Screening Assessment for the Challenge

Oxirane, (butoxymethyl)-
(*n*-Butyl glycidyl ether)

Chemical Abstracts Service Registry Number
2426-08-6

Environment Canada
Health Canada

March 2010

Synopsis

The Ministers of the Environment and of Health have conducted a screening assessment of oxirane, (butoxymethyl)-, also known as *n*-butyl glycidyl ether, Chemical Abstracts Service Registry Number 2426-08-6. This substance was identified in the categorization of the Domestic Substances List as a high priority for action under the Ministerial Challenge. *n*-Butyl glycidyl ether was identified as a substance presenting an intermediate potential for exposure of individuals in Canada and had been classified by other agencies on the basis of carcinogenicity and genotoxicity. As *n*-butyl glycidyl ether did not meet the criteria for persistence, bioaccumulation or inherent toxicity to aquatic organisms, the focus of this assessment relates primarily to human health aspects.

According to data submitted in response to section 71 of CEPA 1999, no companies in Canada reported manufacturing *n*-butyl glycidyl ether in a quantity greater than or equal to the threshold of 100 kg for the 2006 calendar year. However, it was reported that 10 000–100 000 kg were imported into Canada in 2006. *n*-Butyl glycidyl ether is used as a reactive diluent for epoxy resins serving as a viscosity reducer, as a chemical intermediate and as an acid acceptor for stabilizing chlorinated solvents. In Canada, *n*-butyl glycidyl ether is used mainly in epoxy resin formulations, which have applications as coatings, adhesives, binders, sealants, fillers and resins.

Emissions of *n*-butyl glycidyl ether into the ambient environment would likely come from anthropogenic sources, specifically commercial production and use of epoxy resins. Based on reported releases, uses and physicochemical properties, the principal route of exposure for the general population will likely be inhalation of contaminated air; exposure by other routes and from other media is likely to be negligible.

Based on its physical and chemical properties, *n*-butyl glycidyl ether is not expected to be persistent or to bioaccumulate in the environment. The substance does not meet the persistence criteria or the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*. In addition, empirical acute aquatic toxicity data suggest that the substance poses a low to moderate hazard to aquatic organisms. Based on a comparison of predicted no toxic effect concentrations and conservatively estimated environmental exposure concentrations, it is concluded that *n*-butyl glycidyl ether 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.

Although no long-term carcinogenicity assays have been conducted with *n*-butyl glycidyl ether, the substance was genotoxic in several *in vivo* and *in vitro* assays. In addition, substances that are structural analogues of *n*-butyl glycidyl ether have been demonstrated to be carcinogenic in experimental animals and genotoxic in a range of *in vivo* and *in vitro* assays. On the basis of the positive genotoxicity results for *n*-butyl glycidyl ether and the genotoxicity and carcinogenicity of substances analogous to *n*-butyl glycidyl ether, it is concluded that *n*-butyl glycidyl ether is a substance for which there may be a

probability of harm at any level of exposure. Therefore, it is concluded that *n*-butyl glycidyl ether 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 *n*-butyl glycidyl ether meets one or more of the criteria set out in section 64 of CEPA 1999.

Where relevant, research and monitoring will support verification of assumptions used during the screening assessment.

Introduction

Under the *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999), the Minister of the Environment and the Minister of Health conduct screening assessments of substances that were prioritized during the categorization of the Domestic Substances List to determine whether these substances present or may present a risk to the environment or to 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; 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), which 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 *n*-butyl glycidyl ether was identified as a high priority for assessment of human health risk because it was considered to present IPE and had been classified by other agencies on the basis of carcinogenicity and genotoxicity.

The Challenge for *n*-butyl glycidyl ether was published in the *Canada Gazette* on August 30, 2008 (Canada 2008). 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 were received.

n-Butyl glycidyl ether was determined to be a high priority for assessment with respect to human health. It did not meet the ecological categorization criteria for persistence, bioaccumulation or inherent toxicity to aquatic organisms. Therefore, this assessment focuses principally on information relevant to the evaluation of risks to human health.

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

This 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, reviews, assessment documents and stakeholder research reports, as well as from recent literature searches, up to April 2009 for the human health exposure and effects sections of the document. Key studies were critically evaluated; modelling results may have been used to reach conclusions. Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization of the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the conclusion is based.

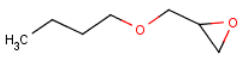
This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. This assessment has undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment, including Bernard Gadagbui (Toxicology Excellence for Risk Assessment), Michael Jayjock (The Lifeline Group) and Susan Griffin (US Environmental Protection Agency). The ecological portions of the assessment have also undergone external written peer review/consultation. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. Although external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada.

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

Substance Identity

For the purposes of this document, this substance will be referred to as *n*-butyl glycidyl ether, as given by the Japan Existing and New Chemical Substances and the Philippine Inventory of Chemicals and Chemical Substances. Information on the identity of *n*-butyl glycidyl ether is summarized in Table 1.

Table 1. Substance identity for *n*-butyl glycidyl ether

CAS RN	2426-08-6
DSL name	Oxirane, (butoxymethyl)-
NCI names	(Butoxymethyl)oxirane (ECL) Butyl 2,3-epoxypropyl ether (EINECS) Butylglycidylether (ENCS) Butyl glycidyl ether (PICCS) *n*-Butyl glycidyl ether (ENCS, PICCS) Normal butyl glycidyl ether (PICCS) Oxirane, (butoxymethyl)- (AICS, ASIA-PAC, NZIoC, PICCS, SWISS, TSCA)
Other names	BGE; *n*-BGE; BGE-C; BGE-R; 1-Butoxy-2,3-epoxypropane; 3-Butoxy-1,2-epoxypropane; 2-(Butoxymethyl)oxirane; 1-Butyl glycidyl ether; (±)-Butyl glycidyl ether; DY-BP; DY-BP (epoxide); Epi-Rez 501; Epodil 741; Epodil 741HP; ERL 0810; 2,3-Epoxypropyl butyl ether; Glycidyl butyl ether; Glycidyl *n*-butyl ether; N 10; N 10 (ether); NSC 83413; Propane, 1-butoxy-2,3-epoxy-
Chemical group (DSL stream)	Discrete organics
Major chemical class or use	Epoxides
Major chemical subclass	Alkyl epoxides; glycidyl ethers
Chemical formula	$C_7H_{14}O_2$
Chemical structure	
SMILES	O(C1COCCCC)C1
Molecular mass	130.185 g/mol

Abbreviations: AICS, Australian Inventory of Chemical Substances; ASIA-PAC, Asia-Pacific Substances Lists; CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substances List; ECL, Korean Existing Chemicals List; EINECS, European Inventory of Existing Commercial Chemical Substances; ENCS, Japanese Existing and New Chemical Substances; NCI, National Chemical Inventories; NZIoC, New Zealand Inventory of Chemicals; PICCS, Philippine Inventory of Chemicals and Chemical Substances; SMILES, simplified molecular input line entry specification; SWISS, Swiss Giftliste 1 and Inventory of Notified New Substances; TSCA, *Toxic Substances Control Act* Chemical Substance Inventory.
Source: NCI 2007

Physical and Chemical Properties

A summary of key physical and chemical properties of *n*-butyl glycidyl ether is presented in Table 2.

Table 2. Physical and chemical properties of *n*-butyl glycidyl ether

Property	Type	Value[1]	Rating[2]	Reference
Melting point (°C)	Modelled	−30.96		MPBPWIN 2000
Boiling point (°C)	Experimental	164		Lewis 2001
Density (g/mL at 25°C)	Experimental	0.908		Lewis 2001
Vapour pressure (Pa @ 25°C)	Experimental	427 (3.2 mmHg)	High	Lewis 2001
Henry's Law constant ($Pa \cdot m^3/mol$)	Modelled (bond method)	0.443 (4.37×10^{-6} $atm \cdot m^3/mol$)	Moderate	HENRYWIN 2000
Water solubility (mg/L @ 20°C)	Experimental	20 000	Very high	Bingham et al. 2001
Log K_{ow} (dimensionless)	Experimental	0.63	Low	Hansch et al. 1995
Log K_{oc} (dimensionless)	Modelled	1.09–1.16	Very low	KOCWIN 2008

Abbreviations: K_{ow}, octanol–water partition coefficient; K_{oc}, organic carbon–water partition coefficient.
[1] Values in parentheses represent the original values reported by the authors.
[2] Qualitative relative rating of the physicochemical parameter of the substance.

Sources

n-Butyl glycidyl ether is not reported to occur naturally. This substance is produced by condensation of epichlorohydrin and *n*-butyl alcohol to form an intermediate chlorohydrin, which is then dehydrochlorinated to form an epoxide group (Bosch et al. 1985; NTP 2004).

n-Butyl glycidyl ether may be released into the environment through emissions from industrial facilities producing, handling or using epoxy-based resins, coatings and adhesives.

According to data submitted in response to section 71 of CEPA 1999, no companies in Canada reported manufacturing *n*-butyl glycidyl ether in a quantity greater than or equal to the threshold of 100 kg for the 2006 calendar year. However, it was reported that between 10 000 and 100 000 kg were imported into Canada in 2006 (Environment Canada 2008).

n-Butyl glycidyl ether is identified as a High Production Volume (HPV) chemical in the United States. Aggregated production and/or import volumes in the United States for 2006 are between 1 million and 10 million pounds (US EPA 2008a).

