

## SCREENING-LEVEL HAZARD CHARACTERIZATION

### SPONSORED CHEMICAL Alkyl (C<sub>12</sub> – C<sub>14</sub>) Glycidyl Ether (CASRN 68609-97-2)

### SUPPORTING CHEMICAL Alkyl (C<sub>12</sub> – C<sub>13</sub>) Glycidyl Ether (CASRN 120547-52-6)

The High Production Volume (HPV) Challenge Program<sup>1</sup> was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set<sup>1,2</sup>) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance<sup>2,3</sup> and is based primarily on hazard data provided by sponsors; however, 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 one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and

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<sup>1</sup> U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

<sup>2</sup> U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

<sup>3</sup> U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

<b>Chemical Abstract Service Registry Number (CASRN)</b>	<b>68609-97-2 (Sponsored) 120547-52-6 (Supporting)</b>
<b>Chemical Abstract Index Name</b>	<b>Oxirane, mono[(C12-14-alkyloxy)methyl] derivs.] – Sponsored Oxirane, mono[(C12-13-alkyloxy)methyl] derivs.] – Supporting</b>
<b>Structural Formula</b>	<b>See Section 1</b>
<b>Summary</b>	
<p>CASRN 68609-97-2 is a liquid mixture consisting of C<sub>12</sub>-C<sub>14</sub> alkoxy-substituted oxiranes with low water solubility and moderate vapor pressure. It is expected to have moderate mobility in soil. Volatilization of this chemical is considered moderate based on its Henry's Law constant. The rate of hydrolysis is considered negligible and CASRN 68609-97-2 is not readily biodegradable. The rate of atmospheric photooxidation is considered moderate. CASRN 68609-97-2 is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).</p> <p>The acute oral toxicity of CASRN 68609-97-2 is low in rats and the acute dermal toxicity of CASRN 120547-52-6 is low in rabbits. A repeated-dose toxicity study in rats with the supporting chemical CASRN 120547-52-6 via the dermal route of exposure showed no systemic toxicity up to the highest tested dose (100 mg/kg/day). However, dermal effects (edema, erythema, fissuring and scaling and thickening of the skin) were observed in this study at the mid-dose of 10 mg/kg/day, resulting in a NOAEL for local effects of 1 mg/kg/day. There were no reproductive toxicity studies performed with either the sponsored or supporting chemicals; however, reproductive organs were evaluated in the repeated-dose dermal study with CASRN 120547-52-6 and were found to be free of measurable effects up to the highest dose tested. A dermal prenatal developmental toxicity study with CASRN 120547-52-6 showed no adverse maternal (systemic) or developmental effects up to the highest tested dose (200 mg/kg/day) aside from local effects (skin irritation) in the dams, resulting in a NOAEL for maternal toxicity of 10 mg/kg/day). There were equivocal genotoxicity findings. CASRN 120547-52-6 induced mutations in one bacterial strain, but did not induce mutations in mammalian cells <i>in vitro</i>. In addition, CASRN 120547-52-6 did not induce micronuclei in an <i>in vivo</i> test with mice. In a separate repeated-dose dermal neurotoxicity study, CASRN 120547-52-6 had effects on the skin (moderate to severe in the high dose animals, lesser effects in mid-dose animals and mild effects at the lowest dose of 1 mg/kg/day) and neurological effects on the visual system (males only) at the mid-dose of 10 mg/kg/day, resulting in a NOAEL for neurotoxicity of 1 mg/kg/day.</p> <p>There is no adequate toxicity data for CASRN 68609-97-2 in fish, aquatic invertebrates, or aquatic plants.</p> <p>Data gaps for acute toxicity to fish, aquatic invertebrates and aquatic plants, and for chronic aquatic toxicity were identified under the HPV Challenge Program.</p>	

The sponsor, Epoxy Resin Systems Task Group, submitted a Test Plan and Robust Summaries to EPA for alkyl (C<sub>12</sub>-C<sub>14</sub>) glycidyl ether (CASRN 68609-97-2; CA Index name: oxirane, mono[(C12-14-alkyloxy)methyl] derivs.) 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/a1214gle/c13351tc.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.

