Docket Numbers EPA-HQ-OPP-2013-0218 & EPA-HQ-OPP-2013-0219

www.regulations.gov

Propylene Glycol, Dipropylene Glycol and Triethylene Glycol Preliminary Work Plan

Registration Review: Initial Docket
Case Numbers: 3126 & 3146

June 2013

Approved by: Susan Lewis

Susan Lewis
Acting Director
Antimicrobials Division

Date: 6/20/2013

Propylene Glycol, Dipropylene Glycol and Triethylene Glycol Registration Review Team

Human Health
Nathan Mottl
Michelle Centra
William Hazel

Environmental Fate and Effects
Siroos Mostaghimi
Srinivas Gowda
Najm Shamim
David Bays

Risk Management
Elizabeth Hernandez
Andrew Bryceland

Office of General Counsel
Philip Ross

Table of Contents

List of Tables

1 Introduction

This document is the Environmental Protection Agency's (EPA or "the Agency") Preliminary Work Plan (PWP) for propylene glycol, dipropylene glycol and triethylene glycol. The PWP document explains what EPA's Office of Pesticide Programs knows about propylene glycol, dipropylene glycol and triethylene glycol, highlighting anticipated data and assessment needs, identifying the types of information that would be especially useful to the Agency in conducting the review, and providing an anticipated timeline for completing the propylene glycol, dipropylene glycol and triethylene glycol review.

Initially, two separate Registration Review cases were scheduled to address triethylene glycol (Case 3146) and propylene glycol and dipropylene glycol (Case 3126). However, because of their similar use patterns, comparable chemical, physical, and environmental fate characteristics, low mammalian toxicity, and low toxicity to non-target aquatic and terrestrial organisms this document will address propylene glycol (PC code 068603), dipropylene glycol (PC code 068604), and triethylene glycol (PC code 083501). The agency is grouping these active ingredients together and merging them into the Propylene Glycol, Dipropylene Glycol and Triethylene Glycol Registration Review case pursuant to 40 CFR Part 155.42(a) and 40 CFR Part 155.42(b)(4).

The registration review process was designed to include a public participation component to solicit input from interested stakeholders. The Agency intends, by sharing this information in the docket, to inform the public of what it knows about propylene glycol, dipropylene glycol and triethylene glycol and what types of new data or other information would be helpful for the Agency to receive as it moves toward a decision on propylene glycol, dipropylene glycol and triethylene glycol. The Agency encourages all interested stakeholders to review the PWP and to provide comments and additional information that will help the Agency's decision-making process for this chemical.

1.1 Statutory and Regulatory Authority

The Food Quality Protection Act (FQPA) of 1996 mandated a registration review program. All pesticides distributed or sold in the United States generally must be registered by the U.S. Environmental Protection Agency (USEPA, EPA, or the Agency) based on scientific data showing that they will not cause unreasonable risks to human health or the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects to human health or the environment. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can be used safely. Information on this program is provided at http://www.epa.gov/oppsrrd1/registration_review/.

The Agency is implementing the registration review program pursuant to Section 3(g) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and will review each registered

pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration. The regulations governing registration review begin at 40 CFR 155.40. The Agency will consider benefits information and data as required by FIFRA. The public phase of registration review begins when the initial docket is opened for each case. The docket is the Agency's opportunity to state what it knows about the pesticide and what additional risk analyses and data or information it believes are needed to make a registration review decision. After reviewing and responding to comments and data received in the docket during this initial comment period, the Agency will develop and commit to a Final Work Plan (FWP) and anticipated schedule for the Propylene Glycol, Dipropylene Glycol and Triethylene Glycol Case.

Documents associated with this registration review can be viewed at http://www.regulations.gov in dockets EPA-HQ-OPP-2013-0218 and EPA-HQ-OPP-2013-0219. Below is a summary of the issues relevant to this registration review case.

Table 1 – Summary of Anticipated Risk Assessments and Data Needs: Propylene Glycol

Risk Assessment	Assessment Necessary to Support Registration Review	Date of Most Recent Assessment	Type of Assessment Required (New/Updated)	Data Anticipated as Needed
Dietary (food)	No (See 3.2.1)	2/5/2007	None	None
Dietary (drinking water)	No (See 3.2.2)	2/5/2007	None	None
Occupational Handler	No (See 3.3.1)	2/5/2007	None	None
Residential Handler	No (See 3.3.2)	2/5/2007	None	None
Residental Post Application	No (See 3.3.3)	2/5/2007	None	None
Aggregate	No (See 3.4.1)	2/5/2007	None	None
Cumulative	No (See 3.4.2)	2/5/2007	None	None
Tolerance Review	No (See 1.5.2)	2/5/2007	Updated	None
Ecotoxicity	No (See 4.3)	2/5/2007	None	None

Table 2 – Summary of Anticipated Risk Assessments and Data Needs: Dipropylene Glycol

Risk Assessment	Assessment Necessary to Support Registration Review	Date of Most Recent Assessment	Type of Assessment Required (New/Updated)	Data Anticipated as Needed
Dietary (food)	No (See 3.2.1)	2/5/2007	None	None
Dietary (drinking water)	No (See 3.2.2)	2/5/2007	None	None
Occupational Handler	No (See 3.3.1)	2/5/2007	None	None
Residential Handler	No (See 3.3.2)	2/5/2007	None	None
Residental Post Application	No (See 3.3.3)	2/5/2007	None	None

Risk Assessment	Assessment Necessary to Support Registration Review	Date of Most Recent Assessment	Type of Assessment Required (New/Updated)	Data Anticipated as Needed
Aggregate	No (See 3.4.1)	2/5/2007	None	None
Cumulative	No (See 3.4.2)	2/5/2007	None	None
Tolerance Review	Yes (See 1.5.2)	2/5/2007	None	None
Ecotoxicity	No (See 4.3)	2/5/2007	None	None

Table 3 – Summary of Anticipated Risk Assessments and Data Needs: Triethylene Glycol

Risk Assessment	Assessment Necessary to Support Registration Review	Date of Most Recent Assessment	Type of Assessment Required (New/Updated)	Data Anticipated as Needed
Dietary (food)	No (See 3.2.1)	1/25/2006	None	None
Dietary (drinking water)	No (See 3.2.2)	1/25/2006	None	None
Occupational Handler	No (See 3.3.1)	1/25/2006	None	None
Residential Handler	No (See 3.3.2)	1/25/2006	None	None
Residental Post Application	No (See 3.3.3)	1/25/2006	None	None
Aggregate	No (See 3.4.1)	1/25/2006	None	None
Cumulative	No (See 3.4.2)	1/25/2006	None	None
Tolerance Review	No (See 1.5.2)	1/25/2006	None	None
Ecotoxicity	No (See 4.3)	1/.25/2006	None	None

Table 4 – Anticipated Registration Review Schedule

Anticipated Activity	Target Date*	Completion Date
Phase 1: Opening the Docket		
Open Docket and 60-Day Comment Period for Preliminary Work Plan	2013-06	2013-06-20
Close Public Comment Period	2013-08	
Phase 2: Case Development		
Issue Final Work Plan	2013-12	
Issue Data Call-In (DCI)	N/A	
Receive Data to be Considered in Risk Assessment	N/A	
Open 30-Day Public Comment Period for Preliminary Risk Assessment(s)	N/A	
Close Public Comment Period	N/A	
Phase 3: Registration Review Decision and Implementation		
Open 60-Day Public Comment Period for Proposed Decision	2014-12	
Close Public Comment Period	2015-02	
Issue Final Decision	2015-06	
Begin Post-Decision Followup	2016-01	

Anticipated Activity	Target Date*	Completion Date
Total (years)	2.5	

*The anticipated schedule will be revised as necessary (*e.g.*, need arising under the Endocrine Disruptor Screening Program with respect to the active ingredients in this case).

1.2 Case Overview

The docket for the propylene glycol, dipropylene glycol and triethylene glycol Case (Case 3126 & 3146) has been established at http://www.regulations.gov in docket numbers EPA-HQ-OPP-2013-0218 and EPA-HQ-OPP-2013-0219.

Initially, separate Registration Review cases were scheduled to address triethylene glycol (Case 3146) and propylene glycol and dipropylene glycol (Case 3126). However, because of their similar use patterns, comparable chemical, physical, and environmental fate characteristics, low mammalian toxicity and low toxicity to non-target aquatic and terrestrial organisms, this document will address propylene glycol (PC code 068603), dipropylene glycol (PC code 068604), and triethylene glycol (PC code 083501). The agency is grouping these active ingredients together and merging them into the Propylene Glycol, Dipropylene Glycol and Triethylene Glycol Registration Review Case.

According to the 2011-2014 public Registration Review schedule, cases 3146 and 3126 were planned to begin in fiscal year 2013. To ensure the public is able to locate information associated with case 3146 and case 3126, EPA has created and will maintain a separate docket for each case. All EPA documents relevant to the two cases will be posted in the two dockets.

This case will be referred to as the Propylene Glycol, Dipropylene Glycol and Triethylene Glycol Case. As a result of this grouping and merger, the Propylene Glycol, Dipropylene Glycol and Triethylene Glycol Case will now include:

1. Case 3146: triethylene glycol (PC code 083501);

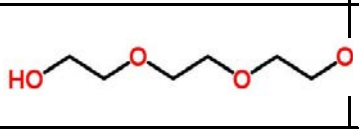
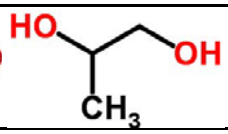
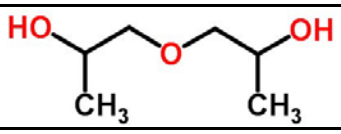
2. Case 3126: propylene glycol (PC code 068603) and dipropylene glycol (PC code 068604)

1.3 Chemical Identification and Properties

Table 5 presents the active ingredients to be assessed in Case 3146: triethylene glycol (PC Code 083501); and Case 3126: propylene glycol (PC Codes 068603) dipropylene glycol (PC Code 068604).

Table 5- Chemical Identification of Triethylene, Propylene and Dipropylene Glycols

Common Name	Triethylene Glycol	Propylene Glycol	Dipropylene Glycol
Classification	Glycol Dihydroxy alcohols Oxygenated Hydrocarbon	Glycol Dihydroxy alcohols	Glycol Dihydroxy alcohols Oxygenated hydrocarbon
Case #	3146	3126	3126

Common Name	Triethylene Glycol	Propylene Glycol	Dipropylene Glycol
PC Code	083501	068603	068604
CAS No.	112-27-6	57-55-6	25265-71-8
Case No.	3146	3126	3126
Molecular Formula	$C_6H_{14}O_4$	$C_3H_8O_2$	$C_6H_{14}O_3$
Molecular Weight	150.17 g/mol	76.09 g/mol	134.20 g/mol
Molecular Structure:			

Triethylene glycol, propylene glycol and dipropylene glycol product chemistry information relevant to the risk assessment is summarized in Table 6 and more detailed product chemistry information is provided in Appendix B. Sources of information used to construct Table 6 consist of MRIDs 42814401, 42814402, 42814403, 43178601, 43178603, 43179501, 43179502, 43179503, and EPI Suite v4.1.

Table 6– Physical-Chemical and Fate Properties for Triethylene, Propylene and Dipropylene Glycols

Guideline No.	Property	Triethylene Glycol	Propylene Glycol	Dipropylene Glycol
830.7000	pH	6.0 - 9.5	Neutral	Neutral
830.7050	UV/Visible Absorption	Does not absorb light at wavelengths >290 nm and therefore it is not expected to be susceptible to direct photolysis by sunlight.	Does not absorb light at wavelengths >290 nm and therefore it is not expected to be susceptible to direct photolysis by sunlight.	Does not absorb light at wavelengths >290 nm and therefore it is not expected to be susceptible to direct photolysis by sunlight.
830.7200	Melting point: Freezing point:	Not applicable. Product is liquid at room temperature. −4.3°C to −7 °C	Not applicable. Product is liquid at room temperature. −59°C	Not applicable. Product is liquid at room temperature. −59°C
830.7220	Boiling point	288.0°C at 760 mm Hg.	188 °C at 760 mm Hg	230 °C at 760 mm Hg
830.7300	Density	1.1255 g/mL at 25°C	1.032 g/ mL at 25°C	1.022 g/ mL at 25°C
830.7370	Dissociation Constant (*pKa*)	Not applicable. Does not dissociate in water.	Not applicable. Does not dissociate in water.	Not applicable. Does not dissociate in water.
830.7550	Partition coefficient (Log *Kow*)	−1.75	− 0.92	− 0.67
830.7840	Solubility in water	Completely soluble.	Completely soluble.	Completely soluble.
830.7950	Vapor pressure (at 25°C)	1.32 $x10^{-3}$ mm Hg	1.3 $x10^{-1}$ mm Hg	1.6 $x10^{-2}$ mm Hg
	Henry law constant ($atm\text{-}m^3$/mole)	3 x 10^{-11}	1.29 x 10^{-8}	6.58 x 10^{-13}
	Ready Biodegradation	YES	YES	YES
	Stability in air (hours)	3.5	10	4

Guideline No.	Property	Triethylene Glycol	Propylene Glycol	Dipropylene Glycol
	Koc (L/kg)	0.089	1	0.45
NG	STP removal (%)	~ 2	~ 2	~ 2
NG	Effluent (%)	98	98	98

NG: non-guideline information

1.4 Use/Usage Description

1.4.1 Registrations

There are two EPA-registered products that contain propylene glycol as an active ingredient (a.i.). The percent a.i. in both products is 4.4% and the formulations include pressurized liquids in aerosol cans and automatic aerosol dispenser. There is no propylene glycol manufacturing use product.

There are two EPA-registered products that contain dipropylene glycol as an a.i. The percent a.i. in the products is 4.4% and 5.31% and the formulations include pressurized liquids in aerosol cans and automatic aerosol dispenser. There is no dipropylene glycol manufacturing use product.

There are 18 EPA-registered products that contain triethylene glycol as an a.i. The percent a.i. ranges from 0.05% to 86% and the formulations include pressurized liquids in aerosol cans, automatic aerosol dispenser, and total release foggers. There is no triethylene glycol manufacturing use product.

1.4.2 Summary of Registered Uses

Table 7 presents a summary of the registered uses of triethylene glycol, propylene glycol and dipropylene glycol that will be assessed in this registration review. Triethylene, propylene and dipropylene glycols can be applied by the following application methods: aerosol can, automatic aerosol dispenser, and total release fogger.