Uses

n-Butyl glycidyl ether is used as a reactive diluent for epoxy resins, as a chemical intermediate and as an acid acceptor for stabilizing chlorinated solvents (Bingham et al. 2001; NTP 2004). The reactive diluent functions in epoxy resin systems as a viscosity lowering agent, allowing easier handling of the resin in the uncured state (Bosch et al. 1985; Lee 1989). Due to the presence of the epoxide functional group, *n*-butyl glycidyl ether participates in polymerization and cross-linking reactions, allowing it to become covalently bound into the epoxy network during the curing process (Bosch et al. 1985; Lee 1989; Hamerton 1996).

According to data submitted under section 71 of CEPA 1999, *n*-butyl glycidyl ether is used in Canada in the formulation of epoxy resins, which have applications as coatings, adhesives, binders, sealants, fillers and resins (Environment Canada 2008). A small quantity (2 kg) was imported as an impurity in a material preservative for paint (Environment Canada 2008). The substance is neither an active ingredient nor a formulant in pest control products registered in Canada, but it may be present as a formulant impurity (PMRA 2009).

n-Butyl glycidyl ether has not been reported in the Cosmetic Notification System (CNS 2009) and is therefore not deliberately added to cosmetics; however, this substance is not currently listed on Health Canada's Cosmetic Ingredient Hotlist, which would prohibit its use in cosmetic products (Health Canada 2007). The European Commission has listed this substance under Annex II of the Cosmetic Ingredients and Substances list, indicating that it must not form part of the composition of a cosmetic product in the European Union (CosIng 2009).

In Canada, *n*-butyl glycidyl ether is not listed in the Drug Product Database, Natural Health Products Ingredients Database or the Licensed Natural Health Products Database (Health Canada 2009a, b, c). As well, use of *n*-butyl glycidyl ether in therapeutic products was not reported under section 71 (Environment Canada 2008); thus, it is not expected that this substance would be present in pharmaceutical or natural health products. The Health Products and Food Branch of Health Canada has indicated that *n*-butyl glycidyl ether is not expected to be used in any current food packaging applications (2009 personal communication from Food Directorate, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced).

The *Controlled Products Regulations* established under the *Hazardous Products Act* require this substance to be disclosed on the material safety data sheet that must accompany workplace chemicals when it is present at a concentration of 0.1% or greater, as specified on the Ingredient Disclosure List (Canada 1988).

Releases to the Environment

n-Butyl glycidyl ether is not manufactured in reportable quantities in Canada; however, releases to the environment may occur from industrial facilities processing, handling or storing imported material. Information gathered under section 71 of CEPA 1999 indicates that Canadian importers of this substance released 100–1000 kg to the air in 2006 (Environment Canada 2008). No releases to water or land were disclosed (Environment Canada 2008).

With respect to exposure from environmental sources, no Canadian environmental monitoring data were identified. *n*-Butyl glycidyl ether is not reportable to Canada's National Pollutant Release Inventory (NPRI 2007); therefore, no release information is available from this source.

Environmental Fate

Based on its physical and chemical properties (Table 2), the results of Level III fugacity modelling (Table 3) suggest that *n*-butyl glycidyl ether will tend to remain in the compartment to which it is released.

Table 3. Results of the Level III fugacity modelling (EQC 2003) of *n*-butyl glycidyl ether

Substance released to:	Fraction of substance partitioning to each medium (%)			
	Air	Water	Soil	Sediment
Air (100%)	64	17	19	0.0
Water (100%)	0.0	99.8	0.0	0.2
Soil (100%)	0.0	20.0	80.0	0.0

Persistence and Bioaccumulation Potential

Table 4a presents empirical degradation data for *n*-butyl glycidyl ether.

Table 4a. Empirical data for degradation of *n*-butyl glycidyl ether

Medium	Fate process	Degradation value	Degradation endpoint, units	Reference
Water	Biodegradation	40	Biodegradation, %	MITI 2002
Water	Biodegradation	25	Biodegradation, %	US EPA 2008b
Water	Biodegradation	4 and 12	Biodegradation, %	US EPA 2008b
Water	Hydrolysis	20.3	Half-life, days	ECB 2006

MITI (2002) reported 40% biodegradation over 28 days in a ready biodegradation test for *n*-butyl glycidyl ether. Assuming first-order degradation kinetics, the predicted half-life

in water is approximately 38 days, suggesting that *n*-butyl glycidyl ether is not persistent in water.

Two additional degradation studies were reported in a robust study summary prepared by the US EPA (2008b). In a closed bottle test (Organisation for Economic Co-operation and Development [OECD] Test Guideline 301D), *n*-butyl glycidyl ether was oxidized to 25% of the theoretical oxygen demand by day 28, indicating that the substance is partially biodegradable. Assuming first-order degradation kinetics, the predicted half-life in water based on this result would be approximately 70 days. In a modified Sturm test (OECD Test Guideline 301B), 4% and 12% of the theoretically possible carbon dioxide formation were observed, leading the authors to conclude that there is "no evidence of biodegradability." There is some uncertainty about the low empirical biodegradation results which could be a result from volatilization. A detailed review of the original studies was not possible, as only the robust study summary prepared by the US EPA (2008b) was available.

A study designed to determine the approximate rate of hydrolysis of *n*-butyl glycidyl ether reported a hydrolysis half-life of 20.3 days (486.7 hours) at 20°C and pH 7. The rate of hydrolysis was observed to slow as the pH was increased (ECB 2006). Based on these results, hydrolysis is likely to be an important environmental fate process for this substance. Although the hydrolysis products are not known, they are likely to be more water soluble and less bioaccumulative than *n*-butyl glycidyl ether itself.

As few experimental data on the degradation of *n*-butyl glycidyl ether are available, a quantitative structure–activity relationship (QSAR)-based weight of evidence approach (Environment Canada 2007) was also applied. Results of the degradation models are presented in Table 4b. Given the ecological importance of the water compartment, the fact that most of the available models apply to water and the fact that *n*-butyl glycidyl ether may be released to this compartment, persistence primarily in water was examined using predictive QSAR models for biodegradation

Table 4b. Modelled data for degradation of *n*-butyl glycidyl ether

Fate process	Model result and prediction	Extrapolated half-life (days)	Model and model basis
Air			
Atmospheric oxidation	$t_{½}$ = 0.54 day	<2	AOPWIN 2000
Ozone reaction	n/a[1]	n/a	AOPWIN 2000
Water			
Biodegradation (aerobic)	3.19[2] "weeks"	<182	BIOWIN 2000 Submodel 3: Expert Survey (ultimate biodegradation)
Biodegradation (aerobic)	3.91[2] "days"	<182	BIOWIN 2000 Submodel 4: Expert Survey (primary biodegradation)

Fate process	Model result and prediction	Extrapolated half-life (days)	Model and model basis
Biodegradation (aerobic)	0.56[3] "biodegrades fast"	<182	BIOWIN 2000 Submodel 5: MITI linear probability
Biodegradation (aerobic)	0.60[3] "biodegrades fast"	<182	BIOWIN 2000 Submodel 6: MITI non-linear probability
Biodegradation (aerobic)	1.0[3] "biodegrades fast"	<182	TOPKAT 2004 Probability
Biodegradation (aerobic)	% BOD = 60 "biodegrades fast"	<182	CATABOL ©2004–2008 % BOD

Abbreviations: BOD, biological oxygen demand; MITI, Ministry of International Trade & Industry, Japan; n/a, not applicable; $t_{½}$, half-life.

[1] Model does not provide an estimate for this type of structure.

[2] Output is a numerical score.

[3] Output is a probability score

In air, a predicted atmospheric oxidation half-life value of 0.54 day (see Table 4b) demonstrates that this substance is likely to be rapidly oxidized. The substance is not expected to react with photo-oxidative species in the atmosphere, such as ozone, nor is it likely to degrade via direct photolysis. Therefore, it is suggested that reactions with hydroxyl radicals will be the most important fate process in the atmosphere for *n*-butyl glycidyl ether. Given the predicted atmospheric half-life of 0.54 day, *n*-butyl glycidyl ether is considered not persistent in air.

Model results indicate that biodegradation is rapid. The four ready biodegradation models—BIOWIN submodels 5 and 6 (BIOWIN 2000), CATABOL (©2004–2008) and TOPKAT (2004)—suggest an ultimate degradation half-life of <182 days. The results of BIOWIN submodels 3 and 4 (BIOWIN 2000) suggest that the substance undergoes primary degradation and ultimate degradation likely in a timeframe much less than 182 days. The predictions for CATABOL (©2004–2008) and TOPKAT (2004) are also within all the domains of both models (and suggest a fast rate of biodegradation). Thus, there is a consensus among the models indicating that the ultimate (and primary) degradation half-life is well below 182 days.

The results of the experimental degradation studies discussed above are conflicting, with one study indicating relatively rapid ultimate degradation (MITI 2002) and others indicating only partial to negligible biodegradability (US EPA 2008b). The conflicting results of the empirical studies are believed to be partially due to the high volatility of the substance. Degradability conclusions are difficult to determine based solely on the empirical ultimate degradation data. However, given the experimental data indicating relatively rapid hydrolysis (ECB 2006) and the model outputs that unanimously predict rapid ultimate degradation, the weight of evidence suggests that *n*-butyl glycidyl ether will have generally a primary and likely also an ultimate biodegradation half-life in water of <182 days.

Using an extrapolation ratio of 1:1:4 for water:soil:sediment biodegradation half-lives (Boethling et al. 1995) and the ultimate degradation half-life of about 38 days for water (MITI 2002), the half-life in soil is estimated to be <182 days and the half-life in sediments is <365 days. *n*-Butyl glycidyl ether is not expected to be persistent in soil or sediment.