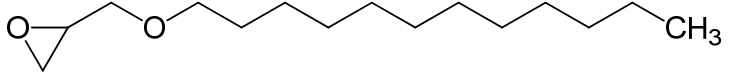
### **Justification for Supporting Chemical**

In 1996, EPA negotiated an Enforceable Consent Agreement (ECA) with several companies to perform some health effects data on alkyl glycidyl ethers (see Federal Register Notice at <http://www.epa.gov/fedrgstr/EPA-TOX/1996/March/Day-22/pr-24125.html>). The sponsored chemical (CASRN 68609-97-2) was identified as a member of the alkyl glycidyl ether category and CASRN 120547-52-6 was chosen as the chemical to be tested and whose results would be used to read across to other category members. Thus, the use of CASRN 120547-52-6 is acceptable as a supporting chemical for the health effects endpoints for the sponsored chemical.

## **1. Chemical Identity**

### **1.1 Identification and Purity**

The following structure is representative of both the sponsored and the supporting chemical:

<b>Chemical Name</b>	<b>CASRN</b>	<b>Structure</b>
Oxirane, 2-[(C12-14-alkyloxy)methyl] derivs.	68609-97-2	 <p>Representative structure (typical C12 alkyl)<sup>1</sup></p>

<sup>1</sup> The representative structure shown has a C12 alkoxy-substituted oxirane, which corresponds to the most prevalent alkyl chain length of the test substance. The sponsor used a C13-alkoxy structure to represent the mixture; however, the oxirane was likely inadvertently substituted with a cyclopropane. This was apparent based on the listed molecular weight and estimated results shown in the test plan. The sponsor does not specify ratio of linear to branched C12-C14 so it is assumed to be linear with mostly even numbered alkyl chains (e.g., C12 and C14).

There were several test substances evaluated by the submitter and the chemical identification and purity were as follows for the different HPV Challenge endpoints:

- Epoxide 8 (distilled C<sub>12</sub>-C<sub>14</sub> glycidyl ether, CASRN 68609-97-2, purity 94%): used in all the physicochemical, environmental fate, environmental effects studies and in the acute toxicity and irritation/sensitization studies for human health effect endpoints

- Alkyl C12-C13 glycidyl ether, CASRN 120547-52-6, purity 98% (consisting of approximately 49% C12 and 39% C13); used in all the health studies except the acute dermal study

## 1.2 Physical-Chemical Properties

The physical-chemical properties of oxirane, 2-[(C12-14-alkyloxy)methyl] derivs. are summarized in Table 1. Oxirane, 2-[(C12-14-alkyloxy)methyl] derivs. is a liquid mixture with low water solubility and moderate vapor pressure.

Property	Value
CASRN	68609-97-2
Molecular Weight	242.40 to 270.45 (C12-C14 alkyl) <sup>2</sup>
Physical State	Liquid
Melting Point	1.7°C (measured)
Boiling Point	216°C at 100 mm Hg (measured) <sup>3</sup> ; 287°C at 760 mm Hg (extrapolated) <sup>4</sup>
Vapor Pressure	0.06 mm Hg at 21°C (measured)
Water Solubility	0.483 mg/L at 20°C (measured)
Dissociation Constant (pK <sub>a</sub> )	Not applicable
Henry's Law Constant	5.2×10 <sup>-5</sup> atm·m <sup>3</sup> /mole (estimated) <sup>5</sup>
Log K <sub>ow</sub>	3.77 at 20°C (measured); 5.01 (estimated) <sup>5</sup>

<sup>1</sup> Epoxy Resin Systems Task Group (ERSTG) The Society of the Plastics Industry, Inc. (SPI). November 14, 2006. Revised Robust Summary for Alkyl (C12-C14) Glycidyl Ether. Available online from: <http://www.epa.gov/hpv/pubs/summaries/a1214gle/c13351tc.htm> as of May 6, 2010.

<sup>2</sup> The representative structure shown has a C12 alkoxy-substituted oxirane, which corresponds to the most prevalent alkyl chain length of the test substance. The sponsor used a C13-alkoxy structure to represent the mixture; however, the oxirane was likely inadvertently substituted with a cyclopropane. This was apparent based on the listed molecular weight and estimated results shown in the test plan. The sponsor does not specify ratio of linear to branched C12-C14 so it is assumed to be linear with mostly even numbered alkyl chains (e.g., C12 and C14).

