Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals

Sponsored Chemical
***n*-Butyl Glycidyl Ether (CAS No. 2426-08-6)**
(9th CI Name: Oxirane, (butoxymethyl)-)

Supporting Chemical
***t*-Butyl glycidyl ether (CAS No. 7665-72-7)**
(9th CI Name: Oxirane, (1,1-dimethyethoxy)methyl-)

Contents:

BACKGROUND

Screening-level hazard, exposure and risk characterizations for high production volume chemicals (HPV) are important contributions to the chemicals cooperation work being done in North America[1] through the EPA Chemical Assessment and Management Program (ChAMP)[2]. These screening-level characterizations are developed by EPA for individual chemicals or chemical categories to support initial Risk-Based Prioritizations (RBPs) for HPV chemicals. These screening-level characterizations are technical documents intended primarily to inform the Agency's internal decision-making process. Accordingly, they are written for assessment professionals and assume a degree of technical understanding. Each of the support documents is described below.

The Risk-Based Prioritizations are found in an accompanying document and are written for a general audience. They present EPA's initial thinking regarding the potential risks presented by these chemicals and future possible actions that may be needed.

Hazard Characterizations for HPV Chemicals

EPA's screening-level hazard characterizations are based primarily on the review of the summaries of studies and other information submitted by the chemical sponsor(s) under the HPV Challenge Program[3]. These studies included in the scope of the HPV Challenge comprise the Screening Information Data Set (SIDS) of the Organization for Economic Cooperation and Development (OECD)[4], an internationally recognized battery of tests that provides the basic data necessary to make an initial evaluation of a chemical's hazards and fate. In preparing the initial hazard characterizations, EPA also consulted a variety of reliable sources[5] for additional relevant information and considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of an HPV submission, EPA also searched publicly available databases[6] for information entered from one year prior to the HPV submission through May 2008. The screening-level hazard characterization is performed according to established EPA guidance[7]. A more detailed description of the hazard characterization process is available on the EPA website[8].

With respect to chemicals for which internationally-accepted OECD SIDS Initial Assessment Profiles (SIAP) and Initial Assessment Reports (SIAR) were available, EPA did not generate its own screening-level hazard characterization, but did check for and incorporate updated information in the risk characterization.

Exposure Characterizations for HPV Chemicals

EPA recently received exposure-related data on chemicals submitted in accordance with the requirements of Inventory Update Reporting (IUR)[9]. The 2006 IUR submissions pertain to chemicals manufactured in

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[1] U.S. EPA – U.S. Commitments to North American Chemicals Cooperation: http://www.epa.gov/hpv/pubs/general/sppframework.htm.
[2] U.S. EPA – ChAMP information: http://www.epa.gov/champ/.
[3] U.S. EPA – HPV Challenge Program information: http://www.epa.gov/hpv.
[4] U.S. EPA – Technical Guidance Document, OECD SIDS Manual Sections 3.4 and 3.5: http://www.epa.gov/chemrtk/pubs/general/sidsappb.htm.
[5] U.S. EPA – Public Database Hazard Information: http://www.epa.gov/hpvis/hazardinfo.htm.
[6] U.S. EPA – Public Database Update Information: http://www.epa.gov/chemrtk/hpvis/updateinfo.htm.
[7] U.S. EPA – Risk Assessment Guidelines: http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[8] U.S. EPA – About HPV Chemical Hazard Characterizations: http://www.epa.gov/hpvis/abouthc.htm.
[9] U.S. EPA – Basic IUR Information: http://www.epa.gov/opptintr/iur/pubs/guidance/basic-information.htm.

(including imported into) the U.S. during calendar year 2005 in quantities of 25,000 pounds or more at a single site. The reports include the identity, the quantity, and the physical form of the chemical manufactured or imported, and the number of workers reasonably likely to be exposed during manufacture of the chemical. For chemicals manufactured or imported in quantities of 300,000 pounds or more at a single site, additional reported information includes: the industrial processing and uses of the chemical; the number of industrial processing sites and workers reasonably likely to be exposed to the chemical at those sites; the consumer and commercial uses of the chemical; and an indication whether the chemical was used in products intended for use by children under 14 years of age.

EPA's screening-level exposure characterizations are based largely on the information submitted under the IUR reporting, although other exposure information submitted to the Agency (for example, in HPV submissions) or readily available through a limited set of publicly accessible databases[10] was also considered. The screening-level Exposure Characterizations identify a potential (high, medium, or low) that each of five populations – the environment, the general population, workers, consumers, and children – might be exposed to the chemical. In most cases, this potential doesn't address the quantity, frequency, or duration of exposure, but refers only to the likelihood that an exposure could occur.

In many instances EPA is not able to fully disclose to the public all the IUR exposure-related data reviewed or relied upon in the development of the screening-level documents because some of the material was claimed as confidential business information (CBI) when it was submitted to the Agency. These CBI claims do limit the Agency's ability to be completely transparent in presenting some underlying exposure and use data for chemicals in public documents. EPA does consider all data, including data considered to be CBI, in the screening-level exposure and risk characterization process, and endeavors whenever possible to broadly characterize supporting materials claimed as confidential in ways that do not disclose actual CBI.

