapson _____

Jonathan Chen _____

Roger Gardner _____

Karen Hamernik _____

Tim McMahon (Chair) _____

Melba Morrow _____

John Redden _____

Sanyvette Williams-Foy _____

Michelle Centra (Executive Secretary) _____

Najm Shamim _____

Timothy Leighton _____

OTHER ATTENDEES:

I. INTRODUCTION

Triethylene glycol is produced commercially as a by-product of ethylene glycol production and it is used as a bacteriostat (against odor-causing bacteria) for air sanitization and deodorization. There are numerous active use sites listed for triethylene glycol that include: air treatment (eating establishments, hospital, commercial, institutional, household, bathroom, transportational facilities); medical premises and equipment, commercial, institutional and industrial premises and equipment; laundry equipment; hard non-porous surface treatments (bathroom facilities); automobiles; air conditioning filters, and refuse and solid waste containers. In combination with other active ingredients, it is used as a fungicide, virucide and miticide for disinfection of hard, non-porous surfaces and as an insecticide (against lice) by direct application to 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. Products contain triethylene glycol in a range of 0.1-9.15% a.i.

II. PHYSICAL/CHEMICAL PROPERTIES [2]

FORMULA: $C_6H_{14}O_4$ / $HOCH_2(CH_2CH_2O)_2CH_2OH$

Active ingredient:	triethylene glycol
Color:	hygroscopic colorless liquid
Physical state:	liquid
Flash point:	165 ^oC
Vapor Pressure:	0.15mmHg at 20 ^oC;
Boiling point:	285 ^oC
Solubility:	Soluble in water, alcohol, benzene
Molecular mass:	150.2
Density:	1.1274 g/cc

III. HAZARD IDENTIFICATION

A. ACUTE AND CHRONIC DIETARY (Acute and Chronic Reference Doses)

At this time, the product labels for triethylene glycol do not include food contact uses. Therefore, dietary endpoints were not selected and acute and chronic dietary risk assessments are not required.

B. INCIDENTAL ORAL EXPOSURE

The Committee determined that there were no incidental oral exposure scenarios for the uses of triethylene glycol as an air sanitizer, and therefore incidental oral toxicity endpoints were not selected at this time.

C. OCCUPATIONAL / RESIDENTIAL EXPOSURE

1. 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 can occur, 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 dermal 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.

2. DERMAL EXPOSURE SCENARIOS (All Durations)

The dermal route of exposure is not considered a major route of exposure for triethylene glycol as an air sanitizer. The chemical is shown to be a non -sensitizer and of low dermal irritancy. 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. Therefore, toxicological endpoints for dermal exposure scenarios were not selected by the Committee.

3. INHALATION EXPOSURE SCENARIOS (All Durations)

Repeat-dose inhalation toxicities studies conducted with triethylene glycol were submitted to the Agency's Office of Pesticide Programs and Toxic Substances. This is an important route of exposure to characterize hazard, as this chemical is used as an air sanitizer. Although the following studies were not conducted according to the OPPTS 870 Harmonized Test Guidelines, they do provide information that is adequate to characterize the toxicity from repeat-dose inhalation exposure to triethylene glycol.

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.

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.

Monkeys exposed by inhalation to approximately 1 ppm vapor from two weeks to 13 months (approximately 0.5 to 1 ppm) showed no adverse reactions or histopathological changes suggestive of toxicity from prolonged exposure to triethylene glycol.

Review of these data show that triethylene glycol is of low toxicity by the inhalation route of exposure. Toxicities are only observed at doses that far exceed the testing limits established for repeat exposure studies. Therefore, toxicological endpoints for inhalation exposure scenarios were not selected by the Committee.

4. RECOMMENDATION OF MARGINS OF EXPOSURE

Margins of exposure were not established for triethylene glycol because there were no toxicological endpoints of concern identified.

5. AGGREGATE EXPOSURE RISK ASSESSMENTS

The ADTC did not identify toxicological endpoints of concern for the active (air sanitization) and the inert (agricultural commodities) uses of triethylene glycol. Therefore, aggregate risk assessments are not required.

IV. CLASSIFICATION OF CARCINOGENIC POTENTIAL

Published literature sources examining the chronic toxicity and carcinogenic potential of triethylene glycol have shown the chemical to be 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.

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. The dosages tested in rats are equivalent to as much as 3 to 4 g/kg/day which are well above the limit dose of 1 g/kg/day (1000 mg/kg/day) for testing pesticides via the oral route in subchronic and chronic toxicity studies. Under the conditions of this study, triethylene glycol was not carcinogenic in rats.

V. 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.

VI. FQPA CONSIDERATIONS

A. ADEQUACY OF THE TOXICITY DATA BASE

The available toxicity 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 Harmonized 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.

B. EVIDENCE OF NEUROTOXICITY

From the available repeat dose toxicity studies, there was no evidence of neurotoxicity of triethylene glycol. However, the existing toxicology data do not fully characterize repeated dose neurotoxicity. Neurotoxicity testing could be required if additional data are needed to support new uses of triethylene glycol.

C. DEVELOPMENTAL & REPRODUCTIVE TOXICITY

(1) Developmental Toxicity

In a published study, triethylene glycol did not appear to cause any developmental effects in rats at a dose of 2.25 g/kg/day. However, the subcutaneous route of administration is not an acceptable route of exposure for determining the potential prenatal developmental toxicity of triethylene glycol.

