Screening Assessment for the Challenge

Oxirane, 2,2',2'',2'''-[1,2-ethanediylidenetetrakis(4,1-phenyleneoxymethylene)]tetrakis-

Chemical Abstracts Service Registry Number
7328-97-4

Environment Canada
Health Canada

September 2010

Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment on Oxirane, 2,2',2",2"'-[1,2-ethanediylidenetetrakis(4,1-phenyleneoxymethylene)]tetrakis- (TGOPE), Chemical Abstracts Service Registry Number 7328-97-4. This substance was identified as a high priority for screening assessment and included in the Challenge because it had been found to meet the ecological categorization criteria for persistence, bioaccumulation potential and inherent toxicity to non-human organisms and is believed to be in commerce in Canada.

TGOPE was not considered to be a high priority for assessment of potential risks to human health, based upon application of the simple exposure and hazard tools developed by Health Canada for categorization of substances on the Domestic Substances List.

TGOPE is a solid epoxy resin that is used in Canada and elsewhere primarily in the manufacture of paints, coatings and adhesives. The substance is not naturally occurring in the environment. It is not reported to be manufactured in Canada; however, between 1000 and 10 000 kg were imported into the country in 2006.

The potential for exposure of the general population to TGOPE from environmental media is expected to be negligible. There is no expected exposure from food. Exposure to TGOPE from consumer products may occur during use of epoxy adhesives; however, such exposure is expected to be low. Therefore, exposure of the general population in Canada is expected to be low to negligible.

During the manufacturing process of items containing TGOPE, virtually all of the TGOPE will chemically react and therefore become chemically transformed and unavailable for release. The very small amount of unreacted TGOPE remaining in manufactured items is assumed to be disposed of in landfill sites. About 1.6% of the mass of TGOPE reported to be sold in Canada is estimated to be released in industrial wastewater during industrial processing, 1% is disposed of in landfills in waste products, and no releases are predicted to air and soil. TGOPE has low predicted water solubility (0.06 mg/L). It is essentially non-volatile. It will partition to sediments (57%) if released to surface waters and will remain in soil if released to soil.

Based on its physical and chemical properties and on data from a chemical analogue, TGOPE is not considered to be persistent in the environment, as it is predicted to hydrolyze in water. Modelled bioaccumulation data that take into account metabolic transformation suggests that this substance has a high potential to accumulate in the lipid tissues of organisms. The hydrolysis product of TGOPE is predicted to have a low potential to bioaccumulate but is expected to persist in the environment. Given that TGOPE hydrolyses to a transformation product with different characteristics, TGOPE does not meet the persistence criteria but does meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*.

Experimental toxicity data for a chemical analogue suggest that saturated solutions of TGOPE cause chronic harm to aquatic organisms. The hydrolysis product of TGOPE is predicted to have low toxicity to aquatic organisms.

For this screening assessment, a conservative site-specific exposure scenario was selected in which an industrial operation discharges TGOPE into the aquatic environment. The predicted environmental concentration in water was below the predicted no-effect concentration for pelagic aquatic organisms.

With regard to human health, while limited toxicity data for TGOPE were identified, the genotoxicity assays identified for TGOPE indicate mutagenic potential *in vitro*. In addition, structural analogues of TGOPE were found to have carcinogenic potential in experimental animals and direct-acting mutagenic potential in a range of *in vitro* assays and mixed results in *in vivo* assays. Therefore, given the positive results for genotoxicity of TGOPE, and the collective evidence from genotoxicity and carcinogenicity data for the analogues of TGOPE, it is considered that TGOPE may cause harm at any level of exposure.

On the basis of the carcinogenic potential of TGOPE, for which there may be a probability of harm at any level of exposure, it is concluded that TGOPE is a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Based on the information available, it is concluded that TGOPE is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends. TGOPE does not meet the persistence criteria but does meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*.

Where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

Based on the information available, it is concluded that TGOPE meets one or more of the criteria set out in section 64 of the *Canadian Environmental Protection Act, 1999*.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or human health.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce in Canada; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE), and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment, and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance Oxirane, 2,2',2",2"'-[1,2-ethanediylidenetetrakis(4,1-phenyleneoxymethylene)]tetrakis- had been identified as a high priority for assessment of ecological risk as it had been found to be persistent, bioaccumulative and inherently toxic to aquatic organisms and is believed to be in commerce in Canada. The Challenge for this substance was published in the *Canada Gazette* on March 14, 2009 (Canada 2009a, 2009b). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information pertaining to the uses of the substance were received.

Although Oxirane, 2,2',2",2"'-[1,2-ethanediylidenetetrakis(4,1-phenyleneoxymethylene)]tetrakis- was determined to be a high priority for assessment with respect to the environment, it did not meet the criteria for GPE or IPE and high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

Screening assessments focus on information critical to determining whether a substance meets the criteria as set out in section 64 of CEPA 1999[1]. Screening assessments examine scientific information and develop conclusions by incorporating a weight-of-evidence approach and precaution.

This final screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to October 2009 for the ecological sections of the document and December 2009 for the health sections of the document. Key studies were critically evaluated; and modelling results were used to reach conclusions.

When available and relevant, information presented in hazard assessments from other jurisdictions is considered. The final screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical studies and lines of evidence pertinent to the conclusion.

This final screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. The ecological portions of the assessment have undergone external peer review/consultation. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment Canada. Approaches used in the screening assessments under the Challenge have been reviewed by an independent Challenge Advisory Panel.

The critical information and considerations upon which the final assessment is based are summarized below.

[1] A determination of whether one or more of the criteria of section 64 are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 on the substances in the Chemicals Management Plan (CMP) Challenge Batches 1-12 is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Controlled Products Regulations*, which is part of regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace use.

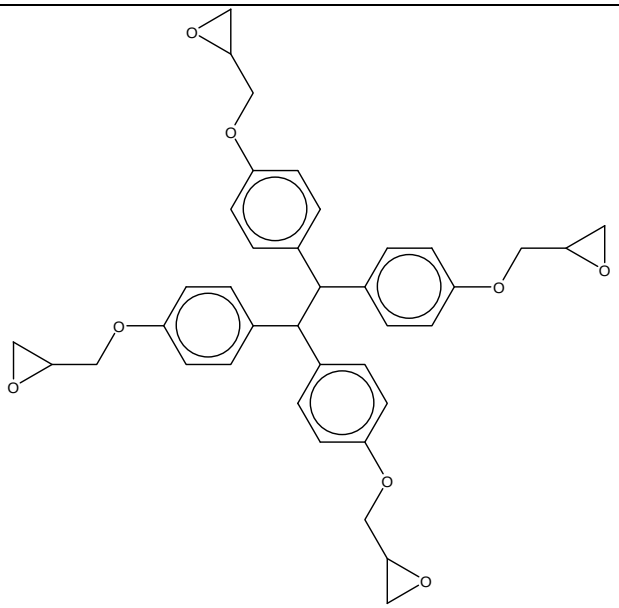
Substance Identity

Substance name

For the purposes of this document, this substance will be referred to as "TGOPE," derived from one of its chemical names *1,1,2,2-(4,4',4'',4'''-tetraglycidyloxyphenyl)ethane*.

Table 1. Substance identity for TGOPE

Chemical Abstracts Service Registry Number (CAS RN)	**7328-97-4**
DSL name	**Oxirane, 2,2',2'',2'''-[1,2-ethanediylidenetetrakis(4,1-phenyleneoxymethylene)]tetrakis-**
National Chemical Inventories (NCI) names[1]	*Oxirane, 2,2',2'',2'''-[1,2-ethanediylidenetetrakis(4,1-phenyleneoxymethylene)]tetrakis-* (TSCA, PICCS, ASIA-PAC, NZIoC, AICS); *2,2',2'',2'''-[ethane-1,2-diylidenetetrakis(p-phenyleneoxymethylene)]tetraoxirane* (EINECS)
Other names	*1,1,2,2-(4,4',4'',4'''-tetraglycidyloxyphenyl)ethane;* *1,1,2,2-tetra(p-hydroxyphenyl)ethane tetraglycidyl ether;* *1,1,2,2-tetrakis(4-glycidoxyphenyl)ethane;* *1,1,2,2-tetrakis(p-glycidyloxyphenyl)ethane;* *1,1,2,2-tetrakis(p-hydroxyphenyl)ethane tetraglycidyl ether;* *ethane, 1,1,2,2-tetrakis[p-(2,3-epoxypropoxy)phenyl]-;* *tetraglycidyl ether of 1,1,2,2-tetrakis(p-hydroxyphenyl)ethane;* *tetraphenylolethane, epichlorohydrin epoxy resin*
Chemical group (DSL Stream)	Discrete organics
Major chemical class or use	Epoxides
Major chemical sub-class	Tetraphenyls; tetraglycidyl ethers
Chemical formula	$C_{38}H_{38}O_8$

Chemical structure	
SMILES[2]	O(C1COc(ccc(c2)C(c(ccc(OCC(O3)C3)c4)c4)C(c(ccc(OCC(O5)C5)c6)c6)c(ccc(OCC(O7)C7)c8)c8)c2)C1
Molecular mass	622.72 g/mol

1 National Chemical Inventories (NCI). 2007: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); EINECS (European Inventory of Existing Commercial Chemical Substances); NZIoC (New Zealand Inventory of Chemicals); PICCS (Philippine Inventory of Chemicals and Chemical Substances); and TSCA (Toxic Substances Control Act Chemical Substance Inventory).

2 Simplified Molecular Line Input Entry System

Physical and Chemical Properties

Table 2a contains experimental and modelled physical and chemical properties of TGOPE that are relevant to its environmental fate. Apart from the melting point, no experimental physical and chemical data for TGOPE were identified. This experimental melting point was used as input when other property values were estimated using EPI Suite (2008) estimation software (Appendix I).

A literature search was performed and the program ChemIDplus® (US NLM 2008) was employed to find appropriate analogue substances of TGOPE with measured data for physical and chemical properties, persistence, bioaccumulation, and toxicity. Because of the lack of analogues with measured data identified through this method, Environment Canada's New Substances database was searched for analogues.

Analogue data were identified through New Substance Notifications received by Environment Canada under the *New Substances Notification Regulations* of CEPA 1999. The structure of the analogue includes phenyl epoxide groups with alkyl substituents. The substance may not be identified due to the confidentiality of this data, and will be referred

to as "Substance A." Physical and chemical property data for Substance A are included in Table 2b.

Table 2a. Physical and chemical properties for TGOPE

Property	Type	Value	Temperature (°C)	Reference
Physical form		Solid		US EPA 2009
Melting point (°C)	Experimental	77–83		Sigma-Aldrich 2009
	Modelled	307.17		MPBPWIN 2008
Boiling point (°C)	Modelled	702.46		MPBPWIN 2008
Density (kg/m^3)		Not available		
Vapour pressure (Pa)	Modelled	5.7×10^{-12} (4.3×10^{-14} mm Hg)	25	MPBPWIN 2008
Henry's Law constant ($Pa\cdot m^3/mol$)	Modelled	3.59×10^{-15} (3.54×10^{-20} $atm\cdot m^3/mol$)	25	HENRYWIN 2008
Log K_{ow}	Modelled	5.5		KOWWIN 2008
Log K_{oc}	Modelled	3.72		KOCWIN 2008
Water solubility (mg/L)	Modelled	0.056[1]	25	WSKOWWIN 2000
pK_a (Acid dissociation constant) (dimensionless	Modelled	Non-ionizing		ACD/pK_aDB 2000-2008

[1] WSKOWWIN estimate generated using a melting point of 80°C.

Table 2b. Physical and chemical properties for an analogue, Substance A

Property	Type	Value[1]	Temp. (°C)	Test Method	Reference
Physical form		Solid		-	Study Submission 1991a
Molecular weight		354.44		-	Study Submission 1991a
Melting point (°C)	Experimental	97.7–105.9		OECD (1981a)	Study Submission 1991a
	Modelled	188		-	MPBPWIN 2008
Boiling point (°C)	Experimental	> 280		OECD (1981b)	Study Submission 1991a
	Modelled	458		-	MPBPWIN 2008
Density (kg/m^3)	Experimental	1.152		Hydrostatic balance method	Study Submission 1991a
Vapour pressure (Pa)	Experimental	< 0.00026	84.5	EEC[2] Directive 67/548, Annex V, A4	Study Submission 1991a
	Modelled	0.048	25	-	MPBPWIN 2008
Log K_{ow}	Experimental	2.90	20	OECD (1981c)[3]	Study Submission 1991a
	Modelled	5.19		-	KOWWIN 2008
Log K_{oc}	Modelled	3.7		-	KOCWIN 2008
Water solubility (mg/L)	Experimental	≥0.30	20	OECD (1981d))	Study Submission 1991a
	Modelled	0.29	25	-	WSKOWWIN 2000

[1] Modelled values were generated in EPI Suite (2008) with experimental melting point (100°C) and boiling point (300°C) as input.
[2] EEC = European Economic Community
[3] Flask containing test substance and octanol were shaken together for 3 hours (instead of 24 hours stipulated in the OECD Guideline (1981c).

Many of the modelled or measured properties of TGOPE are similar to the values for Substance A. Both substances are solids with similar melting points. Substance A has a low vapour pressure, while the vapour pressure of TGOPE is considered very low. The predicted log K_{OW} values for TGOPE and Substance A are similar, and the predicted log K_{OC} values are very similar. While the measured and predicted log K_{OW} values of Substance A are not similar; it should be noted that the experimental K_{OW} determination method did not conform to the OECD Guideline.

However, there are differences between the two molecules. For example, the molecular weight of Substance A is just over half that of TGOPE, and the predicted and experimental water solubility values of Substance A are approximately one order of magnitude higher than that predicted for TGOPE.

Empirical data for persistence and toxicity for Substance A are used as analogue data for TGOPE to support the modelled data (see the Persistence and the Potential to Cause Ecological Harm sections of this report). Substance A is considered to be an adequate analogue for these endpoints. Substance A has similar structural features to TGOPE, so it is likely to be hydrolyzed and biodegraded similarly to TGOPE—though probably at a faster rate due to its higher bioavailability. The predicted log K_{OW} value of Substance A is similar to that of TGOPE and its predicted water solubility is higher but within an order of magnitude of TGOPE. Assuming similar modes of toxic action, K_{OW} and water solubility are the main parameters affecting toxicity predictions.

Sources

TGOPE is not known to be naturally occurring in the environment.

Information was collected through surveys conducted for the years 2005 and 2006 under *Canada Gazette* notices issued pursuant to section 71 of CEPA 1999 (Canada 2006, Canada 2009b). These notices requested data on the Canadian manufacture and import of TGOPE. The 2006 survey also requested information on uses of TGOPE.

Information gathered from the survey notices indicates that TGOPE was not manufactured in Canada in 2005 or 2006. Fewer than 4 companies reported a total import of this substance in the 1000–10 000 kg/year range in 2006 and one company reported importing in the 1000–100 000 kg/year range in 2005. This quantity is consistent with the DSL nomination data, which indicated that 1000-10 000 kg/year of TGOPE were manufactured or imported in 1986. In addition, in 2006 one other company identified itself as having a stakeholder interest in this substance (Environment Canada 2009a).

TGOPE is a U.S. high production volume (HPV) chemical (US EPA 2009). In the U.S., production quantities of TGOPE were in the range of 225-450 tonnes in 1986, 4.5-225 tonnes in 1990, and of 450–4500 tonnes/year in 1994, 1998, 2002 and 2006 (US EPA 2006, 2009). TGOPE is not listed as an HPV or low production volume (LPV) chemical in Europe (ESIS 2009); however, it is on the 2004 Organisation for Economic Co-operation and Development list of HPV chemicals (OECD 2004).

Uses

The following North American Industry Classification System (NAICS) code was reported for TGOPE in 2005 (Environment Canada 2006): 32551 – Paint, Coating and Adhesive Manufacturing: This industry comprises establishments primarily engaged in (1) mixing pigments, solvents and binders into paints and other coatings, such as stains, varnishes, lacquers, enamels, shellacs, and water repellent coatings for concrete and masonry; and/or (2) manufacturing allied paint products, such as putties, paint and varnish removers, paint brush cleaners, and frit. More specific usage information was reported in 2006 but this is considered to be confidential business information

(Environment Canada 2009a). This confidential information was taken into consideration in this risk assessment. The substance uses that were reported were primarily in industrial settings and would likely not result in any exposure to the public. However, based on one submission received, TGOPE is found in an adhesive product that may have consumer uses. Uses listed for the DSL nomination in 1986 included paints and coatings, and plastics and synthetic resins.

In Canada, TGOPE is not approved for any food additive use nor has Health Canada ever received a submission for its use in food packaging materials or in formulations of incidental additives (2010 personal communication from Foods Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

From the literature, TGOPE has been reported to be used in manufacturing high-performance epoxy systems, specially formulated for high-accuracy, elevated-temperature transducer applications (Davidson Measurement 2005). TGOPE has been used in the production of multifunctional epoxy resins, which can be used to improve the properties of cured epoxy resin systems, particularly at elevated temperatures. These epoxy resins may find application in electrical laminates, high-performance composites and adhesives (Brenntag NV 2009; Hexion Specialty Chemicals 2001; US EPA 2006).

In the United States, TGOPE has been used as an adhesive and binding agent in semiconductor and other electronic component manufacturing, and in the resin and synthetic rubber manufacturing sectors (US EPA 2006). In addition, 15 tonnes of TGOPE were used in Sweden in 2005 as an adhesive/binding agent (SPIN 2009).