Risk Characterizations for HPV Chemicals

EPA combines the information from the screening-level exposure characterization with the screening-level hazard characterization to develop a qualitative screening-level risk characterization, as described in the Agency's guidance on drafting risk characterizations[11]. These screening-level risk characterizations are technical documents intended to support subsequent priority-setting decisions and actions by OPPT. The purpose of the qualitative screening-level risk characterization is two-fold: to support initial risk-based decisions to prioritize chemicals, identify potential concerns, and inform risk management options; and to identify data needs for individual chemicals or chemical categories.

These initial characterization and prioritization documents do not constitute a final Agency determination as to risk, nor do they determine whether sufficient data are available to characterize risk. Recommended actions reflect EPA's relative judgment regarding this chemical or chemical category in comparison with others evaluated under this program, as well as the uncertainties presented by gaps that may exist in the available data.

[10] U.S. EPA – Summary of Public Databases Routinely Searched: http://www.epa.gov/chemrtk/hpvis/pubdtsum.htm.
[11] U.S. EPA – Risk Characterization Program: http://www.epa.gov/osa/spc/2riskchr.htm.

QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

***n*-Butyl Glycidyl Ether (CAS No. 2426-08-6)**
[9th CI Name: Oxirane, (butoxymethyl)-]

SUPPORTING CHEMICALS

***t*-Butyl glycidyl ether (CAS No. 7665-72-7)**
[9th CI Name: Oxirane, (1,1-dimethyethoxy)methyl-]

July 2008

Prepared by

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QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION FOR *n*-Butyl glycidyl ether (CAS No. 2426-08-6)

1. Physical-Chemical Properties and Environmental Fate

n-Butyl glycidyl ether is a liquid at room temperature, and has high water solubility and high vapor pressure. *n*-Butyl glycidyl ether is expected to have high mobility in soil and moderate volatility. The rate of atmospheric photooxidation is moderate and the rate of biodegradation is moderate. The hydrolysis rate of *n*-butyl glycidyl ether is rapid under acidic conditions and moderate to slow at neutral and alkaline pH. *n*-Butyl glycidyl ether is judged to have low persistence (P1) and low bioaccumulation potential (B1).

2. Hazard Characterization

The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of *n*-butyl glycidyl ether is low for fish and aquatic plants and moderate for aquatic invertebrates.

Acute oral toxicity of the supporting chemical *t*-butyl glycidyl ether is low. *n*-Butyl glycidyl ether is not a sensitizer. Repeated exposures of the supporting chemical, *t*-butyl glycidyl ether, to rabbits, rats and mice by the inhalation route for 13 weeks, resulted in reduced body weight and irritation of the nasal mucosa. No gross or histopathological findings were noted in the reproductive organs in these studies. A prenatal developmental toxicity study in rats showed evidence of developmental toxicity at the high-dose, but there was no evidence of maternal toxicity. *n*-Butyl glycidyl ether was mutagenic *in vitro* in bacterial and mammalian cells and produced chromosomal aberrations in an *in vitro* assay. A dominant lethal assay was equivocal.

The potential health hazard of *n*-butyl glycidyl ether is moderate based on the repeated-dose and developmental toxicity.

3. Exposure Characterization

n-Butyl glycidyl ether has an aggregated production and/or import volume in the United States of greater than 1 million pounds but less than 10 million pounds. Non-confidential IUR information indicates that *n*-butyl glycidyl ether is processed by incorporation into a formulation, mixture, or reaction product, and in other non-incorporative uses. These formulations and mixtures have commercial and consumer uses as sealants.

The Hazardous Substances Data Bank (HSDB) indicates that a major use of *n*-Butyl Glycidyl Ether is as reactive diluent for epoxy resins, viscosity reducing agent, acid acceptor for stabilizing chlorinated compounds, and chemical intermediate.

Potential Exposures to the General Population and the Environment. Based on the use information, it is likely that there would be some releases to water or air during manufacturing, processing, and use. Based on the totality of the information considered, i.e., the moderate biodegradation rate, the P1, B1 ratings, the use of this chemical in epoxies, and the Agency's expert judgment, EPA identifies, for purposes of risk-based prioritization, that the potential for exposure to the general population and the environment is medium.

Potential Exposure to Workers. Based on the totality of the information considered including IUR data in combination with Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a high relative ranking for the potential worker exposure. This high relative ranking is based on the relatively high production volume and the potential for significant dermal exposure and for inhalation of mists and vapors by a large number of workers in commercial settings including spray application of products containing the subject substance. OSHA has promulgated a Permissible Exposure Limit (PEL) for this chemical of 50 ppm as an 8-hr time-weighted average. NIOSH has published an alert level of 250 ppm at which this chemical is considered immediately dangerous to life and health (IDLH).

Potential Exposures to Consumers. Depending on the consumer product, there may be dermal and/or inhalation exposures to consumers from vapors, mists, or particulates. EPA identifies, for the purposes of risk-based prioritization, that the potential for exposure to consumers from products containing this chemical is high based on IUR data and information from public data sources that indicate this chemical is found in adhesive and sealants.