Table 7– Summary of Triethylene Propylene and Dipropylene Glycols Registered Uses

Use	Application Method	Application Rate
Commercial, Industrial, Institutional, Premises and Equipment		
Space spray and surface treatment	Aerosol can and automatic aerosol dispenser	See footnote[1]
Food Handling/Storage Establishments Premises and Equipment[2]		
Space spray and surface treatment	Aerosol can and automatic aerosol dispenser	See footnote[1]
Residential and Public Access Premises		
Aerosol, fog, space spray and surface	Aerosol can, automatic aerosol dispenser, and total	See footnote[1]

[1] Many of the aerosol labels specify a surface spray to spray until completely wet for 10 minutes; many labels specify to spray upward in center of room for 3-10 seconds in a room of average size 12 by 12 feet.
[2] Dipropylene glycol is the only chemical in this case that has currently registered food uses.

treatment	release fogger	
Medical/Dental/Veterinary Premises and Equipment		
Space spray and surface treatment	Aerosol can and automatic aerosol dispenser,	See footnote[1]

1.4.3 Usage Information

Usage information is not available for the propylene glycol, dipropylene glycol or triethylene glycol. The Kline Biocides Report for 2004/2005 (Kline, 2005) does not include propylene glycol, dipropylene glycol or triethylene glycol.

1.5 Regulatory History

Propylene glycol and dipropylene glycol were first registered in 1950 and 1959, respectively, for use in hospitals as air disinfectants. The Agency completed a Reregistration Eligibility Decision (RED) for propylene glycol and dipropylene glycol in 2006.

Triethylene glycol was first registered in 1947 for use in hospitals as an air disinfectant. The Agency completed a RED for triethylene glycol in 2003.

1.5.1 Recent/Pending Regulatory Actions

There are no recent regulatory actions for propylene glycol, dipropylene glycol or triethylene glycol.

1.5.2 Tolerance Information

EPA has not established a tolerance or tolerance exemption for residues of propylene glycol, dipropylene glycol or triethylene glycol in food resulting from registered uses as an active ingredient. Based on the current uses for dipropylene glycol, the agency has identified the need to establish a tolerance and/or exemption from the requirement of a tolerance in 40 CFR Section 180. As part of this registration review, EPA intends to establish the appropriate tolerance and/or exemption in response to the petitions expected to be received from registrants supporting the following uses for dipropylene glycol: hard nonporous food service use sites. Triethylene glycol and propylene glycol are not used as active ingredients in currently registered food use products. Therefore, tolerances and/or exemptions are not needed for triethylene glycol and propylene glycol. EPA has established exemptions from the requirement of a tolerance when propylene glycol is used as an intentionally-added inert ingredient (solvent or cosolvent) in pesticide formulations (40 CFR 180.910 and 180.930). Dipropylene glycol has been exempted from the requirement of a tolerance when used as an intentionally-added inert ingredient (solvent or cosolvent) in pesticide formulations (40 CFR 180.910). Triethylene glycol is exempted from the requirement of a tolerance when used as an intentionally-added inert ingredient (deactivator) in pesticide formulations (40 CFR 180.920). Propylene glycol has been classified as Generally Recognized as Safe (GRAS) by FDA in association with several uses: as an emulsifying agent (21 CFR 582.4666), as a general purpose food additive (21 CFR 582.1666), and as a direct food additive (21 CFR 184.1666). Dipropylene glycol and triethylene glycol are the subject of the

following indirect food additive regulations: components of adhesives (21 CFR 175.105), components of paper and paperboard in contact with aqueous and fatty foods (21 CFR 176.170), surface lubricants used to make metallic food contact articles (21 CFR 178.3910), defoaming agent used in coatings (176.200), as a component of cellophane (21 CFR 177.1200), in packaging materials for food to be irradiated (21 CFR 179.45), as components of resinous and polymeric coatings (21 CFR 175.300), as adjuvants and production aids as plasticizers in polymeric substances (21 CFR 178.3740), and as an optional adjuvant in resinous and polymeric coatings for polyolefin films. No Food Contact Substance Notifications (FCNs) have been determined to be effective by FDA for propylene glycol, dipropylene glycol or triethylene glycol.

1.6 Incidents

1.6.1 Human Health

No reports of incidents associated with human exposure to propylene glycol and/or dipropylene glycol have been reported in the OPP Incident Data System during the time period from 2001to 2012.

However, for triethylene glycol, there are 413 incidents which have been reported in the OPP Incident Data System (2001 – 2012) which have been specifically associated with exposure to triethylene glycol. However, triethylene glycol is a high production volume chemical with approximately 5,000,000 pounds produced from 2004 to 2012 for pesticide products. Given the high production volume of the chemical and the 11 year period of which incidents occurred, the number of incidents is not unusual. Inhalation exposure is the primary exposure route in these reported cases followed by dermal exposure. Most of the incidents are related to inhalation irritation and/or allergic-type reaction. For inhalation exposure incidents, the reported symptoms include respiratory irritation, coughing, chest tightness, difficulty breathing, shortness of breath and wheezing. For dermal exposure, blisters, hives, welts, rash, and bleeding have been reported. In addition, ocular irritation and fever have also been reported.

1.6.2 Ecological

No ecological incidents reported for triethylene glycol, propylene glycol and dipropylene glycol from 2001-2012 (IDS).

2 Anticipated Data Needs

No data are anticipated to be needed to support a human health or environmental risk assessment for the triethylene glycol, propylene glycol and dipropylene glycol registration review.

3 Human Health Risk Assessment

The agency does not anticipate the need to conduct a human health risk assessment for triethylene, propylene and dipropylene glycols. The agency does not expect to require additional data for use in conducting the registration review. According to the triethylene glycol RED and propylene and dipropylene glycol RED, potential for dermal, inhalation, or incidental ingestion

exposure may occur during application of the glycols as well as post-application following use of glycols may occur following air sanitization, hard surface disinfection and direct use on pets. However, there is no evidence of adverse effects at doses of triethylene glycol, propylene glycol or dipropylene glycol up to the established limit dose in repeat-exposure dermal (1000 mg/kg/day) and inhalation (1 mg/L or 1000 mg/m^3) toxicity studies. Thus, no toxicological endpoints of concern have been established for either of these chemicals based on review of the available mammalian toxicity data. Due to the low order of toxicity and low application rates from the current uses of these chemicals, no risks associated with potential exposures have been quantified for use of triethylene glycol, propylene glycol or dipropylene glycol as active ingredients in pesticide products.

3.1 Existing Toxicological Endpoints

In the September 2006 Propylene Glycol and Diproylene Glycol RED and the September 2003 Triethylene Glycol RED, the Agency concluded that propylene glycol, dipropylene glycol, and triethylene glycol pose no toxicological concerns due to their low toxicity; therefore, no toxicological endpoints of concern were developed. Based on a review of the available toxicity data (see Appendix A), the agency concludes that for registration review these chemicals pose no toxicological concerns when used according to pesticide labeled uses. No additional toxicity data requirements are anticipated at this time for registration review. This conclusion is based on the results of toxicity testing of propylene glycol and dipropylene and triethylene glycol at dose levels near or above testing limits (as established in the OPPTS 870 series harmonized test guidelines). No significant toxicity was observed in any of the animal toxicity studies in the existing toxicological database for registration review. A detailed description of the toxicity studies for triethylene glycol, propylene glycol and dipropylene glycol for registration review is provided in Appendix A .

3.2 Dietary Exposure

3.2.1 Food

Although human dietary exposure to the subject glycols could potentially occur as a result of the registered uses, there is no risk associated with these related compounds because they do not induce adverse systemic effects except at doses much higher than could be expected from pesticidal uses (EPA 2013a and 2013b). As part of this registration review, EPA intends to establish the appropriate tolerance and/or exemption in response to the petitions expected to be received from registrants supporting the following uses for dipropylene glycol: hard nonporous food service use sites. Triethylene glycol and propylene glycol are not used in currently registered food use products. Therefore, tolerances and/or exemptions are not needed for triethylene glycol and propylene glycol.

3.2.2 Drinking Water

Although human dietary exposure via drinking water to the glycols may occur as a result of the registered uses, there is no risk associated with these related compounds because they do not induce adverse systemic effects except at doses much higher than could be expected from pesticidal uses (EPA 2013a and 2013b). Therefore, no additional data are anticipated to be

needed and dietary risk assessments reflecting exposures to the glycols in drinking water are not expected to be necessary.

3.3 Occupational and Residential Exposures

The agency does not anticipate that a new occupational and residential risk assessment will be needed based on the lack of toxicological endpoints. No toxicological endpoints of concern have been established for either of these chemicals based on review of the available mammalian toxicity data. Due to the low order of toxicity and low application rates from the current uses of these chemicals, no risks associated with potential exposures have been quantified for use of triethylene glycol, propylene glycol or dipropylene glycol as active ingredients in pesticide products. The earlier risk assessments for propylene and dipropylene glycol completed in February 5, 2007 and triethylene glycol on May 24, 2005 do not need to be updated (EPA 2007a and EPA 2005).

3.3.1 Occupational Handler Exposure

The agency does not anticipate the need to revise the occupational handler assessments that were already conducted during reregistration. Although there is potential for occupational dermal and/or inhalation exposure, no toxicological endpoints of concern were identified. Therefore no risk assessments can be conducted or are anticipated as needed.

Potential exposure may occur during application of the glycols as well as post-application following air sanitization, hard surface disinfection, and direct use on pets. No chemical-specific handler data were submitted to estimate the potential exposures associated with these uses of triethylene, propylene and dipropylene glycol (nor are they anticipated as needed at this time since a risk assessment cannot be conducted without toxicological endpoints).

Table 8 – Occupational Handler Exposure Scenarios for Triethylene, Propylene and Dipropylene Glycols

Scenario	Exposure Route(s)	Duration
Occupational Exposures		
Applying disinfectant spray to hard surfaces and the air using an aerosol can	Dermal /Inhalation	Short, Intermediate, and Long Term
Applying disinfectant spray to the air using an automatic aerosol dispenser	Inhalation	Short, Intermediate, and Long Term
Applying disinfectant to the air using total release foggers or misters	Inhalation	Short and Intermediate Term

3.3.2 Residential Handler Exposures

EPA does not anticipate the need to revise the residential handler assessment conducted in support of reregistration. Potential for residential dermal and/or inhalation exposure may occur during application of the glycols as well as post-application following air sanitization, hard surface disinfection, and direct use on pets. No chemical-specific handler data were submitted to estimate the potential exposures associated with these uses of triethylene, propylene and dipropylene glycol (nor are they anticipated as needed at this time since a risk assessment cannot

be conducted without toxicological endpoints). However, because no toxicological endpoints of concern were identified, the exposures have not been quantified and no handler data were required in the RED and none are anticipated as needed for registration review.

Table 9 – Residential Handler Exposure Scenarios for Triethylene, Propylene and Dipropylene Glycols

Scenario	Exposure Route(s)	Duration
Residential Exposures		
Applying disinfectant spray to hard surfaces and the air using an aerosol can	Dermal /Inhalation	Short and Intermediate Term
Applying disinfectant spray to the air using an automatic aerosol dispenser	Inhalation	Short and Intermediate
Applying disinfectant to the air using total release foggers or misters	Inhalation	Short and Intermediate Term

3.3.3 Occupational Post-Application Exposures

Potential for occupational post application exposure may occur to individuals reentering treated rooms and/or contacting sprayed surfaces. Disinfectant properties are utilized in the household for hard, nonporous surfaces including windows, shower stalls, countertops, refrigerators, microwave ovens, and tubs (*i.e.*, non-food contact surfaces). As an air sanitizer, this active ingredient has numerous listed active use sites including industrial/institutional use in washrooms, auditoriums, public rooms, hotel lobbies, theaters, hospitals, classrooms, railroads, airplanes, buses, taxicabs, sitting rooms, locker rooms, factories, mills, and department stores. However, because no toxicological endpoints of concern were identified, the exposures have not been quantified and no post application data were required during reregistration and none are anticipated as needed for registration review.

Table 10 – Occupational Post-Application Exposure Scenarios for Triethylene, Propylene, and Dipropylene Glycols

Scenario	Exposure Route(s)	Duration
Post application exposure bystanders to aerosols and vapors released from air deodorizing treatments	Inhalation	Short and Intermediate Term

3.3.4 Residential Post-Application Exposures

Potential for residential post application exposure may occur to individuals reentering treated rooms and/or contacting sprayed surfaces. Disinfectant properties are utilized in the household for hard, nonporous surfaces including windows, shower stalls, countertops, refrigerators, microwave ovens, and tubs (*i.e.*, non-food contact surfaces). Children could become exposed to residues from hand-to-mouth or from dermal contact. As an air sanitizer, this active ingredient has numerous listed active use sites in bathrooms. However, because no toxicological endpoints of concern were identified, the exposures have not been quantified and no post application data were required during reregistration and none are anticipated as needed for registration review.

Table 11 – Residential Post-Application Exposure Scenarios for Triethylene, Propylene, and Dipropylene Glycols

Scenario	Exposure Route(s)	Duration
Postapplication exposure to children from dermal and hand-to-mouth contact from treated floors.	Incidental ingestion/dermal	Short and Intermediate Term
Post application exposure bystanders to aerosols and vapors released from air deodorizing treatments	Inhalation	Short and Intermediate Term

3.4 Aggregate and Cumulative Exposure

3.4.1 Aggregate Exposures

In examining aggregate exposure, EPA takes into account the available and reliable information concerning exposures to pesticide residues in food and drinking water, and non-occupational pesticide exposures. An aggregate risk assessment cannot be conducted because toxicological endpoints for propylene glycol, dipropylene glycol, and triethylene glycol have not been established.

3.4.2 Cumulative Exposures

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 propylene glycol, dipropylene glycol, and triethylene glycol and any 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/.

4 Environmental Risk Assessment

The agency does not anticipate the need to conduct an environmental risk assessment for triethylene glycol, propylene glycol and dipropylene glycol because the indoor air and surface disinfection uses with the given application methods are not expected to result in exposure of terrestrial or aquatic organisms. No changes to the use patterns have occurred for the glycols since the Propylene and Dipropylene Glycol RED or the Triethylene Glycol RED (See Section 1.5.1). There are new models and approaches that the agency has been implementing since the publication of these REDs. Application methods using aerosol cans, automatic aerosol dispensers, and foggers are not expected to result in down-the-drain disposal and there is no direct exposure to non-target organisms. The agency does not anticipate requiring additional data for this registration review.

4.1 Environmental Fate Assessment

The Agency does not anticipate requiring additional environmental fate data at this time because triethylene glycol, dipropylene glycol and propylene glycol are not persistent in the environment.

In 2003, the Agency issued an Ecological Risk Assessment for triethylene glycol which concluded: "Triethylene glycol is miscible in water, mobile in soils, and stable to abiotic hydrolysis, as well as soil and aquatic photolysis. River dye-away tests indicate that triethylene glycol degrades in soils from a few days to weeks. It undergoes ready biodegradation, according to the activated sludge studies." In 2006, the Agency completed an Ecological Risk Assessment for propylene glycol and dipropylene glycol. In its fate assessment, the Agency concluded that " Propylene glycol and dipropylene glycol are miscible in water, mobile in soils, have low absorptivity to soil, and are stable to abiotic hydrolytic degradation as well as it does not undergo abiotic photodegradation in soil and in water. However, in aerobic soils propylene glycol biodegrades to carbon dioxide (CO_2) in 4 days, whereas biodegradation of dipropylene glycol may be a slightly slower process according to biological (biodegradability) screening tests. However, this process may still be an important mechanism for removal of dipropylene glycol from aerobic soils." The physical and chemical properties and fate data are summarized in Table 6.