Thus, *n*-butyl glycidyl ether does not meet the persistence criteria for air (half-life >2 days), water and soil (half-life >182 days) or sediment (half-life >365 days), as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

The low experimental log K_{ow} value for *n*-butyl glycidyl ether (see Table 2 above) suggests that this chemical has low potential to accumulate in biota.

As no experimental bioaccumulation factor (BAF) or bioconcentration factor (BCF) data for *n*-butyl glycidyl ether were available, a predictive approach was applied using available BAF and BCF models. Results are presented in Table 5.

Table 5. Fish BAF and BCF predictions for *n*-butyl glycidyl ether using the Arnot and Gobas (2003) kinetic model with default of no metabolism

Test organism	Log Kow	Endpoint	Value (L/kg wet weight)	Reference
Fish	0.63	BAF	1.173	Arnot and Gobas 2003 (Gobas BAF middle trophic level)
Fish	0.63	BCF	1.173	Arnot and Gobas 2003 (Gobas BCF middle trophic level)
Fish	0.63	BCF	3.162	BCFWIN 2000

The modified Gobas BAF middle trophic level model for fish predicted a BAF of 1.173 L/kg, indicating that *n*-butyl glycidyl ether does not have the potential to significantly bioconcentrate in fish or biomagnify in food webs. The results of BCF model calculations provide additional evidence supporting the low bioconcentration potential of this substance. Based on the available empirical and kinetic-based modelled values, *n*-butyl glycidyl ether does not meet the bioaccumulation criteria (BAF or BCF ≥5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential to Cause Ecological Harm

The approach taken in this assessment was to examine the available scientific 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 the persistence, bioaccumulation, toxicity, sources and fate of the substance.

As described previously, *n*-butyl glycidyl ether has relatively short half-lives in all environmental compartments. It is also expected to have a low bioaccumulation potential. The moderate importation volumes of *n*-butyl glycidyl ether into Canada and information on its uses do not indicate potential widespread release into the Canadian environment. Once released into the environment, *n*-butyl glycidyl ether will tend to remain in the media to which it is released.

There are experimental and modelled ecological effects data available for this substance; the lowest experimental value was used to estimate the potential aquatic toxicity. Tables 6a and 6b contain experimental and predicted ecotoxicity values that were considered to be reliable and were used in the weight of evidence approach for aquatic toxicity (Environment Canada 2007). The experimental and modelled data agree well with each other. The empirical acute median lethal concentration/median effective concentration ((LC_{50}/EC_{50}) values range from 3.9 to 65 mg/L, compared to model data ranging from 3.7 to <967 mg/L, indicating that *n*-butyl glycidyl ether can be expected to pose a low to moderate acute hazard to aquatic organisms.

Table 6a: Empirical data for toxicity of *n*-butyl glycidyl ether in aquatic organisms

Test Organism	Test Type	Endpoint	Value (mg/L)	Reference
Salmo gairdneri	Acute	96-h LC_{50}	65	US EPA 2008a
Daphnia magna	Acute	48-h EC_{50}	3.9	US EPA 2008a
		24-h EC_{50}	22	US EPA 2008a
Pseudokirchneriella subcapitata	Acute	96-h EC_{50} (growth)	35	US EPA 2008a

Abbreviations: EC_{50}, concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms; LC_{50}, concentration of a substance that is estimated to be lethal to 50% of the test organisms.

Table 6b. Modelled data for aquatic toxicity

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Fish	Acute (14 days)	LC_{50}	27.6[1]	ECOSAR 2004
Fish	Acute (96 h)	LC_{50}	41.16[1]	ECOSAR 2004
Fish	Acute (96 h)	LC_{50}	<967.81	OASIS Forecast 2005
Fish	Acute (96 h)	LC_{50}	125	AIES 2003–2005
Daphnia	Acute (48 h)	EC_{50}	97.22	AIES 2003–2005
Daphnia	Acute (48 h)	EC_{50}	3.7	TOPKAT 2004
Alga	Acute (48 h)	EC_{50}	137.05[1]	ECOSAR 2004

Abbreviations: EC_{50}, concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms; LC_{50}, concentration of a substance that is estimated to be lethal to 50% of the test organisms.
[1] ECOSAR values based on monoepoxide SAR class

As *n*-butyl glycidyl ether is used in industrial applications, releases to water are possible. Therefore, a generic scenario using Environment Canada's Industrial Generic Exposure Tool – Aquatic (IGETA) was used to conservatively estimate a concentration of *n*-butyl glycidyl ether resulting from an industrial discharge. The predicted environmental concentration (PEC) of 0.0021 mg/L was based on the maximum quantity used at one facility, the fraction discharged to a sewage treatment plant (STP), the STP removal rate, the STP effluent flow and the dilution capacity of the receiving water body (assumed to be small). Key inputs in the PEC estimate included a 0.25% estimated loss to wastewater during manufacturing or handling. Details regarding the inputs used to estimate this concentration and the output of the model are described in Environment Canada (2009).

A conservative predicted no-effect concentration (PNEC) was also derived from the lowest empirical toxicity value: an acute EC_{50} for *Daphnia* of 3.9 mg/L. This value, selected as the critical toxicity value (CTV), was divided by an assessment factor of 100 to account for uncertainties related to interspecies and intraspecies variability in sensitivity and extrapolation from an estimated EC_{50} to a no-effect value in the field. This yielded a PNEC of 0.039 mg/L.

The resulting conservative risk quotient (PEC/PNEC) of 0.054 indicates that the estimated environmental concentrations would not be sufficient to cause harm to aquatic organisms. The results of fugacity modelling indicate that if released to water, most of the substance will remain in that compartment. Exposures of organisms at other types of locations or in media other than water are less likely. Although releases to air are possible, based on information reported under section 71, effects are unlikely because of the relatively large dilution capacity of the air compartment.

Therefore, based on the information available, *n*-butyl glycidyl ether is unlikely to be causing ecological harm in Canada. This conclusion was made despite the uncertainties from lack of empirical data on environmental concentrations in Canada. Concentrations in water were modelled based on conservative assumptions. There is also uncertainty associated with PNECs used in the risk quotient calculation, including the limited amount of empirical toxicity data. This is addressed in part by dividing the CTV by an assessment factor.

Uncertainties are also associated with the use of QSAR models to estimate substance properties (e.g., persistence and bioaccumulation potential) for *n*-butyl glycidyl ether. However, because the structural composition of the substance was covered by the domains of the models, and since the various QSAR models used gave consistent results, the conclusions drawn are considered credible and comparable to what would be expected for this relatively simple structure. Additional evidence that the QSAR values are credible is that *n*-butyl glycidyl is a low molecular weight substance with no extreme functional groups that cannot be handled by the model and the mono epoxides were used in the ECOSAR model.

Potential to Cause Harm to Human Health

Exposure Assessment

No measured concentrations of *n*-butyl glycidyl ether in air, water or soil were identified. Modelled environmental exposure estimates, based on the upper end of the range of releases reported under the recent section 71 notice (Environment Canada 2008), predict that concentrations of *n*-butyl glycidyl ether in air and water would be low, at approximately 0.8 ng/m^3 and 0.5 ng/L, respectively (ChemCAN 2003). Predicted concentrations for soil and sediment are estimated at less than 10^{-3} ng/g (ChemCAN 2003). Upper bounding estimates of intake for the general population from all environmental media based on these predicted concentrations would therefore be very low (i.e., below 10^{-3} µg/kg bw per day).

A single study was identified in which *n*-butyl glycidyl ether was measured in environmental media. Clark et al. (1991) analysed semivolatile pollutants in effluent streams from three wastewater treatment plants in the state of New Jersey. Three sampling sets were performed at each facility; for each sampling event, three 15 L samples were taken and combined on site. In the effluent from Facility A, *n*-butyl glycidyl ether was detected only in the third sampling set, at a estimated concentration of 0.5 µg/L. *n*-Butyl glycidyl ether was not detected in the other two samples from Facility A or in any of the samples from Facility B or C.

In Canada, *n*-butyl glycidyl ether is used in the production of epoxy resins, which have applications as coatings, adhesives, binders, sealants, fillers and resins (Environment Canada 2008). However, no consumer products containing *n*-butyl glycidyl ether as an intentional ingredient were identified in an extensive search of the publicly available literature or through consultations with various Health Canada programs. The Canadian Paint and Coatings Association has indicated that all coating applications of *n*-butyl glycidyl ether are, to its knowledge, industrial (2009 personal communication from Canadian Paint and Coatings Association to Risk Management Bureau, Health Canada; unreferenced).

No studies were identified on potential exposure to residual *n*-butyl glycidyl ether from cured epoxy resins. It is generally assumed that the glycidyl ether is no longer present in the cured product (IARC 1989). The Dow Chemical Product Safety Assessment report on reactive diluents indicated that "little or no" unreacted glycidyl ether would be present in a finished product (Dow 2009). Thus, exposure to *n*-butyl glycidyl ether from contact with cured epoxy resins is deemed negligible.

n-Butyl glycidyl ether is reportedly present as an impurity in a material preservative used in latex and oleo-resinous paints. The preservative, which reportedly may contain up to 4.2% *n*-butyl glycidyl ether (Environment Canada 2008), is added to interior paints at up to 0.8% by weight (2009 personal communication from Pest Management Regulatory Agency, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced), resulting in a maximum concentration of 336 mg/kg. As only 2 kg of *n*-butyl glycidyl ether were imported as an impurity in a material preservative for paint in 2006 (Environment Canada 2008), few individuals would potentially be exposed to *n*-butyl glycidyl ether during use of this product. Despite the small number of potentially exposed consumers, ConsExpo version 4.1 (ConsExpo 2006) modelling software was used to predict upper bounding estimates of airborne mean event concentration and dermal dose of 6 mg/m^3 and 0.02 mg/kg-bw, respectively (Appendix 1). However, in light of the reactive nature of *n*-butyl glycidyl ether, it is likely that levels remaining in the product used by the end consumer are much lower. Additionally, given the very small amount of the substance imported as an impurity in this type of product, consumer exposure would not be widespread across the general population of Canada.