Potential Exposures to Children. No uses in products specifically intended to be used by children were reported in the IUR, nor were any found in other data sources. However, there may be potential exposure of children through the use of some consumer products, e.g., epoxy, adhesives. Therefore, EPA identifies, for the purposes of risk-based prioritization, that the potential for exposure to children is medium.

4. Risk Characterization

The statements and rationale provided below are intended solely for the purpose of this qualitative screening-level risk characterization and will be used for prioritizing substances for future work in the Chemical Assessment and Management Program (ChAMP).

Risk Statement and Rationale

Potential Risk to Aquatic Organisms from Environmental Releases (LOW/MEDIUM CONCERN). EPA identifies a medium potential for exposure to aquatic organisms from environmental releases. *n*-Butyl glycidyl ether acid has low persistence and low bioaccumulation. These characteristics in combination with the low acute toxicity for fish and aquatic plants, suggests a low concern for potential risk to fish and aquatic plants. These characteristics in combination with the moderate acute aquatic hazard for invertebrates suggest a moderate concern for potential risk to aquatic invertebrates.

Potential Risk to the General Population from Environmental Releases (LOW CONCERN). EPA identifies a medium potential for exposure to the general population from environmental releases. The potential human health hazard is expected to be moderate due to toxicity in animals following repeated exposures. However, *n*-butyl glycidyl ether is irritating and therefore potential exposures will be self-limiting. Given the moderate hazard, the environmental fate characteristics of low persistence and low bioaccumulation, together with low self-limiting exposure suggest a low concern for potential risk to the general population from environmental releases.

Potential Risk to Workers (LOW CONCERN). EPA identifies a high potential for worker exposure. The potential human health hazard is expected to be moderate due to toxicity in animals following repeated exposures. However, adherence to the OSHA PEL will limit the exposure of workers. Therefore, taken together, the available information suggests a low concern for potential risks to workers.

Potential Risk to Consumers from Known Uses (LOW CONCERN). EPA identifies a high potential that consumers may be exposed. The potential human health hazard is expected to be moderate due to toxicity in animals following repeated exposures to high doses. However, *n*-butyl glycidyl ether is an irritant and therefore potential exposures will be self-limiting. Taken together, the available information suggests a low concern for potential risks to consumers.

Potential Risk to Children (LOW CONCERN). EPA identifies a medium potential that children may be exposed. No used in products specifically intended to be used by children were reported in the IUR, nor in any other data sources. Exposures to children, however, may be expected to occur through the household use of some consumer products, e.g., epoxy, adhesives. There are no toxicology data available that assesses the potential toxicity of *n*-butyl glycidyl ether during the postnatal period. However, it is an irritant in adult animal studies, and is likely to be an irritant at earlier life stages; therefore exposures will be self-limiting. Taken together, the available information suggests a low concern for potential risks to children.

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

***n*-Butyl Glycidyl Ether (CAS No. 2426-08-6)**
[9th CI Name: Oxirane, (butoxymethyl)-]

SUPPORTING CHEMICALS

***t*-Butyl glycidyl ether (CAS No. 7665-72-7)**
[9th CI Name: Oxirane, (1,1-dimethyethoxy)methyl-]

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SCREENING-LEVEL HAZARD CHARACTERIZATION
OF HIGH PRODUCTION VOLUME CHEMICALS

SCREENING-LEVEL HAZARD CHARACTERIZATION
n-Butyl glycidyl ether (CAS No. 2426-08-6)

Introduction

The sponsor, Society of the Plastics Industry, Inc. (SPI) Epoxy Resin Systems Task Group, submitted a Test Plan and Robust Summaries to EPA *n*-butyl glycidyl ether (CAS No. 2426-08-6; 9th CI name: oxirane, (butoxymethyl)-) on December 7, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January 14, 2002 (http://www.epa.gov/chemrtk/pubs/summaries/nbtglyet/c13352tc.htm). EPA comments on the original submission were posted to the website on August 1, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on September 30, 2002 and August 28, 2006, which were posted to the ChemRTK website on October 17, 2002 and November 14, 2006, respectively.

This screening level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. In preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from 2006 to May 2008: the NLM databases (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, ATSDR, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. A summary table of SIDS endpoint data with the structure(s) of the sponsored chemical(s) is included in the appendix. In addition, the National Toxicology Program conducted a literature review that is available at: http://ntp.niehs.gov/ntp/htdocs/Chem_Background/ExSumPdf/Butyl_glycidyl_ether.pdf. The screening-level hazard characterization for environmental and human health effects is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Justification for Supporting Chemical

The submitter provided data for a structurally similar chemical, *t*-butyl glycidyl ether (CAS No. 7665-72-7) to address acute, repeated-dose, and reproductive toxicity endpoints and discussed similarities in physicochemical and toxicological properties between *n*-butyl glycidyl ether and *t*-butyl glycidyl ether. Although the tertiary butyl substitution may present some steric hindrance, the functional groups (ethers) are very similar in reactivity. *n*-Butyl alcohol is more readily metabolized to the end carbon, the difference between the *n*- and *t*- butyl alcohols is only a factor of 4. Examination of the data for *n*-and *t*-butyl glycidyl ether demonstrates that they show similar toxicity at comparable dose levels and similar no-observed-adverse-effect levels and positive/negative responses in a battery of mutagenicity studies. EPA agrees that *t*-butyl glycidyl ether is an appropriate analog for *n*-butyl glycidyl ether for the purposes of the HPV Challenge Program.