<sup>3</sup> Waechter, J.M. et al. 2001. Epoxy compounds olefin oxides, aliphatic glycidyl ethers and aromatic monoglycidyl ethers. In: Patty's Toxicology. Volume 9, 5<sup>th</sup> edition. Bingham, E.; Cohnsen, B.; Powell, C.H. (editors). John Wiley & Sons, Inc.

<sup>4</sup> NOMO5. 1987. Programs to Enhance PC-Gems Estimates of Physical Properties for Organic Compounds. The Mitre Corp. Class 3 was used for the boiling point extrapolation of the representative C12-alkyl structure shown in the appendix.

<sup>5</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitd.htm> as of May 6, 2010.

## 2. General Information on Exposure

### 2.1 Production Volume and Use Pattern

According to the 2006 IUR submissions, CASRN 68609-97-2 had an aggregated production and/or import volume in the United States between 1 and 10 million pounds.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other basic organic chemical manufacturing as intermediates; semiconductor and other electronic component manufacturing as adhesives and binding agents; adhesive manufacturing as adhesives and binding agents; paint and coating manufacturing as adhesives and binding agents; resin and synthetic rubber manufacturing as adhesives and binding agents; and all other chemical product and preparation manufacturing as intermediates. Non-confidential commercial and consumer uses of this chemical include adhesives and sealants; paints and coatings; and not readily obtainable (NRO).

### 2.2 Environmental Exposure and Fate

The environmental fate properties of oxirane, 2-[(C12-14-alkyloxy)methyl] derivs. are summarized in Table 2.

Oxirane, 2-[(C12-14-alkyloxy)methyl] derivs. is expected to have moderate mobility in soil. Oxirane, 2-[(C12-14-alkyloxy)methyl] derivs. was not readily biodegradable using the closed bottle test under OECD test guideline (OECD 301D). The rate of hydrolysis is expected to be negligible under environmental pH and temperature. The rate of volatilization is considered moderate based on its Henry's Law constant. Oxirane, 2-[(C12-14-alkyloxy)methyl] derivs. is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).

**Table 2. Environmental Fate Characteristics of Oxirane, 2-[(C12-14-Alkyloxy)methyl] derivs.<sup>1,2</sup>**

Property	Value
Photodegradation Half-life	4.1 hours (estimated) <sup>3</sup>
Hydrolysis Half-life	62 years at pH 7 (estimated) <sup>3</sup>
Biodegradation	34.7% biodegradation in 28 days (not readily biodegradable)
Bioaccumulation Factor	BAF = 140.3 (estimated) <sup>3</sup>
Log K <sub>oc</sub>	3.3 (estimated) <sup>3</sup>
Fugacity (Level III Model) <sup>3</sup>	
Air (%)	5.5
Water (%)	42.7
Soil (%)	49.3
Sediment (%)	2.5
Persistence <sup>4</sup>	P2 (moderate)
Bioaccumulation <sup>4</sup>	B1 (low)

<sup>1</sup> Epoxy Resin Systems Task Group (ERSTG) The Society of the Plastics Industry, Inc. (SPI). November 14, 2006. Revised Robust Summary for Alkyl (C12-C14) Glycidyl Ether. Available online from: <http://www.epa.gov/hpv/pubs/summaries/a1214gle/c13351tc.htm> as of May 6, 2010.

<sup>2</sup> The representative structure shown has a C12 alkoxy-substituted oxirane, which corresponds to the most prevalent alkyl chain length of the test substance. The sponsor used a C13-alkoxy structure to represent the mixture; however, the oxirane was likely inadvertently substituted with a cyclopropane. This was apparent based on the listed molecular weight and estimated results shown in the test plan. The sponsor does not specify ratio of linear to branched C12-C14 so it is assumed to be linear with mostly even numbered alkyl chains (e.g., C12 and C14).