The low K_{ow} of -1.75, -0.92 and -0.67 for triethylene glycol, propylene glycol and, dipropylene glycol, respectively, are not likely to bioaccumulate in aquatic organisms. With a vapor pressure of 0.00132 mmHg at 25 ^{o}C, 0.13 mm Hg and 1.6 x10^{-2} mm Hg at 25 ^{o}C, for triethylene glycol, propylene glycol and dipropylene glycol, respectively, these glycols would exist in large part in the vapor phase in the atmosphere but degrade rapidly (half-life approximately between 3.5 to 10 hours) by reaction with photo-chemically produced hydroxyl radicals. Therefore, the presence of triethylene glycol, propylene glycol, dipropylene glycol in the environment, including the atmosphere, will be transient and not persistent.

Additional fate parameters obtained from the Agency's EPI Suite v 4.1 estimation program indicate that these glycols have low K_{oc} values of 1, 0.45 and 0.089 which make them have a high mobility in soils; but as observed earlier, these glycols degrade fast in soils. All three glycols are ready biodegradable and dye-away testing shows these glycols have a tendency to mineralize within a few days to two weeks. Because of their high solubility in water from 811 to 1000 g/L, these glycols will not likely be adsorbed to sediments. The Agency does not anticipate requiring additional environmental fate data at this time for this registration review.

4.2 Conceptual Models for Environmental Exposure Pathways

All registered pesticide uses of propylene glycol, dipropylene glycol and triethylene glycol as active ingredients are considered to have no exposure to non-target organisms. The indoor air and surface disinfection using aerosol cans, automatic aerosol dispensers, and foggers as application methods are not expected to result in down-the-drain disposal and as a result, there is no direct exposure to non-target organisms. The lack of exposure means, except for spills or accidental releases, there is no ecological risk of concern from their use.

4.3 Ecological Effects Assessment

4.3.1 Mechanism of Action

Propylene glycol, dipropylene glycol and triethylene glycol are all alcohols and dipropylene glycol and triethylene glycol are also esters. They inactivate target pests by denaturing proteins found in cell membranes and viral protein coats. This leads to the target pests losing structural

integrity and losing the ability to cause infections (USEPA, 2004, 2006b). For non-target aquatic animals, these chemicals act acutely by narcosis, a non-specific mechanism of action.

4.3.2 Measures of Effect (Ecotoxicology Endpoints)

Propylene glycol and dipropylene glycol show very low acute toxicity to terrestrial and aquatic animals (Table 12 and Appendix C). The toxicity endpoints presented below are based on the results of toxicity studies submitted by registrants to meet the Agency's ecological effects data requirements for the uses of propylene glycol and dipropylene glycol. Additional information was located in EPA/ORD's ECOTOX database, which provides summary endpoints from the open scientific literature as well as studies submitted to the Agency. For missing data, the structure activity program ECOSAR v1.10 was used to estimate endpoint values. While ECOSAR v1.10 provided estimates for chronic fish and invertebrate endpoints, these results, while in Appendix C, are not in Table 12 because they are not required for the assessment.

Table 12 Selected Endpoints for Assessment of Propylene and Dipropylene Glycols

Receptor Group	Surrogate Species	Risk Scenario	Toxicity Endpoint[a]	Reference (MRID)
Birds	Northern bobwhite quail	Acute oral	LD_{50}>2,000 mg/kg-bw	43762301 43760607
		Subacute dietary	Data not required	--
		Chronic	Data not required	--
Mammals	Rat	Acute	LD_{50} >5,000 mg/kg-bw	See Appendix A
		Chronic	Data not required	
Freshwater fish	Fathead minnow	Acute	96-hr LC_{50} = 790 ppm propylene glycol	ECOSAR v1.10 See Appendix C
		Chronic	Data not required	--
Freshwater invertebrates	Waterflea	Acute	48-hr EC_{50} > 100 ppm[a]	Several MRIDs see Appendix C
		Chronic	Data not required	--
Estuarine/marine fish	Generic fish	Acute	96-hr LC_{50} > 24,000 ppm[a]	ECOSAR v1.10 See Appendix C
		Chronic	Data not required	
Estuarine/marine invertebrates	Eastern Oyster	Acute	Data not required	--
	Mysid	Acute	96-hr LC_{50} >100,000 ppm[a]	ECOSAR v1.10 See Appendix C
		Chronic	Data not required	
Aquatic Plants	Green algae	Nonlisted species	96-hr IC_{50} >5,000 ppm[a]	ECOSAR v1.10 See Appendix C
		Listed Species	96-hr Chv >300 ppm[a]	

[a] For definitive values see Appendix C. Non-definitive values are provided in the table to show that both chemicals have low toxicity, and are considered potentially non-toxic. For the propylene and dipropylene gylcol uses, green algae data and acute animal data were required only for hazard labeling purposes. No risk assessment is anticipated.

Triethylene glycol show very low acute toxicity to terrestrial and aquatic animals (Table 13 and Appendix D). The toxicity endpoints presented below are based on the results of toxicity studies submitted by registrants to meet the Agency's ecological effects data requirements for the uses of triethylene glycol. Additional information was located in EPA/ORD's ECOTOX database, which provides summary endpoints from the open scientific literature as well as studies submitted to the Agency. For missing data, the structure activity program ECOSAR v1.10 was used to estimate endpoint values. However, the ECOSAR v1.10 neutral organics model may not be appropriate for triethylene gylcol. Estimates of acute values were higher than actual

laboratory studies in some cases. While ECOSAR v1.10 provided estimates for chronic fish and invertebrate endpoints, these results, while in Appendix D, are not in Table 13 because they are not required for the assessment.

Table 13 Selected Endpoints for Assessment of Triethylene Glycol

Receptor Group	Surrogate Species	Risk Scenario	Toxicity Endpoint[a]	Reference (MRID)
Birds	Northern bobwhite quail	Acute oral	None	None
		Subacute dietary	Data not required	--
		Chronic	Data not required	--
Mammals	Rat	Acute	LD_{50} = 15,000 mg/kg-bw	See Appendix A
		Chronic	Data not required	
Freshwater fish	Bluegill sunfish	Acute	96-hr LC_{50} = 10,000 ppm	Verschuren, 1983
		Chronic	Data not required	--
Freshwater invertebrates	Waterflea	Acute	48-hr EC_{50} =116,000 ppm[a]	ECOSAR v1.10 See Appendix D
		Chronic	Data not required	--
Estuarine/marine fish	Inland Silverside	Acute	96-hr LC_{50} = 10,000 ppm	Verschuren, 1983
		Chronic	Data not required	
Estuarine/marine invertebrates	Eastern Oyster	Acute	Data not required	--
	Mysid	Acute	96-hr LC_{50} = 11,000 ppm	40228401
		Chronic	Data not required	
Aquatic Plants	Green algae	Nonlisted species	96-hr IC_{50} = 67,640 ppm	ECOSAR v1.10 See Appendix C
		Listed Species	96-hr Chv = 2,486 ppm	

4.4 Exposure Analysis Plan

4.4.1 Aquatic and Terrestrial Wildlife Exposure Estimates

Since the agency does not anticipating conducting an environmental risk assessment, no exposure analysis plan is needed. The agency does not anticipate exposure of aquatic and terrestrial organisms.

4.5 Effects Analysis Plan

Since the agency does not anticipating conducting an environmental risk assessment, no effects analysis plan is needed.

4.5.1 Endangered Species Effects Determination

Based on the low likelihood of exposure of triethylene glycol, dipropylene glycol and propylene glycol in various environmental media like water, soils, and air, the Agency intends to conclude that the registered uses of triethylene glycol, dipropylene glycol and propylene glycol will have 'no effect' on endangered or threatened terrestrial or aquatic species, or their designated critical habitats, as listed by the U.S. Fish and Wildlife Service (USFWS) and the National Oceanic and Atmospheric Administration's (NOAA) National Marine Fisheries Service (NMFS). EPA anticipates conducting no further analysis of potential risks to endangered or threatened species

unless public comment or other submissions provide data or information that would otherwise inform the Agency's determination. However, the Agency will review any comments made by the public on this document and will conduct an environmental risk assessment if new information warrants such action.

5 Endocrine Disruptor Screening Program (EDSP)

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of reregistration decision, for propylene glycol, dipropylene glycol and triethylene glycol, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), propylene glycol, dipropylene glycol and triethylene glycol are subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. Propylene glycol, dipropylene glycol and triethylene glycol are not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Accordingly, as part of registration review, EPA will issue future EDSP orders/data call-ins, requiring the submission of EDSP screening assays for propylene glycol, dipropylene glycol and triethylene glycol.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

6 Guidance for Commenters

6.1 Preliminary Work Plan

The public is invited to comment on EPA's Preliminary Work Plan and rationale. The Agency will carefully consider all comments as well as any additional information or data provided in a timely manner prior to issuing a final work plan for the Propylene Glycol, Dipropylene Glycol and Triethylene Glycol registration review case.

6.1.1 Trade Irritants

Through the registration review process, the Agency intends to solicit information on trade irritants and, to the extent feasible, take steps toward facilitating irritant resolution. The Agency will work to harmonize tolerances and international maximum residue limits (MRLs) and may modify tolerance levels to do so, when possible. **Stakeholders are asked to comment** on any trade irritant issues resulting from lack of MRLs or disparities between U.S. tolerances and MRLs in key export markets, providing as much specificity as possible regarding the nature of the concern.

6.1.2 Water Quality

Glycols, specifically ethylene glycol and propylene glycol (one of the three glycols in the present case) are identified as a cause of impairment of Yeader Creek, Polk County in Des Moines, Iowa. This water body is listed as impaired under section 303(d) of the Clean Water Act[3]. Yeader Creek is across the Des Moines International Airport where the use of ethylene glycol for deicing of planes occurs. All sites listed for pesticides and organics were reviewed and only this site was identified as impaired. Total Maximum Daily Load (TMDL) for Des Moines International Airport to Yeader Creek for ethylene glycol was: 125 mg/L (30-day average), and 190 mg/L for daily maximum. TMDL for propylene glycol was: 100 mg/L (30-day average), and 150 mg/L for the daily maximum. Effects on benthic macroinvertebrates were recognized as the biological target (Index of Biotic Integrity (IBI) = 43[a4]). However, the impairment was due to a non-pesticidal use of propylene glycol.

More information on impaired water bodies and TMDLs can be found at EPA's website[5]. **The Agency invites submission of water quality data for this pesticide.** To the extent possible, data should conform to the quality standards in Appendix A of the *OPP Standard Operating Procedure: Inclusion of Impaired Water Body and Other Water Quality Data in OPP's Registration Review Risk Assessment and Management Process*[6] in order to ensure they can be used quantitatively or qualitatively in pesticide risk assessments.

[3] http://iaspub.epa.gov/tmdl_waters10/attains_nation_cy.cause_detail_303d?p_cause_group_id=885
[4] TMDL for Priority Organics, Yeader Creek, Polk County, 2005
[5] http://www.epa.gov/owow/tmdl/
[6] http://www.epa.gov/oppsrrd1/registration_review/water_quality_sop.htm

6.1.3 Environmental Justice

EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, in the development, implementation, and enforcement of environmental laws, regulations, and policies. To help address potential environmental justice issues, the Agency seeks information on any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical, unusually high exposure to propylene glycol, dipropylene glycol and triethylene glycol compared to the general population. **Please comment if you are aware of any sub-populations that may have atypical, unusually high exposure compared to the general population.**

6.1.4 Structure Activity Relationships

EPA must rely upon information of appropriate quality and reliability for each decision made by the Agency. In the Office of Pesticide Programs (OPP), the evaluation process for a pesticide chemical traditionally begins with the applicant's submission of a set of studies conducted with the specific pesticide chemical of interest. The use of the results of such testing (measured data) is a logical, scientifically rigorous process that identifies the physical, chemical, and environmental fate properties of the pesticide, as well as the dose and endpoints at which an adverse effect can occur in various animal species.

Today, there is significant interest in alternative techniques, *i.e.*, techniques other than data generation that could significantly inform the Agency's decision-making process. Recently, OPP has made increasing use of structure activity relationship (SAR) as part of its regulatory decision-making process. In the SAR process, a chemical's molecular structure is compared to that of other chemicals for which data are available. These structural similarities are then used to make predictive judgments about a chemical's physical, chemical, and biological properties. Thus, the chemical's physical, chemical, and biological properties are a function of (or directly related to) the chemical's molecular structure. Quantitative SAR is referred to as QSAR. To develop a QSAR, a selected set of measured data on a single physical, chemical, or biological property is used to derive a model (an equation) to predict the value of that property.

Since SAR assessments and QSAR modeling are another set of tools that are available to Agency scientists, OPP has begun a process shift that envisions shifting from the current study-by-study approach to an approach in which the use of predicted data, generated using validated models, is considered along with information from open literature and studies specifically generated under Part 161 requirements. All relevant information would be considered as part of a weight-of-the-evidence evaluation.

At this time, EPA believes that for certain endpoints, especially physical/chemical and fate properties, that SAR and QSAR might be effectively utilized to fulfill these data requirements for many antimicrobial pesticide chemicals. When considering biological properties, at this time, EPA believes that SAR and QSAR can be most effectively utilized in the evaluation of chemicals that exhibit lower toxicity for human health and/or ecotoxicity parameters. This is appropriate because the risk assessment for lower toxicity chemicals can be stream-lined, *i.e.*, a screening-level assessment procedure rather than multiple tiers of assessments with progressively more data requirements.

If stakeholders believe that submission of predicted data can fulfill one of the data needs for the Propylene Glycol, Dipropylene Glycol and Triethylene Glycol Case, then the Agency invites submission of this information. The submitter would be expected to supply a rationale describing the utility of the information and provide documentation on the scientific validity of the information. The determination that the predicted data fulfills the data requirement would be at the sole discretion of the Agency. Pre-submission consultation with the Agency is encouraged.

6.1.5 Additional Information

Stakeholders are also specifically asked to provide available information and data that will assist the Agency in refining its risk assessments, including any species-specific ecological effects determinations. The Agency is interested in receiving the following information:

1. Confirmation on the following label information:
    A. Sites of application
    B. Formulations
    C. Application methods and equipment
    D. Maximum application rates
    E. Frequency of application, application intervals and maximum number of applications
    F. Geographic limitations on use
2. Use or potential use distribution
3. Use history
4. Usage/use information for non-agricultural uses (*e.g.*, materials preservation)
5. Typical application interval
6. State or local use restrictions
7. Ecological incidents (non-target plant damage and avian, fish, reptilian, amphibian and mammalian mortalities) not already reported to the Agency
8. Monitoring data

7 Next Steps

After the 60-day comment period closes in August 2013, the Agency will review and respond to any comments received in a timely manner, and then issue a Final Work Plan for the Propylene Glycol, Dipropylene Glycol and Triethylene Glycol case.