Releases to the Environment

To assist in estimating losses of TGOPE to the environment, a spreadsheet (Mass Flow Tool) was used (Environment Canada 2008). No empirical data on releases of TGOPE to the environment were found. TGOPE is not reportable to the National Pollutant Release Inventory (NPRI 2008) or to the U.S. Toxics Release Inventory Program (TRI 2007).

The releases of TGOPE to the environment may result from various losses of the substance during its industrial use and consumer/commercial use. These losses can be grouped into seven types: (1) discharge to wastewater; (2) emission to air; (3) emission to land; (4) chemical transformation; (5) disposal to landfill; (6) disposal by recycling; and (7) disposal by incineration. They are estimated based on regulatory survey data, industry data and data published by different organizations. Unless specific information on the rate or potential for release of the substance from landfills and incinerators is available, the Mass Flow Tool does not quantitatively account for releases to the environment from waste disposal sites.

In the context of the estimation assisted by the Mass Flow Tool, the discharge to wastewater refers to loss to raw wastewater prior to any treatment, by either public or private wastewater systems. In a similar manner, the loss via chemical transformation refers to changes in substance's identity that may occur within the manufacture, industrial use, or consumer/commercial use stages, but excludes those during waste management operations such as incineration and wastewater treatment.

The losses estimated for TGOPE over its life cycle are presented in Table 3 (Environment Canada 2009b). The substance is expected to be released in industrial wastewater at 0.3–1.6% of the total quantity used in Canadian commerce, depending on whether more or less conservative assumptions are made about its releases. In general, wastewater is a common point-of-entry for releases to surface water and to soil through application of biosolids from wastewater systems to agricultural land.

Table 3. Estimated losses of TGOPE during its life cycle

Type of loss	Proportion (%)	Pertinent life cycle stages
Wastewater	0.3–1.6	Industrial use
Air emission	0.0	-
Land emission	0.0	-
Chemical transformation	97.4–99.6	Industrial use
Landfill	0.1–1.0	Consumer/commercial use
Recycling	0.0	-
Incineration	0.0	-

TGOPE is not expected to be released to the environment via routes other than industrial wastewater. TGOPE is used in paints, coating and adhesive manufacturing (Environment Canada 2006; Hexion Specialty Chemicals 2001). During the manufacturing of items containing TGOPE, virtually all of the TGOPE will chemically react and therefore become chemically transformed and unavailable for release. The very small amount of unreacted TGOPE remaining in manufactured items is assumed to be disposed of in landfill sites. TGOPE disposed of in landfill has very low potential to migrate into groundwater, since TGOPE released to soil is expected to be virtually immobile and remain in soil (see Environmental Fate section below).

Environmental Fate

Based on its physical and chemical properties (Table 2a), the results of Level III fugacity modelling (EQC 2003; see Table 4) suggest that TGOPE is expected to predominantly reside in water, soil or sediment, depending on the compartment of release. Values for parameters used in the Equilibrium Criterion (EQC) modelling can be found in Appendix I.

It should be noted that TGOPE is not expected to be stable in air (gas phase) or water (see Environmental Persistence section). In water, TGOPE is expected to biodegrade slowly but to hydrolyze relatively quickly due to the reactivity of the epoxide groups(see Environmental Persistence section).

Table 4. Results of the Level III fugacity modelling (EQC 2003)

	Percentage of substance partitioning into each compartment			
Substance released to:	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	6.45	5.13	86.4	1.97
Water (100%)	<0.01	72.3	<0.01	27.7
Soil (100%)	<0.01	<0.01	100	<0.01

TGOPE is characterized by low water solubility (0.056 mg/L), very low vapour pressure (5.7×10^{-12} Pa), moderately high log K_{oc} (3.72) and very low Henry's Law constant (3.6×10^{-15} Pa·m^3/mol; see Table 2a). Thus, the water, soil and sediment compartments are where the majority of TGOPE is expected to reside, depending on the compartment of release, while the air compartment is of lesser importance for this substance.

If released to air, TGOPE will partition primarily to soil, with small amounts partitioning to air, water and sediment (See Table 4 above). The very low modelled vapour pressure and Henry's Law constant indicate that TGOPE behaves essentially as a non-volatile chemical.

If present in the ambient atmosphere, it is expected to exist almost entirely in the particulate phase. This is further supported by TGOPE's high octanol-air partition coefficient, a log K_{oa} of 23.3 as predicted by KOAWIN (2008), and the fraction of aerosol sorption predicted by AEROWIN (2008) of 1.0, indicating that TGOPE will sorb completely to airborne particulates.

If released to water, the majority of this substance will remain in water. The moderately high log K_{oc} value of 3.72 (Table 2a) indicates that TGOPE is expected to strongly sorb to suspended solids and sediments, with the remainder remaining in water. Volatilization from water surfaces is not expected based upon the very low Henry's Law constant. Thus, if water is a receiving medium, TGOPE will mainly partition to water and, to a lesser extent, to sediment (Table 4).

If released to soil, TGOPE is expected to sorb strongly to soil particles given its moderate to high log K_{oc} value of 3.72. Volatilization from moist soil surfaces seems to be an unimportant fate process based upon the very low Henry's Law constant (Table 2a). Considering the very low vapour pressure, this chemical will not volatilize appreciably from dry soil surfaces either. Therefore, if soil is a receiving medium, TGOPE will likely remain exclusively in soil (Table 4).

Therefore, it can be concluded from the results of the Level III fugacity modelling (Table 4) that when TGOPE is released into the environment, the major media of concern are expected to be soil, water and sediment (depending on the medium of release).

The most likely hydrolysis product, as predicted by CATABOL (2004–2008; see Persistence section), is predicted by EPI Suite (2008) to be much more soluble in water (3.8 mg/L) and have lower log K_{OW} value (1.2) than TGOPE, and hence more of the hydrolysis product will remain in water, and proportionally less will partition to sediment.

Persistence and Bioaccumulation Potential

Environmental Persistence

No experimental data on the degradation of TGOPE were found. Therefore, a quantitative structure-activity relationship (QSAR) and analogue-based weight-of-evidence approach (Environment Canada 2007) was applied using the data described below.

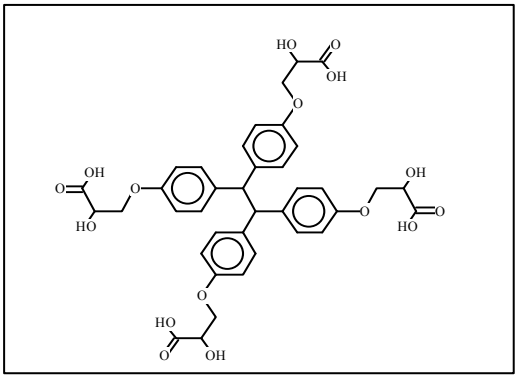
In air, an atmospheric oxidation half-life value of 0.47 hours is predicted by AOPWIN (2008) as a result of reactions with hydroxyl radicals, suggesting that gas-phase TGOPE is rapidly oxidized. AOPWIN (2008) does not provide an estimate for the reaction of this substance with other photo-oxidative species in the atmosphere, such as ozone (O_3). However, based on reactions with hydroxyl radicals, TGOPE is not considered persistent in air. Given that it is not expected to be released to air (see Table 3), only a small amount of TGOPE is expected to remain in air if released to air (see Table 4), and it has a half-life in air of less than 1 hour, modelling of its long-range transport potential was not performed.

Empirical biodegradation and hydrolysis data were identified for an analogue, Substance A, and are presented in Tables 5a and 5b below. Robust study summaries for these studies are found in Appendix II. Substance A has suitable structural similarity to TGOPE as it contains the phenyl oxirane ether functionality of TGOPE, but has approximately half of the structure and molecular weight of TGOPE (refer to Physical and Chemical Properties section). Consequently, this analogue presents a best-case scenario for the biodegradation and hydrolysis of TGOPE because it has a higher bioavailability and solubility in soil and water than TGOPE, and therefore a lower sorption potential (i.e., lower potential for bound residues occurring).

The biodegradation and hydrolysis potential of TGOPE could not be predicted using QSAR models with sufficient reliability. The model training sets do not include oxiranes in their fragment libraries or chemical training sets used to derive predictions. Model predictions are thus not reported for TGOPE. However, epoxides are known to readily hydrolyze, with half-lives between 5 and 15 days at pH 7 (Mabey and Mill 1978). The empirical hydrolysis data for analogue Substance A are consistent with this information,

with hydrolysis half-lives between 5 and 7 days at environmentally relevant pHs (see Table 5a). TGOPE, however, is predicted to be less soluble in water than the analogue Substance A by a factor of 5. The lower water solubility reduces the "chemo-availability" of TGOPE and thus is likely to have a limiting effect on the rate of hydrolysis. The limiting effect is not linearly related to water solubility; thus TGOPE is expected to hydrolyze at a slower rate than Substance A, but the hydrolysis half-life in water is still likely well below 182 days.

Hydrolysis of TGOPE and Substance A is expected to occur via oxirane hydration, which results in the epoxide ring opening up to form linear di-alcohol substituents on the phenyl rings. Further hydroxyl and aldehyde oxidation processes are predicted to produce a stable hydroxylated carboxylic acid transformation product. This transformation product was predicted for TGOPE to form with high probability (p) and reliability (r) using the CATABOL (2004-2008) model (p = 1.0, r = 1.0) (shown in Figure 1 below).



Chemical formula: $C_{38}H_{38}O_{16}$
Molecular mass: 750.72 g/mol

Figure 1. Structure of the predicted hydrolysis product of TGOPE

Table 5a. Empirical data for hydrolysis of analogue substance A

Test method	Temperature (°C)	pH	Half-life (days)	Reference
OECD 1981e (Guideline 111)	25	4 7 9	7 7.1 5.0	Study Submission 1991b

The biodegradation potential of TGOPE and its hydrolysis product are also likely to be limited, based on the empirical biodegradation data for Substance A (Table 5b). The biodegradation data for Substance A (Table 5b) show that a negligible proportion of the

theoretically possible oxygen demand was consumed during the closed bottle test, while in the Sturm test, a negligible proportion of the theoretically possible carbon dioxide was evolved over the 28 days of the test. This indicates that in both tests, Substance A and its hydrolysis product were not significantly degraded in 28 days. These biodegradation studies are considered to be reliable. Substance A was not found to cause microbial inhibition under test conditions. An emulsifier was used to help keep Substance A in solution, which provided an optimal bioavailability for biodegradation (i.e., reduces bound residue interferences). The emulsifier was also found not to have an inhibitory effect on microbial oxygen consumption under the test conditions.

Table 5b. Empirical data for biodegradation of analogue substance A

Test method	Results	Time (d)	Conclusion	Reference
EEC[1] closed bottle (Test Method C4-E)	-3, 3% ThOD[2]	28	Not readily biodegradable	Study Submission 1992a
Modified Sturm (EEC[1] Test Method C4-C)	3 , 4 % $ThCO_2$[3]	28	Not readily biodegradable	Study Submission 1992a

[1]EEC = European Economic Commission Test Methods (EEC 2009)
[2] ThOD = theoretical oxygen demand
[3] $ThCO_2$ = theoretical CO_2 formation

It is likely that the above biodegradation data for Substance A also accounts for the biodegradation potential of the hydrolysis product(s) of Substance A, as nearly complete hydrolysis would be expected to occur within the timeframe of the biodegradation study (28 days). Because minimal biodegradation was observed in the biodegradation studies for Substance A under optimized ready biodegradation conditions (Table 5b), it appears that its hydrolysis product is stable and does not readily biodegrade.

The rate of hydrolysis of TGOPE is expected to be somewhat slower than that of Substance A; complete hydrolysis may not occur within the time frame of a 28-day biodegradation study, especially if solubilizing agents are not used. The hydrolysis product of TGOPE is likely to occur in surface waters within the time frame of Canadian persistence criteria (182 days). This expected product represents primary transformation. Reliable estimates of the biodegradation potential of this hydrolysis product could not be obtained using available models due to lack of sufficient structural coverage in model training sets.

Based on the empirical biodegradation data for the analogue Substance A (Table 5b), which shows that this substance and its hydrolysis product will not biodegrade even under favourable conditions, it is expected that the hydrolysis product of TGOPE will also be persistent. A substance is considered very persistent if inherent biodegradation test results are < 20% biodegradation (Aronson et al. 2006; ECETOC 2006).

Considering that the hydrolysis of TGOPE is likely to occur within 182 days, TGOPE is not considered to be persistent in water as defined in the *Persistence and Bioaccumulation Regulations* (Canada 2000). A similar relatively short half-life may also be expected for sediments and moist soils, but the substance is likely more stable under dry soil conditions. However, it is not likely to be released to soil without being part of a liquid formulation where hydrolysis would occur (e.g., biosludges). TGOPE is also not considered persistent in air, as it does not meet the half-life criteria of ≥ 2 days) as defined in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Based on the analogue and modelled data, the hydrolysis product of TGOPE is considered to be persistent in water as defined in the *Persistence and Bioaccumulation Regulations* (Canada 2000). Using an extrapolation ratio of 1:1:4 for a water: soil: sediment biodegradation half-life (Boethling et al. 1995), the biodegradation half-life in soil is also ≥ 182 days and the half-life in sediments is ≥ 365 days. Therefore, the hydrolysis product of TGOPE is considered to be persistent in water, soil and sediments as defined in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

The predicted log K_{ow} value of 5.5 (Table 2a) suggests that TGOPE has the potential to bioaccumulate in the environment.

Since no experimental bioaccumulation factor (BAF) or bioconcentration factor (BCF) data for TGOPE or Substance A were available, a predictive approach was applied using available BAF and BCF models as shown in Table 6 below. According to the *Persistence and Bioaccumulation Regulations* (Canada 2000) a substance is bioaccumulative if its BCF or BAF is ≥ 5000; however, measures of BAF are the preferred metric for assessing bioaccumulation potential of substances. This is because the BCF may not adequately account for the bioaccumulation potential of substances via the diet, which predominates for substances with log K_{ow} > ~4.0 (Arnot and Gobas 2003). Kinetic mass-balance modelling may provide the most reliable prediction for determining the bioaccumulation potential because it allows for chemical-specific metabolic biotransformation rates to be included as long as the log K_{ow} of the substance is within the log K_{ow} domain of the model.

BCF and BAF estimates, corrected for potential biotransformation, were generated using the BCFBAF model (2008) and are included in Table 6. The BCFBAF model includes a mass balance bioaccumulation screening model. Metabolic rate constant (k_M) estimates are therefore included within the model using quantitative structure-activity relationships described further in Arnot et al. (2008a, 2008b, 2009). Since metabolic rates are related to body weight and temperature (Hu and Layton 2001; Nichols et al. 2007), the BCFBAF model provides a k_M estimate of 0.128 /day for a 10 g fish at 15°C. This value is scaled by the BCFBAF model to the body weight of the middle trophic level fish in the Arnot-

Gobas model (184 g) (Arnot et al. 2008b). The middle trophic level fish was used to represent overall model output as suggested by the model developer and is most representative of fish weight likely to be consumed by an avian or terrestrial piscivore.

Other modelled BCF data for TGOPE are shown in Table 6.

The modelled data contained in Table 6 are considered to be reliable, as TGOPE falls within most of the domains of the models. However, the chemical fragment library of BCFBAF does not include oxirane or tetraphenyl ethane. The structural fragments that were used to determine the BAF and BCF values within BCFBAF included: aromatic ether, aliphatic ether, alkyl substituent on aromatic ring, aromatic CH, aromatic H, -CH2- (linear and cyclic), CH (cyclic) and benzene. TGOPE is considered to be 96% within the structure domain of the Dimitrov et al. (2005) model, which also takes metabolism into account.

Table 6. Fish BAF and BCF predictions for TGOPE

Test organism	Endpoint	Value wet weight (L/kg)	Reference
Fish	Arnot-Gobas BAF, middle trophic level	5263	BCFBAF 2008
Fish	Arnot-Gobas BAF, lower trophic level	8145	BCFBAF 2008
Fish	Arnot-Gobas BCF, middle trophic level	2533	BCFBAF 2008
Fish	BCF	7.7	Dimitrov et al. 2005
Fish	BCF, linear regression	1977	BCFBAF 2008

Predicted BCF values for TGOPE are much lower than predicted BAF values, likely because the BCF models do not account for uptake via the diet. Even among the BCF estimates there is considerable variation, reflecting differences in how the model addresses biotransformation. The BCFBAF (2008) linear regression estimate of BCF does not account for biotransformation at all. The Arnot-Gobas middle trophic level BCF (BCFBAF 2008) uses rate constants (k_M) to account for biotransformation, while the Dimitrov et al. (2005) model uses structure and metabolic transformation pathways to correct for biotransformation.

As noted above, BAFs are the preferred measure for estimating bioaccumulation. The modified Gobas BAF middle trophic level model for fish predicted a BAF of 5263 L/kg (Table 6). This model also predicted a BAF of 8145 L/kg for the lower trophic level fish.

Given that BAF predictions for TGOPE exceed 5000, TGOPE meets the bioaccumulation criteria (BCF or BAF ≥ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Since TGOPE is predicted to hydrolyze in water with a half-life of less than 182 days (see Persistence section), the bioaccumulation of the stable hydrolysis product as predicted by CATABOL (see Figure 1, Persistence Section), was considered. This hydrolysis product was predicted to have a log K_{OW} value of 1.2 (KOWWIN 2008), and a log BAF value of 0.3 L/kg for the middle trophic level fish (BCFBAF 2008). Therefore the hydrolysis product does not meet the bioaccumulation criteria (Canada 2000).