<sup>3</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of April 1, 2010

<sup>4</sup> Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

**Conclusion:** CASRN 68609-97-2 is a liquid mixture consisting of C<sub>12</sub>-C<sub>14</sub> alkoxy-substituted oxiranes with low water solubility and moderate vapor pressure. It is expected to have moderate mobility in soil. Volatilization of this chemical is considered moderate based on its Henry's Law constant. The rate of hydrolysis is considered negligible and CASRN 68609-97-2 is not readily biodegradable. The rate of atmospheric photooxidation is considered moderate. CASRN 68609-97-2 is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).

### 3. Human Health Hazard

The human health data are summarized in Table 4. Data from the supporting chemical is used to read across to the sponsored chemical where indicated.

#### *Acute Oral Toxicity*

##### *Alkyl (C<sub>12</sub> – C<sub>14</sub>) glycidyl ether (CASRN 68609-97-2)*

Sprague-Dawley rats (5/dose, sex distribution not stated) were dosed with 10.0, 14.7, 21.5 or 31.6 mL/kg-bw of Epoxide 8 (approximately 8860, 13,024, 19,049 or 27,998 mg/kg-bw based

on specific gravity at room temperature). Animals were observed for up to 14 days following dosing. No observations (other than the LD<sub>50</sub> value) were reported. Although not considered reliable by the submitter, EPA accepts the limited information (in conjunction with the acute dermal toxicity study summarized below) as adequately covering the acute toxicity endpoint for the purposes of the HPV Challenge Program.

**LD<sub>50</sub> = ~ 17,100 mg/kg-bw**

### *Acute Dermal Toxicity*

#### *Alkyl (C<sub>12</sub> – C<sub>14</sub>) glycidyl ether (CASRN 68609-97-2)*

Male New Zealand White rabbits (10/dose) were dosed with 0, 0.5, 1.5 or 4.5 mL/kg-bw (approximately 0, 443, 1329 or 3987 mg/kg-bw) of Epoxide 8<sup>4</sup> to clipped, intact skin and occluded for 24 hours. After 24 hours, sites were rinsed and observed for 72 hours. There were no deaths; although the observation period was three days post-dosing instead of the normal 14 days.

**LD<sub>50</sub> > ~ 3987 mg/kg-bw**

### *Repeated-Dose Toxicity*

#### *Alkyl (C<sub>12</sub> – C<sub>13</sub>) glycidyl ether (CASRN 120547-52-6, supporting chemical)*

Fischer 344 rats (10/sex/dose) were administered dermal doses of 0, 1, 10 or 100 mg/kg-bw-day (in an acetone vehicle) 5 days/week for 13 weeks. Exposure sites were not abraded or occluded and sites were not wiped clean before the next application. There were no compound-related effects observed on mortality, body weight, food consumption, hematology, clinical chemistry, urinalysis organ weights or histopathology of reproductive organs or any other evaluated tissue, with the exception of the skin. Effects consisted of moderate edema, slight to well-defined erythema and slight fissuring. At necropsy, thickened and scaly skin at the site of application was observed in high-dose animals of males (10/10) and females (9/10) and the mid-dose males (6/10). Histopathological, treatment-related effects were confined to the skin of high-dose males and females and consisted of hyperkeratosis and hyperplasia of the epidermis, hyperplasia of the sebaceous gland and inflammation.

**NOAEL (systemic toxicity) = 100 mg/kg-bw/day** (highest dose tested)

**LOAEL (local effects) = 10 mg/kg-bw/day** (dermal effects)

**NOAEL (local effects) = 1 mg/kg-bw/day**

### *Reproductive Toxicity*

#### *Alkyl (C<sub>12</sub> – C<sub>13</sub>) glycidyl ether (CASRN 120547-52-6, supporting chemical)*

In the 13-week dermal toxicity study described above, both the ovaries and testes were evaluated (organ weight – all treated groups; gross and histopathology – control and high dose groups only). No adverse effects were observed in any of the reproductive organs examined. Given

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<sup>4</sup> In this robust summary, the following description was given for the content of Epoxide 8: "...51.6-57% C12 glycidyl ether, 18.2-20% C14 glycidyl ether, 4.1-5% C16 glycidyl ether; oxirane oxygen 5.4-6.2%; epichlorohydrin 23-25 ppm;....". All other health endpoint studies (acute oral and irritation/sensitization) did not provide a similar description. It may be due to this (acute dermal) study being conducted at a much later date (1980) compared to the other studies (date range of 1961-1973).

these results, in conjunction with the prenatal developmental test described below, the reproductive toxicity endpoint has been met for the purposes of the HPV Program.