Hazard Characterization

n-Butyl glycidyl ether is a liquid at room temperature that has high water solubility and high vapor pressure. *n*-Butyl glycidyl ether is expected to have high mobility in soil and moderate volatility. The rate of atmospheric photooxidation is moderate and the rate of biodegradation is moderate. The hydrolysis rate of *n*-butyl glycidyl ether is rapid under acidic conditions and moderate to slow at neutral and alkaline pH. *n*-Butyl glycidyl ether is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of *n*-butyl glycidyl ether is low for fish and aquatic plants and moderate for aquatic invertebrates.

Acute oral toxicity of the supporting chemical *t*-butyl glycidyl ether is low. *n*-Butyl glycidyl ether did not demonstrate potential to be a sensitizer in one assay in guinea pigs. Repeated exposures of the supporting chemical, *t*-butyl glycidyl ether, to rabbits, rats and mice by the inhalation route for 13 weeks, resulted in reduced body weight and irritation of the nasal mucosa. No gross or histopathological findings were noted in reproductive organs during this study. A prenatal developmental toxicity study in rats showed evidence of developmental toxicity at the high-dose (increased post-implantation loss, decreased litter viability, decreased fetal weight and delayed ossification.), but there was no evidence of maternal toxicity. *n*-Butyl glycidyl ether was mutagenic *in vitro* in bacterial and mammalian cells and produced chromosomal aberrations in an *in vitro* assay. A dominant lethal assay was equivocal.

The potential health hazard of *n*-butyl glycidyl ether is moderate based on the repeated-dose and developmental toxicity.

No data gaps were identified under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

Physical-Chemical Properties Characterization

n-Butyl glycidyl ether is a liquid at room temperature. *n*-Butyl glycidyl ether has high water solubility and high vapor pressure.

Table 1a. Physical-Chemical Properties of n-Butyl Glycidyl Ether[1]

Property	Value
CAS No.	2426-08-6
Molecular Weight	130.2
Physical State	Liquid
Melting Point	-30.96°C (measured)
Boiling Point	164 °C (measured)
Vapor Pressure	3.2 mm Hg at 25°C (measured)
Water Solubility	20,000 mg/L at 20°C (measured)
Henry's Law Constant	1.7×10^{-5} atm-m^3/mole (estimated)[2]
Log K_{ow}	0.63 (measured)

[1] Society of Plastics Industry. Revised Robust Summary and Test Plan for n-Butyl Glycidyl Ether http://www.epa.gov/chemrtk/pubs/summaries/nbtglyet/c13352tc.htm.
[2] US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.

Environmental Fate Characterization

n-Butyl glycidyl ether is expected to have high mobility in soil and moderate volatility. The rate of atmospheric photooxidation is moderate. The substance did not pass ready biodegradation tests, but did show some degradation. Therefore, the biodegradation rate is characterized as moderate. Under acidic conditions (pH 4) the rate of hydrolysis is rapid, while under neutral to alkaline conditions the rate is moderate to slow. Bioconcentration in

aquatic organisms is expected to be low. *n*-Butyl glycidyl ether is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 1b. Environmental Fate Properties of n-Butyl Glycidyl Ether	
Property	**Value** [1]
Photodegradation Half-life	6.466 hours
Hydrolysis Half-life	0.3 hours at pH 4 (20°C) 20 days at pH 7 (20°C) Stable at pH 9
Biodegradation	25% in 28 days (not readily biodegradable); 4-12% in 28 days (not readily biodegradable)
Bioconcentration	3 (estimated)[2]
K_{oc}	3 (estimated)[2]
Fugacity (Level III Model)[2]	Air = 1.7% Water = 46% Soil = 52.2 % Sediment = 0%
Persistence	P1 (low)[3]
Bioaccumulation	B1 (low)[3]

[1] Society of Plastics Industry. Revised Robust Summary and Test Plan for n-Butyl Glycidyl Ether. http://www.epa.gov/chemrtk/pubs/summaries/nbtglyet/c13352tc.htm.
[2] US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.
[3] FR. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) Page 60194-60204.

Conclusion: n-Butyl glycidyl ether is a liquid at room temperature that has high water solubility and high vapor pressure. *n*-Butyl glycidyl ether is expected to have high mobility in soil and moderate volatility. The rate of atmospheric photooxidation is moderate and the rate of biodegradation is moderate. The hydrolysis rate of *n*-butyl glycidyl ether is rapid under acidic conditions and moderate to slow at neutral and alkaline pH. *n*-Butyl glycidyl ether is expected to have low persistence (P1) and low bioaccumulation potential (B1).