Potential to Cause Ecological Harm

Ecological Effects Assessment

A – In the Aquatic Compartment

TGOPE is predicted to cause harm to aquatic organisms at relatively low concentrations (Table 7), based on analogue data.

A range of aquatic toxicity values were obtained from the various QSAR models, including ECOSAR (2008), OASIS (2005) and AIEPS (2003–2007). However, none of these models have substances in their training sets that are very similar to TGOPE, such as oxiranes or tetraphenyls. This reduces the reliability of the model predictions. Because good quality empirical data for analogue Substance A were available, the aquatic toxicity assessment of TGOPE is based on the analogue data, which are presented in Table 7. The robust study summary for the algae toxicity study is found in Appendix II.

Substance A is a smaller molecule with higher solubility and a slightly lower predicted K_{OW} than TGOPE (see Tables 2a,b); it is therefore likely more bioavailable than TGOPE and its toxicity may be higher than that of TGOPE.

Toxicity tests for Substance A were conducted according to OECD Guidelines 203 and 201 (OECD 1992, 2006). The tests were static, non-renewal for the algae and daphnid studies and static with daily renewal for the test with Rainbow Trout. Acetone was used as a solubilizer at a concentration of 10 µL/L (10 ppm) in the algae and daphnid tests, and at a concentration of 100 µL/L (100 ppm) in the Rainbow Trout test. Only one concentration of Substance A was tested in each of these toxicity studies. However, range-finding tests at nominal concentrations of 0.002, 0.02 and 0.2 mg/L had also been conducted with the algae *P. subcapitata* (*S. capricornutum*). No toxicity was observed at any concentration during the range-finding tests. These toxicity results were considered valid, as they are below the measured water solubility of 0.30 mg/L for Substance A. These results for Substance A are above, but within ten times of, the estimated water solubility of TGOPE (0.06 mg/L). Given that concentrations for both toxicity and water solubility are often uncertain, toxicity values that exceeded solubility estimates by up to a factor of 10 are considered to be acceptable.

Table 7. Empirical data for aquatic toxicity of analogue Substance A

Test organism	Type of test	Test methods	Results	Reference
Algae (*Pseudokirchneriella subcapitata*)	(72 hours), growth inhibition	Official Journal of the European Communities, Parts C1 (Fish), C2 (Daphnia) and L133 (Algae)	16.9% and 3.8% inhibition after 72 hours; LOEC[1] = 0.15 mg/L NOEC[2] < 0.15 mg/L	Study Submission 1992b
Daphnia magna	Acute (48 hours)		0% immobilized after 48 h; NOEC[2] > 0.15 mg/L	Study Submission 1992b
Rainbow Trout (*Oncorhynchus mykiss*)	Acute (96 hours)		No effects at 0.1 mg/L; NOEC[2] > 0.1 mg/L	Study Submission 1992b

[1] LOEC – The lowest-observed-effect concentration is the lowest concentration in a toxicity test that caused a statistically significant effect in comparison to the controls.
[2] NOEC – The no-observed-effect concentration is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls.

The above toxicity data for Substance A indicate effects to algae at a concentration of 0.15 mg/L. Therefore, Substance A has been shown to have the potential to harm algae at relatively low concentrations. Based on these analogue data, it is predicted that TGOPE will also have the potential to harm algae at low concentrations.

Predictions of the toxicity of the hydrolysis product of TGOPE (see Persistence section), were made using ECOSAR (2008). It is predicted to be much more soluble (3.8 mg/L) in water than TGOPE (EPI Suite 2008) and to have a much lower ecotoxicity potential. It was modelled by ECOSAR as part of the class "Neutral organics – acid." Acute predicted mean lethal concentration (LC_{50}) values for fish, daphnia and algae for the hydrolysis product ranged from 4900 to 44 000 mg/L (ECOSAR 2008), which exceed its predicted water solubility by factors exceeding 1000. Therefore, the hydrolysis product of TGOPE has a low predicted toxicity.

B – In Other Environmental Compartments

When TGOPE is released into a water body, it is predicted to partition into suspended particulate matter and to bottom sediments (see Table 4), where sediment-dwelling organisms would be exposed to the substance. However, no environmental monitoring data or toxicity data specific to sediment-dwelling organisms are available for this substance

No suitable ecological effects studies were found for this substance in media other than water.

Ecological Exposure Assessment

No data concerning concentrations of TGOPE in water in Canada or elsewhere have been identified; therefore, environmental concentrations are estimated from available information, including estimated substance quantities, release rates, and size of receiving water bodies.

A – Industrial Release

As TGOPE is used industrially and is expected to be released to water, a realistic but conservative industrial release scenario was used to estimate the aquatic concentration of the substance with the help of Environment Canada's (2009c, 2009d) Industrial Generic Exposure Tool – Aquatic (IGETA). The IGETA equation is given below:

$$C_I = \frac{1000 \times Q_I \times L \times (1 - R)}{N \times S \times D}$$

where:
C_I: Aquatic concentration due to industrial release, mg/L
Q_I: Total substance quantity used annually, kg/yr
L: Loss to wastewater, %
R: wastewater treatment plant removal rate, fraction
N: Number of annual release days, d/yr
S: wastewater treatment plant effluent flow, m^3/d
D: Dilution
factor of receiving water, unitless

Wastewater treatment plant removal rates after primary and secondary treatment of 70%, 89% and 67% were predicted using the models SimpleTreat (1997), STP (2001) and ASTreat (2006), respectively (Environment Canada 2009e). The predicted environmental concentration (PEC) calculation used the most conservative removal rate of 67%, as modelled by ASTreat (2006).

The quantity of TGOPE used in this scenario (which is confidential) is the amount used by the largest customer of the Canadian importer, as reported to Environment Canada for the year 2006 (Environment Canada 2009a). All of this quantity is used at one site. The dilution factor into the receiving creek is the actual dilution factor (assuming instantaneous mixing in the receiving water) based on a relatively low (10th percentile) flow at this location (Environment Canada 2009f). The local wastewater treatment plant effluent flow has also been used (Environment Canada 2009f). A conservative (high) loss to wastewater is used in this scenario: 1.6% of the total quantity resulting from the cleaning of chemical containers and other industrial processes (refer to the Releases to the Environment section). The scenario also assumes that the release occurs 250 days per year, typical for small and medium-sized facilities, and is sent to a local wastewater treatment plant with a 67% removal rate for the substance, but no removal (e.g., by degradation) in the receiving surface water.

The PEC is based on exposure to the unreacted parent substance (TGOPE), as the average residence time inside of a wastewater treatment plant is less than one day (Crechem 2005) whereas the hydrolysis half-life of this substance is at least 5–7 days (see Persistence section). It is assumed that there is continuous flow of TGOPE into and out of the wastewater treatment plant. Also, the hydrolysis product of TGOPE is predicted to have lower toxicity than TGOPE (see Ecological Effects Assessment section). Based on the above conservative exposure scenario, the aquatic PEC for TGOPE is 0.0003 mg/L (Environment Canada 2009d).

B – Consumer Release

No estimate of releases to water from consumer uses was made, as TGOPE is not expected to be released to water or other environmental compartments from consumer uses (refer to Releases to the Environment section).

Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine various supporting information and develop conclusions based on a weight-of-evidence approach and using precaution as required under CEPA 1999. Lines of evidence considered include results from a conservative risk quotient calculation, as well as information on persistence, bioaccumulation, toxicity, sources and fate of the substance.

TGOPE hydrolyzes, and therefore is not considered to be persistent in water, but has the potential to bioaccumulate. The hydrolysis product of TGOPE is considered to be persistent in water, soil and sediment, but has properties sufficiently different from the parent substance that it is considered not bioaccumulative. The importation volumes of TGOPE into Canada, along with information on its uses, indicate low potential for releases into the Canadian environment. Releases of TGOPE will be mainly to surface

waters via industrial wastewater releases (refer to Releases to the Environment section), though it will ultimately reside mainly in sediments (see Table 4). TGOPE has also been predicted to have the potential to harm sensitive aquatic organisms at relatively low concentrations (see Ecological Effects Assessment section).

A risk quotient analysis, integrating conservative estimates of exposure with toxicity information, was performed for TGOPE for the aquatic medium to help determine whether there is potential for ecological harm in Canada. The industrial scenario presented above yielded a PEC of 0.0003 mg/L (Environment Canada 2009c). A predicted no-effect concentration (PNEC) was derived from the analogue alga toxicity lowest-observed-effect concentration (LOEC) of 0.15 mg/L (see Table 7a). This value was selected for PNEC derivation as it is the lowest analogue toxicity value, and the predicted data were deemed to be of low quality. The PNEC was derived by dividing this toxicity value by an assessment factor of 10, to account for interspecies and intraspecies variability in sensitivity, to give a PNEC of 0.015 mg/L. The resulting risk quotient (PEC/PNEC) = 0.02. Therefore harm to aquatic pelagic organisms from industrial use of TGOPE in Canada is unlikely.

A risk quotient for TGOPE based on exposure in sediment pore water may be calculated based on the aquatic compartment PEC and PNEC values presented above. In the calculation, bottom sediment and its pore water are assumed to be in equilibrium with the overlying water, and benthic and pelagic organisms are assumed to have similar sensitivities to the substance. Therefore the PEC and PNEC for pore water is considered to be the same as for the aquatic compartment. This equilibrium approach would result in a risk quotient (PEC/PNEC) for the sediment compartment that is the same as for the aquatic compartment. Therefore, harm to sediment-dwelling organisms from TGOPE in Canada is unlikely.

No risk quotient analysis was prepared for the hydrolysis product of TGOPE, as it is predicted to be much less toxic than TGOPE (see Ecological Effects Assessment section), and therefore would have a lower risk quotient than TGOPE.

This information suggests that TGOPE and its hydrolysis product are unlikely to cause ecological harm in Canada.

Uncertainties in Evaluation of Ecological Risk

There are no experimental data for most of the physical and chemical properties, persistence, bioaccumulation, and toxicity of TGOPE. Therefore, this ecological assessment was based on modelled and analogue data. The empirical analogue data were considered to be of high quality, and modelled data were used where it was considered to be of acceptable reliability.

Regarding ecotoxicity, based on the predicted partitioning behaviour of this chemical, the significance of sediment as an important medium of exposure is not well addressed by the effects data available. Indeed, the only effects data identified apply to pelagic aquatic exposures, although the water column may not be the only medium of concern based on partitioning estimates.

Potential to Cause Harm to Human Health

Exposure Assessment

Environmental Media and Food

From the published literature, no empirical data were identified for TGOPE measured concentrations in environmental media (air, water, soil and sediment) in Canada or elsewhere. In addition, no studies were identified reporting the presence of TGOPE in food. In the absence of release data from publicly available inventories and the section 71 survey of CEPA 1999 (Environment Canada 2009a), as a conservative approach, environmental concentrations were conservatively estimated using the loss percentages predicted by the Mass Flow Tool (see Table 3) applied to the maximum of the import quantity range of TGOPE in Canadian commerce in 2006 (10 000 kg) (Environment Canada 2009c).

The maximum loss quantities of 160 kg to water through industrial wastewater and 100 kg to soil or landfill leachate through migration from landfills were estimated while the majority of the substance is chemically transformed during industrial use (up to 99.6%). These loss quantities to water and soil/landfill are likely overestimates as wastewater treatment is not considered nor that only a small fraction of the substance would be expected to escape from landfills (e.g., in leachate).

Based on these estimated losses, ChemCAN, a Canada-specific environmental exposure model (ChemCAN 2003), was used to predict concentrations of TGOPE in various environmental media. The resulting conservative upper-bounding daily intakes of TGOPE for the general population of Canada were in the order of nanograms per kg-bw (kilogram of body weight) per day.

Consumer Products

TGOPE is used in epoxy resins in Canada and elsewhere. One submission received has reported the use of TGOPE in an epoxy-patch adhesive resin consumer product containing between 10 and 30% of TGOPE (Environment Canada 2009a, Henkel 2009). It is a general purpose adhesive with high temperature performance, when applied to different materials such as wood, metal, ceramics, and most plastics (Environment Canada 2009a; Henkel 2009; Loctite 2001). While consumers could order this product directly from the distributor, it is unlikely that this product is widely available to the general population of Canada.

Exposure to TGOPE from the use of epoxy adhesives (such as for home repair projects) were estimated using ConsExpo v.4.1 (ConsExpo 2006). The upper-bounding concentration of 30% was used to derive conservative upper-bounding exposure

estimates (Environment Canada 2009a, Henkel 2009). A mixing ratio of 1:1 (resin: hardener) was applied, resulting in an upper-bounding TGOPE concentration of 15% in epoxy adhesives (Henkel 2009, 2010 personal communication from Industry to Risk Management Bureau, Health Canada; unreferenced). An estimate of exposure to TGOPE from use of epoxy adhesives predicts air concentrations during use ranging from 4.1×10^{-9} to 8.5×10^{-7} mg/m^3 (Appendix III). The selected scenarios correspond to gluing a handle on a coffee mug or gluing a large vase. However, it is expected that the majority of exposures will occur at the lower end of this range.

Dermal exposure may also result from the use of this product, and the upper-bounding potential intake per use for adults was estimated to be 0.212 mg/kg-bw as applied dose (Appendix III). Confidence in these estimates is low, as they are based on a number of assumptions; however it is likely that they overestimate actual exposures from this source. Skin permeability of TGOPE is expected to be very low based on data reported for similar aromatic glycidyl ethers (Boogaard et al. 2000a) (refer to Health Effects Assessment section).

Health Effects Assessment

Appendix IV contains a summary of the available health effects information for TGOPE.

No classifications and assessments of the health effects of TGOPE by national or international regulatory agencies were identified. *In vitro* genotoxicity data for TGOPE suggested potential direct-acting mutagenic effects. Ames assays and chromosomal aberration assays were positive in the presence or absence of metabolic activation (S9) when tested with Epon resin 1031-B-80 (containing 80% TGOPE and 20% methyl ethyl ketone) (Shell Development Company 1984a, c). A mouse lymphoma assay tested with Epon resin 1031-B-80 was positive in the absence and negative in the presence of S9 (Shell Development Company 1984b). The negative result with metabolic activation suggests that TGOPE may be mutagenic as a primary compound but that treatment with S9 may have masked the direct-acting mutagenic potential, as the reactive groups in TGOPE could be occupied by macromolecules in the S9 fraction. Since methyl ethyl ketone has not demonstrated genotoxicity in a battery of tests including Ames assays, mouse lymphoma assays, unscheduled DNA synthesis, chromosomal aberration and sister chromatid exchange *in vitro* and micronucleus induction *in vivo* (IRIS 2003), the positive genotoxicity observed for Epon resin 1031-B-80 could be reasonably attributed to TGOPE. As only limited data were available with respect to the potential toxicity of TGOPE, relevant information on potential analogues of this substance were also considered. The outputs of predictive QSAR models (TOPKAT 2004; CASETOX 2008; DEREK 2008; Model Applier 2008) on TGOPE generated mixed results for carcinogenicity and genotoxicity endpoints (Appendix V).

Data on several analogue substances (Appendix VI) were examined to better inform the understanding of the potential health effects associated with exposure to TGOPE. The use

of analogue substances as surrogates is an approach that has been employed by several national and international regulatory agencies. The U.S. Environmental Protection Agency's HPV Challenge program, the European Chemical Agency's REACH regulation, and the Organisation for Economic Co-operation and Development's HPV Chemicals programme have all developed guidance documents relating to such an approach. The approach used in the present assessment is consistent with the general principles described by the above-mentioned authorities; i.e., the selection of chemical analogues included in this report is based on the presence of the aromatic glycidyl ether functional group and other structural similarities, physical and chemical properties, and the availability of carcinogenicity and genotoxicity data. The epoxide ring of the aromatic glycidyl ether group was identified as the most important criteria for assessing the carcinogenic and mutagenic potential due to the presence of the epoxy ring. Epoxides are reactive due to their three-membered ring structure which is highly strained, and act as alkylating agents *in vivo* with the ability to covalently bind with DNA (Koskinen and Plná 2000; Solomon 1999). Aliphatic epoxides had been shown to be genotoxic with the ability to induce DNA adduct, chromosomal aberration and sister chromatid exchange (Das et al. 1993; Giri et al. 1989; Koskinen and Plná 2000). Toxicity data on related aromatic epoxides are summarized in the sections below.

No empirical toxicity data were identified for chemical analogues containing 4 benzene rings. Suitable analogues containing 2 benzene rings and glycidyl ether functional groups, with similar physical and chemical properties and available empirical toxicity data, are bisphenol A diglycidyl ether (BADGE) and Substance A. Substance A has been described earlier in the "Physical and Chemical Properties" section of this assessment. Two other analogues containing a benzene ring and glycidyl ether functional group(s) were diglycidyl resorcinol ether (DGRE) and phenyl glycidyl ether (PGE). Toxicity data for these analogues were included in this assessment for a better understanding of the aromatic glycidyl ethers as a class. As limited empirical toxicity data for TGOPE suggested genotoxic potential and the 4 epoxy functional groups contained in TGOPE are a hazard concern, genotoxicity and carcinogenicity data for the 4 analogues of TGOPE are described below and summarized in Appendix VII.