### *Developmental Toxicity*

#### ***Alkyl (C<sub>12</sub> – C<sub>13</sub>) glycidyl ether (CASRN 120547-52-6, supporting chemical)***

In a prenatal screening developmental toxicity study, pregnant female Sprague-Dawley rats (8/dose) were administered doses of 0, 1, 10, 50, 100 or 200 mg/kg-bw/day of the test chemical (in acetone vehicle) to clipped areas of skin on their backs from gestation day 6 through 15. The backs were washed six hours after application. The study was identified as a screening study because fetuses were not examined for visceral or skeletal anomalies. There were no significant effects on body weight, food consumption or gross pathological findings. Dermal irritation was observed at 50 mg/kg-bw/day and higher in a dose-related manner in terms of severity (incidence information not provided). No irritation occurred at 10 mg/kg-bw/day. There were no other compound-related effects on systemic maternal toxicity, fertility, intrauterine growth or survival, or fetal parameters (viability, body weight, external anomalies).

**NOAEL (maternal toxicity) = 10 mg/kg-bw/day**

**LOAEL (maternal toxicity) = 50 mg/kg-bw/day** (local skin effects)

**NOAEL (developmental toxicity) = 200 mg/kg-bw/day** (highest dose tested)

### *Genetic Toxicity – Gene Mutation*

#### ***In vitro***

#### ***Alkyl (C<sub>12</sub> – C<sub>13</sub>) glycidyl ether (CASRN 120547-52-6, supporting chemical)***

(1) *Salmonella typhimurium* (strains TA98, TA100, TA1535 and TA1537) and *Escherichia coli* WP2 *uvrA* were exposed to six concentrations ranging from 10 to 5000 µg/plate (depending on the tester strain based on results in a preliminary cytotoxicity assay in which 10 concentrations were tested) in the presence or absence of metabolic activation. Testing was conducted in triplicate, and positive and negative controls were also tested. Cytotoxicity was observed at > 333 µg/plate in some *Salmonella* strains with activation. Positive controls responded appropriately. Test compound induced a significant increase in the number of revertant colonies in strain TA 1535 with and without metabolic activation. No other positive responses were observed in the other bacterial strains.

**Alkyl (C<sub>12</sub> – C<sub>13</sub>) glycidyl ether was mutagenic in this assay.**

(2) Chinese hamster ovary (CHO) cells were exposed to concentrations of 100, 250, 750, 2000 or 5000 µg/mL without metabolic activation and 25, 50, 75, 125 or 150 µg/mL in the presence of metabolic activation. Positive and negative controls were conducted concurrently and were stated to have responded appropriately. The test chemical did not induce gene mutations at the HGPRT locus under the conditions of this assay.

**Alkyl (C<sub>12</sub> – C<sub>13</sub>) glycidyl ether was not mutagenic in this assay.**

### *Genetic Toxicity – Chromosomal Effects*

#### *In vivo*

##### ***Alkyl (C<sub>12</sub> – C<sub>13</sub>) glycidyl ether (CASRN 120547-52-6, supporting chemical)***

ICR mice (15/sex/dose @ ≤ 2000 mg/kg-bw; 20/sex @ 4000 mg/kg-bw) were administered single intraperitoneal doses of 0, 1000, 2000 or 4000 mg/kg-bw (in corn oil). Five animals per sex were sacrificed at 24, 48 and 72 hours after administration and bone marrow samples were taken. Positive and negative controls were tested concurrently and responded appropriately. The number of micronucleated polychromatic erythrocytes was not statistically increased at any dose level relative to vehicle control.