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

n-Butyl glycidyl ether (CAS No. 2426-08-6)
Salmo gairdneri (10/concentration) were exposed to nominal concentrations of 0, 10, 20, 50, 100 or 200 mg/L under static-renewal conditions for 96 hours.
96-h LC_{50} = 65 mg/L

Acute Toxicity to Aquatic Invertebrates

n-Butyl glycidyl ether (CAS No. 2426-08-6)
Daphnia magna (30/concentration) were exposed to nominal concentrations of test substance in a log series ranging from 1 to 1000 mg/L. Ten daphnia were tested per dish and tests were conducted in triplicate.
24-h EC_{50} = 22 mg/L
48-h EC_{50} = 3.9 mg/L

Toxicity to Aquatic Plants

n-Butyl glycidyl ether (CAS No. 2426-08-6)
Pseudokirchneriella subcapitata were exposed to nominal concentrations of 0, 10, 14, 19, 25, 35, 45, 60, 85, 120, 160, 220 or 300 mg/L for 96 hours. One replicate was tested for each concentration level and six negative controls were tested.
96-h EC_{50} (growth) = 35 mg/L
Conclusion: The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of *n*-butyl glycidyl ether is low for fish, moderate for aquatic invertebrates, and low for aquatic plants.

3. Human Health Effects

Acute Oral Toxicity

t-Butyl glycidyl ether (CAS No. 7665-72-7, supporting chemical)
Rats (2/dose, strain not specified) were administered the test substance via oral gavage at 126, 252, 500, 1000 or 2000 mg/kg-bw and observed for 2 weeks after dosing. One animal per dose was subjected to gross necropsy. One rat at the highest dose died. No other adverse effects were observed. No effects on body weight gain, gross pathological changes or mortality were seen at the three lowest doses. At 1000 and 2000 mg/kg-bw, there was a slight accumulation of darkened material around the external nares and the mucosal surface of the stomach was edematous.
LD_{50} = 2000 mg/kg-bw

Repeated-Dose Toxicity

t-Butyl glycidyl ether (CAS No. 7665-72-7, supporting chemical)
(1) New Zealand White rabbits (4/sex/concentration) were exposed via inhalation to vapor of *t*-butyl glycidyl ether at concentrations of 0, 25, 75 and 225 ppm (approximately 0, 0.13, 0.4 and 1.19 mg/L) for 6 hours per day, 5 days per week for 13 weeks. No mortalities were reported. Nasal exudation was noted in male and females at the high-dose. No effects were noted in hematology, clinical chemistry or urinalysis. At the high dose, there was a significant decrease in body weights, decrease in body fat and decrease in thymic size in both sexes. Gross pathology revealed increased thickness or hyperplasia of the tracheal epithelium in both sexes of the mid- and high-dose levels.
LOAEL = 0.4 mg/L/day (based on hyperplasia of the tracheal epithelium)
NOAEL = 0.13 mg/L

(2) Fischer 344 rats (10/sex/ concentration) were exposed via inhalation to vapor of *t*-butyl glycidyl ether at concentrations of 0, 25, 75 and 225 ppm (approximately 0, 0.13, 0.4 and 1.19 mg/L) for 6 hours/day, 5 days/week for 13 weeks. No mortalities were reported. There was a significant decrease in body weight in the high-dose group (both sexes). No effects were observed in hematology, clinical chemistry or urinalysis. Decreases in body fat, thymic size and corneal cloudiness were observed at the high-dose. Loss of cells/thickening or flattening of the nasal olfactory epithelium was seen at the mid- and high-dose males and high-dose females. Hyperplasia of nasal respiratory epithelium and decreased hepatocyte size were reported in both sexes at the high-dose. Increased subepithelial inflammatory cell infiltrate in nasal turbinates. Decreased thymocytes were observed in both sexes at the high-dose.
LOAEL = 0.4 mg/L/day (based on inflammation of the nasal mucosa)
NOAEL = 0.13 mg/L/day

(3) B6C3F1 mice (10/sex/ concentration) were exposed via inhalation to vapor of *t*-butyl glycidyl ether at concentrations of 0, 25, 75 and 225 ppm (approximately 0, 0.13, 0.4 and 1.19 mg/L) for 6 hours/day, 5 days/week for 13 weeks. No mortalities were reported. There was a significant decrease in body weight at the high dose. No effects in hematology, clinical chemistry or urinalysis were observed. Decreases in body fat, thymic size and nasal discharge were observed at the high-dose. Increased subepithelial inflammatory cell infiltrate in nasal turbinates,

hyperplasia in respiratory epithelium and loss of cells, thickening or flattening of olfactory epithelium was observed in both sexes at the mid- and high-doses.
LOAEL = 0.4 mg/L/day (based on inflammation of the nasal mucosa and hyperplasia of the respiratory epithelium)
NOAEL = 0.13 mg/L

Reproductive Toxicity

Data are not available to address the reproductive toxicity endpoint for this chemical. Evaluation of reproductive organs from the 13-week studies on *t*-butyl glycidyl ether showing no effects and available developmental toxicity study on *n-b*utyl glycidyl ether addressed this endpoint for the purposes of the HPV Challenge Program.

t-Butyl glycidyl ether (CAS No. 7665-72-7, supporting chemical)
(1) In the 13-week inhalation repeated-dose toxicity study in rabbits described previously, the reproductive organs/tissues were examined grossly and histologically. No adverse effects were observed in any of the organs or tissues examined at any dose.