Identification of BADGE as a potential analogue for TGOPE was further confirmed with similarity searches in SciFinder (72% similarity) and ChemIDplus® (74% similarity) (CAS 2009; US NLM 2008). The International Agency for Research on Cancer (IARC 1989, 1999a) classified BADGE as a Group 3 carcinogen (not classifiable as to its carcinogenicity to humans). The European Food Safety Authority (EFSA) reviewed toxicity data for BADGE, its chlorohydrins and its hydrolysis products and concluded that BADGE has direct-acting mutagenic effects *in vitro* and is not mutagenic *in vivo* (EFSA 2004). However, it should be noted that the assessment by EFSA focused on the oral route and considered BADGE-related compounds that do not contain the DNA alkylating epoxy rings. In a 2-year oral gavage toxicity study, no significant increased incidence of tumours were observed in Fischer 344 rats administrated 0, 2, 15 or 100 mg/kg-bw per day of BADGE (Stebbins and Dryzga 2003). In a dermal study using pure BADGE, mice were exposed to 0, 1 or 10% solution of BADGE (corresponding to approximately 0, 70 or 700 mg/kg-bw per day respectively) by dermal application for 2

years (Persitianis et al. 1988). A low increased incidence of tumours that was not statistically significant was noted at the site of application and at other sites. In addition, a statistically significant trend was observed for the occurrence of thymic lymphosarcoma in females. In terms of *in vitro* genotoxicity studies, some mutagenic responses were observed in certain strains of *Salmonella typhimurium* and *S. cerevisiae* (Brooks et al. 1981; Canter et al. 1986). Induction of chromosomal aberration *in vitro* was also identified in mammalian cells (Brooks et al. 1981). In *in vivo* genotoxicity studies, DNA adduct was observed in isolated epidermal DNA in male mice given a single topical dose of BADGE under occluded conditions (Steiner et al. 1992). Negative results were observed in micronucleus assays, DNA damage assays and dominant lethal assays (Hine et al. 1981; Pullin 1977; Wooder and Creedy 1981).

The identity of Substance A is confidential. Substance A was not found in the SciFinder or ChemID database, and the available toxicity information presented here was based on Health Canada's New Substances database. References to the toxicity data for Substance A may not be identified due to confidentiality. No chronic or long-term studies were identified to assess carcinogenicity, as the only repeated-dose study identified was a 28-day study. Positive *in vitro* genotoxicity data were identified, including Ames assays, mouse lymphoma assays and chromosomal aberration in Chinese hamster ovary cells suggesting a mutagenic potential. The only *in vivo* genotoxicity study identified showed no induction of micronucleus in mice.

Diglycidyl resorcinol ether (DGRE) is classified by IARC (1985, 1999b) as a Group 2B carcinogen (possibly carcinogenic to humans) and by the European Commission (ESIS 2009) as a Category 3 carcinogen for carcinogenicity (causes concern to humans owing to limited evidence of a carcinogenic effect). With respect to carcinogenicity, 2-year oral gavage studies in Fischer 344/N rats and B6C3F1 mice showed induction of squamous-cell carcinomas and papillomas of the forestomach in animals of both species and both sexes. In female mice, significantly increased incidences of hepatocellular carcinomas were observed (NTP 1985). Although a human counterpart for the rodent forestomach does not exist, development of forestomach tumour through a genotoxic mechanism is relevant to humans (Proctor et al. 2007). Based on a limited study, no skin tumours were induced in a dermal carcinogenicity study in mice (Van Duuren et al. 1965). For genotoxicity, *in vitro* studies indicated mutagenicity in certain strains of *Salmonella typhimurium* in Ames tests and in mouse lymphoma assays (Canter et al. 1986; McGregor et al. 1988, 1996; Seiler 1984). Chromosomal aberration and sister chromatid exchange were positive in Chinese hamster ovary cells (Gulati et al. 1989; Seiler 1984). Mixed results were identified for micronucleus induction *in vivo* (Seiler 1984; Shelby et al. 1993). In terms of mutagenicity in germ cells, positive results were observed for sex-linked recessive lethal and reciprocal translocation assays in *Drosophila melanogaster* (Valencia et al. 1985).

Phenyl glycidyl ether (PGE) is classified as a Group 2B carcinogen by IARC (1999f) and as a Category 2 carcinogen (should regard as carcinogenic to humans with adequate animal evidence) and a Category 3 mutagen (suspect agent but with limited information available) by the European Commission (ESIS 2009). In the only identified

carcinogenicity study for PGE, rats were exposed to 0, 6 or 74 mg/m^3 for 24 months by inhalation (Lee et al. 1983). Exposure-related nasal tumours were observed at 74 mg/m^3 (statistical significance not specified). Increased incidences of rhinitis and squamous metaplasia were also observed at 74 mg/m^3 and were considered to be related to the nasal tumours. *In vitro* genotoxicity studies were generally positive in micro-organisms, showing direct-acting mutagenic response in *Salmonella typhimurium* TA97, TA100, TA1535 (Canter et al.1986; Greene et al. 1979; Ivie et al. 1980; Neau et al. 1982; Ohtani and Nishioka 1981; Seiler 1984), *Klebsiella pneumoniae* and *Escherichia coli* (Hemminki et al. 1980a; Ohtani and Nishioka 1981; von der Hude et al. 1990; Voogd et al. 1981). No effect on chromosomal aberration was observed in Chinese hamster ovary cells (Greene et al. 1979). The *in vivo* genotoxicity studies were negative, including micronucleus induction, chromosomal aberration and dominant lethal assays (Greene et al. 1979; Seiler 1984; Terrill et al. 1982).

Generally, the analogues showed direct-acting mutagenic effects *in vitro* and some evidence of carcinogenicity, although *in vivo* genotoxicity results were mixed. In addition to the analogues, a number of aliphatic glycidyl ethers such as n-butyl glycidyl ether, propylene oxide, 1,2-epoxybutane and epichlorohydrin were shown to have mutagenic effects and carcinogenic potential, and classified by national and international regulatory agencies for carcinogenicity (ESIS 2009; Health Canada 2009; IARC 1976, 1994, 1999c,d; NTP 2004, 2005a,b; US EPA 1994a,b).

Epoxy dermatitis, sensitization to epoxy compounds, had been reported in occupational settings where a number of low-molecular-weight epoxy compounds can induce direct or airborne contact dermatitis (Jolanki et al. 2000). TGOPE was a minimal irritant to skin and eyes and was not a skin sensitizer in animals (Mellon Institute 1979; Shell Development Company 1983). Substance A was minimally irritating to eyes and was not a skin irritant or sensitizer in animals. In contrast, BADGE and PGE are both known contact allergens in exposed workers, while DGRE can cause severe burns and skin sensitization (IARC 1989, 1999a,b,f).

The epoxide functional group is expected to be the most reactive site for TGOPE. The epoxide moiety in glycidyl compounds can be hydrolyzed to the corresponding (bis-)diols both through the epoxide hydrolase enzymatically and nonenzymatically or conjugated with endogenous tripeptide glutathione (GSH) catalyzed by glutathione S-transferase (GST) (Boogaard et al. 2000b; IARC 1989, 1999a). Empirical toxicokinetic data for TGOPE and Substance A were not identified. Oral administration of BADGE is metabolized in mice to its corresponding bis-diol followed by mono-oxygenase-mediated dealkylation in forming the corresponding phenol and glyceraldehyde (Climie et al. 1981). BADGE can also be directly oxidized with the release of glycidaldehyde, which is a Group 2B carcinogen classified by IARC (1999e). Urinary and fecal metabolites included glucuronides and sulfates of the bis-diol and corresponding carboxylic acids. Empirical data on DGRE metabolizing to its corresponding bis-diol were also identified (Seiler 1984). With respect to PGE, metabolic data catalyzed by epoxide hydrolase and by GST were identified (de Rooij et al. 1998; Wit and Snel 1968).

In one study, where metabolism of five glycidyl ethers were compared using human liver and lung isolates (Boogaard et al. 2000b). The glycidyl ethers containing two aromatic glycidyl ethers functional groups, including BADGE and Epikote YX4000 were found to have much higher affinity for epoxide hydrolase than the GST enzymatic route when compared to glycidyl ethers containing 1 benzene ring or alkyl glycidyl ethers (Boogaard et al. 2000b). An *in vitro* dermal penetration study of the same five glycidyl ethers found that skin permeation correlates with lipophilicity, expressed as log $K_{ow,}$ and molecular weight (Boogaard et al. 2000a). The two glycidyl ethers containing two aromatic glycidyl ether functional groups, (BADGE and Epikote YX4000), were found to be much less permeable through the skin compared to the other glycidyl ethers due to higher molecular weight and lipophilicity. The percentage penetration of applied dose over 24hrs were calculated to range from 0.01 to 0.73% for Epikote YX4000 and 0.14 – 2.99% for BADGE of which only a small fraction remained as the parent aromatic glycidyl ether. The rest (> 97%) was detected as the metabolites indicating extensive metabolism in the skin (Boogaard et al. 2000a).

While specific metabolism and toxicokinetic data on TGOPE were not available, predictions can be made based on similar physical chemical properties to Epikote YX4000 and BADGE[2]. It would be expected that glycidyl ether groups of TGOPE would rapidly metabolized by epoxide hydrolase to the bis-diol. Since the molecular weight and lipophilicity of TGOPE are greater than that of either Epikote YX4000 or BADGE, dermal penetration of TGOPE would be expected to be very low (likely <1%) and involving extensive metabolism in the skin.

The confidence in the toxicity database of TGOPE is considered to be low to moderate; limited empirical data were identified, but analogues with substantial toxicity data increase the overall confidence in the hazard assessment for this substance.

Characterization of Risk to Human Health

Empirical data identified for TGOPE suggested direct-acting mutagenic potential *in vitro*. The 4 epoxy rings contained in TGOPE are the critical health effects concern, as each epoxy ring can bind covalently with DNA. Four aromatic glycidyl ether analogues that contained epoxy ring(s) were identified and informed the assessment of risk to human health of TGOPE. Some of the analogues were classified by national and international regulatory agencies for carcinogenicity and mutagenicity. The analogues, which contained the alkylating epoxy ring(s), had similar direct-acting mutagenic profiles as TGOPE *in vitro*. Some analogues were also shown to be carcinogenic in animal studies although *in vivo* genotoxicity data were mixed. The collective evidence from genotoxicity and carcinogenicity data for TGOPE and its analogues suggested that TGOPE has a potential for genotoxicity and carcinogenicity. Therefore it cannot be

[2] Molecular weight (MW) and Octanol-water partition coefficient (P_{OW}) of Epikote YX4000 and BADGE (Boogaard et al. 2000a): Epikote YX4000 (MW=354, logPow=5.2), BADGE (MW=341, logPow=3.8)

precluded that TGOPE could induce tumours via a mode of action involving direct interaction with genetic material.

The potential for exposure of the general population to TGOPE from environmental media is expected to be negligible. There is no expected exposure from food. In addition, exposure to TGOPE from consumer products (e.g., epoxy adhesives) is expected to be low. Exposure of the general population in Canada based on the use of the substance as an epoxy adhesive is expected to be low to negligible.

Uncertainties in Evaluation of Risk to Human Health

The scope of this screening assessment does not include a full analysis of the mode of action of TGOPE or its analogues, nor does it take into account possible differences between humans and experimental species in sensitivity. Empirical data for TGOPE are very limited. In addition, the majority of toxicity data identified were tested with a commercial product containing 80% TGOPE and 20% methyl ethyl ketone. Methyl ethyl ketone may have a confounding effect on the toxicity data, but a battery of *in vitro* and *in vivo* genotoxicity studies indicated the lack of genotoxic potential. The use of analogues as surrogates is an approach that is recognized by national and international regulatory agencies, but bias may be present in selecting analogues containing substantial toxicity data that generally possess a hazard potential. For one of the analogues, DGRE, some of the toxicity studies were tested with 88% pure DGRE. NTP (1985) gas chromatography analysis identified 30 unspecified impurities including major impurities: 1.9% 3-methylbenzoic acid ethyl ester, 1.6% 3-chloropropoxy-benzene and 2.8% dihydroxypropoxylbenzene. Impurities might have a confounding effect although no toxicity studies were identified for the major impurities. There is also uncertainty surrounding the use of data on analogue substances to extrapolate the potential carcinogenicity and genotoxicity of TGOPE.

Confidence in the exposure characterization for environmental media is considered to be low to moderate. There is uncertainty in the exposure to TGOPE from environmental media in Canada, as no literature data were identified. However, environmental media estimates that have been made are based on conservative assumptions and are considered to be conservative upper-bounding estimates. There is no expected exposure from food. Confidence in the estimate for consumer product exposure is considered to be moderate. The inhalation and dermal exposure estimates resulting from the use of epoxy adhesives for gluing a vase and a coffee mug were considered to be conservative.

Conclusion

Based on the information presented in this final screening assessment, it is concluded that TGOPE is not entering the environment in a quantity or concentration or under

conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends. Additionally, TGOPE does not meet the criteria for persistence but does meet the criteria for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

On the basis of the genotoxicity of TGOPE, and the collective evidence from genotoxicity and carcinogenicity data of the analogues of TGOPE, and applying a precautionary approach, it is considered that TGOPE is a substance for which there may be a probability of harm at any level of exposure. It is therefore concluded that TGOPE is a substance that may be entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on human life and health.

It is therefore concluded that TGOPE meets one or more of the criteria under section 64 of CEPA 1999.

Where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

References

ACD/pK_aDB [Prediction Module]. 2000-2008. Version 9.04. Toronto (ON): Advanced Chemistry Development. [cited 2009 Jan 23]. Available from: http://www.acdlabs.com/products/phys_chem_lab/pka/ [restricted access].

[AEROWIN] Aerosol Sorption Program for Windows [Estimation Model]. 2008. Version 1.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

[AIEPS] Artificial Intelligence Expert Predictive System. 2003–2007. Version 2.05. Ottawa (ON): Environment Canada. Model developed by Stephen Niculescu. Available from: Environment Canada, Ecological Assessment Division, New Chemicals Evaluation Section.

Andersen M, Kiel P, Larsen H, Maxild J. 1978. Mutagenic action of aromatic epoxy resins. Nature 276:391-392.

[AOPWIN] Atmospheric Oxidation Program for Windows [Estimation Model]. 2008. Version 1.92. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Arnot JA, Gobas FAPC. 2003. A generic QSAR for assessing the bioaccumulation potential of organic chemicals in aquatic food webs. QSAR Comb Sci 22(3):337–345.

Arnot JA, Mackay D, Bonnell M. 2008a. Estimating metabolic biotransformation rates in fish from laboratory data. Environ Toxicol Chem 27(2):341–351.

Arnot JA, Mackay D, Parkerton TF, Bonnell M. 2008b. A database of fish biotransformation rates for organic chemicals. Environ Toxicol Chem 27(11):2263–2270.

Arnot JA, Meylan W, Tunkel J, Howard PH, Mackay D, Bonnell M, Boethling RS. 2009. A quantitative structure-activity relationship for predicting metabolic biotransformation rates for organic chemicals in fish. Environ Toxicol Chem 28(6):1168–1177.

Aronson, D, Boethling R, Howard P, Stiteler W. 2006. Estimating biodegradation half-lives for use in chemical screening. Chemosphere 63:1953–1960.

ASTreat Model [sewage treatment plant removal model]. 2006. Version 1.0. Cincinnati (US): Procter & Gamble Company. [cited 2009 Nov 4]. Available from Procter & Gamble Company, P.O. Box 538707, Cincinnati, OH 45253-8707, U.S.

[BCFBAF] Bioaccumulation Program for Windows [Estimation Model]. 2008. Version 3.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

[BIOWIN] Biodegradation Probability Program for Windows [Estimation Model]. 2008. Version 4.10. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Boethling RS, Howard PH, Beauman JA, Larosche ME. 1995. Factors for intermedia extrapolations in biodegradability assessment. Chemosphere 30(4):741−752.

Boogaard PJ, de Kloe KP, Bierau J, Kuiken G, Borkulo PE, Watson WP, van Sittert NJ. 2000b. Metabolic inactivation of five glycidyl ethers in lung and liver of humans, rats and mice in vitro. Xenobiotica 30(5):485–502.

Boogaard PJ, Denneman MA, Van Sittert NJ. 2000a. Dermal penetration and metabolism of five glycidyl ethers in human, rat and mouse skin. Xenobiotica 30(5):469–83.

Brenntag NV. 2009. EPON Product Information Page. [cited 2001 Jan 6]. Available from: http://www.brenntag.be/prd/product/eponen.php

Brooks TM, Meyer AL, Hodson-Walker G, Crabtree AN, Jones L, Wiggins DE. 1981. Toxicity studies with epoxy resins: in vitro genotoxicity studies with diglycidyl ether of bispheno1 A, Epikote 828, Epikote 1001. Epikote 1007. Shell Toxicology Laboratory TLGR.80.123.

Canada. 1999. *Canadian Environmental Protection Act, 1999*. S.C., 1999, c. 33, Canada Gazette. Part III, vol. 22, no. 3. Available from: http://www.gazette.gc.ca/archives/p3/1999/g3-02203.pdf

Canada. 2000. *Canadian Environmental Protection Act, 1999: Persistence and Bioaccumulation Regulations,* P.C. 2000-348, 23 March, 2000, SOR/2000-107, Canada Gazette, Part II, vol. 134, no. 7, p. 607−612. Available from: http://www.gazette.gc.ca/archives/p2/2000/2000-03-29/pdf/g2-13407.pdf

Canada, Dept. of the Environment. 2006. *Canadian Environmental Protection Act, 1999*: *Notice with respect to selected substances identified as priority for action*. Canada Gazette, Part I, vol. 140, no. 9, p. 435–459. Available from: http://www.gazette.gc.ca/archives/p1/2006/2006-03-04/pdf/g1-14009.pdf

Canada, Dept. of the Environment, Dept. of Health. 2009a. *Canadian Environmental Protection Act, 1999: Notice of ninth release of technical information relevant to substances identified in the Challenge.* Canada Gazette, Part I, vol. 143, no. 11, p. 558–562. Available from: http://canadagazette.gc.ca/rp-pr/p1/2009/2009-03-14/pdf/g1-14311.pdf#page=4

Canada, Dept. of the Environment. 2009b. *Canadian Environmental Protection Act, 1999: Notice with respect to Batch 9 Challenge substances.* Canada Gazette, Part I, vol. 143, no. 11, p. 562–579. Available from: http://canadagazette.gc.ca/rp-pr/p1/2009/2009-03-14/pdf/g1-14311.pdf#page=4

Canter DA, Zeiger E, Haworth S, Lawlor T, Mortelmans K, Speck W. 1986. Comparative mutagenicity of aliphatic epoxides in Salmonella. Mutat Res 172:105–138.