**Alkyl (C<sub>12</sub> – C<sub>13</sub>) glycidyl ether did not induce micronuclei under the conditions of this assay.**

#### *Additional Information*

There were several irritation studies submitted by the sponsor which used Epoxide 8 as the test substance (identified as the sponsored chemical, distilled C<sub>12</sub>-C<sub>14</sub> glycidyl ether, CASRN 68609-97-2, purity 94% - except for the acute dermal toxicity case; see footnote 4). In all cases except for the acute dermal toxicity study, the submitter considered the information not reliable because the exact nature of the test material was not known. Although EPA agrees with this fact, the available data reviewed in this hazard characterization clearly show that both the sponsored chemical and the supporting chemical cause dermal irritation. The supporting chemical information includes repeated-dose (two separate 13-week studies) and a prenatal developmental toxicity study – all using the dermal route of exposure and all showing local, irritation effects at relatively low doses (LOAELs of 1–50 mg/kg/day). Therefore, the individual irritation studies will be summarized and presented below.

#### *Eye Irritation*

##### ***Alkyl (C<sub>12</sub>-C<sub>14</sub>) glycidyl ether (CASRN 68609-97-2)***

New Zealand albino rabbits (three per sex per group – rinsed/unrinsed) were dosed with 0.1 ml of undiluted test material (Epoxide 8) in the right eye. Treated eyes were evaluated one hour and 1, 2, 3, 4 and 7 days (and weekly for up to five weeks if irritation continues) post-instillation. Corneas were also evaluated at each time point. Results showed no corneal involvement and mild, transient conjunctivitis that was cleared in two days (rinsed and unrinsed eyes).

**Alkyl (C<sub>13</sub> – C<sub>14</sub>) glycidyl ether was considered minimally irritating to the rabbit eye.**

#### *Skin Irritation*

##### ***Alkyl (C<sub>12</sub>-C<sub>14</sub>) glycidyl ether (CASRN 68609-97-2)***

New Zealand albino rabbits (three to six per group, gender not stated) were dosed with 0.5 ml of undiluted test material (Epoxide 8) on abraded and unabraded skin sites. The back of each rabbit was shaved and part of the shaved area was abraded (each animal had an abraded and non-abraded test site). Both occluded and non-occluded patch techniques were used (details on the number of animals for each not provided). Occluded sites were wrapped for 24 hours; test sites were evaluated for erythema and edema at 14 hours and 72 hours post treatment. Only total primary irritation index scores were presented and they ranged from 3.5-5.7 and there was no

difference between abraded vs. non-abraded sites. There was no discussion of whether there were differences in occluded vs. non-occluded sites.

**Alkyl (C<sub>13</sub> – C<sub>14</sub>) glycidyl ether was considered a moderate dermal irritant in rabbits.**

### *Neurotoxicity*

#### ***Alkyl (C<sub>12</sub> – C<sub>13</sub>) glycidyl ether (CASRN 120547-52-6, supporting chemical)***

Fischer 344 rats (12/sex/dose) were administered dermal doses of 0, 1, 10 or 100 mg/kg-bw/day (in an acetone vehicle) 5 days/week for 14 weeks in a study designed to evaluate neurotoxicity. The following parameters were evaluated: cageside observations (including skin integrity because it was a dermal study as well as clinical signs); body weight; functional observational batter (FOB) and motor activity (MA) – included hand-held and open field observations, grip performance, landing foot splay), evoked potentials (visual, auditory, somatosensory, and caudal nerves), and comprehensive neuropathological exam of both the peripheral and central nervous systems. Exposure sites were not abraded or occluded and sites were not wiped clean before the next application. There were no compound related effects observed on mortality, clinical signs or body weight. As seen in the 13-week repeated-dose study with rats, dermal effects were observed (erythema, edema, moderate scabbing and moderate to severe scaling in high dose males; lesser effects in high dose females; and very slight edema in mid-dose males). There were no exposure-related effects in most of the FOB/MA measurements and no effects observed in the neuropathology examinations. Flash evoked potential (FEP) from male mid- and high-dose rats were smaller than control, but FEPs from female high-dose rats were larger than control. Confirmatory examination included electroretinography (ERG) of control and high-dose males showed ERG response was smaller in high-dose males, suggesting a retinal effect which was not corroborated following histopathological analysis.