(2) In the 13-week inhalation repeated-dose toxicity study in rats described previously, the reproductive organs/tissues were examined grossly and histologically. No adverse effects were observed in any of the organs or tissues examined at any dose.

(3) In the 13-week inhalation repeated-dose toxicity study in mice described previously, the reproductive organs/tissues were examined grossly and histologically. No adverse effects were observed in any of the organs or tissues examined at any dose.

Developmental Toxicity

n-Butyl glycidyl ether (CAS No. 2426-08-6)
Pregnant female Crj: CD(SD) rats (25/dose) were administered doses of 0, 40, 100 or 250 mg/kg-bw/day (in the vehicle 0.5% methylcellulose with 0.1% polysorbate 80) by oral gavage on gestation days 0 to 19. All animals survived until the end of the study. Mean maternal body weights, body weight gains, net body weights, net body weight gains and food consumption were unaffected by treatment. Intrauterine growth and survival were unaffected by administration of the test substance. Increased post-implantation loss with corresponding decreased litter viability was observed at the high-dose. Decreased fetal weight was noted at the high-dose and, in combination with the increased post-implantation loss, resulted in lower gravid uterine weight. There was an increase in delayed ossification in the high-dose group.
LOAEL (maternal toxicity) > 250 mg/kg-bw/day
NOAEL (maternal toxicity) = 250 mg/kg-bw/day
LOAEL (developmental toxicity) = 250 mg/kg-bw/day (based on increased post-implantation loss, decreased litter viability, decreased fetal weight and delayed ossification)
NOAEL (developmental toxicity) = 100 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro
n-Butyl glycidyl ether (CAS No. 2426-08-6)
(1) *Salmonella typhimurium* (strains TA98, TA100, TA1535, TA1537 and TA1538) were exposed to concentrations of 8.2, 24.7, 74, 222.2, 666.7 or 2000 μg/plate with and without metabolic activation. Each concentration was tested in triplicate. The highest concentration produced signs of cytotoxicity. Positive controls were tested concurrently but responses were not provided. An increase in mutations was noted in TA100 and TA1535 with and without metabolic activation compared with the negative control.
***n*-Butyl glycidyl ether was mutagenic in this assay.**

(2) The National Toxicology Program (NTP) evaluated *n*-butyl glycidyl ether in a bacterial reverse mutation assay in *S. typhimurium* and it was found to be mutagenic.
***n*-Butyl glycidyl ether was mutagenic in this assay.**

(3) Mouse lymphoma L5178Y cells were tested for mutations at the thymidine kinase (TK) locus at 12 concentrations ranging from 84 – 800 μg/mL with and without metabolic activation. Concentrations were selected based on toxicity, but details about cytotoxicity were not presented in the robust summary. Positive controls were tested concurrently, but responses were not provided.
***n*-Butyl glycidyl ether was mutagenic in this assay.**

Genetic Toxicity – Chromosomal Aberrations

In vitro
n-Butyl glycidyl ether (CAS No. 2426-08-6)
Chinese hamster ovary (CHO) cells were exposed to concentrations of 37.5 – 500 μg/mL for the 4 hours and 18.75 – 350 μg/ml for 20 hours, in two separate groups, in the presence and absence of metabolic activation. A solvent control group was tested, but the testing of a positive control group was not stated in the robust summary. The cytotoxic concentration was 400 μg/mL in the 4-hour group, without metabolic activation. Cytoxicity was seen at 200 μg/mL concentration without metabolic activation and at 350 μg/mL with metabolic activation in the 20-hour group. The percentage of cells with structural chromosomal aberrations in the activated and non-activated 4-hour exposure groups were statistically significantly ($p<0.05$) increased compared with the solvent controls. The percentage of cells with structural chromosomal aberrations in the non-activated 20-hour exposure group was within the range of the historical controls.
***n*-Butyl glycidyl ether was clastogenic in this assay.**

In vivo
n-Butyl glycidyl ether (CAS No. 2426-08-6)
Male BDF hybrid mice (number per dose not indicated) were dosed dermally 3 times per week with 0, 0.37, 0.75 or 1.5 g/kg-bw for 8 weeks. Following the last treatment, each male was mated with three virgin females per week for 3 weeks. Positive controls were not conducted concurrently. There was no effect on pregnancy rate or number of implants. An increase in fetal death rate at the highest dose could not be confirmed due to a similar rate in controls in a repeat experiment. Analysis of testes failed to demonstrate any compound-related effects on sperm viability or morphology.
***n*-Butyl glycidyl ether produced equivocal dominant lethal effects in this assay.**