8 References

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. Toxicological Profile for Propylene Glycol. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. 176 pp. http://www.atsdr.cdc.gov/ToxProfiles/tp189.pdf

Amdur, M.O., J. Doull, et al. (1991). Casarett and Doull's Toxicology: The Basic Science of Poisons. pp 705. MRID 46892501

ATSDR. 2008. Addendum to the Toxicological Profile for Propylene Glycol. Division of Toxicology and Environmental Medicine, Atlanta, GA. 17 pp. http://www.atsdr.cdc.gov/toxprofiles/propylene_glycol_addendum.pdf

Bartsch, W., G. Sponer, et al. (1976). Acute Toxicity of Various Solvents in the Mouse and Rat. LD_{50} of Ethanol, Diethylacetamide, Dimethylformamide, Dimethyl-Sulfoxide, Glycerine, N-Methylpyrrolidone, Polyethylene Glycol 400, 1, 2-Propanediol and Tween 20. Arzneimittelforsch 26:1581-1583.

Braun, H.A. and G.F. Cartland. (1936). The Toxicity of Propylene Glycol. J. Am. Pharm. Assoc. 25:746-749.

Budden, R., U.G. Kuehl, et al. (1979). Experiments on the Toxic, Sedative, and Muscle Relaxant Potency of Various Drug Solvents in Mice. Methods Toxicol. 102:467-474.

Bridie, A.L., C.J.M. Wolff, and M. Winter. 1979. The Acute Toxicity of Some Petrochemicals to Goldfish. Water Res. 13(7):623-626. (ECOTOX reference #623).

Bossert, N.L., et al. (1992) Reproductive Toxicity of Triethylene Glycol and its Diacetate and Dimethyl ether Derivatives in a Continuous Breeding Protocol in Swiss CD-1 mice. Fund. Appl. Pharmacol. 18: 602-608.

Budavari, S., M.J. O'Neill, A. Smith, and P.E. Heckelman (eds.)1989. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. Rahway (eleventh edition), NJ: Merck & Co., Inc.

Campbell and Beavers, 1995. Acute oral toxicity of dipropylene glycol to Northernbobwhite. Unpublished data. MRID 43760807.

Campbell and Beavers, 1995. Acute oral toxicity of propylene glycol to Northern bobwhite. Unpublished data. MRID 43762301.

Clark C.R., T.C. Marshall, et al. (1979). Toxicological Assessment of Heat Transfer Fluids Proposed for Use in Solar Energy Applications. Toxicology and Applied Pharmacology 51:529-535.

Clayton, G.D. and F.E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982. 3839.

Collins, 1995. Acute toxicity of propylene glycol to the waterflea (Daphnia magna). Unpublished data. MRID 43888003.

Conquet, P., et al. (1977). Evaluation of Ocular Irritation in the Rabbit: Objective versus Subjective Assessment. Toxicology and Applied Pharmacology 39:129-139. MRID 46892502

Cornell, J.S., D.A. Pillard, and M.T. Hernandez. 2000. Comparative Measures of the Toxicity of Component Chemicals in Aircraft Deicing Fluid. Environ. Toxicol. Chem. 19(6):1465-1472. (ECOTOX reference #48385).

Davis, K. (1993) Compilation of Toxicology Data References for Triethylene Glycol: Lab Project Number: TEGTOX. Unpublished study prepared by RegWest Co. 131 (MRID 42814404)

Draize, J.H., et al. (1944). Journal of Pharmacology and Experimental Therapy 82:377.

Driscoll, C.D., M.F. Kubena, et al. (1993). Propylene Glycol: Developmental Toxicity Gavage Study III in CD-1 Mice. Danbury (CT): Industrial Chemicals Division, Union Carbide Chemicals and Plastics Company Inc.

Gaunt, I.F., F.M.B. Carpanini, et al.(1972). Long-Term Toxicity of Propylene Glycol in Rats. Food Cosmetics and Toxicology 10:151-162. MRID 46892504

Gimeno, S., Komen, H., Gerritsen, A.G., and Bowner, T. (1998a): Feminisation of young males of the common carp, *Cyprinus carpio*, exposed to 4-tert-pentyphenol during sexual differentiation. Aquatic Toxicology (Amsterdam) 43: 77-92.

Guillot, J.P., et al. (1982) Safety Evaluation of Some Humectants and Moisturizers Used in Cosmetic Formulations. International J. Cosmetic Sci., 4: 67.

Goldstein, I., et al. (1970) Toxicity of Glycol Derivatives. Igenia.

Graves and Swigert, 1995. Acute toxicity of dipropylene glycol to the waterflea (Daphnia magna). MRID 43760808.

Graves and Swigert, 1995. Acute toxicity of propylene glycol to the waterflea (Daphnia magna). Unpublished data. MRID 43762302.

Guzzie, P., Slesinski, F. Frank, et al. (1986a) Triethylene Glycol Salmonella/Microsome (Ames) Bacterial Mutagenicity Assay. Bushy Run Research Center, Export, PA. Project Report 49-58. April 29, 1986. NTIS Report No. OTS0527779-1. Unpublished.

Guzzie, P., Slesinski, F. Frank, et al. (1986b) Triethylene Glycol: *In vitro* Chromosome Aberration Study. Bushy Run Research Center, Export, PA. Project Report 49-82. July 1, 1986. NTIS Report No. OTS0527779-1. Unpublished.

Hayashi, M., et al. (1988). Micronucleus Tests in Mice on 39 Food Additives and Eight Miscellaneous Chemicals. Food Chemistry and Toxicology 26:487-500. MRID 46892506

FDRL (1973). Food and Drug Research Laboratories, Inc. Teratologic Evaluation of

FD 71-56 (Propylene Glycol). Report No. PB-223 822. July.

Fischer, L., R. Kopf, et al. (1949). Chemical Structure and Pharmacological Effects of Glycols, Particularly 1,3-Butylene Glycol. A. Gesamte Exp. Med. 115:22-39.

Florin, I., L. Rutberg, et al. (1980). Screening of Tobacco Smoke Constituents for Mutagenicity Using the Ames' Test. Toxicology 18:219-232. MRID 46892503

Guerrant, N.B., et al. (1947). Bull. Natn. Formul. Comm. 15:205.

Guillot, J.P., et al. (1982). International Journal of Cosmet. Science 4:67.

Hanzlik, P.J., A.J. Lehman, et al. (1939). General Metabolic and Glycogenic Actions of Propylene Glycol and Some Other Glycols. Journal of Pharmacol. Exp. Ther. 67:114-126.

Kavlock, R.J., et al. (1987). Further Evaluation of an In Vivo Teratology Screen.

Teratogenesis Carcinog Mutagen 7:7-16. MRID 46892508

Kero, M. and Hannuksela, M. (1980). Guinea Pig Maximization Test, Open Epicutaneous Test and Chamber Test in Induction of Delayed Contact. Contact Dermatitis 6:341-344.

Konradova, V., V. Vavrova, et al. (1978). Effect of the Inhalation of a Surface Tension-Reducing Substance (Propylene Glycol) on the Ultrastructure of Epithelium of the Respiratory Passages in Rabbits. Folia Morphol. (Praha) 26:28-34.

LaKind, J.S., E.A. McKenna, et al. (1999). A Review of the Comparative Mammalian Toxicity of Propylene Glycol. Critical Reviews in Toxicology 29.4:331-365. MRID 46892509

Latven, A.R. and H. Molitor. (1939). Comparison of the Toxic, Hypnotic and Irritating Properties of Eight Organic Solvents. Journal of Pharmacol. Exp. Ther. 65:89-94.

Laug, E.P. et al. (1939). Journal Ind. Hyg. Toxicol. 21:173.

Layton, D.W., B.J. Mallon, et al. (1987). Deriving Allowable Daily Intakes for Systemic Toxicants Lacking Chronic Toxicity Data. Regulatory Toxicology and Pharmacology 7:96-112. MRID 46892510

Kuhn, R., M. Pattard, K. Pernak, and A. Winter. 1989. Results of the Harmful Effects of Selected Water Pollutants (Anilines, Phenols, Aliphatic Compounds) to Daphnia magna. Water Res. 23(4):495-499. (ECOTOX reference #846).

Lamb, I.V. et al. (1997) Triethylene Glycol. Environ. Health Perspectives, 105(Suppl 1): 235-236. (Also available as an NTP Report No. PB85-137073).

Lauter, W.M. and V.L. Vria (1940) Toxicity of Triethylene Glycol and the Effect of Para-amino-benzene Sulfonamide Upon the Toxicity of this Glycol. J. Am. Pharmaceutical Assoc. 29: 5-8.

McKennis, Jr., et al. (1962) The Excretion and Metabolism of Triethylene Glycol. Toxic. Appl. Pharmacol., 91: 52.

Monographs on Fragrance Raw Materials: Special Issue V (1979). Food and Cosmetic Toxicology, 17(suppl): 913.

Morrissey, R.E., et al. (1989). Results and Evaluations of 48 Continuous Breeding Reproduction Studies Conducted in Mice. Fundamentals of Applied Toxicology 13:747-777. MRID 46892201

Morris, H.J., A.A. Nelson, et al. (1942). Observations on the Chronic Toxicities of Propylene Glycol, Ethylene Glycol, Diethyl Glycol, Ethylene Glycol Mono-Ethyl-Ether, and Diethylene Glycol Mono-Ethyl-Ether. Journal of Pharm. Exper. Ther. 74:266-273.

Morshed, K.M., J.P. Nagpaul, et al. (1991). The Effect of Propane-Diols on the Intestinal Uptake of Nutrients and Brush Border Membrane Enzymes in the Rat. Biochem. Med. Metab. Biol. 45:161-170.

Majewski, H.S., J.F. Klaverkamp, and D. P. Scott. 1978. Acute Lethality and Sub-Lethal Effects of Acetone, Ethanol, and Propylene Glycol on the Cardiovascular and Respiratory Systems of Rainbow Trout. Water Res. 12(4):217-221. (ECOTOX reference # 991).

Nachreiner, D.J. (1991) Triethylene Glycol (TEG) Acute Aerosol Inhalation Toxicity Test in Rats. Bushy Run Research Center; Project Report 53-139 (BRCC No. 90-22-40272), MarcH 4, 1991; NTIS Report No. OTS0527779-1. Unpublished.

NCI. (1986). Salmonella/ Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test): Dipropylene Glycol. National Cancer Institute Test Article Code No.: 00812 Microbiological Associates, Inc. pp 10.

NCI (1987). Mouse Lymphoma Mutagenesis Assay: Dipropylene Glycol. National Cancer Institute Test Article Code No.: 00812 (ML-NCI #185). Microbiological Associates, Inc. pp 11.

National Institute For Occupational Safety and Health (NIOSH). (1981). Toxic Substances List. Washington, DC: U.S. Government Printing Office.

Nomura, T. (1977). Similarity of the Mechanism of Chemical Carcinogen-initiated Teratogenesis and Carcinogenesis in Mice. Cancer Research 37:969-973. MRID 46892203

Norris, J. and W. Kintigh (1994) Triethylene Glycol: Nine-day Aerosol Inhalation (Nose- only Exposure) toxicity study in Rats. Bushy Run Research Center, Union Carbide Corporation, Inc., Export, PA. Laboratory Project ID: 93U1293, October 26, 1994. NTIS Report No. OTS0537563-1. Unpublished.

NTP (2003b). Toxicology and Carcinogenesis Studies of Dipropylene Glycol CAS No. 25265-71-8) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). NTP Report # TR-511, Draft Abstract. 3-Month Study in Mice. http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr511.html. MRID 46892101

NTP (1985). Propylene Glycol (CAS No. 57-55-6): Reproduction and Fertility Assessment in CD-1 Mice When Administered in Drinking Water. NTP Report # RACB84068, DraftAbstract. http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr511.html. MRID 46892204

NTP (1973). Teratologic Evaluation of FDA 71-56 (Propylene Glycol) in Mice and Rats. NTP CERHR-PG-03 National Toxicology Program Center Final Reports. Food and Drug Research Laboratories, Inc. Laboratory Reports Numbered 1573j-1574j. Prepared for U.S. Food and Drug Administration. FDRL, Waverly Division, Waverly, N.Y., 1973.

NTP (2003d). Toxicology and Carcinogenesis Studies of Dipropylene Glycol (CAS No. 25265-71-8) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). NTP Report # TR-511, Draft Abstract. 2-Year Study in Mice. http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr511.html.

NTP (2003e). Toxicology and Carcinogenesis Studies of Dipropylene Glycol (CAS No. 25265-71-8) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). NTP Report # TR-511, Draft Abstract. 2-Year Study in Rats. http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr511.html.

NTP (1992a). Developmental Toxicity of Dipropylene Glycol (CAS No. 25265-71-8) in New Zealand White Rabbits. NTP Report # TER90014. http://ntp-server.niehs.nih.gov/htdocs/LT-studies/TER90014.html. MRID 46892205

NTP (1992b). Final Report on the Developmental Toxicity of Dipropylene Glycol (CAS No. 25265-71-8) in Sprague-Dawley CD® Rats. NTP Report # TER91013. http://ntp-server.niehs.nih.gov/htdocs/LT-studies/TER91013.html. MRID 46892206

NTP (2003a). NTP-CERHR Expert Panel Report on the Reproductive and

Developmental Toxicity of Propylene Glycol. NTP-CERHR-PG-03. National Toxicology Program Center for the Evaluation of Risks to Human Reproduction. U.S. Department of Health and Human Services. pp 82. MRID 46892207

NTP (2003c). Toxicology and Carcinogenesis Studies of Dipropylene Glycol

(CAS No. 25265-71-8) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). NTP Report # TR-511, Draft Abstract. 3-Month Study in Rats. . http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr511.html. MRID 46892208

Opitz, K. (1958). The Glycogen-Forming Effect of the Glycols. Nauyn-Schmiedeberg's Arch. Exp. Pathol. Pharmakol. 234:448-454.

Pfeiffer, EA and Dunkelberg. (1979). Mutagenicity of Ethylene Oxide and Propylene Oxide and of the Glycols and Halohydrins Formed from Them During the Fumigation of Foodstuffs. Food and Cosmetics Toxicology 18:115-118. MRID 46892102

Pedersen, 1995. Acute oral toxicity of propylene glycol to Northern bobwhite. Unpublished data. MRID 43888002.

Pillard, D.A. 1995. Comparative Toxicity of Formulated Glycol Deicers and Pure

Ethylene and Propylene Glycol to Ceriodaphnia dubia and Pimephales promelas. Environ. Toxicol. Chem. 14(2):311-315. (ECOTOX reference #13727).

Price, K.S., G.T. Waggy, and R. A. Conway. 1974. Brine Shrimp Bioassay and Seawater

BOD of Petrochemicals. J. Water Pollut. Control Fed. 46(1):63-77.(ECOTOX reference #2408).