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, however, there were no treatment-related increases in external, visceral, or skeletal malformations.

In this same study, 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 only at the high dose level of 11.27 g/kg/day.

(2) Reproductive Toxicity

Published literature examined the effect of triethylene glycol on reproduction in Swiss CD-1 mice. Doses of 0, 0.3, 1.5, and 3% triethylene glycol were administered in drinking water using a continuous breeding protocol. No effects on reproductive function were observed at any dose level tested. Although reduced pup weight was observed in the mid and high-dose (1.5% and 3% triethylene glycol, approximate equivalent doses of 3390 mg/kg/day and 6780 mg/kg/day, respectively) treated mice, this effect occurred at doses in excess of the established testing limit doses (1000 mg/kg/day) for this type of study.

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

The ADTC concluded that the toxicity observed from these data were not significant and were apparent only at doses of triethylene glycol in excess of limit doses for animal studies. Therefore, there is no concern for reproductive toxicity of this chemical.

D. DETERMINATION OF SUSCEPTIBILITY

The ADTC concluded from the available animal data that there is no evidence of increased susceptibility to fetuses or offspring following exposure to triethylene glycol. As there are no active food uses registered by the Agency for triethylene glycol, the ADTC recommended that the special hazard-based safety factor under the FQPA be reduced to 1x. This issue can be revisited if direct or indirect food uses for triethylene glycol become active in the future.

E. DETERMINATION OF THE NEED FOR A DEVELOPMENTAL NEUROTOXICITY STUDY

The ADTC has not identified a basis for requesting a developmental neurotoxicity study at this time.

F. DATABASE UNCERTAINTY FACTOR

No additional database uncertainty factor is needed at this time for triethylene glycol.

VII. HAZARD CHARACTERIZATION

The hazard of triethylene glycol is characterized by reports in the open scientific literature, submitted by the CSMA Glycol Joint Venture in response to Phase IV under FIFRA. 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. [1-6]

Repeated oral dosing studies of triethylene glycol toxicity showed in general that the chemical was without any adverse effects. Only one study, a 90-day oral toxicity study in rats used more than one dose level and reported the doses in mg/kg. In this study, oral doses of 748, 1522, or 3849 mg/kg/day (males), and 848, 1699, or 4360 mg/kg (females) were administered in the diet. Significant effects were noted at the high dose in male and female rats, including decreases in body weight, slight decreases in hemoglobin and hematocrit, slight increase in mean corpuscular volume, and increased kidney and brain weight. As noted, however, these effects were seen at doses in excess of the Agency's limit dose (1000 mg/kg/day) for repeated oral toxicity testing. [7, 8]

Repeated dose inhalation toxicity studies conducted with triethylene glycol show the chemical to be without adverse effects in experimental animals at doses up to an exceeding the limit dose (1 mg/L). Therefore there are no inhalation toxicity concerns for the chemical. [9,10,11]

Published literature sources examining the chronic toxicity and carcinogenic potential of triethylene glycol have shown the chemical to be negative in rodent species. [11,12,13, 14]

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. [15 -18]

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. [19]

Developmental toxicity testing of triethylene glycol showed unremarkable effects. Studies in rats and

mice tested the chemical at very high dose levels (11.27 g/kg/day, 4.4 g/kg/day, and 2.25 g/kg/day) without developmental effects. 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, however, there were no treatment-related increases in external, visceral, or skeletal malformations. In this same study, 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 only at the high dose level of 11.27 g/kg/day. [20, 21]

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). Reduced pup weight was observed at the 1.5 and 3% doses of triethylene glycol. 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. [22, 23]

VIII. DATA GAPS / REQUIREMENTS

The toxicological database for triethylene glycol is currently comprised of published and unpublished studies either submitted to the Agency or obtained directly from the published literature. These acceptable non-guideline studies include: acute, subchronic, developmental, and reproductive toxicity; carcinogenicity, mutagenicity, metabolism/pharmacokinetics and dermal absorption studies. Although the available studies do not meet the requirements of the Agency's OPPTS harmonized test guidelines published in 1998, the ADTC concluded that the existing toxicological data base is adequate for hazard characterization of triethylene glycol. Therefore, the Agency has determined that there are no data gaps for the labelled non-food uses of this chemical as an air sanitizer and deodorizer. If a direct or indirect food-use is sought in the future for triethylene glycol, the existing data base would be considered inadequate and additional data may be required to support these new uses.

IX. ACUTE TOXICITY

Acute Toxicity Profile for Triethylene Glycol

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	42814404	LD_{50} = 15-22 g/kg	IV
81-2	Acute Dermal	42814404	LD_{50} not established	Study Requirement Waived
81-3	Acute Inhalation	42814404	LC_{50} not assigned	II (irritant)
81-4	Primary Eye Irritation	42814404	mild irritant	III
81-5	Primary Skin Irritation	42814404	slight irritant	IV
81-6	Dermal Sensitization	00104805	non- sensitizer	N/A

X. SUMMARY OF TOXICOLOGICAL DOSE AND ENDPOINT SELECTION

There were no toxicological endpoints of concern for triethylene glycol.

XI. REFERENCES

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