Genetic Toxicity – Other

In vitro
n-Butyl glycidyl ether (CAS No. 2426-08-6)
Human cells (WI38) were exposed to concentrations of 0, 0.24, 0.36, 0.53, 0.8 or 1.2 μg/mL in the absence of metabolic activation and 0, 0.5, 1.0, 2.0, 4.0 or 8.0 μg/mL in the presence of metabolic activation and examined for increased DNA repair determined by monitoring thymidine incorporation into DNA. Positive controls were tested concurrently and responded appropriately.
***n*-Butyl glycidyl ether did not induce unscheduled DNA synthesis in this assay.**

Additional Information

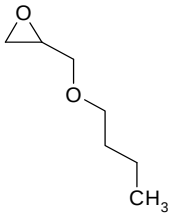
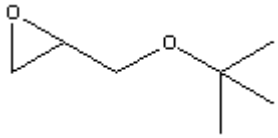
Skin Sensitization

n-Butyl glycidyl ether (CAS No. 2426-08-6)
During the induction phase, guinea pigs (10/group) were treated with a series of four administrations of 0.1 mL of undiluted test substance (96.8% pure with 90 μg/mL epichlorohydrin content) or positive control. The test substance was administered by patches that remained in contact with the skin for 48 hours each, with the exception of the fourth patch which was removed after 24 hours. At the time of the third patch application, 0.2 mL of Freund's Adjuvant was injected intradermally at multiple points adjacent to the induction site. Two weeks after the last exposure, all animals were challenged with 0.1 mL test material but not covered with patches. Sites were scored at 24 and 48 hours. There was no positive skin sensitization reaction to the test substance, but concurrent positive control groups treated with several epoxy resins showed positive responses.
***n*-Butyl glycidyl ether is not a dermal sensitizer.**

Conclusion: Acute oral toxicity of the supporting chemical *t*-butyl glycidyl ether is low. *n*-Butyl glycidyl ether did not demonstrate potential to be a sensitizer in one assay in guinea pigs. Repeated exposures of the supporting chemical, *t*-butyl glycidyl ether, to rabbits, rats and mice by the inhalation route for 13 weeks, resulted in reduced body weight and irritation of the nasal mucosa. No gross or histopathological findings were noted in reproductive organs in these studies. A prenatal developmental toxicity study in rats showed evidence of developmental toxicity at the high-dose (increased post-implantation loss, decreased litter viability, decreased fetal weight and delayed ossification.), but there was no evidence of maternal toxicity. *n*-Butyl glycidyl ether was mutagenic *in vitro* in bacterial and mammalian cells and produced chromosomal aberrations in an *in vitro* assay.

The potential health hazard of *n*-butyl glycidyl ether is moderate based on the repeated-dose and developmental toxicity.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program		
Endpoints	**SPONSORED CHEMICAL** ***n*-Butyl glycidyl ether** **(2426-08-6)**	**SUPPORTING CHEMICAL** ***t*-Butyl glycidyl ether** **(7665-72-7)**
Structure		
Summary of Environmental Effects – Aquatic Toxicity Data		
Fish **96-h LC_{50} (mg/L)**	65	—*
Aquatic Invertebrates **48-h EC_{50} (mg/L)**	3.9	—*
Aquatic Plants 96-h EC_{50} (mg/L) (growth)	35	—*
Summary of Human Health Data		
Acute Oral Toxicity **LD_{50} (mg/kg-bw)**	—	2000
Repeated-Dose Toxicity **(mg/L/day)** **NOAEL/LOAEL**	—	NOAEL = 0.13 LOAEL = 0.4
Reproductive Toxicity **NOAEL/LOAEL**	—	No effects were seen following evaluation of reproductive organs in a 13-wk inhalation repeated-exposure toxicity study in rats, rabbits and mice
Developmental Toxicity **NOAEL/LOAEL** **(mg/kg-bw/day)**		
Maternal Toxicity	NOAEL = 250 (highest dose tested)	—*
Developmental Toxicity	NOAEL =100 LOAEL = 250	—*
Genetic Toxicity – Gene Mutation ***In vitro***	Positive	—*
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	Positive	—*
Genetic Toxicity – Chromosomal Aberrations ***In vivo*** **Dominant Lethal Effects**	Equivocal	—*
Genetic Toxicity – Other **Unscheduled DNA synthesis**	Negative	—*

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program		
Endpoints	**SPONSORED CHEMICAL *n*-Butyl glycidyl ether (2426-08-6)**	**SUPPORTING CHEMICAL *t*-Butyl glycidyl ether (7665-72-7)**
Additional Information Skin Sensitization	Negative	—*

— indicates that endpoint was not addressed for this chemical; * indicates endpoint not necessary for supporting chemical.