Robbins, G. (1995). Dipropylene Glycol: Acute Oral Toxicity in Rats. Lab Project Number A3435. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 21 p. The CSPA Glycols Joint Venture Project ID A3435. Work Assignment No. 2-28A. MRID 43760801

Robbins, G. (1995). Dipropylene Glycol: Acute Dermal Toxicity on Rabbits. Lab Project Number E3435. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 23 p. The CSPAGlycols Joint Venture Project ID B3435. Work Assignment No. 2-28B. MRID 43760802

Robbins, G. (1995) Dipropylene Glycol: Acute Inhalation Study in Rats: Lab Project Number: C3435. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 35 p.The CSPA Glycols Joint Venture Project ID C3435. Work Assignment No. 2-28C. MRID 43760803

Robbins, G. (1995) Dipropylene Glycol: Primary Eye Irritation in Rabbits: Lab Project Number: D3435. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 22 p. The CSPA Glycols Joint Venture Project ID D3435. Work Assignment No. 2-28D. MRID 43760804

Robbins, G. (1995). Dipropylene Glycol: Primary Dermal Irritation on Rabbits. Lab Project Number E3435. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 18p. The CSPA Glycols Joint Venture Project ID E3435. Work Assignment No. 2-28E. MRID 43760805

Robbins, G. (1995) Dipropylene Glycol: Dermal Sensitization (Buehler) on Guinea Pigs: Lab Project Number: F3435. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 45 p. The CSPA Glycols Joint Venture Project ID F3435. Work Assignment No. 2-28F. MRID 43760806

Robertson, O.H., et al. (1947) Tests for the Chronic Toxicity of Propylene Glycol and Triethylene Glycol on Monkeys and Rats by vapor inhalation and Oral Administration. J. Pharm. Exp. Ther., 91: 52.

Robertson, O.H., et al. (1947). Tests for the Chronic Toxicity of Propylene Glycol and Triethylene Glycol on Monkeys and Rats by Vapor Inhalation and Oral Administration. J. Pharmac. Exp. Ther. 91:52-76.

Salter, W.T., P.D. Robb, et al. (1935). Liver Glycogen from Derivatives of Glucose. Journal Nutr. 9:11-23.

Sax, N.I. (1979). Dangerous Properties of Industrial Materials. New York: Van Nostrand Reinhold, p 943.

Seidenfeld, M.A. and P.G. Hanzlik (1932). The General Properties, Actions and Toxicity of Propylene Glycol. Journal of Pharm. Exper. Ther. 44:109-121.

Safety Assessment of Triethylene Glycol and PEG-4: Final Report of the Cosmetic Ingredient Review Expert Panel, Fegruary 7, 2003.

Slensinski, R., F. Frank, and P. Guzzie (1986a) Triethylene Glycol: *In vitro* Mammalian Cell Gene Mutation Assay in CHO Cells. Bushy Run Research Center, Export, PA. Project Report 49-82. June 26, 1986. NTIS Report No. OTS0527779-1. Unpublished.

Slensinski, R., F. Frank, and P. Guzzie (1986b) Triethylene Glycol: *In vitro* Genotoxicity Studies: CHO/HGPRT Mutation Test; Sister Chromatid Exchange Assay. Bushy Run Research Center, Export, PA. Project Report 49-83. June 26, 1986. NTIS Report No. OTS0527779-1. Unpublished.

Smeets, J.M.W., van Holsteijn, I., Giesy, J., Seinen, W., and van den Berg, M. (1999) Estrogenic potencies of several environmental pollutants, as determined by vitellogenin induction in a carp hepatocyte assay. Toxicological Sciences 50: 206-213.

Smyth, H.F. et al (1941) The single dose toxicity of some glycol derivatives. J. Ind. Hyg. Toxicol. 23(6): 259-268.

Smyth, H.F. Jr., et al. (1941). J. Ind. Hyg. Toxicol. 23:259.

Stenger, E.G., er al. (1968) Zur Toxikologie des Triathylenglkol. Arzneimittel-Forsch, 18: 1536.

Stenback, F. and P. Shubik. (1974). Lack of Toxicity and Carcinogenicity of Some Commonly Used Cutaneous Agents. Toxicol. Appl. Pharmacol. 30:7-13. MRID 46892301

Suber, R.L., et al. (1989). Subchronic Nose-Only Inhalation Study of Propylene Glycol in Sprague-Dawley Rats. Food Chemistry and Toxicology 27.9:573-584. MRID 46892103

Swenberg, J.A. G.L. Petzold, et al. (1976). In vitro DNA Damage/Alkaline Elution Assay for Predicting Carcinogenic Potential. Biochem Biophys Res. Commun 72:732-738.

Sun, J. and W. Kintigh (1992) Triethylene Glycol: Nine-day Aerosol Inhalation study in Rats. Bushy Run Research Center, Union Carbide Chemicals and Plastics Company, Inc., Export, PA. Laboratory Project ID: 91U0027, December 14, 1992. NTIS Report No. OTS0537563-1 with cover letter dated 010693 (1992). Unpublished.

Union Carbide (1989) Triethylene Glycol: Fourteen-day Dietary Toxicity Study in Fischer 344 Rats. NTIS Report No. OTS0527779-1. Unpublished.

Union Carbide (1990a) Triethylene Glycol: Ninety-day Dietary Toxicity Study in Fischer 344 Rats. NTIS Report No. OTS0527779-1. Unpublished.

Union Carbide (1990b) Developmental Toxicity Study of Triethylene Glycol Administered by Gavage to CD-1 Mice. NTIS Report No. OTS0527779-1. Unpublished.

Union Carbide (1991) Developmental Toxicity Study of Triethylene Glycol Administered by Gavage to CD (Sprague-Dawley) Rats. NTIS Report No. OTS0527779-4. Unpublished.

USEPA (1993) ID # 083501: Triethylene glycol. Review of Phase IV response submissions in support of FIFRA 88. EPA Record No. S444604, S444216. Caswell No. 888. PC Code: 083501. HED Project No(s). D193163, D192934. (Memorandum: G. Reddy, 12/22/93, TXR #:010715).

USEPA (2005a) *TRIETHYLENE GLYCOL*: Revised Toxicology Chapter in Support of Issuance of the Registration Eligibility Decision (RED) Document. PC Code: 083501. Reregistration Case Number: 3146. CAS Registry Number: 112-27-6. DP#: 325786 (Memorandum: M. Centra, 10/11/05).

USEPA (2005b) *TRIETHYLENE GLYCOL:* Revised Report of the Antimicrobials Division Toxicology Endpoint Selection Committee (Memorandum: T. McMahon, 11/21/05).

USEPA (2013) TRIETHYLENE GLYCOL: Toxicology Chapter/Hazard Characterization in Support of Registration Review. PC Code: 083501. CAS Registry Number: 112-27-6. Registration Review Case Number: 3146. DP Barcode: 408350 (Memorandum: M. Centra, 6/11/13).

U.S. Environmental Protection Agency (EPA). 2002. ECOTOX User Guide: ECOTOXicology Database System. Version 3.0. Available: http://www.epa.gov/ecotox/

U.S. Environmental Protection Agency (EPA). 2003. AD's Occupational and Residential Exposure Chapter for the Triethylene Glycol Reregistration Eligibility Decision (RED) Document (Case No. 3146). PC Code 083501 (Memorandum: T. Leighton, 9/26/03).

U.S. Environmental Protection Agency (EPA). 2004. Ecological Hazard and Environmental Risk Characterization. PC Code 083501, Case 3146, Antimicrobials Division, (Memorandum, Kathryn Montague, August 4, 2004).

U.S. Environmental Protection Agency (EPA). 2005. AD's Occupational and Residential Exposure Chapter for the Triethylene Glycol Reregistration Eligiblity Decision (RED) Document (Case No. 3146). PC Code083501 (Memorandum: T. Leighton, 5/24/05).

U.S. Environmental Protection Agency (EPA). 2006a. ***TRIETHYLENE GLYCOL:*** Revised Antimicrobials Division's Review of the Disciplinary Sciences for Issuance of the Reregistration Eligibility Decision (RED)Document. Reregistration Case No.: 3146. PC Code: 083501. CAS Registry No.: 112-27-6. DP#: 305169. (Memorandum M. Centra, January 25, 2006).

U.S. Environmental Protection Agency (EPA). 2006b. Propylene/Dipropylene Glycol Revised Ecological Hazard and Environmental Risk Characterization Chapter for the Reregistration Eligibility Decision (RED) Document, Case 3126. (Memorandum Kathryn Montague, February 14, 2006).

U.S. Environmental Protection Agency (EPA). 2007a. AD's Revised Occupational and Residential Exposure Chapter for the Propylene and Dipropylene Glycol Reregistration Eligibility Decision (RED) Document. Case No. 3126. PC Code 068603, 068604. (Memorandum: Timothy Leighton, February 5, 2007).

U.S. Environmental Protection Agency (EPA). 2007b. AD's Risk Assessment for Issuance of the Reregistration Eligibility Decision (RED) Document. Reregistration Case No.: 3126. PC Codes: 068603, 068604. CAS Registry No.: Propylene Glycol, 57-55-6; Dipropylene Glycol, 25265-71-8. (Memorandum M. Centra, February 5, 2007).

U.S. Environmental Protection Agency (EPA). 2013a. ***PROPYLENE GLYCOL/ DIPROPYLENE GLYCOL*:** Hazard Characterization/Toxicology Chapter in Support of Registration Review. DP Barcode(s)/No(s): 408349 . (Memorandum M. Centra, March 13, 2013).

U.S. Environmental Protection Agency (EPA). 2013b. ***TRIETHYLENE GLYCOL*:** Hazard Characterization/Toxicology Chapter in Support of Registration Review. DP Barcode(s)/No(s): 408349 . (Memorandum M. Centra, March 13, 2013).

U.S. Environmental Protection Agency. High Production Volume Information System (HPVIS). http://www.epa.gov/hpvis/

Van Winkle, W., Jr. (1941). Quantitative Gastrointestinal Absorption and Renal Excretion of Propylene Glycol. Journal Pharmacol. 72:344-353.

Weatherby, J.H. and H.B. Haag. (1938). Toxicity of Propylene Glycol. Journal of Amer. Pharm. Assoc. 27:466-471.

Weil, C.S. and R.A. Scala. (1971). Study of Intra- and Inter-laboratory Variability in the Results of Rabbit Eye and Skin Irritation Tests. Toxicology and Applied Pharmacology 19:276. MRID 46892104

Appendix A Toxicology Profile

Acute Toxicity for Product Labeling

Dipropylene glycol

The dipropylene glycol (DiPG) toxicological database is comprised of studies submitted by the Glycols Joint Venture Consortium and published literature studies. Low acute toxicities for DiPG were established in rodents, rabbits, and guinea pigs. Acute LD_{50} values appear to be relatively high concentrations and fall within the toxicity classification of category IV for all of the acute experiments (Table 1). Acute oral LD_{50} values were greater than 5010 mg/kg/day when DiPG was administered to Sprague-Dawley male and female rats (43760801). When DiPG was administered topically to NZW rabbits, the dermal LD_{50} was also greater than 5010 mg/kg/day (highest dose tested). No toxicological effects were observed at the doses tested in the acute dermal toxicity study (43760802).

In a 4-hour inhalation whole-body exposure study with Sprague-Dawley rats, the LC_{50} was found to be greater than 2.34 mg/L. There were no treatment-related effects observed in rats exposed to DiPG and all of the animals survived the exposure and observation period with no indication of toxicity (43760803).

Instillation of 0.1 mL DiPG in eyes of New Zealand White (NZW) rabbits showed no evidence of corneal damage and was classified as a slight irritant based on observed conjunctival irritation that subsided within 24 hours (43760804). DiPG (0.5 mL of 100% TGAI) was administered to NZW rabbits in a primary dermal irritation study. There was evidence of erythema in a single site that subsided in 24 hours while there were no traces of edema observed in treated animals; DiPG was classified as a non irritant (43760805).

A study for dermal sensitization assessed a single challenge application of 0.5 mL DiPG (100% purity) to guinea pigs that had previously been treated with DiPG. The topical administration did not produce any evidence of dermal sensitization in treated animals (43760806).

In multiple open literature reports, when rats were exposed to DiPG, the acute oral toxicity LD_{50} values were similar to PG values and ranged from greater than 5000 to 15000 mg/kg/day for treated animals (46892504). DiPG was found to be an irritant to rabbits when administered in an undiluted dose of 510 mg in a primary eye irritation study (NIOSH, 1981).

Intraperitoneal and intravenous injections to rodents resulted in toxicity values similar to other acute studies, with LD_{50} values ranging from 4600-10000 and 5800-11500 mg/kg/day, respectively (Latven, 1939; Bartsch, 1976; Sax, 1979; Fischer, 1949; Weatherby, 1938; Budden, 1979).

Table 14 Acute Toxicity Profile of Dipropylene Glycol

Guideline	Study Type	MRID Number and/or Citation	Results	Toxicity Category
870.1100	Acute Oral - Rat	43760801	LD_{50} = > 5010 mg/kg	IV
870.1100	Acute Oral - Rat	46892504; NIOSH, 1981	LD_{50} > 5000-15000 mg/kg	IV
870.1200	Acute Dermal - Rabbit	43760802	LD_{50} = > 5010 mg/kg	IV
870.1300	Acute Inhalation - Rat	43760803	LC_{50}= > 2.34 mg/L	IV
870.2400	Acute Eye Irritation - Rabbit	43760804	Slight irritant	IV
870.2400	Acute Eye Irritation - Rabbit	NIOSH, 1981	Irritant	IV
870.2500	Acute Skin Irritation - Rabbit	43760805	Non irritant	IV
870.2600	Skin Sensitization - Guinea Pig	43760806	Non sensitizer	N/A

N/A = Not applicable

Propylene glycol

The toxicological database for propylene glycol (PG) is comprised of published literature studies (Table 1). Acute oral toxicity studies yielded similar, low acute toxicities with relatively high LD_{50} values (all considered to be Toxicity Category IV) ranging from 8000-46000 mg/kg/day PG for rodents and 18000-20000 mg/kg/day for both rabbits and guinea pigs. Signs of nervous system toxicity were reported in the rabbit and guinea pig at lethal doses whereas effects of this nature (loss of balance, marked depression, and analgesia) were only evident in one study with mice at LD_{50} values of 23000-24900 mg/kg/day (46892501; 46892509; Clark, 1979; Bartsch, 1976; Sax, 1979; Layton, 1987).

PG induced degeneration of goblet cells (+69%) in the tracheal lining of rabbits after 20 and 120 minutes of aerosol exposure in an acute inhalation toxicity study; no other toxicological effects were observed (Konradova, 1978). In primary eye irritation studies, PG was instilled in the eyes

of rabbits (0.1-0.5 mL). There were no treatment-related effects on the corneas of the animals and PG was classified as a non-irritant (46892104; 46892502; 46892507; Clark, 1979; Draize, 1944; Guillot, 1982). Acute dermal toxicity studies were not available for PG. In a series of skin sensitization tests, no reactions were observed in guinea pigs exposed to solutions of PG up to 70% active ingredient (46892104).