[CAS] CAS: A division of the American Chemical Society. 2009. SciFinder program. Updated March 2009. [cited 2009 Dec 16]. Available from https://scifinder.cas.org

CASETOX [Prediction module]. 2008. Version 2.0. Beachwood (OH): MultiCASE. [cited 2009 Dec 16]. Available from: http://www.multicase.com/products/prod03.htm [restricted access].

[CATABOL] Probabilistic assessment of biodegradability and metabolic pathways [Computer Model]. c2004−2008. Version 5.10.2. Bourgas (BG): Bourgas Prof. Assen Zlatarov University, Laboratory of Mathematical Chemistry. Available from: http://oasis-lmc.org/?section=software&swid=1 [included in the CPOPs 2008 model suite].

ChemCAN [Level III fugacity model of 24 regions of Canada]. 2003. Version 6.00. Peterborough (ON): Trent University, Canadian Centre for Environmental Modelling and Chemistry. [cited 2009 Dec 30]. Available from: http://www.trentu.ca/academic/aminss/envmodel/models/CC600.html

Climie IJ, Hutson DH, Stoydin G. 1981. Metabolism of the epoxy resin component 2,2-bis[4-(2,3-epoxypropoxy)phenyl]propane, the diglycidyl ether of bisphenol A (DGEBPA) in the mouse. Par II.

Identification of metabolites in urine and faeces following a single oral dose of 14C-DGEBPA. Xenobiotica 11:401–424 [cited in IARC 1989, 1999a].

Consumer Exposure (ConsExpo) Model [Internet]. 2006. Version 4.1. The Netherlands: The National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu). Available from: http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp#tcm:13-42840

[CPOPs] Canadian POPs Model. 2008. Gatineau (QC): Environment Canada, Ecological Assessment Division; Bourgas (BG): Bourgas Prof. Assen Zlatarov University, Laboratory of Mathematical Chemistry. [Model developed based on Mekenyan et al. 2005]. Available from: Environment Canada, Ecological Assessment Division.

Crechem Technologies Inc. 2005. Validation of Sewage Treatment Plant Emission Models. Volume II/II – Appendices. Prepared for Environment Canada, New Substances Branch. March 2005. 703 pp.

Das L, Das SK, Chu EH, Sinsheimer JE. 1993. Chromosomal aberrations in mouse lymphocytes exposed in vivo and in vitro to aliphatic epoxides. Mutat Res 299(1):19–24.

Davidson Measurement. 2005. [MSDS] Material Safety Data Sheet. M-BOND 450 (Part A). August 2005. [accessed 2009 Dec. 30]. Available from: http://www.davidson.com.au/products/strain/mg/msds/pdf/MBOND-450-PartA.pdf

de Rooij BM, Commandeur JN, Hommes JW, Aalbers T, Groot EJ, Vermeulen NP. 1998. Urinary metabolite profile of phenyl and o-cresyl glycidyl ether in rats: identification of a novel pathway leading to N-acetylserine O-conjugates. Chem Res Toxicol 11(2):111-8.

[DEREK] Deductive Estimation of Risk from Existing Knowledge [Prediction module on CD ROM]. 2008. Version 10.0.2. Cambridge (MA): Harvard University, LHASA Group. Available from: http://lhasa.harvard.edu/?page=toxicology.htm [restricted access].

Dimitrov S, Dimitrova N, Parkerton T, Comber M, Bonnell M, Mekenyan O. 2005. Base-line model for identifying the bioaccumulation potential of chemicals. SAR QSAR Environ Res 16(6):531–554 [included in the CPOPs 2008 model suite].

[ECETOC] European Centre for Ecotoxicology and Toxicology of Chemicals. 2006. Workshop on Biodegradation and Persistence. Workshop Report No. 10. Brussels.

[ECOSAR] Ecological Structural Activity Relationships [Internet]. 2008. Version 1.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

[EEC] European Economic Community. 2009. Annex V to Directive 67/548/EEC. Test Methods. C.4. Determination of 'Ready' Biodegradability. [cited 2009 Dec 21], Available from: http://ecb.jrc.ec.europa.eu/testing-methods/

[EFSA] European Food Safety Authority. 2004. Opinion of the E.U. scientific panel on food additives flavourings, processing aids and materials in contact with food (AFC) on a request from the commission related to 2,2-bis(4-hydroxyphenyl)propane bis(2,3-epoxypropyl)ether (bisphenol A diglycidyl ether. BADGE) Ref. No. 13510 and 39700 (EFSA-Q-2003-178). Available from http://www.efsa.europa.eu/en/scdocs/doc/afc_op_ej86_badge1,3.pdf

Environment Canada. 2006. Data for selected substances collected under the *Canadian Environmental Protection Act, 1999*, Section 71: *Notice with respect to selected substances identified as priority for action*. Data compiled by: Environment Canada, Program Development and Engagement Division.

Environment Canada. 2007. Guidance for Conducting Ecological Assessments under CEPA, 1999, Science Resource Technical Series, Technical Guidance Module: QSARs. Reviewed Draft Working Document. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Environment Canada. 2008. Guidance for Conducting Ecological Assessments under CEPA, 1999, Science Resource Technical Series, Technical Guidance Module: Mass Flow Tool. Working Document. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Environment Canada. 2009a. Data for Batch 9 substances collected under the *Canadian Environmental Protection Act, 1999*, Section 71: *Notice with respect to certain Batch 9 Challenge substances.* Data compiled by: Environment Canada, Program Development and Engagement Division.

Environment Canada. 2009b. Mass Flow Tool for TGOPE, CAS RN 7328-97-4. Oct. 27, 2009, Internal draft document. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Environment Canada. 2009c. Guidance for Conducting Ecological Assessments under CEPA, 1999, Science Resource Technical Series, Technical Guidance Module: The Industrial Generic Exposure Tool – Aquatic (IGETA). Working document. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Environment Canada. 2009d. IGETA report: CAS RN 7328-97-4, 2009-11-03. Unpublished report. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Environment Canada. 2009e. STP Removal Predictions for Batch 9 CAS# 7328-97-4. Ecological Assessment Division. Report dated 09 July 2010.

Environment Canada 2009f. Exposure Database 2009, Environment Canada, Ecological Assessment Division, Exposure Unit. [Cited on 2009-08-07].

[EPI Suite] Estimation Programs Interface Suite for Microsoft Windows [Estimation Model]. 2008. Version 4.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuitedl.htm

[EQC] Equilibrium Criterion Model. 2003. Version 2.02. Peterborough (ON): Trent University, Canadian Environmental Modelling Centre. Available from: http://www.trentu.ca/academic/aminss/envmodel/models/EQC2.html

[ESIS] European Chemical Substances Information System [database on the Internet]. 2009. European Chemicals Bureau (ECB). [2009 Dec 31]. Available from: http://ecb.jrc.it/esi

Giri AK, Messerly EA, Sinsheimer JE. 1989. Sister-chromatid exchange and chromosome aberrations for 4 aliphatic epoxides in mice. Mutat Res 224(2):253–61.

Girolami GS. 1994. A simple 'back of the envelope' method for estimating the densities and molecular volumes of liquids and solids. J Chem Educ 71(11):962–964.

Greene EJ, Friedman MA, Sherrod JA, Salerno AJ. 1979. In vitro mutagenicity and cell transformation screening of phenylglycidyl ether. Mut Res 67:9-19.

Gulati D, Witt K, Anderson B, Zeiger E, Shelby M. 1989. Chromosome aberration and sister chromatid exchange test in Chinese hamster ovary cells in vitro III: Results with 27 chemicals. Environ Mol Mutagen 13:133-193.

Health Canada. 1998. Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Unpublished report. Ottawa (ON): Health Canada, Environmental Health Directorate.

Health Canada. 2009. Final screening assessment for the challenge: Oxirane, (butoxymethyl)- (n-butyl glycidyl ether) CAS RN 2426-08-6. Ottawa (ON): Health Canada, Risk Assessement Bureau. Available from: http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_2426-08-6_en.pdf

Hemminki K, Falck K, Vainio H. 1980a. Comparison of alkylation rates and mutagenicity of directly acting industrial and laboratory chemicals. Arch Toxicol 46:277-285.

Hemminki K, Vainio H. 1980b. Alkylation of nucleic acid bases by epoxides and phenyl glycidyl ethers. Dev Toxicol Environ Sci 8:241-244.

Henkel. 2009. [MSDS] Material Safety Data Sheet. Hysol 9340 EPK 2.7OZ KT Resin. July 2009. [accessed 2010 Jan. 29]. Available from: http://henkelconsumerinfo.com/products/henkel.datasheets.Search.pdf?BUSAREA=0006&DOCTYPE=MSDS&LANG=EN&COUNTRY=CA&MATNR=702137&VKORG=3400

[HENRYWIN] Henry's Law Constant Program for Microsoft Windows [Estimation Model]. 2008. Version 3.20. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Hexion Specialty Chemicals. 2001. [TDS] Technical Data Sheet. EPON™ Resin 1031-B-80. [accessed 2009 Dec 30]. Available from: http://www.hexion.com/Products/TechnicalDataSheet.aspx?id=3586

Hine CH, Guzman RJ, Coursey MM, Wellington JS. 1958. An investigation of the oncogenic activity of two representative epoxy resins. Cancer Res 18:20–26.

Hine CH, Rowe VK, White ER, Darmer KI, Yougblood GT. 1981. Epoxy compounds. In Clayton GD, Clayton FE, editors. Patty's Industrial Hygiene and Toxicology. Vol. 2A. 3rd rev. ed. New York (NY): Interscience. Chap. 32.

Holland JM, Gosslee DG, Williams NJ. 1979. Epidermal carcinogenicity of bis(2,3-epoxycyclopentyl)ether, 2,2-b(p-glycidoloxyphenyl)propane, and m-phenylenediamine in male and female C3H and C57BL/6 mice. Cancer Res 39:1718–1725.

Hu TM, Layton WL. 2001. Allometric scaling of xenobiotic clearance: uncertainty versus universality. AAPS PharmSci [Internet]. Vol. 3(4): Article 29. Available from: http://www.aapsj.org/view.asp?art=ps030429

Hubinski H, Gutzke GE, Kubinski Z. 1981. DNA-cell-binding (DCB) assay for suspected carcinogens and mutagens. Mutat Res 89:95-136.

[IARC] International Agency for Research on Cancer. 1976. Epichlorohydrin. IARC Monogr Eval Carcinog Risk Chem Man 11:131–139.

[IARC] International Agency for Research on Cancer. 1985. Diglycidyl resorcinol ether. IARC Monogr Eval Carcinog Risk Chem Man 36:181–8.

[IARC] International Agency for Research on Cancer. 1989. Some glycidyl ethers. IARC Monogr Eval Carcinog Risks Hum 47:237–261.

[IARC] International Agency for Research on Cancer. 1994. Propylene oxide. IARC Monogr Eval Carcinog Risks Hum 60:181–213.

[IARC] International Agency for Research on Cancer. 1999a. Bisphenol A diglycidyl ether. IARC Monogr Eval Carcinog Risk Chem Man 71(3):1285–1289.

[IARC] International Agency for Research on Cancer. 1999b. Diglycidyl resorcinol ether. IARC Monogr Eval Carcinog Risk Chem Man 71(3):1417–20.

[IARC] International Agency for Research on Cancer. 1999c. Epichlorohydrin IARC Monogr Eval Carcinog Risk Chem Man 71(2):603–628.

[IARC] International Agency for Research on Cancer. 1999d. 1,2-Epoxybutane. IARC Monogr Eval Carcinog Risk Chem Man 71(2):629–40.

[IARC] International Agency for Research on Cancer. 1999e. Glycidaldehyde. IARC Monogr Eval Carcinog Risk Chem Man 71(3):1459–1463.

[IARC] International Agency for Research on Cancer. 1999f. Phenyl glycidyl ether. IARC Monogr Eval Carcinog Risk Chem Man 71(3):1525–1528.

[IRIS] Integrated Risk Information System [database on the Internet]. 2003. Methyl ethyl ketone (CAS RN 78-93-3). IRIS Record No. 0071. Washington (DC): U.S. Environmental Protection Agency. [cited 2009 Dec 30]. Available from http://www.epa.gov/NCEA/iris/subst/0071.htm

Ivie GW, MacGregor JT, Hammock BD. 1980. Mutagenicity of psoralen epoxides. Mutat Res 79:73–77.

Jolanki R, Kanerva L, Estlander T. 2000. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, editors. Handbook of Occupational Dermatology. New York (NY): Springer. Chap. 73.

[KOAWIN] Octanol Air Partition Coefficient Program for Microsoft Windows [Estimation Model]. 2008. Version 1.10. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

[KOCWIN] Soil Adsorbtion Coefficient Program for Microsoft Windows [Estimation Model]. 2008. Version 2.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Koskinen M, Plná K. 2000. Specific DNA adducts induced by some mono-substituted epoxides in vitro and in vivo. Chem Biol Interact 129(3):209–29.

[KOWWIN] Octanol-Water Partition Coefficient Program for Microsoft Windows [Estimation Model]. 2008. Version 1.67. Washington (DC): U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. [cited 2009-12-15]. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Lee KP, Schneider PW, Trochimowicz HJ. 1983. Morphologic expression of glandular differentiation in the epidermoid nasal carcinomas induced by phenylglycidyl ether inhalation. Am Asso Pathol 111:140–148.

Loctite. 2001. Product Description Sheet. Hysol Product 9340. August 2001. [accessed 2010 Jan. 29]. Available from: http://www.shanghailoctite.com/template/ying/pdf/docs/HYSA9340-EN.PDF

Mabey WR, Mill T. 1978. J Phys Chem Ref Data 7:383 [cited in Mill 1982].

McGregor D, Brown A, Cattanach P, Edwards I, McBride D, Riach C, Caspary W. 1988. Responses of the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. Environ Mol Mutagen 12:85–154.

McGregor DB, Riach C, Cattanach P, Edwards I, Shepherd W, Caspary WJ. 1996. Mutagenic responses of L5178Y mouse lymphoma cells at the tk and hprt loci. Toxicol In Vitro 10:643–647.

Mekenyan G, Dimitrov SD, Pavlov TS, Veith GD. 2005. POPs: A QSAR system for creating PBT profiles of chemicals and their metabolites. SAR QSAR Environ Res 16(1-2):103−133.

Mellon Institute. 1979. Epoxy Resin ERRA-0163 Range Finding Toxicity Studies by Carnegie Mellon Univ With Cover Letter From Union Carbide. EPA Doc No. 878214012, OTS No. 0206476.

Mill T. 1982. Hydrolysis and oxidation processes in the environment. Environ Toxicol Chem 1:135–141.

[MPBPWIN] Melting Point Boiling Point Program for Microsoft Windows [Estimation Model]. 2008. Version 1.43. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

[Model Applier] Leadscope FDA Model Applier [Prediction module on CD ROM]. 2008. Version 1.2.0-3. Columbus (OH): Leadscope, Inc. Available from: http://www.leadscope.com/model_appliers/ [restricted access].

[NCI] National Chemical Inventories [database on CD-ROM]. 2007. Issue 1. Columbus (OH): American Chemical Society, Chemical Abstracts Service. [cited 2009 Oct. 12]. Available from: http://www.cas.org/products/cd/nci/index/html

Neau SH, Hooberman BJ, Frantz SW, Sinsheimer JE. 1982. Substituent effects on the mutagenicity of phenyl glycidyl ethers in *Salmonella typhimurium*. Mutat Res 93: 297–304.

Nichols JW, Fitzsimmons PN, Burkhard LP. 2007. In vitro – in vivo extrapolation of quantitative hepatic biotransformation data for fish. II. Modeled effects on chemical bioaccumulation. Environ Toxicol Chem 26:1304−1319.

[NPRI] National Pollutant Release Inventory [database on the Internet]. 2008. Gatineau (QC): Environment Canada. [cited 2009 Dec 30]. Available from: http://www.ec.gc.ca/pdb/querysite/query_e.cfm

[NTP] National Toxicology Program. 1985. Toxicology and carcinogenesis studies of diglycidyl resorcinol ether (technical grade) (CAS No. 101-90-6) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park (NC): National Toxicology Program. TR-257 (NTIS No. PB87-146734) [cited in IARC 1985, 1999b].