Screening Level Exposure Characterization for HPV Challenge Chemical

n-Butyl Glycidyl Ether

CAS # 2426-08-6

July 2008

Prepared by

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Chemical Engineering Branch
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Environmental Protection Agency
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Screening Level Exposure Characterization
n-Butyl Glycidyl Ether (CAS #2426-08-6)

Non-CBI Executive Summary

n-Butyl Glycidyl Ether (CAS # 2426-08-6) has an aggregated production and/or import volume in the United States of greater than 1 million pounds but less than 10 million pounds.[12] Non-confidential information in the Inventory Update Rule (IUR) indicates that this chemical was manufactured and/or imported at the following companies and sites: Ciba Specialty Chemicals Corp., West Memphis, AR; Hercules Incorporated, Hopewell, VA; Hexion Specialty Chemicals, Inc., Norco, LA; Huntsman Corporation, McIntosh, AL; and Kemira Chemicals, Inc., Columbus, GA. There may be other sites manufacturing n-butyl glycidyl ether which were designated as confidential. Persons submitting IUR information for 2005 asserted that some or all of the information was confidential. Only non-confidential IUR data are included in this summary.

Non-confidential IUR information indicates that *n*-butyl glycidyl ether is processed by incorporation into a formulation, mixture, or reaction product, and in other non-incorporative uses. These formulations and mixtures have commercial and consumer uses as sealants. There may be other confidential industrial functions and consumer and commercial uses which were designated as confidential.

The High Production Volume submission for this chemical did not include information on use[13].

The Hazardous Substances Data Bank (HSDB) indicates that a major use of *n*-Butyl Glycidyl Ether is as reactive diluent for epoxy resins, viscosity reducing agent, acid acceptor for stabilizing chlorinated compounds, and chemical intermediate.[14]

Potential Exposures to the General Population and the Environment. Based on the information under the release section, it is likely that there would be some releases to water or air during manufacturing, processing, and use. Based on the totality of the information considered, i.e., the moderate biodegradation rate, the P1, B1 ratings, the use of this chemical in epoxies, and the Agency's expert judgment, EPA identifies, for purposes of risk-based prioritization, that the potential for exposure to the general population and the environment is medium.

Potential Exposure to Workers. Based on the totality of the information considered including IUR data in combination with Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a high relative ranking for the potential worker exposure. This high relative ranking is based on the relatively high production volume and the potential for significant dermal exposure and for inhalation of mists and vapors by a large number of workers in commercial settings including spray application of products containing the subject substance.

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[12] USEPA, 2006 Partial Updating of TSCA Chemical Inventory.
[13] USEPA, 2007a. http://www.epa.gov/chemrtk/pubs/summaries/dbe/c13453tc.htm.
[14] HSDB, 2008. Hazardous Substances Data Bank. Accessed, 4/11/08, n-Butyl Glycidyl Ether. http://toxnet.nlm.nih.gov/.

OSHA has promulgated a permissible exposure limit for this chemical of 50 ppm as an 8-hr time-weighted average.[15] NIOSH has published an alert level of 250 ppm at which this chemical is considered immediately dangerous to life and health (IDLH).

Potential Exposures to Consumers. Depending on the consumer product, there may be dermal and/or inhalation exposures to consumers from vapors, mists, or particulates. EPA identifies, for the purposes of risk-based prioritization, that the potential for exposure to consumers from products containing this chemical is high based on IUR data and information from public data sources that indicate this chemical is found in adhesive and sealants.

Potential Exposures to Children. No uses in products specifically intended to be used by children were reported in the IUR, nor were any found in other data sources. However, there may be potential exposure of children through the use of some consumer products, e.g., epoxy, adhesives. Therefore, EPA identifies, for the purposes of risk-based prioritization, that the potential for exposure to children is medium.

Below are tables summarizing non-confidential processing and use information in the IUR for *n*-butyl glycidyl ether.

This exposure characterization was completed using both public, non-confidential sources, and one or more IUR submissions that were available as of this writing.

[15] NIOSH, 1988. OSHA PEL Project Documentation. Accessed, 4/7/08. http://www.cdc.gov/niosh/pel88/npelcas.html.

Non Confidential IUR Data Summary

Manufacturing/ Import Information

Production (including import) volume:	1 million to 10 million pounds
List of non-CBI companies/ sites:	Ciba Specialty Chemicals Corp., West Memphis, AR; Hercules Incorporated, Hopewell, VA Hexion Specialty Chemicals, Inc., Norco, LA; Huntsman Corporation, McIntosh, AL; and Kemira Chemicals, Inc., Columbus, GA;
Highest non-CBI maximum concentration:	greater than 90%
Non-CBI physical forms:	CBI

Table 1
Industrial Processing and Use
Information Reported in 2006 IUR

Processing Activity	Industrial Sector	Function in Ind. Sector
Use—non-incorporative activities	All Other Chemical Product and Preparation and Manufacturing	Intermediates
Processing--incorporation into formulation, mixture, or reaction product	Resin and Synthetic Rubber Manufacturing	Adhesives and binding agents
Processing--incorporation into formulation, mixture, or reaction product	Adhesive Manufacturing	Adhesives and binding agents
Processing--incorporation into formulation, mixture, or reaction product	Paint and Coatings Manufacturing	Adhesives and binding agents
Claimed as CBI		

Table 2 **Commercial/ Consumer Uses** **Information Reported in 2006 IUR**		
Commercial/ Consumer Product Category Description	Highest maximum concentration range	Use in Children's Products
Paints and coatings	Confidential	Confidential
Not Readily Obtainable	NRO	No
Adhesives and sealants	30%	No
Claimed as CBI		