In the recently published Initial Risk-Based Prioritization of High Production Volume Chemicals for *n*-butyl glycidyl ether, the US Environmental Protection Agency (US EPA) characterized the potential for consumer exposure as high, based on the Inventory Update Rule and the use of *n*-butyl glycidyl ether in adhesives and sealants (US EPA 2008a). However, the US EPA consumer exposure characterization is based on the production volumes and general use categories, not on specifically identified products containing this substance (2009 personal communication from Chemical Control Division, US EPA, to Risk Assessment Bureau, Health Canada; unreferenced).

There are significant uncertainties in the characterization of human exposure. In the absence of measured environmental data, estimates of exposure have been based on the upper bound of the range of environmental releases from industrial facilities. The confidence in the relevant exposure database is considered to be very low. Despite the very limited data, the reactive nature of the oxirane group, the predominant application in cured epoxy resins in which *n*-butyl glycidyl ether participates in cross-linking reactions and the very low predicted daily intake estimates lend confidence to the prediction that exposure of the general population would be low.

Health Effects Assessment

Appendix 2 contains a summary of the available health effects information for *n*-butyl glycidyl ether.

The European Commission has classified *n*-butyl glycidyl ether as Category 3 for carcinogenicity (causes concern to humans owing to limited evidence of a carcinogenic effect) and as Category 3 for mutagenicity (causes concern to humans owing to possible risk of irreversible effects) (ESIS 2009). Due to the lack of long-term data for *n*-butyl glycidyl ether, the European Commission's carcinogenicity classification was based on both the weight of evidence from the genotoxicity data for *n*-butyl glycidyl ether and the carcinogenicity data from the structural analogue allyl glycidyl ether. The mutagenicity classification was based principally on positive results from *in vivo* micronucleus assays.

For this assessment, data on several analogous substances (Appendix 3) were examined to inform understanding of the potential health effects associated with exposure to *n*-butyl glycidyl ether. The use of analogous substances as surrogates is an approach that has been employed by several national and international regulatory agencies, including the US EPA (HPV Challenge programme), the European Chemicals Agency (Registration, Evaluation, Authorisation and Restriction of Chemicals [REACH] regulation) and the OECD (HPV Chemicals program). The approach used in the present assessment is consistent with the general principles described by the above-mentioned authorities—that is, the selection of the chemical analogues included in this report is based on the presence of the glycidyl (ether) functional group and other structural similarities, physicochemical properties, availability of carcinogenicity data and their identification as an analogue to *n*-butyl glycidyl ether by various regulatory agencies. Hence, some structural analogues, such as *t*-butyl glycidyl ether, were not considered due to a lack of carcinogenicity data. The glycidyl (ether) group was identified as the most important criterion for assessing carcinogenic potential due to the presence of the epoxy ring. Epoxides act as alkylating agents and can interact with deoxyribonucleic acid (DNA) (NTP 2004), thus making them likely to be involved in the potential carcinogenicity of *n*-butyl glycidyl ether.

Although allyl glycidyl ether was the only surrogate used by the European Commission to classify *n*-butyl glycidyl ether and is considered the most closely related substance with carcinogenicity data available, other substances, including glycidol and phenyl glycidyl ether, may also be used to better support the body of evidence with respect to carcinogenicity. In addition, NTP (2004) also included another substance, bisphenol A diglycidyl ether (BADGE, the most common active component in epoxy resins), in its review of the toxicological literature relevant to *n*-butyl glycidyl ether. A brief overview of the relevant data on the carcinogenicity and genotoxicity of these substances is presented below, and more details are provided in Appendix 4.

The available carcinogenicity database for allyl glycidyl ether is limited to a 2-year inhalation study in which male and female rats and mice were exposed to 0, 23 or 47 mg/m^3 (NTP 1990a). The authors concluded that there was equivocal evidence of carcinogenicity in male Osborne-Mendel rats, some evidence in male B6C3F1 mice and

equivocal evidence in female B6C3F1 mice, based on the presence of various types of nasal neoplasms. Although the incidences of primary tumours were not statistically significant, they were considered to be biologically significant due to the fact that primary nasal tumours are rare in rodents; in addition, non-neoplastic lesions preceded or accompanied the neoplasia, and preneoplastic lesions were observed in exposed mice.

For glycidol, there is stronger evidence for carcinogenicity, as it induced tumours in a wide range of tissues in multiple species exposed via oral administration. Male and female rats and mice were exposed to glycidol at doses 0, 37.5 or 75 mg/kg-bw per day (rats) and 0, 25 or 50 mg/kg-bw per day (mice) via gavage for 2 years (NTP 1990b). It was concluded that there was clear evidence of carcinogenicity in males and females of both species based on multiple neoplastic lesions in various tissues, including the uterus, tunica vaginalis, clitoral gland, Harderian gland, mammary gland, brain, oral mucosa, forestomach, intestine, liver, lung, skin, subcutaneous tissue, blood, Zymbal gland and thyroid gland. In a study using genetically modified haploinsufficient mice, animals were exposed to glycidol at 0, 25, 50, 100 or 200 mg/kg-bw per day via gavage for 40 weeks (NTP 2007). The authors concluded that there was clear evidence of carcinogenicity in males based on the occurrence of histiocytic sarcomas and some evidence of carcinogenicity in females based on the occurrence of alveolar/bronchiolar adenomas. Increased incidences of alveolar/bronchiolar adenomas in males and forestomach papillomas in females were also considered to be related to glycidol administration. In a study in which hamsters were exposed to 100 mg/kg-bw per day by gavage for 60 weeks, tumours were observed in the spleen, adrenal cortex, forestomach and uterus/cervix (Lijinsky and Kovatch 1992). The authors indicated that adrenal cortex tumours are common in this strain of hamster, but that hemangiomas and hemangiosarcomas of the spleen are very rare. However, no increased incidence of skin damage or neoplasm was observed in mice exposed to a 5% solution of glycidol through skin application for 520 days (Van Duuren et al. 1967).

In the only identified carcinogenicity study for phenyl glycidyl ether, 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 the higher concentration only (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.

With respect to BADGE, most of the carcinogenicity studies involved the commercial-grade resin. Only one study using pure BADGE was identified. Mice were exposed to a 0%, 1% or 10% solution of BADGE by dermal application for 2 years (Peristianis et al. 1988). Although tumours were noted at the site of application and at other sites, the incidences were not statistically significant. A statistically significant trend was observed for the occurrence of thymic lymphosarcoma in females. However, the authors noted a relatively high background incidence of lymphoreticular/hematopoietic neoplasia for this particular strain in their laboratory, which may have been caused by viral infection.

Although no carcinogenicity bioassays have been conducted with *n*-butyl glycidyl ether, the substance has been tested in a range of short-term genotoxicity tests with positive

results in several assays. *In vivo*, it induced chromosomal aberrations and micronucleus formation in mice exposed via intraperitoneal injection, although it did not cause micronucleus formation when administered orally. *n*-Butyl glycidyl ether also induced dominant lethal mutations in mice, with the exception of one trial in which fetal death rate was elevated in controls. *n*-Butyl glycidyl ether also tested positive in a number of *in vitro* genotoxicity assays. Reverse mutations were observed in several, but not all, strains of *Salmonella typhimurium*, with and without activation. When tested in urine and host-mediated assays, results were negative. However, *n*-butyl glycidyl ether induced mutations in mouse lymphoma cells, Chinese hamster cells and human peripheral blood lymphocytes.

The results of genotoxicity assays for the analogous substances considered relevant are summarized in Appendix 4. In general, there is convincing evidence of the genotoxicity of allyl glycidyl ether and glycidol, with results comparable to those for *n*-butyl glycidyl ether, whereas phenyl glycidyl ether and BADGE appeared to be only weakly genotoxic.

In order to further inform the database with respect to the potential carcinogenicity of *n*-butyl glycidyl ether, QSAR models were used to predict its toxicity and that of the related substances considered here. In general, the predictions for all substances were similar, as CASETOX (2008), DEREK (2008) and TOPKAT (2004) indicated that genotoxicity was probable/plausible for *n*-butyl glycidyl ether and its analogues, due to the presence of the glycidyl (ether) moiety, consistent with available empirical data. With respect to predictions for carcinogenicity, DEREK (2008) predicted that *n*-butyl glycidyl ether and its analogues were plausible carcinogens, CASETOX (2008) predictions were mostly positive and TOPKAT (2004) predictions were negative. Although different models may provide varying results for a substance (likely principally due to the different model assumptions and supporting datasets), it is the similarity in predictions of each model across this group of compounds that provides support for the consideration of information on allyl glycidyl ether, glycidol, phenyl glycidyl ether and BADGE in the assessment of the carcinogenic potential of *n*-butyl glycidyl ether.