[NTP] National Toxicology Program (US). 2004. n-Butyl Glycidyl Ether (BGE) [CAS No. 2426-08-6] Review of toxicological literature. Research Triangle Park (NC): National Toxicology Program. Available from: http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/Butyl_glycidyl_ether.pdf

[NTP] National Toxicology Program (US). 2005a. 11th Report on carcinogens. Substance profile: epichlorohydrin. Research Triangle Park (NC): National Toxicology Program. Available from: http://www.iso.org/en/prods-services/iso3166ma/02iso-3166-code-lists/index.html

[NTP] National Toxicology Program (US). 2005b. 11th Report on carcinogens. Substance profile: propylene oxide. Research Triangle Park (NC): National Toxicology Program. Available from: http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s155prop.pdf

[OASIS Forecast] Optimized Approach based on Structural Indices Set [Internet]. 2005. Version 1.20.

Bourgas (BG): Bourgas Prof. Assen Zlatarov University, Laboratory of Mathematical Chemistry. Available from: http://oasis-lmc.org/?section=software [included in the CPOPs 2008 model suite].

[OECD] Organisation for Economic Co-operation and Development. 1981a. OECD Guideline For Testing of Chemicals., No. 102: Melting Point/Melting Range. [12 May, 1981].] Available from: http://www.oecd.org/document/43/0,3343,en_2649_34377_45121835_1_1_1_1,00.html

[OECD] Organisation for Economic Co-operation and Development. 1981b. OECD Guideline For Testing of Chemicals., No. 103: Boiling Point/Boiling Range. [12 May, 1981].] Available from: http://www.oecd.org/document/43/0,3343,en_2649_34377_45121835_1_1_1_1,00.html

[OECD] Organisation for Economic Co-operation and Development. 1981c. OECD Guideline For Testing of Chemicals., No. 107: Partition Coefficient (n-octanol/water): Shake Flask Method. [12 May, 1981].] Available from: http://www.oecd.org/document/43/0,3343,en_2649_34377_45121835_1_1_1_1,00.html

[OECD] Organisation for Economic Co-operation and Development. 1981d. OECD Guideline For Testing of Chemicals, No. 105: Water Solubility. [12 May, 1981].] Available from: http://www.oecd.org/document/43/0,3343,en_2649_34377_45121835_1_1_1_1,00.html

[OECD] Organisation for Economic Co-operation and Development. 1981e. OECD Guideline For Testing of Chemicals. Test No. 111: Hydrolysis as a function of pH. [12 May 1981]. Available from: http://www.oecd.org/document/43/0,3343,en_2649_34377_45121835_1_1_1_1,00.html

[OECD] Organisation for Economic Co-operation and Development. 2004. The 2004 OECD list of high production volume chemicals [Internet]. Paris (FR): OECD, Environment Directorate. [cited 2009 June 29]. Available from: http://www.oecd.org/dataoecd/55/38/33883530.pdf

Ohtani H, Nishioka H. 1981. Mutagenic activity of epoxide compounds as constituents of resins in bacterial test systems. Sci Eng Rev 21:247–265.

Persitianis GC, Doak SM, Cole PN, Hend RW. 1988. Two-year carcinogenicity study on three aromatic epoxy resins applied cutaneously to CF1 mice. Food Chem Toxicol 26(7):611–624.

Proctor DM, Gatto NM, Hong SJ, Allamneni KP. 2007. Mode-of-action framework for evaluating the relevance of rodent forestomach tumors in cancer risk assessment. Toxicol Sci 98(2):313–26.

Pullin T. 1977. Report to the Dow Chemical Company Integrated Mutagenicity Testing Program, Galveston (TX): University of Texas Medical Branch. 71 pp. [Submitted to EPA pursuant to TSCA Section 8(e) by Rhone-Poulenc, Inc. and Shell Oil Company].

Ringo DL, Brennan EF, Cota-Robles EH. 1982. Epoxy resins are mutagenic: Implications for electron microscopists. J Ultrastruct Res 80:280–287.

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu. 2007. Do-It-Yourself Products Fact Sheet.

Seiler JP. 1984. The mutagenicity of mono- and di-functional aromatic glycidyl compounds. Mutat Res 135:159–167.

Shelby MD, Erexson GL, Hook GJ, Tice RR. 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. Environ Molec Mutag 21:160–179.

Shell Development Company. 1983. Acute toxicity studies of Epon Resin 1031-B-80. EPA Doc No. 878214967. OTS No. 0206735. p. 1–79.

Shell Development Company. 1984a. Assay of Epon Resin B-80 for gene mutation in Salmonella typhimurium. EPA Doc No. 878214965, OTS No. 0206735. p. 1–16.

Shell Development Company. 1984b. Assay of Epon Resin 1031-B-80 for gene mutation in mouse lymphoma cells. EPA Doc No. 878214966, OTS No. 0206735. p. 1–33.

Shell Development Company. 1984c. In vitro chromosome aberration assay in Chinese hamster ovary cells of Epon 1031-B-80. EPA Doc No. 878214964, OTS No. 0206735. p. 1–99.

Sigma-Aldrich. 2009. Data for Tetraphenylolethane gycidyl ether, CAS No. 7328-97-4. [accessed 2009 Aug 17]. Available from: www.sigmaaldrich.com

SimpleTreat [sewage treatment plant removal model]. 1997. Version 3.0. Bilthoven (NL): National Institute for Public Health and the Environment (RIVM). [cited 2009 Nov 04]. Available from: National Institute for Public Health and the Environment (RIVM), Laboratory for Ecological Risk Assessment, PO Box 1, 3720 BA Bilthoven, The Netherlands.

Solomon JJ. 1999. Cyclic adducts and intermediates induced by simple epoxides. IARC Sci Publ 150:123–35.

[SPIN] Substances in Preparations in Nordic Countries [database on the Internet]. 2009. Copenhagen (DK): Nordic Council of Ministers. [cited 2009 Dec. 15] Available from: http://195.215.251.229/Dotnetnuke/Home/tabid/58/Default.aspx

Stebbins KE, Dryzga MD. 2003. Bisphenol A Diglycidyl Ether (BADGE): Two-year gavage chronic toxicity/oncogenicity study in Fischer 344 rats. Midland(MI): The Dow Chemical Company. Study ID: 011134. [cited in EFSA 2004].

Steiner S, Hönger G, Sagelsdorff P. 1992. Molecular dosimetry of DNA adducts in C3H mice treated with bisphenol A diglycidylether. Carcinogenesis 13:969–972.

STP Model [sewage treatment plant removal model]. 2001. Version 1.5. Peterborough (ON): Trent University, Canadian Environmental Modelling Centre. [cited 2009 Nov 05]. Available from: http://www.trentu.ca/academic/aminss/envmodel/models/VBSTP.html

Study Submission. 1991a. Physicochemical tests on Substance A. Unpublished confidential data submitted to Environment Canada under the New Substances Program. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Study Submission. 1991b. Hydrolysis as a function of pH. Unpublished confidential data submitted to Environment Canada under the New Substances Program. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Study Submission. 1992a. An assessment of ready biodegradability. Unpublished confidential data submitted to Environment Canada under the New Substances Program. Available as Robust Study Summaries (See Appendix II – Aerobic Biodegradation, Closed Bottle Method and Modified Sturm Method). Gatineau (QC): Environment Canada, Ecological Assessment Division.

Study Submission. 1992b. Acute toxicity to Oncorhynchus mykiss, Daphnia magna and Selenastrum capricornutum. Unpublished confidential data submitted to Environment Canada under the New Substances Program. Available as Robust Study Summary (See Appendix II –Toxicity to Algae). Gatineau (QC): Environment Canada, Ecological Assessment Division.

Terrill JB, Lee KP, Culik R, Kennedy GL Jr. 1982. The inhalation toxicity of phenylglycidyl ether: reproduction, mutagenic, teratogenic, and cytogenetic studies. Toxicol Appl Pharmacol 64:204–212.

[TOPKAT] Toxicity Prediction by Komputer Assisted Technology [Internet]. 2004. Version 6.2. San Diego (CA): Accelrys Software Inc. [cited 2009 Dec 18]. Available from: http://www.accelrys.com/products/topkat/index.html

[TRI] Toxics Release Inventory [database on the Internet]. 2007. TRI Explorer 4.8. Washington (DC): US Environmental Protection Agency. [cited 2009 Dec 30]. Available from: http://www.epa.gov/triexplorer/

[US EPA] United States Environmental Protection Agency. 1994a. Epichlorohydrin (CAS RN 106-89-8). Washington (DC): US Environmental Protection Agency, Integrated Risk Information System (IRIS). Available at: http://www.epa.gov/iris/subst/0050.htm

[US EPA] United States Environmental Protection Agency. 1994b. Propylene oxide (CAS RN 75-56-9). Washington (DC): US Environmental Protection Agency, Integrated Risk Information System (IRIS). Available at: http://www.epa.gov/ncea/iris/subst/0403.htm

[US EPA] United States Environmental Protection Agency. 2006. Non-confidential 2006 Inventory Update Reporting (IUR) records by chemical. Search results for CAS RN 7328-97-4. Washington (DC): US EPA, Office of Pollution Prevention and Toxics. [cited 2009 Aug 13]. Available from: http://cfpub.epa.gov/iursearch/index.cfm?s=chem

[US EPA] United States Environmental Protection Agency. 2009. High Production Volume Information System (HPVIS) [Internet]. Washington (DC): US EPA, Office of Pollution Prevention and Toxics. [cited 2009 July] Available from: http://www.epa.gov/hpvis/index.html

[US NLM] United States National Library of Medicine. 2008. ChemIDplus program. Division of Specialized Services. [updated May 2008; cited 2009 Dec 29]. Available from: http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp

Valencia R, Mason JM, Woodruff RC, Zimmering S. 1985. Chemical mutagenesis testing in Drosophila: III. Results of 48 coded compounds tested for the National Toxicology Program. Environ Mutagen 7:325–348.

Van Duuren BL, Orris L, Nelsoon N. 1965. Carcinogenicity of epoxides, lactones, and peroxy compounds. Part II. J Natl Cancer Inst 35:707–717. [cited in IARC 1986, 1999a].

Von der Hude W, Seelbach A, Basler A. 1990. Epoxides: Comparison of the induction of SOS repair in *Escherichia coli* PQ37 and the bacterial mutagenicity in the Ames test. Mutat Res 231(2):205–218.

Voogd CE, Stel Van JJ, Jacobs JA. 1981. The mutagenic action of aliphatic epoxides. Mutat Res 89:269–282.

Wade MJ, Moyer JW, Hine CH. 1979. Mutagenic action of a series of epoxides. Mut Res 66(4):367–371.

Weil CS, Condra N, Haun C, Striegel JA. 1963. Experimental carcinogenicity and acute toxicity of representative exposides. Am Ind Hyg Journal 24(4):305–324.

Wit JG, Snel J. 1968. Enzymatic glutathione conjugations with 2,3-epoxyphenylprophyether and diethylmaleate by wild bird liver supernatant. Eur J Pharmacol 3:370–373. [cited in IARC 1989].

[WSKOWWIN] Water Solubility for Organic Compounds Program for Microsoft Windows [Estimation Model]. 2000. Version 1.41. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Wooder MF, Creedy CL. 1981. Studies on the effects of diglycidyl ether of bisphenol A on the liver DNA in vivo. Shell Research Report TLGR.81.102.

Zakova N, Zak F, Froehlich E, Hess R. 1985. Evaluation of skin carcinogenicity of technical 2,2-bis-(p-glycidyloxyphenyl)-propane in CF1 mice. Fd Chem Toxic 23:1081–1089.

Appendix I – PBT Model Inputs Summary Tables

Table 1. TGOPE

	Phys-Chem/Fate	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model input parameters	EPI Suite (2008) (all models, including: AOPWIN, KOCWIN, BCFBAF, BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC	Canadian POPs (including: Catabol, Dimitrov Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIEPS)
SMILES code	O(C1COc(ccc(c2)C(c(ccc(OCC(O3)C3)c4)c4)C(c(ccc(OCC(O5)C5)c6)c6)c(ccc(OCC(O7)C7)c8)c8)c2)C1				
Molecular weight (g/mol)	622.72	622.72	622.72		
Melting point (ºC)	80		80		
Boiling point (ºC)					
Data temperature (ºC)			20		
Density (kg/m^3)		1.42[1]			
Vapour pressure (Pa)		5.7 x 10^{-12}	5.7 x 10^{-12}		
Henry's Law constant (Pa·m^3/mol)		3.59 x 10^{-15}	Calculated from vapour pressure and water solubility		
Log K_{ow} (Octanol-water partition coefficient) (dimensionless)	5.5	5.5	5.5		
Water solubility (mg/L)		0.056	0.056		
Solids-water partition coefficient (L/kg)[2]		20 000			
Half-life in air (hours)			0.5		
Half-life in water (days)			14		
Half-life in sediment			14		

(days)					
Half-life in soil (days)			14		
Biodegradation rate constant (1/days) or (1/hr) -specify		(3, 1/hr) (2, 1/days)			
Biodegradation half-life in primary clarifier ($t_{1/2-p}$) (hr)		1521			
Biodegradation half-life in aeration vessel ($t_{1/2-s}$) (hr)		152			
Biodegradation half-life in settling tank ($t_{1/2-s}$) (hr)		152			

[1] Estimated by method of Girolami (1994)
[2] Derived from log K_{OW}
[3] Default value

Table 2. Hydrolysis Product of TGOPE

	Phys-Chem/Fate	**PBT Profiling**
Model input parameters	EPI Suite (all models, including: AOPWIN, KOCWIN, BCFBAF, BIOWIN and ECOSAR)	Canadian-POPs (including: Catabol, Dimitrov Model, OASIS Toxicity Model)
SMILES code	c1(C(c3ccc(OCC(O)C(=O)O)cc3)C(c4ccc(OCC(O)C(=O)O)cc4)c2cc(OCC(O)C(=O)O)cc2)ccc(OCC(O)C(=O)O)cc1	
Molecular weight (g/mol)	750.7	750.7

Appendix II – Robust Study Summaries

Aerobic Biodegradation, Closed Bottle Method

Test Substance
Identity: Analogue Substance A

Remarks: Purity of test substance: 85%, based on gel permeation chromatography. The proton nuclear magnetic resonance (NMR) spectrum suggests, if anything, a higher degree of purity (study author).

Method

Method/guideline followed: EEC Test Methods C.5 - Closed Bottle method
Type *(test type)*: Aerobic [X] Anaerobic [ ]
Year: *(study performed):* 1992
Contact time *(units):* 28 days
Inoculum: Mixed micro-organisms usually derived from sewage treatment plants

Test Conditions: (*Detail and discuss any significant protocol deviations, whether there was bacterial inhibition, and detail differences from the guideline followed including the following as appropriate:* A microbial inhibition study was done, and no microbial inhibition by the test substance or emulsifying agent (DOBANE PT) was found.

• *Inoculum (concentration and source):* Mineral salts medium was inoculated with 0.5 mL/L coarse-filtered secondary effluent from Canterbury Sewage Works (England)
• *Concentration of test chemical, vehicle used, pre-acclimation conditions:* Test substance added to test medium from a stock emulsion to give an initial concentration of 3 mg/L
• *Temperature of incubation(°C):* 20 ± 1°C
• *Dosing procedure:*
• *Sampling frequency:* Dissolved oxygen (DO) measured at 5, 15 and 28 days
• *Appropriate controls and blank system used:* Sodium benzoate (reference substance control), salt solution blanks, inoculum blanks and emulsion blanks
• *Analytical method used to measure biodegradation:* Winkler iodometric method
• *Method of calculating measured concentrations (i.e., arithmetic mean, geometric mean, etc.):* Calculations of BOD on day 5, ThOD on days 5 and 28 - methods provided in Appendix to the study.

Results

• % ThOD, Day 28: -3, 3 (results for sodium benzoate: 51, 72)
• Kinetic *(for sample, positive and negative controls):* ♦ For each time period %:
• Breakdown products: Yes [ ] No [X]. *(If yes, describe breakdown products and whether they were transient or stable in the Remarks field for Results).*

Remarks: *(Describe additional information that may be needed to adequately assess data for*

reliability and use, e.g., lag time, observed inhibition, excessive biodegradation, excessive standard deviation, kinetics, number of micro-organisms present, time required for 10% degradation and total degradation at the end of the test, e.g., 10-day window.)

Conclusions

Remarks: *(*Identify source of comment, i.e. author and/or submitter)

Author: Based on results, test substance cannot be classed as "readily biodegradable."

Reliability: 1 – High confidence

Remarks: *(The rationale for the reliability code should be described clearly as should the process by which the "Reliability" decision was made)*

Guideline study:
- Thoroughly validated and comparable to guideline study
- Test procedures according to national standards followed
- Good laboratory practice (GLP) principles implemented
- All necessary data are presented and documentation is sufficient for assessment

Study is GLP compliant and met U.S. EPA, UK, OECD and Japanese GLP requirements.

References *(Free Text)*

Other

Last changed: *(administrative field for updating)* Jan. 28, 2010

Remarks: *(Use for any other comments necessary for clarification)*

Aerobic Biodegradation, Modified Sturm Method

Test Substance
Identity: Analogue Substance A

Remarks: Purity of test substance: 85%, based on gel permeation chromatography. The proton nuclear magnetic resonance (NMR) spectrum suggests, if anything, a higher degree of purity (study author).

Method

Method/guideline followed: EEC Test Method C.6 (Modified Sturm method)
Type *(test type)*: Aerobic [X] Anaerobic [ ]
Year: *(study performed):* 1992
Contact time *(units):* 28 days
Inoculum: Mixed micro-organisms usually derived from sewage treatment plants

Test Conditions: (*Detail and discuss any significant protocol deviations, whether there was bacterial inhibition, and detail differences from the guideline followed including the following as appropriate:* A microbial inhibition study was done, and no microbial inhibition by the test substance or emulsifying agent (DOBANE PT) was found.