Additionally, several studies established intraperitoneal and intravenous LD_{50} values for mice, rats, and rabbits. The acute LD_{50} values for intraperitoneal injection of PG ranged from 11200-13000 mg/kg/day for rodents. Similar, but lower, values were observed in intravenous injections experiments; with LD_{50} ranges of 6200-8000 mg/kg/day for rodents and 6500 mg/kg/day for rabbits (Latven, 1939; Bartsch, 1976; Sax, 1979; Fischer, 1949; Weatherby, 1938; Budden, 1979).

Table 15 Acute Toxicity Profile of Propylene Glycol

Guideline	Study Type	MRID Number and/or Citation	Results	Toxicity Category
870.1100	Acute Oral - Rat	46892501; 46892509; Clark, 1979; Bartsch, 1976; Sax, 1979; Layton, 1987	LD_{50} = 8000-46000 mg/kg	IV
870.1300	Acute Inhalation - Rat	Konradova, 1978	LC_{50} > 2.0 mg/L (no deaths)	IV
870.2400	Acute Eye Irritation - Rabbit	46892104; 46892502; 46892508; Clark, 1979; Draize, 1954; Guillot, 1982	Non irritant	IV
870.2500	Acute Skin Irritation - Rabbit	Clark, 1979	Non irritant	IV
870.2600	Skin Sensitization – Guinea pig	Kero, 1980	Non sensitizer	NA

N/A = Not applicable

Triethylene Glycol

Published literature studies submitted by the Glycols Joint Venture consortium show low toxicity (Toxicity Categories III and IV) following acute exposures (Table 16). 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

dermaltoxicity were not sufficient 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 (Safety Assessment of Triethylene Glycol and PEG-4, 2003; Budavari, 1989; Clayton, 1981-1982; Smyth, 1941).

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 Agency 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 is considered adequate for regulatory purposes and it now replaces the earlier submitted acute inhalation information (Nachreiner, 1991).

Table 16 Acute Toxicity Profile of Triethylene Glycol

Guideline	Study Type	MRID Number and/or Citation	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	Nachreiner, 1991	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	Son- sensitizer	N/A

Subchronic Toxicity Subchronic Toxicity

Propylene glycol

Subchronic toxicity studies for PG were available from published open literature studies. With relatively high-dose and no-observed-adverse-effect levels (NOAEL), PG exhibits low toxicity to animals exposed over a moderate period of time. In a 15-week feeding study, there were no adverse toxicological effects observed in rats administered 2500 mg/kg/day PG (46892504). In another subchronic toxicity study, PG was administered to rats in drinking water for 140 days. Although there were clinical signs (CNS depression and minor liver toxicity) exhibited in animals at a dose of 13200 mg/kg/day, these effects occurred well above the testing limit dose of 1000 mg/kg/day established for an oral subchronic toxicity study in rats (Seindenfeld, 1932).

In a 90-day inhalation study, female rats were exposed to PG vapors (1.0 or 2.2 mg/L) for 6 hours/day, 5 days/week over a period of 90 days. Animals experienced decreases in body weight and food consumption, although there were no changes in respiratory rates, minute volumes, or tidal volumes during exposure. With the exception of a significant increase in the number of goblet cells in the nasal passages of the mid- and high-dose animals (both male and female) males were unaffected by PG treatment (0.16, 1.0, or 2.2 mg/L) in this subchronic inhalation study (46892103).

Dipropylene glycol

Two published literature studies were available to address the subchronic toxicity of DiPG. In a drinking water study, DiPG was administered to mice at concentrations of 715, 1350, 2620, 4790, or 11000 mg/kg/day for males and 1230, 2140, 4020, 7430, or 14700 mg/kg/day for females over a period of 90 days. There were treatment-related increases in mortality at the high-dose for both males and females and increased body weight in females treated with 2140 mg/kg/day DiPG. Minimal toxicity was observed at these relatively high doses of DiPG; 11000 and 14700 mg/kg/day for males and females, respectively (46892101).

In a similar study, male and female rats exhibited reductions in body weight at 425 and 1690 mg/kg/day, respectively, when exposed to DiPG in drinking water for 90 days (425, 890, 1840, 3890, or 12800 mg/kg/day for males and 460, 920, 1690, 3340, or 8950 mg/kg/day for females). Water consumption increased at the high-dose for all animals by the second week and continued throughout the remainder of the study. There were increases in weight and the appearance of lesions in liver and kidneys of treated animals at concentrations exceeding those that induced body weight reductions. High-dose (12800 mg/kg/day) males experienced testicular effects, hypoactivity and poor hair coats (46892208).

Triethethylene Glycol

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 (Lauter, 1940). 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 (Union Carbide, 1989). 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 Union Carbide, 1990).

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 (Guillot, 1982). These results are supported by triethylene glycols' low dermal irritancy a negative response as a skin sensitizer (42814404).

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 high-dose group rats 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 (Sun, 1992).

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 (Norris, 1994).

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 (Robertson, 1947).

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 (Stenger, 1968).

Developmental and Reproductive Toxicity

Open literature studies examining the developmental and reproductive toxicity of propylene/dipropylene/triethylene glycol showed minimal evidence of toxicity at relatively high concentrations (10000 mg/kg/day) that exceed the established limit dose of 1000 mg/kg/day.

Propylene glycol

PG, administered to mice at a concentration of 10000 mg/kg/day in drinking water, did not produce any overt adverse effects in fetal development (46892201). In a second study, PG administered to mice via subcutaneous injections at a dose of 10400 mg/kg/day on gestation day (GD) 9, 10, and 11 did not exhibit significant increases in fetal malformations (46892203). Two additional studies involving oral administration of PG in mice up to concentrations of 10400 mg/kg/day did not induce any maternal, reproductive, or developmental toxicity in this study (46892508; Driscoll, 1993).

Several developmental studies were performed on rats, mice, rabbits, and hamsters in which oral doses of PG, that ranged from 12.3-1600 mg/kg/day, were administered during gestation. In all four studies, there were no incidents of treatment-related maternal, reproductive, or developmental toxicities observed in this study (46892207; FDRL, 1973; NTP, 1973).

PG was administered to rats (1600-6200 mg/kg/day), mice (1550-10000 mg/kg/day), and rabbits (1230 mg/kg/day) during gestation via a stomach tube. There were no adverse reproductive effects observed in any of these experiments. However, a slight maternal toxicity was noted in mice treated with 10000 mg/kg/day PG (highest dose administered) on GD 8-12 (46892508; FDRL, 1973).

In a second reproductive toxicity study, rats from three successive generations were orally administered 2.5, 5, 7.5, 10, 20, or 30% PG. No adverse effects were observed up to the 20% dose (equivalent to a dietary level of approximately 11900 mg/kg/day), where 50% of the animals failed to produce offspring. No offspring were produced by any of the rats in the 30% high-dose PG group (Guerrant, 1947).

Mice were administered 1820, 4800, or 10100 mg/kg/day in drinking water over a course of 18 weeks in a third reproductive toxicity study. There were no treatment-related maternal, reproductive, or offspring effects observed at any of the PG doses tested in this study (46892204).

Dipropylene glycol

DiPG was administered to NZW rabbits in a developmental toxicity study at concentrations up to 1200 mg/kg/day on GD 6-19. No treatment-related maternal, reproductive, or developmental toxicities were observed in treated animals (46892205). However, there were decreases in maternal food consumption and body weight in rats treated with 2000 and 5000 mg/kg/day DiPG. Increases in liver weight were also observed in these dose groups. No reproductive or developmental toxicity effects were observed in rats at any dose levels of DiPG from 800-5000 mg/kg/day (46892206).

Triethylene glycol

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 tested. 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 observed for external or visceral malformations in offspring. Some evidence of delayed ossification was observed at the high dose level (Union Carbide, 1990).

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 Union Carbide, 1991). 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 (Bossert, 1992; Lamb, 1997).

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 (Robertson, 1947; Goldstein, 1970).

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.

Chronic Toxicity and Carcinogenicity

Published literature studies examining the chronic toxicity and carcinogenic potential of propylene/dipropylene/triethylene glycol have shown the chemicals to be noncarcinogenic in rodent and non-rodent species under the conditions of each study protocol. In addition, systemic adverse effects were noted only at doses of propylene, dipropylene, and triethylene glycol that exceed the limit dose of 1000 mg/kg/day established for mammalian chronic toxicity studies.

Propylene glycol

Several studies in the rat involving dietary, drinking water, and inhalation exposure to PG comprise the chronic toxicity database. There was little evidence of adverse toxicological effects at the relatively high concentrations used within these studies and chronic toxicity associated with PG was low. With the exception of slight liver damage in treated animals, there were no signs of toxic effects when PG was administered 1230 or 2450 mg/kg/day in the diet for 2 year (Morris, 1942). In another study, slight liver damage and no other effects were observed in a 2-year drinking water study that administered 1834 mg/kg/day PG to rats (46892509; Braun, 1936).

In a continuous-exposure inhalation study, rats were exposed to 0.17-0.35 mg/L PG for 18 months and a chronic toxicity lowest observed adverse effect level (LOAEL) of 0.35 mg/L was established based on a 50% increase in body weight. There were no other effects observed in treated animals in this study (Robertson, 1947).

A carcinogenicity study in rats fed PG at dietary concentrations of 200, 400, 900, or 1700 mg/kg/day for males and 300, 500, 1000, or 2100 mg/kg/day for females was carried out for 2 years with little evidence of chronic toxicity or significant treatment-related neoplasms (46892504). In a dermal carcinogenicity study conducted in mice, there was no change in longevity or increase in dermal tumors following chronic treatment with 0.02 mL of 10, 50 or 100% (46892301).

Dipropylene glycol

There were decreases in survival and body weight of male and female rats treated with 3040 and 2330 mg/kg/day DiPG, respectively, in drinking water for 2 years. Clinical signs of toxicity were noted in males with an increase in focal histiocytic and focal granulomatous inflammation in the liver. There was no evidence of carcinogenic activity in rats treated with DiPG over the course of 24 months (NTP, 2003e). In a similar mouse study, animals experienced decreased survival and body weight at the high-dose (2390 mg/kg/day for males and 1950 mg/kg/day for females) of DiPG tested in the study. Males in the 2390 mg/kg/day dose group also exhibited reduced water consumption. After 2 years of DiPG administration in drinking water, mice failed to show any evidence of carcinogenic activity (NTP, 2003d).

Triethylene glycol

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 glycol saturated air) showed no adverse effects in physiological function or organ histopathology (Robertson, 1947).

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 doses 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 (Fitzhugh, 1946).

Mutagenicity

Open published literature studies comprise the mutagenicity database for propylene/dipropylene glycol/triethylene glycol. In a battery of studies, propylene and dipropylene glycol did not exhibit mutagenic or genotoxic activity.

Propylene glycol

There were no signs of mutagenicity in several bacterial reverse mutation tests in tester strains TA 1535, TA 1537, TA 100, TA 98, and TA 1538 that were performed with concentrations of PG ranging from 1-10000 μg/plate. PG did not induce mutant colonies and was negative in all cases (46892102; 46892503; Clark, 1979). Similar negative results were observed in additional mutagenicity studies, including an *in vitro* mammalian cell gene mutation test, an *in vitro* mammalian chromosome aberration test, a mammalian erythrocyte micronucleus test, and a dominant lethal assay (46892506; Litton Bionetics, 1974; Swenberg, 1976).

Dipropylene glycol

Non-mutagenic results were observed in both a bacterial reverse mutation and *in vitro* mammalian cell gene mutation test. There was no increase in mutant frequencies when DiPG was administered (100-10000 μg/plate) to the bacterial tester strains TA 98, TA 100, TA 1535, and TA 1537 (NCI, 1986). In an *in vitro* mammalian cell gene mutation test, mice were given 0.005, 0.01, 0.05, 0.1, 0.5, 1.0, 5.0, 10, or 50 μL/mL DiPG and failed to produce a positive response in either the presence or absence of metabolic activation (NCI, 1987).

Triethylene glycol

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 (Guzzie, 1986a; Guzzie, 1986b; Slensinski, 1986a; Slensinski, 1986b).

Neurotoxicity

From the available toxicity studies, evidence of neurotoxicity was observed in mice, rabbits, and guinea pigs following a single dose of propylene glycol; loss of balance, marked depression, and analgesia observed at lethal doses of 18400-24900 mg/kg/day (Braun, 1936; Laug, 1939; Smyth, 1941; Latven, 1939). Central nervous system (CNS) depression was also noted in rats administered propylene glycol at greater than 13200 mg/kg/day in drinking water for 140 days (Seidenfeld, 1932). However, these CNS effects were observed only at a dose level that far exceeds the established limit dose (1000 mg/kg/day) for an oral subchronic toxicity study. Based on a weight-of-evidence evaluation of the available data, the Agency does not anticipate needing neurotoxicity testing, including a developmental neurotoxicity study for either propylene or dipropylene glycol.

Metabolism and Excretion

Propylene glycol

In an elimination and metabolism study a maximum concentration of 29.21∀2.92 mmol/L PG was found in the blood of rats 2 hours with the high-dose administration of PG (treatment with 4.83, 9.66, 19.32, 38.64, and 77.28 mmol/kg PG) (Morshed, 1988). PG was readily absorbed in the gastrointestinal tract of several animals in other studies. The absorption was rapid and complete and PG was broken down into glycogen (Hanzlik, 1939; Opitz, 1958; Salter, 1935; Van Winkle, 1941). PG was administered orally to humans (70 g) and dogs (150 g) in a NTIS study in which a portion of PG was metabolized and an appreciable fraction was excreted in the urine. Within 10 hours, 20-25% of the 70 g dose given to the human subjects was excreted. The dogs excreted 20% of the 150 g dose within 24 hours (Hanzlik, 1939).

Dipropylene glycol

No metabolism studies conducted with DiPG are available in the toxicity data base.

Triethylene glycol

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 (McKennis, 1962).

Dermal Absorption

Propylene glycol

There have been no reports dealing with PG and skin absorption. PG has been found to penetrate the outermost layer of the epidermis; however, because of this property, PG is commonly used as a cosmetic ingredient in many products. Although absorption through the skin is possible, it is doubtful any appreciable systemic/dermal injury would occur based on the lack of irritation in acute dermal studies, no evidence of chronic toxicity or tumor response following a 2-year dermal application study, and the widespread use in cosmetics that is considered safe (46892301; Clark, 1979).

Dipropylene glycol

No dermal penetration/skin absorption studies were identified for dipropylene glycol. Similar to PG, DiPG is used in many cosmetic formulations and has been generally recognized as a low toxicity chemical by the FDA. Dermal and systemic injury from skin exposure to DiPG is unlikely considering its widespread use in cosmetics, the lack of evidence of dermal toxicity in acute studies, and the lack of evidence of skin sensitization in repeat-exposure studies (43760802; 43760805; 43760806).