Although a mode of action for tumour induction by analogues of *n*-butyl glycidyl ether has not been elucidated, the potential of the epoxy ring contained in the glycidyl group to interact with DNA suggests a genotoxic mechanism of carcinogenicity. The possibility that *n*-butyl glycidyl ether could act as a direct carcinogen is supported by the available genotoxicity data.

n-Butyl glycidyl ether also induced non-neoplastic effects in experimental animals, among which skin irritation and sensitization are the most documented. Exposure of the eyes of rabbits to the undiluted substance resulted in conjunctivitis and severe ocular damage (Rhone-Poulenc Inc. 1973). As well, dermal applications of pure or diluted *n*-butyl glycidyl ether (1% or 25% solutions) induced light to moderate erythema in rabbits and guinea pigs (Rhone-Poulenc Inc. 1973; Reichhold Chemical Company 1978).

Sensitization tests were performed in guinea pigs in several studies (Weil et al. 1963; Ciba-Geigy 1977; Reichhold Chemical Company 1978), all of which provided evidence

of sensitization in the majority of the animals after exposure to the diluted substance (0.1–25% solutions) intracutaneously or via patch application followed by a challenge dose.

Allergic reactions in humans were also investigated in several studies, predominantly in occupationally exposed workers. The response rate was generally lower than in laboratory animals, ranging from 0/343 to 3/20 positive allergic reactions.

Although no long-term studies have been identified, the toxicity of *n*-butyl glycidyl ether has been investigated in a limited number of shorter-term studies. In a 4-week inhalation study in rats, a lowest-observed-effect concentration (LOEC) for short-term exposure of 500 mg/m^3 (94 ppm) was identified for degeneration of the olfactory mucosa and hyperplastic/metaplastic changes in the ciliated respiratory epithelium (Ciba-Geigy 1985a, b). With respect to dermal exposure, a lowest-observed-effect level (LOEL) of 100 mg/kg-bw per day was identified for lesions in the livers of rabbits exposed 5 times/week for 4 weeks (NTP 2004). Other target tissues following short-term exposure to *n*-butyl glycidyl ether include the blood, liver, kidney and lungs.

No studies specifically designed to assess reproductive or developmental toxicity of *n*-butyl glycidyl ether were identified. However, information is available from sub-chronic studies and dominant lethal assays. In rats exposed to *n*-butyl glycidyl ether concentrations up to 1600 mg/m^3 via inhalation for 10 weeks, testicular atrophy was observed at 400 mg/m^3 and above (Shell Oil Company 1957). In a dominant lethal assay, females mated with males exposed to 1500 mg/kg-bw per day 3 times/week for 3 weeks via skin application had decreased pregnancy rates, increased fetal death rates and decreased number of implants (Rhone-Poulenc Inc. 1977). Testicular atrophy as well as reduced reproductive capacity have also been observed in rats exposed to allyl glycidyl ether and phenyl glycidyl ether (IARC 1989; NTP 1990a, 2004).

The confidence in the toxicity database is considered to be moderate. There is sufficient information to address effects that may be of concern following short-term exposure. Despite the absence of chronic carcinogenicity studies for *n*-butyl glycidyl ether, information can be drawn from studies conducted using analogous substances to inform assessment of the potential carcinogenicity of *n*-butyl glycidyl ether. The carcinogenicity data are supported by the results from both *in vivo* and *in vitro* genotoxicity testing of *n*-butyl glycidyl ether as well as its analogues.

Characterization of Risk to Human Health

Based principally on the weight of evidence assessment of the European Commission, a critical effect for characterization of risk to human health for *n*-butyl glycidyl ether is carcinogenicity. Although *n*-butyl glycidyl ether has not been tested in a long-term cancer bioassay, exposure to analogous substances via inhalation, topical application or ingestion increased the incidence of tumours in various organs in rodents.

n-Butyl glycidyl ether was also genotoxic in a range of *in vivo* and *in vitro* assays; likewise, the structural analogues allyl glycidyl ether and glycidol also tested positive for various endpoints in both *in vivo* and *in vitro* genotoxicity assays. Considering that the glycidyl ether functional group is present in each of the analogues, that the epoxide moiety contained therein is known to alkylate DNA, that all analogues have tested positive in several *in vitro* genotoxicity assays and some have tested positive in *in vivo* assays, that all show some evidence for carcinogenicity and that similar health effects were observed for other endpoints (irritation, sensitization and reproductive toxicity), it can be reasonably concluded that *n*-butyl glycidyl ether and the selected analogues cause similar health effects and that the use of such analogues is appropriate to better inform understanding of the hazards associated with exposure to *n*-butyl glycidyl ether. Therefore, in light of the genotoxicity of *n*-butyl glycidyl ether and the carcinogenicity and genotoxicity of structurally similar compounds, it cannot be precluded that *n*-butyl glycidyl ether would induce tumours via a mode of action involving direct interaction with genetic material.

With respect to non-cancer effects, the lowest LOEC for inhalation exposure was 400 mg/m^3 based on testicular atrophy observed in rats exposed 5 days/week for 10 weeks (Shell Oil Company 1957). Comparison of this effect level with the modelled estimate of outdoor air concentration for *n*-butyl glycidyl ether (i.e., <1 ng/m^3) results in a predicted margin of exposure of approximately eight orders of magnitude. Although *n*-butyl glycidyl ether is used in the manufacture of epoxy resins and other formulations that are used in various products, the available information indicates that consumer exposure is expected to be minimal. Therefore, in light of the very low predicted exposures, the margin of exposure is considered sufficient to be protective against the induction of non-cancer effects in the general population in Canada.

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 *n*-butyl glycidyl ether or its analogues, nor does it take into account possible differences between humans and experimental species in sensitivity or potential differences in toxicity due to route of exposure. Furthermore, there is uncertainty surrounding the extrapolation of data on analogous substances to predict the potential carcinogenicity of *n*-butyl glycidyl ether; although analogues were carefully chosen based on common structural features and similar profiles of health effects, it is possible that other characteristics specific to each substance may influence their toxic potential. There is also uncertainty concerning the reproductive and developmental toxicity of *n*-butyl glycidyl ether, as the available information was limited to effects observed on reproductive organs in shorter-term studies and dominant lethal assays, although it is likely that these effects would be induced only at doses or concentrations greater than those to which the general population is exposed.

Despite the very limited data available with which to quantify population exposure, in view of the lack of information on the presence of the substance in consumer products, the reactive nature of the oxirane group and the very low predicted daily intake estimates

based on conservative assumptions, there is confidence that exposure of the general population to *n*-butyl glycidyl ether would be low. Additional data on residual concentrations (if any) within cured epoxy resins as well as environmental monitoring data would permit more confident characterization of the potential human exposure to *n*-butyl glycidyl ether in Canada.

Conclusion

Based on the information presented in this screening assessment, it is concluded that *n*-butyl glycidyl ether 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.

On the basis of the genotoxicity of *n*-butyl glycidyl ether and the genotoxicity and carcinogenicity of substances analogous to *n*-butyl glycidyl ether, it is concluded that *n*-butyl glycidyl ether is a substance for which there may be a probability of harm at any level of exposure. Thus, *n*-butyl glycidyl ether is concluded to be 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.

It is therefore concluded that *n*-butyl glycidyl ether meets one or more of the criteria set out in section 64 of CEPA 1999. Additionally, *n*-butyl glycidyl ether does not meet the criteria for persistence or bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Where relevant, research and monitoring will support verification of assumptions used during the screening assessment.

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Appendix 1: Upper-bounding estimates of potential exposure to *n*-butyl glycidyl ether from consumer products

Consumer product scenario	Assumptions	Estimated exposure
Paint	Weight percent of *n*-butyl glycidyl ether: 0.0336% Exposure frequency of 1/year (ConsExpo 2006) Body weight of 70.9 kg (Health Canada 1998) Applied amount of 1.3×10^3 g (ConsExpo 2006) **Inhalation model: exposure to vapour, evaporation** Exposure duration of 132 min (ConsExpo 2006) Room volume of 20 m^3 (ConsExpo 2006) Ventilation rate of 0.6 air changes/h (ConsExpo 2006) Inhalation uptake of 100% Inhalation rate of 16.2 m^3/day (Health Canada 1998) **Dermal model: direct dermal contact with product, constant rate** Exposed area of 0.367 m^2 (ConsExpo 2006, general fact sheet for hands and arms) Contact rate of 30 mg/min (ConsExpo 2006) Release duration of 7.2×10^3 s (ConsExpo 2006) Dermal uptake of 100%	**Inhalation** Mean event concentration **6 mg/m^3** **Dermal** Acute dose **0.02 mg/kg-bw**

Appendix 2: Summary of health effects information for *n*-butyl glycidyl ether (BGE)