• *Inoculum (concentration and source):* 3 L aliquots of mineral salts test medium was inoculated with 10 mL/L coarse-filtered supernatant of homogenized activated sludge obtained from Canterbury Sewage Treatment Works (England)
• *Concentration of test chemical, vehicle used, pre-acclimation conditions:* Test substance added to test medium from a stock emulsion to give an initial concentration of 20 mg/L
• *Temperature of incubation(°C):* 20 ± 1°C
• *Dosing procedure:*
• *Sampling frequency:* CO_2 evolution measured every few days during Modified Sturm test
• *Appropriate controls and blank system used:* Sodium benzoate (reference substance control), inoculated mineral medium blanks, and e inoculated mineral medium + DOBANE PT blanks
• *Analytical method used to measure biodegradation:* CO_2 evolution determined by titrating the contents of the $Ba(OH)_2 \cdot 8H_2O$ absorber bottles proximal to the units against standard HCl. In order to measure CO_2 trapped as inorganic carbonates in the medium, the contents of each Sturm vessel were acidified with 1 mL concentrated H_2SO_4 on Day 27 of the test.
Biodegradation was also measured by determining DOC in blank and sodium benzoate vessels at the start and end of incubation.
• *Method of calculating measured concentrations (i.e., arithmetic mean, geometric mean, etc.):* Methods provided in Appendix to the study.

Results

• Degradation % after time: 3 - 4% of the $ThCO_2$ produced after 28 days by test substance, as compared to 84 - 85% for sodium benzoate
• Results:

• Kinetic *(for sample, positive and negative controls):* ♦ For each time period %:
• Breakdown products: Yes [ ] No [X]. *(If yes, describe breakdown products and whether they were transient or stable in the Remarks field for Results).*

Remarks: *(Describe additional information that may be needed to adequately assess data for reliability and use, e.g., lag time, observed inhibition, excessive biodegradation, excessive standard deviation, kinetics, number of micro-organisms present, time required for 10% degradation and total degradation at the end of the test, e.g,. 10-day window.)*

Mean net $ThCO_2$ production at the end of the 10-day window for sodium benzoate was 74%.

Conclusions

Remarks: *(Identify source of comment, i.e. author and/or submitter)*

Author: Test substance was not degraded with a negligible portion of the $ThCO_2$ being evolved in 28 days.

Reliability: 1 – High confidence

Guideline study:
- Thoroughly validated and comparable to guideline study
- Test procedures according to national standards followed
- Good laboratory practice (GLP) principles implemented
- All necessary data are presented and documentation is sufficient for assessment

Study is GLP compliant and met U.S. EPA, UK, OECD and Japanese GLP requirements.

References *(Free Text)*

Other

Last changed: Jan 28, 2010

Remarks: *(Use for any other comments necessary for clarification)*

Toxicity to Algae

Test Substance: Analogue Substance A

Identity: Confidential

Remarks: Purity of test substance: 85%, based on gel permeation chromatography. The proton nuclear magnetic resonance (NMR) spectrum suggests, if anything, a higher degree of purity (study author).

Test substance is not stable in water (hydrolyzes slowly), but concentrations measured each day.

Method

Method/guideline followed*:* Official Journal of the European Communities, L251, Part C.
Test type *(static/other):*Static
Good laboratory practice: Yes [X] No [ ]
Year *(study performed):*1992
Species/strain # and source: *S. capricornutum* inoculum derived from axenic culture derived from strain ATCC 22662 obtained from the American Type Culture Collection, Maryland, USA.
Element basis*:* growth inhibition - area under the curve, specific growth rate.
Exposure period *(Duration*): 3 days (72 hours)
Analytical monitoring: Cell concentrations, concentrations of test substance at 0 and 72 hours.
Statistical methods: Analysis of variance using Duncan's multiple comparison test for both areas under the growth curves and the average specific growth rate.

Test Conditions *(Detail and discuss any significant protocol deviations and detail differences from the guideline followed including the following as appropriate):*

As I was unable to locate EC L251, Part C, I compared the test methods to OECD 201 (2006).

• *Test organisms*

- ♦ *Laboratory culture:*
- ♦ *Method of cultivation*: Given in report
- ♦ *Controls:*

• *Test Conditions*

- ♦ *Test temperature range:* Range was 23–26°C (± not indicated), rather than 21–24°C ± 2°C
- ♦ *Growth/test medium chemistry (hardness, alkalinity, pH, TOC, TSS, dissolved oxygen, salinity, EDTA*): "The water quality parameters were generally in the preferred ranges for all of the tests."
- ♦ *Dilution water source:* From water main, then filtered (10 µm) and passed through activated carbon.
- ♦ *Exposure vessel type (e.g., size, headspace, sealed, aeration, number per treatment):*
- ♦ *Water chemistry in test (pH) in at least one replicate of each concentration (at start and end of the test):* Yes. All of the recorded pHs were within 1 pH unit at the beginning and end of the test.
- ♦ *Stock solutions preparation (vehicle, solvent, concentrations):10 µg/L acetone*

♦ *Light levels and quality during exposure:*

• *Test design (number of replicates, concentrations):* One concentration (0.2 mg/L) x 4 replicates + 4 solvent control replicates + 7 algae blank replicates
• *Method of calculating mean measured concentrations (i.e., arithmetic mean, geometric mean, etc.):* Geometric means calculated

Results

• Nominal concentrations (mg/L): 0.20 mg/L
• Measured concentrations (mg/L): mean = 0.15 mg/L
• Element value *(e.g., ErC50,ErL50,EbC50,EbL50,EC10-CD, EL10-CD, EC50-CD, EL50-CD, EL90-CD, EC90-CD, EC0,orEL0 at 24, 48, 72 or 96 hours). Note whether cells removed prior to measurement.* Does not include this information.

NOEC, LOEC, or NOEL, LOEL: LOEC = 0.15 mg/L; NOEC < 0.15 mg/L, based on 16.9% and 3.8% growth inhibition by test substance after 72 h based on area under the growth curves and average specific growth rate, respectively (significant at 95% level).
Was control response satisfactory: Yes [X] No [ ] Unknown [ ]
Statistical results (as appropriate):
Remarks: *(Discuss if the effect concentration is greater than the solubility of the substance in the test medium. Describe additional information that may be needed to adequately assess data for reliability and use including the following):*

• *Biological observations*

♦ Cell density at each flask at each measuring point: yes
♦ Growth curves: Yes
♦ Percent biomass/growth rate inhibition per concentration: yes
♦ Observations:

Conclusions

Remarks: *(Identify source of comment, i.e., author and/or submitter)*

Reliability: Satisfactory reliability

Remarks:
- Not OECD study but test procedure comparable to guidelines/standards with acceptable restrictions
- Study that has met basic scientific principles
- All necessary data are presented and documentation is sufficient for assessment

References *(Free Text)*

Other

Last changed: Feb. 4, 2010

Appendix III – Upper-bounding Estimates of Potential Exposure to TGOPE from Consumer Products

Consumer product scenarios	Assumptions	Estimated exposure
Two-component epoxy adhesive – gluing the handle of a coffee mug[1,2]	**Inhalation** • Used ConsExpo (2006) model version 4.1, exposure to vapour: evaporation from an increasing area as mode of release.. • Assume saturation conditions (i.e., select "limit air concentration to vapour pressure of pure substance" check box). • Based on 30% TGOPE in epoxy resins and a mix ratio in epoxy adhesives of 1:1 (resin: hardener), epoxy adhesives consist of 15% TGOPE (Environment Canada 2009a, Henkel 2009, 2010 personal communication from Industry to Risk Management Bureau, Health Canada; unreferenced). • Assume amount of product used is 0.5 g/event to cover a surface area of 2 cm^2, and an application duration of 5 minutes. • Assume a room volume of 20 m^3, exposure duration of 240 minutes, a ventilation rate of 0.6 times/hr, a mass transfer rate based on Langmuir's method and a molecular weight matrix of 3000 g/mol (RIVM 2007).	Mean event concentration = 4.09×10^{-6} µg/m^3
Two-component epoxy adhesive – gluing a large vase[2]	**Inhalation** • Used ConsExpo (2006) model version 4.1, exposure to vapour: evaporation from an increasing area as mode of release. • Assume saturation conditions (i.e., select "limit air concentration to vapour pressure of pure substance" check box). • Based on 30% TGOPE in epoxy resins and a mix ratio in epoxy adhesives of 1:1 (resin: hardener), epoxy adhesives consist of 15% TGOPE (Environment Canada 2009a, Henkel 2009, 2010 personal communication from Industry to Risk Management Bureau, Health Canada; unreferenced). • Assume amount of product used is 20 g/event	Mean event concentration = 0.000845 µg/m^3

	to cover a surface area of 500 cm^2, an application duration of 30 minutes, a room volume of 20 m^3, exposure duration of 240 minutes, a ventilation rate of 0.6 times/hr, a mass transfer rate based on Langmuir's method and a molecular weight matrix of 3000 g/mol (RIVM 2007).	
	Dermal • Used ConsExpo model (2006) version 4.1, direct dermal contact with product: instant application as mode of release. • Based on 30% TGOPE in epoxy resins and a mix ratio in epoxy adhesives of 1:1 (resin: hardener), epoxy adhesives consist of 15% TGOPE (Environment Canada 2009a, Henkel 2009, 2010 personal communication from Industry to Risk Management Bureau, Health Canada; unreferenced). • Assume the exposed area of skin is 43 cm^2, and an amount of 0.1 g of product is applied (RIVM 2007). • Assume adult exposed weighs 70.9 kg (Health Canada 1998). • Assume 100% uptake.	Acute dose per event = 212 µg/kg-bw

[1]Possible exposure of teenagers (12–19 years old) and adults (20 years old and older). Scenarios were completed for adults only.
[2] Adult body weight assumed to be using a weight value of 70.9 kg (Health Canada 1998).

Appendix IV – Summary of Health Effects Information for TGOPE

TGOPE	
Endpoint	**Lowest effect levels/results**
Experimental animals and *in vitro*	
Acute toxicity	**Oral LD_{50}** (rat) > 5000 mg/kg-bw (Mellon Institute 1979). **Other oral LD_{50}** (rat) > 5 mL/kg-bw (Epon resin 1031-B-80 containing 80% TGOPE and 20% methyl ethyl ketone) (Shell Development Company 1983). **Dermal LD_{50}** (rabbit) > 8000 mg/kg-bw (Mellon Institute 1979). **Other dermal LD_{50}** (rabbit) > 2 mL/kg-bw (Epon resin 1031-B-80 containing 80% TGOPE and 20% methyl ethyl ketone) (Shell Development Company 1983). No inhalation studies were identified.
Short-term repeated-dose toxicity	No studies were identified.
Subchronic toxicity	No studies were identified.
Chronic toxicity/ carcinogenicity	No studies were identified.
Reproductive toxicity	No studies were identified.
Developmental toxicity	No studies were identified.
Genotoxicity and related endpoints: *in vivo*	No studies were identified.
Genotoxicity and related endpoints: *in vitro*	**Mutagenicity-Ames test:** **Positive:** *Salmonella typhimurium* TA100 and TA98 with Epon resin 1031-B-80 (containing 80% TGOPE and 20% methyl ethyl ketone) dose ranged 0–5000 µg/mL; 9 dose levels in the absence or presence of metabolic activation S9. No significant toxicity observed at all dose levels, and testing chemical precipitated at 500 µg/mL or higher in dimethyl sulfoxide (DMSO) (Shell Development Company 1984a). **Positive:** Mouse lymphoma L5175Y TK(±) cells with Epon resin 1031-B-80 (containing 80% TGOPE and 20% methyl ethyl ketone) dose ranged 0–10 µg/mL; 7 dose levels in the absence of metabolic activation S9 (Shell Development Company 1984b). **Negative:** Mouse lymphoma L5175Y TK(±) cells with Epon resin 1031-B-80 (containing 80% TGOPE and 20% methyl ethyl ketone) dose ranged 0–1000 µg/mL; 9 dose levels in the presence of metabolic activation S9. Cytotoxicity observed and testing chemical precipitated at 300 µg/mL or higher in DMSO (Shell Development Company 1984b). **Chromosomal aberration:** **Positive:** Chinese hamster ovary cells with Epon resin 1031-B-80 (containing 80% TGOPE and 20% methyl ethyl ketone) dose ranged 0–300 µg/mL; 4 dose levels in the absence or presence of metabolic activation S9. No toxicity observed at all dose levels (Shell Development Company 1984c).
Sensitization	No sensitization responses observed when tested with Epon resin 1031-B-80 (containing 80% TGOPE and 20% methyl ethyl ketone) in Duncan-Hartley albino guinea pigs (5/sex/group) (Shell Development Company 1983).

TGOPE	
Endpoint	**Lowest effect levels/results**
Irritation	**Skin irritation:** Minimal irritation to intact and abraded skin when tested with Epon resin 1031-B-80 (containing 80% TGOPE and 20% methyl ethyl ketone) in New Zealand white rabbits (3/sex/group) (Shell Development Company 1983). No irritation to intact skin when tested with Epon resin 1031-B-80 (containing 80% TGOPE and 20% methyl ethyl ketone) in rabbits (5, strain and sex not specified) (Mellon Institute 1979).
	Eye irritation: Mild irritation to non-washed and washed (tested in males only) eyes treated with Epon resin 1031-B-80 (containing 80% TGOPE and 20% methyl ethyl ketone) in New Zealand white rabbits (6 males, 3 females) (Shell Development Company 1983). No irritation when tested with the powder of TGOPE and minor irritation observed when tested with 20% TGOPE in PEG 400 in rabbits (5, strain and sex not specified (Mellon Institute 1979).
Epidemiology studies	
	No studies were identified.

LD_{50} = median lethal dose

Appendix V – QSAR Predictions for TGOPE and Its Analogues

Carcinogenicity Predictions

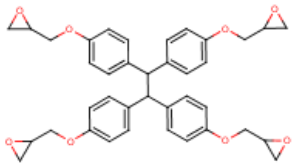
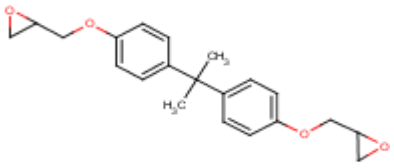
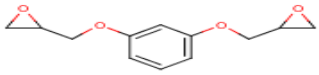
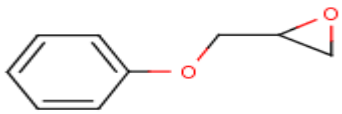
ID	CAS	DEREK	TOPKAT (TK)				Model Applier (MA)				CASETOX (CT)			
		Cancer	Rat		Mice		Rat		Mice		Rat		Mice	
			M	F	M	F	M	F	M	F	M	F	M	F
TGOPE	7328-97-4	Pl	IC	IC	IC	IC	N	N	N	N	P	P*	P	P
BADGE	1675-54-3	Pl	IC	IC	IC	IC	N	N	N	N	P	P*	P	P
Substance A		Pl	IC	IC	IC	IC	N	N	IC	N	P	P*	P	P
DGRE	101-90-6	Pl	IC	P	IC	IC	N	N	N	N	P	P*	P	P
PGE	122-60-1	Pl	N	IC	IC	IC	N	N	N	N	P	P*	P	P

Genotoxicity Predictions

ID	CAS	Ames				ChrAb		Micronuclei Induction	
		DEREK	TK	MA	CT	MA	CT[#]	MA	CT
TGOPE	7328-97-4	Pl	IC	IC	P	IC	P	N	N
BADGE	1675-54-3	Pl	P	P	P	P	P	N	N
Substance A		Pl	IC	IC	P	N	P	N	IC
DGRE	101-90-6	Pl	IC	P	P	P	P	IC	N
PGE	122-60-1	Pl	N	P	P	N	P	IC	N

[#] *in vitro* test (in cultured Chinese hamster ovary cells)
*weakly
ChrAb – chromosomal aberration
M – male; F – female;
TK – TOPKAT (2004); CT – CASETOX (2008); MA – Model Applier (2008); DEREK (2008)
IC – inconclusive; P – positive; Pl – plausible; N- negative

Appendix VI – Structures and Classification for TGOPE and Analogues Considered in This Assessment

Name / CAS RN	Classification		Structure
	IARC	European Commission	
TGOPE 7328-97-4 MW: 622.71, solid			
Bisphenol A diglycidyl ether (BADGE) 1675-54-3 MW: 340.42, crystalline	3; Not classifiable		
Substance A[1] MW: 354.45, waxy solid			
Diglycidyl resorcinol ether (DGRE) 101-90-6 MW: 222.24, liquid	Carc. Group 2B	Carc. Cat. 3	
Phenyl glycidyl ether (PGE) 122-60-1 MW: 150.18, liquid	Carc. Group 2B	Carc. Cat. 2 Muta. Cat. 3	

Abbreviations: Carc. - carcinogenicity; CAS RN - Chemical Abstracts Service Registry Number; Cat. - category; Muta. - mutagenicity.

[1] Structure of Substance A may not be identified due to confidentiality.