Triethylene glycol

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 may occur, it is doubtful any appreciable systemic/dermal injury would occur because triethylene glycol has 1) a low order of dermal irritancy (42814404), (2) is not a skin sensitizer (42814404) 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 (Guillot, 1982).

Appendix B Product Chemistry

Triethylene glycol, Propylene glycol and Dipropylene glycol product chemistry information is summarized in Table B1 (source: MRIDs 42814401, 42814402, 42814403, 43178601, 43178603, 43179501, 43179502, 43179503, and EPI Suite v4.1).

Table 17– Product Chemistry of Triethylene, Propylene and Dipropylene Glycols

Guideline No.	Physical and Chemical Properties	Triethylene Glycol	Propylene Glycol	Dipropylene Glycol
830.1550	Product identity and composition	Refer to Table 5	Refer to Table 5	Refer to Table 5
830.1600	Description of materials used to produce the product	Confidential Business Information (CBI)	CBI	CBI
830.1620	Description of production process	CBI	CBI	CBI
830.1650	Description of Formulation Process	CBI	CBI	CBI
830.1670	Discussion of formulation of impurities	CBI	CBI	CBI
830.1700	Preliminary analysis	CBI	CBI	CBI
830.1750	Certified limits	CBI	CBI	CBI
830.1800	Enforcement analytical method	Gas Chromatography (GC)	GC	GC
830.1900	Submittal of samples	CBI	CBI	CBI
830.6302	Color	Colorless viscous liquid	Colorless viscous liquid	Colorless viscous liquid
830.6303	Physical State	Liquid	Liquid	Liquid
830.6304	Odor	Mild, characteristic odor.	Slight acrid to none.	Practically odorless.
830.6313	Stability to normal and elevated temperature, metals/metal ions	Stable at normal temperatures of use and storage. Exposure to elevated temperatures can cause decomposition.	Stable at normal temperatures of use and storage. Exposure to elevated temperatures can cause decomposition.	Stable at normal temperatures of use and storage. Exposure to elevated temperatures can cause decomposition.
830.6314	Oxidation/Reduction: Chemical Incompatibility:	Not applicable. Product contains no oxidizing or reducing agents. Incompatible with strong acids, strong bases, and strong oxidizers.	Not applicable. Product contains no oxidizing or reducing agents. Incompatible with strong acids, strong bases, and strong oxidizers.	Not applicable. Product contains no oxidizing or reducing agents. Incompatible with strong acids, strong bases, and strong oxidizers.
830.6315	Flammability	Flash point: 177°C (Closed Cup). Flash point: 191°C (Open Cup).	Flash point: 103 ^{o} C	Flash point: 124 ^{o} C
830.6316	Explodability	Not applicable. Product is not explosive.	Not applicable. Product is not explosive.	Not applicable. Product is not explosive.
830.7000	pH	6.0 - 9.5	Neutral	Neutral
830.7050	UV/Visible Absorption	Does not absorb light at	Does not absorb light at	Does not absorb light at

Guideline No.	Physical and Chemical Properties	Triethylene Glycol	Propylene Glycol	Dipropylene Glycol
		wavelengths >290 nm and therefore it is not expected to be susceptible to direct photolysis by sunlight.	wavelengths >290 nm and therefore it is not expected to be susceptible to direct photolysis by sunlight.	wavelengths >290 nm and therefore it is not expected to be susceptible to direct photolysis by sunlight.
830.7200	Melting point: Freezing point:	Not applicable. Product is liquid at room temperature. −4.3°C to −7 °C	Not applicable. Product is liquid at room temperature. −59°C	Not applicable. Product is liquid at room temperature. −59°C
830.7220	Boiling point	288.0°C at 760 mm Hg.	188 °C at 760 mm Hg	230 °C at 760 mm Hg
830.7300	Density	1.1255 g/mL at 25°C	1.032 g/ mL at 25°C	1.022 g/ mL at 25°C
830.7370	Dissociation Constant (*pKa*)	Not applicable. Does not dissociate in water.	Not applicable. Does not dissociate in water.	Not applicable. Does not dissociate in water.
830.7520	Particle size, fiber length, & diameter distribution	Not Applicable; soluble in water	Not Applicable; soluble in water	Not Applicable; soluble in water
830.7550	Partition coefficient (Log *Kow*)	−1.75	− 0.92	− 0.67
830.7840	Solubility in water	Completely soluble.	Completely soluble.	Completely soluble.
830.7860	Solubility in organic solvents	Soluble in alcohol, benzene, toluene, sparingly soluble in ether and insoluble in petroleum ether.	Soluble in ethanol, acetone, and most organic solvents.	Soluble in ethanol, acetone, and most organic solvents.
830.7950	Vapor pressure	0.00132 mm Hg at 25°C	0.13 mm Hg at 25°C	0.016 mm Hg at 25°C

Appendix C Ecotoxicology Profile for Propylene Glycol and Dipropylene Glycol

Toxicity to Terrestrial Animals

Avian acute oral and dietary toxicity

To establish the toxicity of propylene glycol and dipropylene glycol to birds, the Agency required an acute oral toxicity study using the technical grade of the active ingredient (TGAI). The preferred test species was either mallard duck (a waterfowl) or bobwhite quail (an upland game bird). The results of submitted studies are provided in the following table (Table 18). The results indicate that both propylene and dipropylene glycol are practically non-toxic to birds on an acute oral basis. The studies are acceptable and fulfill guideline requirements (71-1/OPPTS 850.2100).

A subacute dietary study using the TGAI was not required for propylene glycol or dipropylene glycol because of a lack of acute toxicity in the bobwhite quail (Table 16).

Table 18 Acute Oral Toxicity of Propylene and Dipropylene Glycol to Birds

Species	% Active Ingredient (ai)	Endpoint (mg/kg)	Toxicity Category (TGAI)	Satisfies Guidelines/ Comments	Reference
Propylene Glycol					
Northern bobwhite (*Colinus virginianus*)	100	LD_{50} > 2000 NOEL = 2000	Practically non-toxic	Yes	Campbell and Beavers, 1995 MRID 43762301
Northern bobwhite (*Colinus virginianus*)	99.88	LD_{50} > 2150 NOEL = 2150	Practically non-toxic	Yes	Pedersen, 1995 MRID 43888002
Dipropylene Glycol					
Northern bobwhite (*Colinus virginianus*)	100	LD_{50} > 2000 NOEL = 2000	Practically non-toxic	Yes • core study • 14-day test duration	Campbell and Beavers, 1995 MRID 43760807

Mammals

Both propylene and dipropylene glycol show low acute toxicity to mammals in laboratory studies, and do not produce developmental or reproductive effects at fairly high doses (Table 12, Appendix A).

Table 19 Toxicity of Propylene and Dipropylene Glycol to Mammals (excerpted from Appendix A)

Species	Test Type	Results
Propylene Glycol		
Rat	Acute oral	LD_{50} 8000 - 46000 mg/kg (Toxicity Category IV)
Rat	15-week Subchronic (feeding)	NOAEL = 2500 mg/kg/day
Mouse	Developmental	maternal, reproductive, developmental NOAEL = 10400 mg/kg/day (oral)
Dipropylene Glycol		
Rat	Acute oral	LD_{50} >5010 mg/kg (Toxicity category IV)
Mouse	90-day Subchronic (drinking water)	NOAEL = 4790mg/kg/day male, 7430 mg/kg/day female
Rat	Developmental	reproductive, developmental NOAEL = 5000 mg/kg/day

Toxicity to Aquatic Animals

Freshwater Fish, Acute

In order to establish the acute toxicity of an antimicrobial pesticide to freshwater fish for the listed propylene and dipropylene glycol use patterns, the Agency required a freshwater fish toxicity study using the TGAI. Data are generally required on only one species for these use patterns unless the active ingredient or principal transformation products are stable in the environment and the LC_{50} in the first species is less than or equal to 1 ppm. The preferred test species was rainbow trout (a coldwater fish) or bluegill sunfish (a warmwater fish). No fish acute toxicity testing has been submitted to the Agency. A survey of the EPA/ORD database ECOTOX provided multiple freshwater fish acute toxicity endpoints for propylene glycol, which are summarized in Table 20.

The results indicate that propylene glycol, dipropylene glycol and triethylene glycol are practically non-toxic to freshwater fish on an acute basis. Since these data are supplemental information, Guideline 72-1/850.1075 is not fulfilled; however, because multiple published studies demonstrate very low toxicity to freshwater fish, no further testing is required for propylene glycol, dipropylene glycol, triethylene glycol.

Table 20 Acute Toxicity of Propylene and Dipropylene Glycol to Freshwater Fish

Species	Endpoints	Toxicity Category	Reference
Propylene Glycol			
Goldfish (*Carassius auratus*)	Static 24 hr. LC_{50} >5000 ppm ai	Practically non-toxic	Bridie *et al*., 1979 (ECOTOX reference #623)
Rainbow trout (*Oncorhynchus mykiss*)	Static 24-hr LC_{50} = 50,000 ppm	Practically non-toxic	Majewski *et al*., 1978 (ECOTOX reference # 991)
Fathead minnow (*Pimephales promelas*)	48 hr LC_{50} = 790 ppm	Practically non-toxic	Pillard, 1995 (ECOTOX reference #13727)
Fathead minnow (*Pimephales promelas*)	96 hr LC_{50} = 710 ppm	Practically non-toxic	Pillard, 1995 (ECOTOX reference #13727)

Species	Endpoints	Toxicity Category	Reference
Fathead minnow (*Pimephales promelas*)	96 hr LC_{50} = 62,000 ppm ai	Practically non-toxic	Pillard, 1995 (ECOTOX reference #13727)
Dipropylene Glycol			
Goldfish (*Carassius auratus*)	24 hr. LC_{50} >5000 ppm ai	Practically non-toxic	Bridie *et al*., 1979 (ECOTOX reference #623)

Freshwater Invertebrates, Acute

The Agency required a freshwater aquatic invertebrate toxicity study using the TGAI to establish the acute toxicity of an antimicrobial pesticide to freshwater invertebrates. The preferred test species is *Daphnia magna*.

The results of the studies in Table 19 indicate that propylene and dipropylene glycol are both practically non-toxic to freshwater invertebrates. The testing guideline requirement has been fulfilled (850.1010/72-2). Additional data on the acute toxicity of propylene glycol to freshwater invertebrates were retrieved from the ECOTOX database. This information is provided in Table 22. Because the agency has acceptable, albeit limit[7] study data, no formal agency review of the public literature studies were conducted. The results from the following studies do provide further weight –of-evidence that propylene and dipropylene glycol demonstrate very low toxicity to freshwater invertebrates. While not reviewed these results do provide further weight-of-evidence that propylene and dipropylene glycol demonstrate very low toxicity to freshwater invertebrates.

Table 21 Acute Toxicity of Propylene/Dipropylene Glycol to Freshwater Invertebrates

Species	% Active Ingredient (ai)	Endpoints (ppm)	Toxicity Category (TGAI)	Satisfies Guidelines/ Comments	Reference
Propylene Glycol					
Waterflea (*Daphnia magna*)	100	48-hr. EC_{50} >110 ppm ai NOEC $\geq$ 110 ppm ai	Practically non-toxic	Yes	Graves and Swigert, 1995. MRID 43762302
Waterflea (*Daphnia magna*)	99.76	48-hr. EC_{50} >1,000 ppm ai NOEC $\geq$ 1,000 ppm ai	Practically non-toxic	Yes	Collins, 1995 MRID 43888003
Dipropylene Glycol					
Waterflea (*Daphnia magna*)	100	48-hr. EC_{50} > 109 ppm ai NOEC $\geq$ 109 ppm ai	Practically non-toxic	Yes	Graves and Swigert, 1995. MRID 43760808

[7] A limit study or Tier I study refers here to a study where instead of testing several concentrations to establish a dose response and a definitive endpoint value, only a single concentration of at least 100 mg/L (ppm) or the solubility limit, whichever is lower, is tested.

Table 22 Open Literature Freshwater Invertebrate Acute Toxicity Data for Propylene Glycol

Species	Endpoints	Toxicity Category	Reference
Waterflea (*Ceriodaphnia dubia*)	48 hr. LC_{50} = 1,020 ppm ; NOEC = 660 ppm	Practically non-toxic	Pillard, 1995 (ECOTOX reference #13727)
Waterflea (*Ceriodaphnia dubia*)	48 hr LC_{50}= 18,340 ppm ai; NOEC = 13,020 ppm ai	Practically non-toxic	Pillard, 1995 (ECOTOX reference #13727)
Waterflea (*Ceriodaphnia dubia*)	48 hr LC_{50} = 4,919 ppm ai	Practically non-toxic	Cornell *et al*., 2000 (ECOTOX reference #48385)
Waterflea (*Daphnia magna*)	48 hr EC_{50} > 10,000 ppm	Practically non-toxic	Kuhn *et al*., 1989 (ECOTOX reference #846)

Estuarine and Marine Organisms, Acute Toxicity

Acute toxicity testing with estuarine and marine organisms using the TGAI is required when the end-use product is intended for direct application to the marine/estuarine environment or effluent containing the active ingredient is expected to reach this environment. Neither propylene glycol nor dipropylene glycol has such uses on their labels and neither is exposure expected to occur. Therefore, testing with marine/estuarine organisms is not anticipated to be required. Some information on the acute toxicity of propylene glycol to an inland saltwater lake invertebrate species, brine shrimp,was found in ECOTOX, and the results are provided in Table 23. Estimates of propylene gylcol and dipropylene gylcol (neutral organics class) acute toxicity using ECOSAR v1.10 are 24,391 mg/L and 32,012 mg/L, respectively, for a saltwater fish and 119,000 mg/L and 142,000 mg/L, respectively, for a mysid.

Table 23 Acute Toxicity of Propylene Glycol to Inland Saltwater Lake Species

Species	Endpoints	Toxicity Category	Reference
Brine Shrimp (*Artemia salina*)	Static 24 hr. LC_{50} > 10000 ppm	Practically non-toxic	Price *et al*., 1974 (ECOTOX reference #2408)

Aquatic Animals, Chronic Toxicity

There are no submitted chronic data in the files and no comparable endpoints were found in the open literature ECOTOX database. Estimates of propylene gylcol and dipropylene gylcol (neutral organics class) chronic toxicity to aquatic animals using ECOSAR v1.10 range from 413 to 1,894 mg/L for freshwater animals and 484 to 26,858 mg/L for saltwater animals (Table 24). Chronic toxicity testing (Fish early life stage, 850.1300/72-4a and aquatic invertebrate life cycle, 850.1400/72-4b) is not required for the currently registered uses of propylene glycol or dipropylene glycol. Therefore, aquatic animal chronic testing is not anticipated to be required at this time.