Endpoint	Lowest effect levels[1]/Results
Laboratory animals and in vitro	
Acute toxicity	**Lowest oral LD_{50}** (mouse) = 1530 mg/kg-bw in Webster mouse (Shell Oil Company 1956) **Lowest dermal LD_{50}** (rabbit) = 788 mg/kg-bw in rabbits (strain not stated) (Lockwood and Taylor 1982) **Lowest inhalation LC_{50}** (rat) = 5.484 g/m^3 (1030 ppm) in Long-Evans rats (Shell Oil Company 1956) [Additional studies: Hine et al. 1956; ACGIH 1986]
Short-term repeated-dose toxicity	**LOEL (oral):** No studies identified. **LOEC (inhalation):** 500 mg/m^3 (94 ppm) based on degeneration of the olfactory mucosa and hyperplastic/metaplastic changes in the ciliated respiratory epithelium in male and female rats. Effects were slightly more pronounced in males than in females. Additional effects were observed at 1000 mg/m^3 (188 ppm), including decreased body weights in males along with elevated aspartate transaminase levels and increased hemoglobin. The effect on hemoglobin was reversible when exposure was ceased and animals were allowed to recover for 2 weeks. Exposure protocol was as follows: rats were exposed 6 h/day, 5 days/week, for 28 days to 0, 100, 500 or 1000 mg/m^3 (0, 18, 94 or 188 ppm) (Ciba-Geigy 1985a, b). [No additional inhalation studies identified.] **LOEL (dermal):** 100 mg/kg-bw per day based on the appearance of small white lesions on the liver in one of five rabbits. BGE was applied 5 times/week for 4 weeks. No further information reported in secondary source (Confidential 1964). [No additional dermal studies identified.]
Subchronic toxicity	**LOEC (inhalation):** 400 mg/m^3. Male rats were exposed to BGE at concentrations of 0, 200, 400, 800 or 1600 mg/m^3 (0, 38, 75, 150 or 300 ppm) 7 h/day, 5 days/week, for 10 weeks. At 800 mg/m^3 (150 ppm), retarded growth and the death of one rat were observed. Exposure to 1600 mg/m^3 (300 ppm) resulted in liver necrosis, emaciation, rough appearance and increased kidney to body weight and lung to body weight ratios (Shell Oil Company 1957). See also Reproductive toxicity. [No additional subchronic studies identified.]
Chronic toxicity/ carcinogenicity	No chronic toxicity/carcinogenicity studies identified.
Developmental toxicity	See Genotoxicity and related endpoints: *in vivo*, dominant lethal assays results.
Reproductive toxicity	**LOEC (inhalation):** 400 mg/m^3. Testicular atrophy was observed in 1/10 rats at 400 mg/m^3 and in 4/5 rats at 1600 mg/m^3. Small testes were observed in 1/10 rats at 800 mg/m^3. (Shell Oil Company 1957). US EPA (1979) considered the effects related to BGE exposure. See Shell Oil Company (1957) in Subchronic toxicity for study protocol details. See also Genotoxicity and related endpoints: *in vivo*, dominant lethal assays results.
Genotoxicity and related endpoints: *in vivo*	**Dominant lethal assay** **Positive:** A minimum of 10 B6D2F1 male mice (8–10 weeks old) were exposed topically with >95% pure BGE at a dosage of 1500 mg/kg-bw 3 times/week for 8 weeks. The study included unexposed controls and positive controls exposed to triethylenemelamine. After exposure, males were mated with three virgin females per week for the following 3 weeks. A significant increase in the proportions of deaths per pregnancy ($p = 0.04$) was observed. Significant decreases were detected

Endpoint	Lowest effect levels[1]/Results
	in both the numbers of implants per pregnancy ($p = 0.01$) and the number of pregnant females ($p = 0.05$) when compared with unexposed controls (Rhone-Poulenc Inc. 1977). **Equivocal:** Groups of 36–44 male BDF mice were exposed to BGE (95% purity) at 0, 375, 750 or 1500 mg/kg-bw per day through dermal application 3 times/week for 8 weeks. Controls were exposed to 0.9% saline. The males were mated to three unexposed females each week for 3 weeks following initial exposure. Two trials using the same protocol were conducted. A significant increase in the fetal death rate at the high dose was observed in experiment 1, as well as when the data from the two trials were combined ($p < 0.05$). When considering only the second trial, there was no significant increase in fetal death rate, as it was unusually high in the control group for this experiment. No changes in pregnancy rate or number of implants per pregnant female were observed in either trial (Shell Oil Company 1957; Whorton et al. 1983). **Chromosomal aberrations** **Positive:** Sprague-Dawley CR-1 rats were injected intraperitoneally with 0, 31.3, 104.2 or 312.5 mg/kg-bw 5 times over 5 days. Exposure to triethylenemelamine was used as a positive control. A dose-related increase in chromosomal aberrations was observed in rat bone marrow cells. Aberrations included chromatid and chromosome breaks, marker-type aberrations and severe chromosome damage (Procter and Gamble Company 1979). **Micronucleus assay** **Negative:** Mice (female, BDF) exposed orally for 5 days with 200 mg/kg-bw (Connor et al. 1980a). **Positive:** Mice (female, BDF) injected intraperitoneally with 225, 450, 675 or 900 mg/kg-bw for 1 or 2 days. Response was dose related (Connor et al. 1980a). **Positive:** Mice injected intraperitoneally with 200, 225 or 675 mg/kg-bw for 5, 2, or 1 day, respectively. Increased micronuclei at 225 mg/kg-bw for 2 days and 675 mg/kg-bw for 1 day (CMA 1984).
Genotoxicity and related endpoints: *in vitro*	**Mutagenicity** **Positive for bacterial reverse mutation:** Ames test, *Salmonella typhimurium* strains TA100 and TA1535 with and without metabolic activation. Occasionally positive in TA97 and TA1538 (Confidential 1977; Rhone-Poulenc Inc. 1977; Shell Oil Company 1978; Procter and Gamble Company 1979; Wade et al. 1979; Connor et al. 1980a; Thompson et al. 1981; Canter et al. 1986). **Negative:** Urine assay, *Salmonella typhimurium* strain TA1535. Urine obtained from female B6D2F1 or female ICR mice exposed orally to 200 mg/kg-bw per day for 4 days (Rhone-Poulenc Inc. 1977). **Negative:** Urine assay, *Salmonella typhimurium* strains TA98 and TA1535. Urine obtained from male BDF mice treated topically with 1500 mg/kg-bw, 3 times/week for 8 weeks, or with 750, 1500 or 3000 mg/kg-bw, 3 times/week for 16 weeks (Connor et al. 1980a). **Negative:** Urine assay, *Salmonella typhimurium* strain TA1535 using urine obtained from female ICR mice treated orally with 200 mg/kg-bw once per day for 4 days (Connor et al. 1980a). **Negative:** Host-mediated assay, *Salmonella typhimurium* (strains not stated). Ten female ICR mice treated orally for 5 days were inoculated with *Salmonella typhimurium.* Bacteria were recovered and screened for reverse mutation (Rhone-Poulenc Inc. 1977). **Positive:** Mouse lymphoma cells (TK deficient mutants) with and without activation (Thompson et al. 1981). **Sister chromatid exchange**

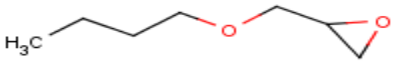
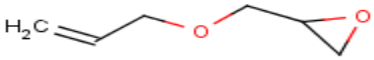
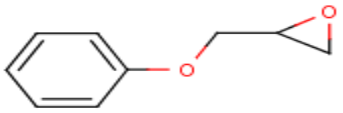
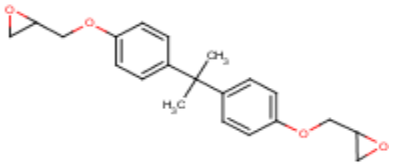
Endpoint	Lowest effect levels[1]/Results
	Positive: Chinese hamster V79 cells (von der Hude et al. 1991). **Transformation** **Negative:** Mouse BALB/3T3 cells exposed once for 2 h or twice for 2 h with a 24-h recovery period in between (Connor et al. 1980a). **DNA damage** **Positive:** Unscheduled DNA synthesis in human peripheral blood lymphocytes (Rhone-Poulenc Inc. 1977; Frost and Legator 1982). **Equivocal:** Weak unscheduled DNA synthesis response in W138 cells, not considered positive by the authors (Thompson et al. 1981). **Positive:** Damaged DNA present in cultured human lymphocytes (exposure protocol not provided in secondary source: IARC 1999) (Connor et al. 1980b).
Irritation/sensitization	0.1 ml of undiluted BGE was administered into one eye in each of three New Zealand White Albino rabbits. BGE caused severe ocular damage in one eye, which was considered irreversible. The remaining eyes had diffuse areas of corneal translucency and slight to moderate conjunctivitis that cleared within 4 days (Rhone-Poulenc Inc. 1973). 0.5 ml of undiluted BGE was applied to gauze pads that were taped onto both normal and abraded sites on the backs of New Zealand White Albino rabbits. Experiments were performed under both occluded and unoccluded conditions. After 24 h, pads were removed and animals were observed. BGE elicited severe irritation under all conditions (Rhone-Poulenc Inc. 1973; Reichhold Chemical Company 1978). Guinea pigs were injected intracutaneously with 0.1 ml of diluted BGE 3 times/week, on alternate days, for a total of eight injections. A challenge dose, assumed to be a 0.1 ml injection of diluted BGE, although this was not stated by the authors, was given after an incubation of 3 weeks. Animals were observed for sensitization 24 and 48 h later. Sensitization was observed in 16 of 17 animals (Weil et al. 1963). Ten male and 10 female Pirbright guinea pigs were injected intracutaneously with 0.1 ml of 0.1% BGE on the back or right flank every other day for a total of 10 injections. Challenge doses of the same magnitude were given 2 weeks later on the left flank. Eleven of 19 animals showed sensitization. One animal died (Ciba-Geigy 1977). Twelve female albino guinea pigs received 0.1 ml intradermal injections of 10% BGE 3 times. A 48-h topical application followed 1 week later. After a 2-week incubation, guinea pigs were patch tested with 0.1% BGE. Six of 12 animals showed sensitization (Reichhold Chemical Company 1978).[2] Hartley guinea pigs were exposed to 25% BGE by patch application, on the back, once per week for 3 weeks. After a 2-week rest period, animals were administered a challenge dose (1% BGE). Observations were made at 24 h and 48 h post-challenge. One of 20 animals showed moderate erythema. Eighteen of 20 animals showed slight confluent or moderate patchy erythema (Reichhold Chemical Company 1978).
Humans	
Immunotoxicity	Patients with known contact allergies to epoxy resins were exposed to 0.25% BGE in acetone (no further details given). Three of 20 patients reacted positively (Fregert and Rorsman 1964).