Appendix VII – Summary of Health Effects Information for Analogues Considered in This Assessment

Bisphenol A diglycidyl ether (BADGE)	
Endpoint	**Lowest effect levels/results**
Experimental animals and *in vitro*	
Chronic toxicity/ carcinogenicity	**Oral:** Fischer 344 rats (65/sex/group) were orally (gavage) administered 0, 2, 15 or 100 mg/kg-bw per day BADGE (> 99% purity) for up to 2 years. Ten/sex/group were sacrificed after 1 year of treatment. No significant increased incidence of neoplasms was observed in males or females at any dose level. In males, statistically significant decrease in body weights and body weight gains were observed at 15 and 100 mg/kg-bw per day and an increase in serum cholesterol levels was observed at 100 mg/kg-bw per day after 1 year but not observed after 2 years of treatment. In females, a significant increase in serum cholesterol level was observed at 15 and 100 mg/kg-bw per day after 1 year but not observed after 2 years of treatment. After 2 years of treatment, a statistically significant decrease in absolute and relative spleen weights was observed at 100 mg/kg-bw per day in males. A statistically significant increase in cecal size and weight was observed in males and females at 100 mg/kg-bw per day with no histopathological alterations (Stebbins and Dryzga 2003). **Dermal:** Groups of 50 CF1 mice of each sex (99 male and 100 females for controls) were exposed to 0, 1 or 10% (0.2 mL) (corresponding to approximately 0, 70, 700 mg/kg-bw per day respectively) pure BADGE in acetone topically 2 times/week for 103 weeks. Controls were exposed to acetone only, and 1/199 (sex not specified) developed dermal tumour. A positive control group was also exposed to β-propiolactone. Exposure did not affect survival. Three males (3/50) from the 10% group and 1 female (1/50) from the 1% group developed tumours at the site of exposure. Three females (3/50) from the 1% group developed skin tumours distant from the exposed site. The incidence of skin tumours was not significant at the treated site or at all sites combined. No treatment-related systemic tumours were identified in males. A statistically significant trend was observed in females for thymic lymphosarcoma. The authors noted a relatively high background incidence of lymphoreticular hematopoietic neoplasia for this particular strain in their laboratory, which they suggested could be caused by a virus (Persitianis et al. 1988). Other dermal studies identified for BADGE were of lower quality and tested impure forms of the substance and so are not considered in this assessment (Hine et al. 1958; Holland et al. 1979; Weil et al. 1963; Zakova et al. 1985). No inhalation studies were identified.

Bisphenol A diglycidyl ether (BADGE)	
Endpoint	**Lowest effect levels/results**
Experimental animals and *in vitro*	
Genotoxicity and related endpoints: *in vivo*	**DNA adduct** **Positive:** Male C3H mice were treated with 20 mg/mL BADGE dermally under occluded conditions. Animals were sacrificed at 48, 96, or 122 h and epidermal DNA was isolated. BADGE metabolites were found to bind to adenine bases in the DNA at a frequency of approximately 0.1–0.8 adducts per 10^6 nucleotides (Steiner et al. 1992). **DNA damage** **Negative:** A single 500 mg/kg-bw oral dose was administered to male and female Wistar rats. Alkaline elution assay was used to measure DNA damage. No detectable DNA single strand damage was detected in the liver 6 h after dosing (Wooder and Creedy 1981). **Micronucleus induction** **Negative:** 10 female B6D2F1 mice were given 1000 mg/kg-bw per day orally for 5 consecutive days. No increased incidence of micronuclei was observed in comparison to unexposed controls (Pullin 1977). **Dominant lethal assay** **Negative:** 10 male B6D2F1 mice were treated topically with 3000 mg/kg-bw, 3 times per week, for a minimum of 8 weeks. After exposure, male mice were cohabitated with 3 virgin females per week for 2 weeks. Two weeks after mating, females were sacrificed and examined for pregnancies, number of implants and fetal deaths. No effects in the measured parameters were observed in comparison to controls (Pullin 1977). **Negative:** Another dominant lethal study also reported no adverse effects due to BADGE treatment. However, no details were reported in this study (Hine et al. 1981).
Genotoxicity and related endpoints: *in vitro*	**Mutagenicity** **Ames tests:** **Positive:** – *Salmonella typhimurium* strains TA1535, TA1537, with metabolic activation induced mutation 7- to 10- fold more than background (Brooks et al. 1981). **Positive:** BADGE was tested in TA100 and TA1538 *Salmonella typhimurium* using 10–10 000 µg/plate (Canter et al. 1986). **Positive:** *S. cerevisiae* JD1 cells were positive for mitotic gene conversion when incubated with BADGE with or without microsomal enzymes (Brooks et al. 1981). **Negative:** *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 without metabolic activation (S9). *Salmonella typhimurium* strains TA1538, TA98 and TA100 with S9. BADGE was not mutagenic in *E. coli* WP2 or WP2 uvr*A* (Brooks et al. 1981). Other bacterial mutation studies: Andersen et al. 1978; Pullin 1977; Ringo et al. 1982; Wade et al. 1979. **Host-mediated assay** **Negative:** *S. typhimurium* inoculated into the peritoneal cavity of mice treated by gavage for 5 days with 1000 mg/kg BADGE. No increase in revertants was observed (Pullin 1977).

Bisphenol A diglycidyl ether (BADGE)	
Endpoint	**Lowest effect levels/results**
Experimental animals and *in vitro*	
	Urine Assay **Negative:** The urine of mice dosed by gavage once per day with 1000 mg/kg BADGE was not mutagenic in strain TA1535 (Pullin 1977). **Chromosomal aberration** **Positive:** Rat liver cells were cultured in the presence of BADGE (3.75, 5, 7.5, 10, 15 and 20 µg/mL). Dose-related increases in chromosomal aberrations were evident in cells treated with 10 to 20 µg/mL (Brooks et al. 1981). **Positive:** BADGE's ability to induce neoplastic transformation was assessed in baby hamster kidney cells. A 5-fold increase in transformation frequency was observed. No additional information was given in secondary reference (Brooks et al. 1981).

Substance A[1]	
Endpoint	**Lowest effect levels/results**
Experimental animals and *in vitro*	
Short-term repeated-dose toxicity	**Lowest oral LOEL** = 250 mg/kg-bw per day based on increased liver weights in Fischer 344 rats (7/sex/group) administered 0, 50, 250 or 1100 mg/kg-bw per day for 28 days. In males, significant reduction in body weight gain observed at 1100 mg/kg-bw per day and significant increase in mean plasma alkaline phosphatase levels observed at 50, 250 and 1100 mg/kg-bw per day. In females, significant decrease in mean erythrocyte count, hemoglobin and hematocrit concentrations observed at 250 and 1100 mg/kg-bw per day and significant increase in cholesterol levels, absolute and relative liver weights observed at 250 and 1100 mg/kg-bw per day and significant increase in mean plasma alkaline phosphatase observed at 1100 mg/kg-bw per day. No other studies were identified.
Chronic toxicity/ carcinogenicity	No studies were identified.
Genotoxicity and related endpoints: *in vivo*	**Micronucleus induction:** **Negative:** CD-1 mice (5/sex/group) administered with 0 or 1300 mg/kg-bw per day intraperitoneally for 2 days.
Genotoxicity and related endpoints: *in vitro*	**Mutagenicity** **Ames test** **Positive:** *Salmonella typhimurium* TA1535, TA100; *E. Coli* WP2 urvaA with dose ranged 0–5000 µg/mL in the presence of metabolic activation S9. **Negative:** *Salmonella typhimurium* TA1535, TA100; *E. Coli* WP2 urvaA with dose ranged 0–5000 µg/mL in the absence of metabolic activation S9. **Negative:** *Salmonella typhimurium* TA98, TA1537, TA1538 with dose ranged 0–5000 µg/mL in the presence or absence of metabolic activation S9. **Positive:** Mouse lymphoma L5178Y TK(±) cells with dose ranged 0–75 µg/mL without metabolic activation S9 and dose ranged 0–125 µg/mL with metabolic activation S9. Positive results observed at 3.125 µg/mL or higher and toxicity observed at 30 µg/mL or higher without S9. Positive results observed at 50 µg/mL or higher with S9 and no toxicity observed at all concentrations. **Chromosomal aberration** **Positive:** Chinese hamster ovary (CHO-K1) cells with dose ranged 0–12.5 µg/mL in the absence of metabolic activation S9 and dose ranged 0–100 µg/mL in the presence of metabolic activation S9. Positive results observed at 5 µg/mL or higher without S9 and at 100 µg/mL with S9.

LOEL = lowest-observed-effect concentration

[1] References for toxicity data of Substance A may not be identified due to confidentiality.

Diglycidyl resorcinol ether (DGRE)	
Endpoint	**Lowest effect levels/results**
Experimental animals and *in vitro*	
Chronic toxicity/ carcinogenicity	**Oral carcinogenicity in rats:** Fischer 344/N rats (50/sex/group) were orally (gavage) administered 0, 12, 25 or 50 mg/kg-bw per day DGRE (approximately 88% purity with 30 unspecified impurities, including 1.9% 3-methylbenzoic acid ethyl ester, 1.6% 3-chloropropoxy-benzene, 2.8% dihydroxypropoxylbenzene) 5 times/week for 103 weeks. Significant increased incidence of hyperkeratosis, hyperplasia, papillomas and squamous-cell carcinomas of the forestomach observed in both sexes at 12 mg/kg-bw per day or higher. Excessive mortality observed in males at 12 mg/kg-bw per day or higher and in females at 25 mg/kg-bw per day or higher due to bronchopneumonia (not consistent with chemical pneumonitis but was characterized by polymorphonuclear leucocytes in the centriacinar alveoli) (NTP 1985). **Oral carcinogenicity in mice:** B6C3F1 mice (50/sex/group) were orally (gavage) administered 0, 50 or 100 mg/kg-bw per day DGRE (approximately 88% purity with 30 unspecified impurities, including 1.9% 3-methylbenzoic acid ethyl ester, 1.6% 3-chloropropoxy-benzene, 2.8% dihydroxypropoxylbenzene) 5 times/week for 103 weeks. Significant increased incidences of hyperkeratosis, hyperplasia, papillomas and squamous-cell carcinomas of the forestomach were observed in both sexes at 50 mg/kg-bw per day or higher. Significant increased incidence of hepatocellular carcinomas observed at 100 mg/kg-bw in females. No effect in mortality observed in males, but 60–80% of females died during experiment in all dose levels including control due to suppurative and necrotizing inflammation of the reproductive tract (NTP 1985). **Dermal carcinogenicity in mice:** Swiss ICR/Ha mice (30 treated, 60 control, female) administered 1% solution DGRE (purity not specified) in benzene (approximately 100 mg/application according to IARC 1985, thrice weekly for life. No skin tumours observed and median survival was 491 days (Van Duuren et al. 1965). No inhalation studies were identified.
Genotoxicity and related endpoints: *in vivo*	**Micronucleus induction** **Positive:** B6C3F1 mice (5/group, male) intraperitoneally administered 0, 90, 180 or 270 mg/kg-bw per day for a single dose (Shelby et al. 1993). **Negative:** ICR mice (male and female, 4/group) orally administered 0 or 600 mg/kg-bw for a single dose (Seiler 1984). **Negative:** B6C3F1 mice (5/group, male) intraperitoneally administered 0, 15, 30, 60 or 90 mg/kg-bw per day for 3 days (Shelby et al. 1993). **Sex-linked recessive lethal** **Positive:** *Drosophila melanogaster,* 0 or 50 000 ppm DGRE (purity 87.9%) feeding in a solution of 5% aqueous sucrose (Valencia et al. 1985). **Reciprocal translocation** **Positive:** *Drosophila melanogaster,* 0 or 50 000 ppm DGRE (purity 87.9%) feeding in a solution of 5% aqueous sucrose (Valencia et al. 1985).
Genotoxicity and related endpoints: *in vitro*	**Mutagenicity** **Ames test** **Positive:** *Salmonella typhimurium* TA100 dose ranged 0–500 µg/mL in the absence

Diglycidyl resorcinol ether (DGRE)	
Endpoint	**Lowest effect levels/results**
	of metabolic activation with mutagenic response observed at 25–100 µg/mL and cytotoxicity observed at 250 µg/mL or higher (Seiler 1984). **Positive:** *Salmonella typhimurium* TA100, TA1535 dose ranged 0–2000 µg/mL (purity 87.9%) in the presence or absence of metabolic activation (Canter et al. 1986). **Negative:** *Salmonella typhimurium* TA98, TA1537 with dose up to 167 µg/mL in the presence or absence of metabolic activation S9 (NTP 1985). **Mouse lymphoma assay** **Positive:** Mouse lymphoma L5178Y TK(±) cells dose ranged 0–4 µg/mL in the absence of metabolic activation. Mutagenic response observed at 0.125 µg/mL or higher. Lethal response observed at 4 µg/mL (McGregor et al. 1988). **Positive:** Mouse lymphoma L5178Y TK(±) cells dose ranged 0–0.7 µg/mL in the absence of metabolic activation with chromosomal aberrations observed at 0.1 µg/mL or higher (McGregor et al. 1996). **Negative:** Mouse lymphoma cells, hprt locus in the absence of metabolic activation with dose up to 0.4 µg/mL (McGregor et al. 1996). **Chromosomal aberrations** **Positive:** Chinese hamster ovary (CHO) cells with DGRE (purity 87.9%) dose ranged 0–25 µg/mL in the absence of metabolic activation (Seiler 1984) **Positive:** CHO cells with dose ranged 0–50 µg/mL in the absence or presence of metabolic activation (Gulati et al. 1989). **Sister chromatid exchange** **Positive:** CHO cells with dose ranged 0–1.6 µg/mL in the absence or presence of metabolic activation (Gulati et al. 1989).

Phenyl glycidyl ether (PGE)	
Endpoint	**Lowest effect levels/results**
Experimental animals and *in vitro*	
Chronic toxicity/ carcinogenicity	**Inhalation:** Sprague-Dawley rats (100 animals per sex per dose group) were exposed (whole body) to 0, 6 or 74 mg/m^3 (0, 1 or 12 ppm respectively) of phenyl glycidyl ether (99.6% pure) 6 h/day, 5 days/week for 24 months. No details on survival were given. Exposure-related nasal tumours were observed at 74 mg/m^3 (statistical significance not specified) with incidences of 0/89, 0/83 and 9/85 in males and 1/87, 0/88 and 4/89 in females at 0, 6 and 74 mg/m^3, respectively. Incidences of rhinitis and squamous metaplasia were also higher at 74 mg/m^3 and were related to nasal tumours. IARC (1989) indicates p-values of 0.007 and 0.06 for incidences of rhinitis and metaplasia at the high doses in males and females, respectively (Lee et al. 1983).
Genotoxicity and related endpoints: *in vivo*	**Chromosomal aberration** **Negative:** Male rats were exposed to 0, 12.3, 36.8, or 67.6 mg/m^3 PGE (0, 2, 6, or 11 ppm) for 6 h/day for 19 consecutive days. No increased incidence in chromosomal aberrations was observed in bone marrow cells (Terrill et al. 1982). **Micronucleus induction** **Negative:** Mice treated with a single oral dose of up to 1000 mg/kg-bw were sacrificed 24 h after treatment and bone marrow cells were examined for micronucleated erythrocytes. No increase in micronuclei was observed (Seiler 1984). **Dominant lethal assay** **Negative:** Male rats were exposed to 0, 12.3, 36.8, or 67.6 mg/m^3 (0, 2, 6, or 11 ppm) for 6 h/day for 19 consecutive days and mated with 3 untreated females each for 6 weeks. No changes were observed that would be indicative of a dominant lethal effect (Terrill et al. 1982). **Testicular DNA synthesis** **Negative:** Mice were treated with a single oral dose of 500 mg/kg. Testicular DNA synthesis was examined. PGE did not affect the ability of [^{3}H]thymidine to reach the testes or the rate of testicular DNA synthesis as measured by the specific activity of [^{3}H]thymidine incorporated into DNA (Greene et al. 1979).
Genotoxicity and related endpoints: *in vitro*	**Mutagenicity** **Ames-test** **Positive:** *Salmonella typhimurium* strains TA97, TA100, and TA1535 (sensitive to base pair mutagens) but not in strains TA98, TA1537, and TA1538 (sensitive to frame-shift mutagens) with and without metabolic activation (Canter et al. 1986; Greene et al. 1979; Ivie et al. 1980; Neau et al. 1982; Ohtani and Nishioka 1981; Seiler 1984). **Positive:** *Klebsiella pneumoniae* and *Escherichia coli* WP2 uvrA (Voogd et al. 1981; Hemminki and Vainio 1980b; Ohtani and Nishioka 1981). **Host-mediated assay** **Positive:** C57BL/6 X C3H mice (5/group, sex not specified) received a single dose of 2500 mg/kg-bw orally or intramuscularly (IM). Positive results observed in 2/5 animals (oral) and 1/5 animals (IM). Positive control was not included (Greene et al. 1979). **Negative:** C57BL/6 X C3H mice (5/group, sex not specified) received a single dose

Phenyl glycidyl ether (PGE)	
Endpoint	**Lowest effect levels/results**
	of 2500 mg/kg-bw intraperitoneally (IP). Positive control was not included (Greene et al. 1979). **SOS chromotest** **Positive**: When 250 µL *Escherichia coli* PQ37 were incubated with 10 µL of dissolved PGE for 2 hours (von der Hude 1990). **Chromosomal aberration** **Negative:** Chinese hamster ovary cells (CHO) were incubated with PGE (6.25–100 µg/mL) for 6 or 18–24 hr without metabolic activation (S9) or for 6 hr with S9. None of the conditions tested resulted in mutations in CHO cells (Greene et al. 1979). **DNA adduct** **Positive:** PGE was reported to alkylate DNA in 4-(p-nitrobenzyl)-pyridine (NBP) reaction (Hemminki et al. 1980a). **Negative:** PGE did not bind to DNA in *Escherichia coli* with or without metabolic activation in a DNA-cell-bind assay (Hubinski et al. 1981).