Table 24 Chronic Toxicity of Propylene Glycol and Dipropylene Glycol to Aquatic Animals

Species	Propylene Glycol *Chv*	Dipropylene Glycol *Chv*	Reference
Fish, Freshwater	1,422 mg/L	1,894 mg/L	ECOSAR v1.10
Daphnid, Freshwater Invertebrate	413 mg/L	569 mg/L	ECOSAR v1.10
Fish, Saltwater	484 mg/L	693 mg/L	ECOSAR v1.10
Mysid, Estuarine/Marine Invertebrate	23,526 mg/L	26,858 mg/L	ECOSAR v1.10

Chv = geometric mean of a NOEC and LOEC value

Toxicity to Plants

No data, such as phytotoxicity, were available from submitted studies or open literature to address the risk to plants. Estimates for toxicity to green algae for propylene gylcol and dipropylene gylcol, as neutral organics, from ECOSAR v1.10 consist of 96-h IC_{50} values of 5,611 mg/L and 7,567 mg/L, respectively, and *Chv* (geometric mean of a NOEC and LOEC) values of 329 mg/L and 476 mg/L, respectively. This information is sufficient for any hazard labeling. Additionally, exposure to plants is not expected from the current registered uses of propylene glycol and dipropylene glycol. Therefore, plant toxicity testing is not anticipated to be required at this time.

ECOSAR Version 1.10 Results Page—Propylene Glygol

```
SMILES : OCC(O)C
CHEM   : 1,2-Propanediol
CAS Num: 000057-55-6
ChemID1:
MOL FOR: C3 H8 O2
MOL WT : 76.10
Log Kow: -0.782     (EPISuite Kowwin v1.68 Estimate)
Log Kow:            (User Entered)
Log Kow: -0.92      (PhysProp DB exp value - for comparison only)
Melt Pt:            (User Entered for Wat Sol estimate)
Melt Pt: -60.00     (deg C, PhysProp DB exp value for Wat Sol est)
Wat Sol: 1E+006     (mg/L, EPISuite WSKowwin v1.43 Estimate)
Wat Sol:            (User Entered)
Wat Sol: 1E+006     (mg/L, PhysProp DB exp value)


-------------------------------------
Values used to Generate ECOSAR Profile
-------------------------------------
Log Kow: -0.782     (EPISuite Kowwin v1.68 Estimate)
Wat Sol: 1E+006     (mg/L, PhysProp DB exp value)

-----------------------------------------------
Available Measured Data from ECOSAR Training Set
-----------------------------------------------

   No Data Available


-------------------------------------
```

```
ECOSAR v1.1 Class-specific Estimations
-------------------------------------
Neutral Organics
```

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Neutral Organics	Fish	96-hr	LC50	19700.475
Neutral Organics	Fish	14-day	LC50	18018.713
Neutral Organics	Daphnid	48-hr	LC50	8688.484
Neutral Organics	Green Algae	96-hr	EC50	5611.575
Neutral Organics	Fish		ChV	1422.289
Neutral Organics	Daphnid		ChV	412.807
Neutral Organics	Green Algae		ChV	329.329
Neutral Organics	Fish (SW)	96-hr	LC50	24391.777
Neutral Organics	Mysid	96-hr	LC50	1.19e+005
Neutral Organics	Fish (SW)		ChV	484.236
Neutral Organics	Mysid (SW)		ChV	23526.172
Neutral Organics	Earthworm	14-day	LC50	257.073

```
 Note:  * = asterisk designates: Chemical may not be soluble enough to
        measure this predicted effect. If the effect level exceeds the
        water solubility by 10X, typically no effects at saturation (NES)
        are reported.


------------------------------
Class Specific LogKow Cut-Offs
------------------------------
If the log Kow of the chemical is greater than the endpoint specific cut-offs
presented below, then no effects at saturation are expected for those endpoints.

Neutral Organics:
----------------
Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50)
Maximum LogKow: 6.0 (Fish 14-day LC50; Earthworm LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
```

ECOSAR Version 1.10 Results Page—Dipropylene Glycol

```
SMILES : CC(O)COCC(O)C
CHEM   : Propanol, oxybis-
CAS Num: 025265-71-8
ChemID1:
MOL FOR: C6 H14 O3
MOL WT : 134.18
Log Kow: -0.639     (EPISuite Kowwin v1.68 Estimate)
Log Kow:            (User Entered)
Log Kow:            (PhysProp DB exp value - for comparison only)
Melt Pt:            (User Entered for Wat Sol estimate)
Melt Pt: -40.00     (deg C, PhysProp DB exp value for Wat Sol est, <-40)
Wat Sol: 1E+006     (mg/L, EPISuite WSKowwin v1.43 Estimate)
Wat Sol:            (User Entered)
Wat Sol: 1E+006     (mg/L, PhysProp DB exp value)


-------------------------------------
Values used to Generate ECOSAR Profile
-------------------------------------
Log Kow: -0.639     (EPISuite Kowwin v1.68 Estimate)
Wat Sol: 1E+006     (mg/L, PhysProp DB exp value)
```

Available Measured Data from ECOSAR Training Set

No Data Available

ECOSAR v1.1 Class-specific Estimations

Neutral Organics

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Neutral Organics	Fish	96-hr	LC50	25833.533
Neutral Organics	Fish	14-day	LC50	23787.684
Neutral Organics	Daphnid	48-hr	LC50	11541.943
Neutral Organics	Green Algae	96-hr	EC50	7567.450
Neutral Organics	Fish		ChV	1894.386
Neutral Organics	Daphnid		ChV	569.086
Neutral Organics	Green Algae		ChV	476.003
Neutral Organics	Fish (SW)	96-hr	LC50	32012.744
Neutral Organics	Mysid	96-hr	LC50	1.42e+005
Neutral Organics	Fish (SW)		ChV	693.606
Neutral Organics	Mysid (SW)		ChV	26857.861
Neutral Organics	Earthworm	14-day	LC50	438.047

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported.

Class Specific LogKow Cut-Offs

If the log Kow of the chemical is greater than the endpoint specific cut-offs presented below, then no effects at saturation are expected for those endpoints.

Neutral Organics:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50)
Maximum LogKow: 6.0 (Fish 14-day LC50; Earthworm LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)

Appendix D Ecotoxicology Profile for Triethylene Glycol

Toxicity to Terrestrial Animals

Avian acute oral and dietary toxicity

To establish the toxicity of triethylene glycol to birds, the Agency required an acute oral toxicity study using the technical grade of the active ingredient (TGAI). The preferred test species was either mallard duck (a waterfowl) or bobwhite quail (an upland game bird). The results of submitted studies are provided in the following table . The results indicate that triethylene glycol is practically non-toxic to birds on an acute oral basis. The studies are acceptable and fulfill guideline requirements (71-1/OPPTS 850.2100).

Mammals

Triethylene glycol shows low acute toxicity to mammals in laboratory studies (see Table Appendix A).

Table 25 Toxicity of Triethylene Glycol to Mammals (excerpted from Appendix A)

Species	Test Type	Results
Rat	Acute oral	LD_{50} 15,000 - 22,000 mg/kg-bw (Toxicity Category IV)

Toxicity to Aquatic Receptors

Freshwater Fish, Acute

The results indicate that triethylene glycol is practically non-toxic to freshwater fish on an acute basis. Since these data are supplemental information, Guideline 72-1/850.1075 is not fulfilled; however, because multiple published studies demonstrate very low toxicity to freshwater fish for the glcols, no further testing is anticipated to be required for triethylene glycol at this time.

Table 26 Acute Toxicity of Triethylene Glycol to Freshwater Fish

Species	Endpoints	Toxicity Category	Reference
Bluegill sunfish (*Lepomis macrochirus*)	96 hr LC_{50} = 10,000 ppm	Practically non-toxic	Verschuren, 1983
Fathead minnow (*Pimephales promelas*)	96 hr LC_{50} = 59,900 – 77,400 ppm	Practically non-toxic	Geiger *et al*., 1988

Freshwater Invertebrates, Acute

The Agency requires a freshwater aquatic invertebrate toxicity study using the TGAI to establish the acute toxicity of an antimicrobial pesticide to freshwater invertebrates. The preferred test species is *Daphnia magna*.

No data have been submitted for triethylene glycol and no data was found in the EPA/ORD ECOTOX database. An estimate of triethylene gylcol (neutral organics class) acute toxicity using ECOSAR v1.10 is 116,000 mg/L for a freshwater daphnid (see ECOSAR results page at end of this appendix). Triethylene glycol is expected to be practically nontoxic on an acute basis to freshwater invertebrates. No additional acute data are anticipated to be required for the assessment.

Estuarine and Marine Organisms, Acute Toxicity

Acute toxicity testing with estuarine and marine organisms (a fish, a mollusk, and a shrimp) using the TGAI is required when the end-use product is intended for direct application to the marine/estuarine environment or effluent containing the active ingredient is expected to reach this environment. The triethylene glycol uses are not expected to result in such exposure. Therefore, testing with marine/estuarine organisms is not anticipated to be required. However, a sheepshead minnow study and a mysid study were conducted by EPA (Mayer, 1986). Additionally, the acute toxicity of triethylene glycol to another fish species (Inland silverside) was found in ECOTOX, and the results are provided in Table 27. Triethylene glycol is practically nontoxic to estuarine/marine fish and invertebrates based on this data. No additional acute data are anticipated to be required for the assessment.

Table 27 Open Literature Estuarine/Marine Fish and Invertebrate Acute Toxicity Data for Triethylene Glycol

Species	Endpoints	Toxicity Category	Reference
Sheepshead minnow (*Cyprinodon variegatus*)	96 hr LC_{50} = 48,000 ppm	Practically non-toxic	Mayer, 1986 MRID 40228401
Inland silverside *Menidia beryllina*	96 hr LC_{50} = 10,000 ppm	Practically non-toxic	Verschuren, 1983
Mysid (*Mysidopsis bahia*)	96 hr LC_{50} = 11,000 ppm	Practically non-toxic	Mayer, 1986 MRID # 40228401

Aquatic Animals, Chronic Toxicity

There are no submitted chronic data in the files and no comparable endpoints were found in the open literature ECOTOX database. Estimates of triethylene gylcol (neutral organics class) chronic toxicity to aquatic animals using ECOSAR v1.10 range from 4,288 to 18,640 mg/L for freshwater animals and 3,885 to 873,000 mg/L for saltwater animals (Table 28). The model appears to underestimate chronic toxicity to aquatic animals. There is a laboratory acute study for a mysid with a 96-hr LC_{50} (concentration at which 50% of exposed organisms are expected to die) of 11,000 ppm but the modeled chronic value is 873,000 ppm, which is not appropriate. Chronic toxicity testing (Fish early life stage, 850.1300/72-4a and aquatic invertebrate life cycle, 850.1400/72-4b) is not anticipated to be required for the currently registered uses of triethylene glycol.

Table 28 Chronic Toxicity of Triethylene Glycol to Aquatic Animals

Species	Triethylene Glycol *Chv*	Reference
Fish, Freshwater	18,640 mg/L[a]	ECOSAR v1.10
Daphnid, Freshwater Invertebrate	4,288 mg/L	ECOSAR v1.10
Fish, Saltwater	3,885 mg/L	ECOSAR v1.10
Mysid, Estuarine/Marine Invertebrate	873,000 mg/L[b]	ECOSAR v1.10

Chv = geometric mean of a NOEC and LOEC value

[b] Model may not be appropriate for triethylene gylcol as the laboratory acute 96-hr LC_{50} values for freshwater fish of 10,000 to 77,400 ppm is lower than the modeled 96-hr LC_{50} value for freshwater fish of 287,000 ppm (see Table 27).

[b] Model is not appropriate for triethylene gylcol as the chronic value is above the laboratory 96-hr LC_{50} value of 11,000 ppm (see Table 27).

Toxicity to Plants

No data, such as phytotoxicity, were available from submitted studies or open literature to address the risk to plants. Estimates for toxicity to green algae for triethylene gylcol, as a neutral organic, from ECOSAR v1.10 consist of a 96-h IC_{50} value of 67,639 mg/L and a *Chv* (geometric mean of a NOEC and LOEC) value of 2,486 mg/L. This information is sufficient for any hazard labeling. Additionally, exposure to plants is not expected from the current registered uses of triethylene glycol. Therefore, plant toxicity testing is not anticipated to be required at this time.

ECOSAR Version 1.10 Results Page – Triethylene Glycol

```
SMILES : O(CCOCCO)CCO
CHEM   : Ethanol, 2,2 -[1,2-ethanediylbis(oxy)]bis-
CAS Num: 000112-27-6
ChemID1:
MOL FOR: C6 H14 O4
MOL WT : 150.18
Log Kow: -1.748     (EPISuite Kowwin v1.68 Estimate)
Log Kow:            (User Entered)
Log Kow: -1.75      (PhysProp DB exp value - for comparison only)
Melt Pt:            (User Entered for Wat Sol estimate)
Melt Pt: -7.00      (deg C, PhysProp DB exp value for Wat Sol est)
Wat Sol: 1E+006     (mg/L, EPISuite WSKowwin v1.43 Estimate)
Wat Sol:            (User Entered)
Wat Sol: 1E+006     (mg/L, PhysProp DB exp value)


-------------------------------------
Values used to Generate ECOSAR Profile
-------------------------------------
Log Kow: -1.748     (EPISuite Kowwin v1.68 Estimate)
Wat Sol: 1E+006     (mg/L, PhysProp DB exp value)


-----------------------------------------------
Available Measured Data from ECOSAR Training Set
-----------------------------------------------
```

CAS No	Organism	Duration	End Pt	Measured mg/L (ppm)	Ecosar Class	Reference
000112-27-6	Fish	96-hr	LC50	59900	Neutral organics	DUL
000112-27-6	Fish	96-hr	LC50	70200	Neutral organics	DUL
000112-27-6	Fish	96-hr	LC50	77400	Neutral organics	DUL
000112-27-6	Fish	14-day	LC50	62601.4	Neutral organics	Konemann, 1981

ECOSAR v1.1 Class-specific Estimations

Neutral Organics

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Neutral Organics	: Fish	96-hr	LC50	2.87e+005
Neutral Organics	: Fish	14-day	LC50	2.51e+005
Neutral Organics	: Daphnid	48-hr	LC50	1.16e+005
Neutral Organics	: Green Algae	96-hr	EC50	67639.422
Neutral Organics	: Fish		ChV	18639.736
Neutral Organics	: Daphnid		ChV	4288.514
Neutral Organics	: Green Algae		ChV	2486.059
Neutral Organics	: Fish (SW)	96-hr	LC50	3.53e+005
Neutral Organics	: Mysid	96-hr	LC50	3.32e+006 *
Neutral Organics	: Fish (SW)		ChV	3885.237
Neutral Organics	: Mysid (SW)		ChV	8.73e+005
Neutral Organics	: Earthworm	14-day	LC50	639.014

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported.

Class Specific LogKow Cut-Offs

If the log Kow of the chemical is greater than the endpoint specific cut-offs presented below, then no effects at saturation are expected for those endpoints.

Neutral Organics:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50)
Maximum LogKow: 6.0 (Fish 14-day LC50; Earthworm LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