Endpoint	Lowest effect levels[1]/Results
	Workers with previous skin eruptions who were employed at a bisphenol A-based epoxy resin plant were patch tested with a variety of chemicals used in the manufacturing process. One of 19 subjects reacted positively to BGE (Prens et al. 1986). One hundred and forty patients with contact dermatitis to epoxy resins were patch tested. A solution of 0.25% BGE was applied on the upper back and occluded for 24 or 48 h. Tests were read at 24 and 48–120 h after removal. Two of the 140 tested patients had positive reactions (Jolanki et al. 1990). Patch testing was performed on 343 subjects using the same method as in Jolanki et al. (1990). None of the 343 patients showed any reaction to 0.25% BGE (Tarvainen 1995). Patients with suspected occupational dermatoses were patch tested with 0.25% BGE under occluded conditions for 48 h. Examinations were performed 2, 3 and 4–6 days after removal. Two allergic reactions and one irritant reaction were observed in a group of 310 patients (Kanerva et al. 1997, 1999).
Other studies	Case reports: Two men were exposed to an approximately 3.5 L spillage of grouting compound containing BGE. Inhalation produced gastrointestinal irritation, which resulted in short-term anorexia and vomiting. Persistent and severe headache was also reported (Wallace 1979). Survey of reproductive health: A survey of reproductive health was performed due to a cluster of miscarriages among employees at a plastic fabrication facility. BGE was found in several products used in the plant (Epibond 8543-A, Epocast 167-A and epoxy resins). BGE was found to be associated with one miscarriage. No single causative agent was identified (Boeing Company 1986).

[1] LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOEC, lowest-observed-effect concentration; LOEL, lowest-observed-effect level.

[2] Method described may contain errors due to poor quality of Microfiche No. OTS0523514 (NTP 2004).

Appendix 3: Structures and classifications for *n*-butyl glycidyl ether and similar substances considered in this assessment

Name / CAS RN	Classification		Structure
	IARC	European Commission	
n-Butyl glycidyl ether 2426-08-6		Carc. Cat. 3 Muta. Cat. 3	
Allyl glycidyl ether 106-92-3		Carc. Cat. 3 Muta. Cat. 3 Repro. Cat. 3	
Phenyl glycidyl ether 122-60-1	Carc. Group 2B	Carc. Cat. 2 Muta. Cat. 3	
Bisphenol A diglycidyl ether 1675-54-3	Not classifiable		
Glycidol 556-52-5	Carc. Group 2A	Carc. Cat. 2 Muta. Cat. 3 Repro. Cat. 2	

Abbreviations: Carc., carcinogenicity; CAS RN, Chemical Abstracts Service Registry Number; Cat., category; Muta., mutagenicity; Repro., reproductive toxicity.

Appendix 4: Summary of available information on carcinogenicity and genotoxicity of substances considered similar to *n*-butyl glycidyl ether in this assessment

Allyl glycidyl ether (AGE)
Carcinogenicity
Inhalation: Osborne-Mendel rats and B6C3F1 mice (50 animals per sex per group) were exposed to 0, 23 or 47 mg/m^3 (0, 5 and 10 ppm), 6 h/day, 5 days/week, for 102 or 103 weeks via whole body inhalation. Statistically significant nasal lesions (inflammation, degeneration, metaplasia and hyperplasia) were observed in rats and mice at both exposure levels. In male Osborne-Mendel rats exposed to 47 mg/m^3, one papillary adenoma of respiratory epithelial origin, one squamous cell carcinoma of respiratory epithelial origin and one adenocarcinoma of olfactory epithelial origin were observed. In male mice, three adenomas of the respiratory epithelium, four occurrences of dysplasia and seven occurrences of focal basal cell hyperplasia were observed at 47 mg/m^3. In female mice, one adenoma of the respiratory epithelium and seven occurrences of focal basal cell hyperplasia were noted at 47 mg/m^3. The incidences of primary tumours were not statistically significant but were considered biologically meaningful (NTP 1990a).
Genotoxicity
In vivo **Intraperitoneal:** Three male C3H/Hej mice were injected intraperitoneally with a 40 mg/mL solution of AGE dissolved in tricaprylin for a total dose of 148 mg/kg-bw per mouse. Animals were sacrificed 24 h after treatment, and tissues were collected. DNA was isolated from the liver of exposed and unexposed mice and assayed for the presence of AGE–DNA adducts. AGE was bound to both guanine and adenine bases in DNA from the livers of AGE-exposed mice (Plna and Segerbäck 1997). **Dermal:** AGE was applied topically, onto a 4 × 4 cm depilated area, on the backs of three C3H/Hej mice at a total dose of 60.5 mg/kg-bw. Twenty-four hours after exposure, mice were sacrificed and the skin was removed. DNA was isolated from the skin of treated and untreated mice and assayed for the presence of DNA-bound AGE. AGE was demonstrated to form adducts with both adenine and guanine bases (Plna and Segerbäck 1997). **Oral:** Male Canton-S *Drosophila melanogaster* were fed 5.5 mg/mL (5500 ppm) AGE in 5% sucrose solution for 3 days. Increased sex-linked recessive mutations were observed. At the same dose, AGE did not increase the incidence of reciprocal translocations (NTP 1990a). ***In vitro*** Ames tests: AGE induced mutations in *Salmonella typhimurium* base-substitution strains TA100 and TA1535 at doses in the range of 10–10 000 µg/plate. AGE was mutagenic in the presence and absence of S9. AGE was not mutagenic in frame-shift strains TA98 and TA1537 with or without S9 (Canter et al. 1986; NTP 1990a). Chinese hamster ovary (CHO) cells were incubated for 2 h at 37ºC with AGE (1–50.2 µg/mL −S9 or 3.3–100 µg/ml +S9). All concentrations strongly induced sister chromatid exchange and chromosomal aberrations ($p < 0.001$ by trend test under all conditions). At the highest concentrations, cell cycle delay was evident (NTP 1990a). SOS chromotest: Positive when 250 µl *Escherichia coli* PQ37 was incubated with 10 µl of dissolved AGE for 2 h (von der Hude 1990). Salmon testes DNA was incubated directly with AGE (500 mM) for 24 h at 37ºC. AGE reacted directly with adenine and guanine to form DNA adducts (Plna and Segerbäck 1997).
Glycidol
Carcinogenicity
Oral: Groups of 15 haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice of each sex were exposed to glycidol administered in deionized water at 0, 25, 50, 100 or 200 mg/kg-bw per day by gavage, 5 days/week for 40 weeks. The deleted CDKN2A locus is responsible for two suppressor proteins, one that regulates cell

cycle ($p16^{Ink4a}$) and one that induces G1 phase and apoptosis ($p19^{Arf}$). Deletion of CDKN2A thus predisposes mice to cancer in multiple sites. Therefore, studies using these mice require shorter exposures and fewer animals. Statistically significant increases of histiocytic sarcomas, compared with controls, were observed at 50 and 200 mg/kg-bw in males (incidence also increased in all groups of both sexes exposed to 50 mg/kg-bw and above without being statistically significant) and of alveolar/ bronchiolar adenoma at 100 mg/kg-bw in males and at 200 mg/kg-bw in females. A statistically significant increase in epithelial hyperplasia of the forestomach was observed in males and females at 200 mg/kg-bw. Non-neoplastic effects included enlarged spleen and liver foci in males at 200 mg/kg-bw, neuropathy, gliosis and hemorrhage of the brain at 200 mg/kg-bw in males and at 100 and 200 mg/kg-bw in females, and a decrease in male reproductive organ weight and sperm count at 200 mg/kg-bw (NTP 2007).

F344N1 rats and B6C3F1 mice were exposed to glycidol (94% pure) at 0, 37.5 or 75 mg/kg-bw per day and 0, 25 or 50 mg/kg-bw per day, respectively, 5 days/week for 103 weeks via oral gavage. Each exposure group contained 50 animals of each sex. The following incidences were considered clear evidence of carcinogenicity: mesotheliomas of the tunica vaginalis (3/49, 34/50, 39/47), fibroadenomas of the mammary gland (3/45, 8/39, 7/17), gliomas of the brain (0/46, 5/50, 6/30) and neoplasms of the forestomach (1/46, 2/50, 6/32), intestine (0/47, 1/50, 4/37), skin (0/45, 5/41, 4/18), Zymbal gland (1/49, 3/50, 6/48) and thyroid gland (1/46, 4/42, 6/19) in male rats; fibroadenomas (14/49, 32/46, 29/44) and adenocarcinomas (1/50, 11/48, 16/48) of the mammary gland, gliomas of the brain (0/49, 4/46, 4/46), leukemia (13/49, 14/44, 20/41) and neoplasms of the oral mucosa (1/46, 3/37, 7/26), forestomach (0/47, 4/38, 11/30), clitoral gland (5/49, 9/47, 12/45) and thyroid gland (0/49, 1/38, 3/35) in female rats; neoplasms of the Harderian gland (8/46, 12/41, 22/44) , forestomach (1/50, 2/50, 10/50), skin (0/50, 0/50, 4/50), liver (24/50, 31/50, 35/50) and lung (13/50, 11/50, 21/50) in male mice; and neoplasms of the Harderian gland (4/46, 11/43, 17/43), mammary gland (2/50, 6/50, 15/50), uterus (0/50, 3/50, 3/50), subcutaneous tissue (3/50, 3/50, 9/50) and skin (0/50, 0/50, 2/50) in female mice. No compound-related clinical or non-neoplastic toxicity signs were observed in rats or mice (NTP 1990b).

Syrian golden hamsters (20 animals of each sex) were exposed to glycidol (in a 1:1 solution with ethyl acetate and corn oil) at 100 mg/kg-bw per day, twice a week for 60 weeks, via gavage. Control groups consisted of 12 animals per sex exposed to the solution without glycidol for 90 weeks. The number of tumour-bearing animals in exposed male/female and control male/female groups, respectively, for the most prevalent tumour types are as follows: spleen (2, 4, 0, 0), adrenal cortex (3, 2, 4, 3), forestomach (3, 0, 0, 0) and uterus/cervix (0, 1, 0, 2). No statistical analyses were presented. It is unclear how many animals were examined for tumours in each group. The authors indicated that adrenal cortex tumours are common in this strain of hamsters, but that hemangiomas and hemangiosarcomas of the spleen are very rare (Lijinsky and Kovatch 1992).

Dermal: A group of 20 IRC/Ha female Swiss mice were exposed to glycidol 5% solution in acetone by dorsal skin application 3 times/week for 520 days. Control groups consisted of three groups of 40, 50 or 30 animals (same sex and species) exposed to the solvent and three groups of 100 animals receiving no treatment. Survival was comparable between exposed and control groups, and no skin damage or neoplasm was observed (Van Duuren et al. 1967).

Genotoxicity

In vivo
Intraperitoneal: B6C3F1 male mice (five per group) were injected intraperitoneally with two doses, 24 h apart, of glycidol (27.5, 75 or 150 mg/kg) dissolved in phosphate buffered saline. The total volume of each dose was 0.4 mL. Negative control animals were injected intraperitoneally with phosphate buffered saline only. Mitomycin C was administered to positive control animals. Mice were sacrificed 24 h after the second injection, and polychromatic erythrocytes were examined for micronucleated cells. The incidence of micronucleated cells was increased significantly (Trial 1, $p < 0.001$; Trial 2, $p < 0.05$) at the high dose in each of two trials (NTP 1990b).

Oral: *Drosophila melanogaster* males were fed a solution of 5% sucrose containing 1.23 mg/mL (1230 ppm) glycidol for 3 days. Males were then mated to three females for 3 days and given new virgin females at 2-day intervals, producing a total of three broods. Glycidol induced sex-linked recessive mutations. The same dose also induced reciprocal translocations (NTP 1990b).

In vitro
Ames test: Glycidol was mutagenic at doses ranging from 1 to 10 000 µg/plate in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 with or without S9 metabolic activation (NTP 1990b).
[Additional studies (Ames test): McCann et al. 1975; Loquet et al. 1981]

L1578Y/TK cells were exposed to glycidol at concentrations ranging from 0.313 to 40 nL/mL. Cells were exposed at 37ºC for 4 h followed by a 48-h incubation in glycidol-free medium. Cells were then assayed for trifluorothymidine resistance. Glycidol induced trifluorothymidine resistance at concentrations as low as 1.25 nL/mL. The test was performed without metabolic activation only (NTP 1990b).

CHO cells treated with 1.1–150 µg/mL in the presence or absence of S9 were strongly positive for sister chromatid exchange at all doses tested (NTP 1990b).

CHO cells incubated with glycidol (12.5–400 µg/mL) both with and without activation were strongly positive for chromosomal aberrations at all doses (NTP 1990b).

DNA damage was assessed by the single cell gel/comet assay. CHO cells exposed for 3 h to 5, 10, 20 or 30 µg/mL sustained increased DNA damage at all doses. Statistically significant increases ($p < 0.05$) were observed at 20 and 30 µg/mL (El Ramy et al. 2007).

Phenyl glycidyl ether (PGE)

Carcinogenicity

Inhalation: Sprague-Dawley rats (100 animals per sex per dose group) were exposed to 0, 6 or 74 mg/m^3 (0, 1 or 12 ppm) of PGE (99.6% pure) 6 h/day, 5 days/week, for 24 months by whole body inhalation (Lee et al. 1983). No details on survival were given. Exposure-related nasal tumours were observed at 74 mg/m^3 only (statistical significance not specified), with incidences of 0/89, 0/83 and 9/85 and 1/87, 0/88 and 4/89 in males and females, respectively. Incidences of rhinitis and squamous metaplasia were also higher at 74 mg/m^3 and were related to nasal tumours. The International Agency for Research on Cancer 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

In vivo
Inhalation: Dominant lethal assay: 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 three untreated females each for 6 weeks. No changes were observed that would be indicative of a dominant lethal effect (Terrill et al. 1982).

Inhalation: Male rats were exposed to 0, 12.3, 36.8 or 67.6 mg PGE/m^3 (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).

Oral: 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 1984a).

Oral: Mice were treated with a single dose of 500 mg/kg-bw. 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).

In vitro
Ames test: PGE was mutagenic in *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 (Greene et al. 1979; Ivie et al. 1980; Ohtani and Nishioka 1981; Neau et al. 1982; Seiler 1984b; Canter et al. 1986).

Host-mediated assay: Mice received a single dose of 2500 mg/kg-bw orally, intraperitoneally or intramuscularly. Weak positive responses were found in mice treated orally and intramuscularly. The test was negative when PGE was administered intraperitoneally (Greene et al. 1979).

CHO cells were incubated with PGE (6.25–100 µg/mL) for 6 or 18–24 h without S9 or for 6 h with S9. None of the conditions tested resulted in mutations in CHO cells (Greene et al. 1979).

PGE was mutagenic in *Klebsiella pneumoniae* and *Escherichia coli* WP2 uvrA (Hemminki and Vainio 1980; Ohtani and Nishioka 1981; Voogd et al. 1981).

SOS chromotest: Positive when 250 µL of *Escherichia coli* PQ37 was incubated with 10 µL of dissolved PGE for 2 h (von der Hude et al. 1990).

PGE was reported to alkylate DNA *in vitro* (Hemminki et al. 1980).

PGE did not bind to DNA in *Escherichia coli* with or without metabolic activation (Hubinski et al. 1981).

Bisphenol A diglycidyl ether (BADGE)

Carcinogenicity

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) pure BADGE in acetone topically 2 times/week for 103 weeks. Controls were exposed to acetone only. A positive control group was also exposed to β-propiolactone. Exposure did not affect survival. Three males from the 10% group and one female from the 1% group developed tumours at the site of exposure. Three females 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 for thymic lymphosarcoma was observed in females. 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 (Peristianis et al. 1988).
[Additional dermal studies: Hine et al. 1958; Weil et al. 1963; Holland et al. 1979; Zakova et al. 1985]

Genotoxicity

In vivo

Oral: Ten female B6D2F1 mice were given 1000 mg/kg-bw per day for 5 consecutive days. No increased incidence of micronuclei was observed in comparison with unexposed controls (Rhone-Poulenc Inc. 1977).

Oral: BADGE's ability to induce DNA damage was examined. A single 500 mg/kg-bw 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).

Dermal: Dominant lethal assay: Ten male B6D2F1 mice were treated topically with 3000 mg/kg-bw, 3 times/week, for a minimum of 8 weeks. After exposure, male mice were mated with three 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 adverse effects were observed in comparison with controls (Rhone-Poulenc Inc. 1977).

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).

Dermal: Male C3H mice were treated with 20 mg BADGE/mL 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).

In vitro

Ames test: *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were treated with BADGE with and without metabolic activation. BADGE was negative in all strains in the absence of metabolic activation. With activation, BADGE induced 7- to 10-fold more mutations in TA1535 and TA1537 compared with background. Results were negative in all other strains tested. BADGE was not mutagenic in *Escherichia coli* WP2 or WP2 uvr*A* (Brooks et al. 1981).

BADGE was tested in TA100 and TA1538 using 10–10 000 µg/plate. A weak positive response was seen without activation. Positive responses were observed with metabolic activation by either rat liver- or hamster liver-derived S9 (Canter et al. 1986).

[Additional bacterial mutation studies: Rhone-Poulenc Inc. 1977; Andersen et al. 1978; Wade et al. 1979; Ringo et al. 1982]

Urine assay, negative: The urine of mice dosed by gavage once per day with 1000 mg BADGE/kg-bw was not mutagenic in strain TA1535 (Rhone-Poulenc Inc. 1977).

Host-mediated assay, negative: *Salmonella typhimurium* was inoculated into the peritoneal cavity of mice treated by gavage for 5 days with 1000 mg BADGE/kg-bw. No increase in revertants was observed (Rhone-Poulenc Inc. 1977).

Saccharomyces cerevisiae JD1 cells were positive for mitotic gene conversion when incubated with BADGE with or without microsomal enzymes (Brooks et al. 1981).

Rat liver cells were cultured in the presence of BADGE (3.75, 5, 7.5, 10, 15 or 20 µg/mL). Dose-related increases in chromosomal aberrations were evident in cells exposed to concentrations between 10 and 20 µg/mL (Brooks et al. 1981).

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 the secondary reference (Brooks et al. 1981).