**LOAEL = 10 mg/kg-bw/day** (based on changes in flash evoked potentials)

**NOAEL = 1 mg/kg-bw/day**

**Conclusion:** The acute oral toxicity of CASRN 68609-97-2 is low in rats and the acute dermal toxicity of CASRN 120547-52-6 is low in rabbits. A repeated-dose toxicity study in rats with the supporting chemical CASRN 120547-52-6 via the dermal route of exposure showed no systemic toxicity up to the highest tested dose (100 mg/kg/day). However, dermal effects (edema, erythema, fissuring and scaling and thickening of the skin) were observed in this study at the mid-dose of 10 mg/kg/day, resulting in a NOAEL for local effects of 1 mg/kg/day. There were no reproductive toxicity studies performed with either the sponsored or supporting chemicals; however, reproductive organs were evaluated in the repeated-dose dermal study with CASRN 120547-52-6 and were found to be free of measurable effects up to the highest dose tested. A dermal prenatal developmental toxicity study with CASRN 120547-52-6 showed no adverse maternal (systemic) or developmental effects up to the highest tested dose (200 mg/kg/day) aside from local effects (skin irritation) in the dams, resulting in a NOAEL for maternal toxicity of 10 mg/kg/day). There were equivocal genotoxicity findings. CASRN 120547-52-6 induced mutations in one bacterial strain, but did not induce mutations in mammalian cells *in vitro*. In addition, CASRN 120547-52-6 did not induce micronuclei in an *in vivo* test with mice. In a separate repeated-dose dermal neurotoxicity study, CASRN 120547-52-6 had effects on the skin (moderate to severe in the high dose animals, lesser effects in mid-dose animals and mild effects at the lowest dose of 1 mg/kg/day) and neurological effects on the

visual system (males only) at the mid-dose of 10 mg/kg/day, resulting in a NOAEL for neurotoxicity of 1 mg/kg/day.

Table 4: Summary Table of the Screening Information Data Set as submitted under the U.S. HPV Challenge Program: Human Health Data		
Endpoints	SPONSORED CHEMICAL Alkyl (C <sub>12</sub> -C <sub>14</sub> ) glycidyl ether (68609-97-2)	SUPPORTING CHEMICAL Alkyl (C <sub>12</sub> -C <sub>13</sub> ) glycidyl ether (120547-52-6)
Acute Oral Toxicity LD <sub>50</sub> (mg/kg-bw)	~ 17,100	–
Acute Dermal Toxicity LD <sub>50</sub> (mg/kg-bw)	> ~ 3987	–
Repeated-Dose Toxicity NOAEL/LOAEL Dermal (mg/kg-bw/day)	No Data (RA) NOAEL (systemic) = 100 (hdt) LOAEL (local) = 10 NOAEL (local) = 1	NOAEL (systemic) = 100 (hdt) LOAEL (local) = 10 NOAEL (local) = 1
Reproductive Toxicity	No Data (RA) Reproductive organs were evaluated in 13 week repeated dose study. No effects were observed.	Reproductive organs were evaluated in 13 week repeated dose study. No effects were observed.
Developmental Toxicity NOAEL/LOAEL Dermal (mg/kg-bw/day)	No Data (RA)	
Maternal (systemic)	NOAEL = 200 (hdt)	NOAEL = 200 (hdt)
Maternal (local)	LOAEL = 50	LOAEL = 50
Developmental	NOAEL = 10	NOAEL = 10
	NOAEL = 200 (hdt)	NOAEL = 200 (hdt)
Genetic Toxicity – Gene Mutation <i>In vitro</i>	No Data (RA) Positive (1 of 5 bacteria strains) Negative (mammalian cells)	Positive (1 of 5 bacteria strains) Negative (mammalian cells)
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	No Data (RA) Negative	Negative
Additional Information Skin Irritation	–	Highly irritating
Neurotoxicity	–	Positive (males only)
– indicates that endpoint was not addressed for this chemical. (RA) = read across (hdt) = highest dose tested		

**4. Hazard to the Environment**

The environmental hazard data are summarized in Table 5.

*Acute Toxicity to Fish*

No adequate data were available concerning CASRN 68609-97-2 for fish.

*Acute Toxicity to Aquatic Invertebrates*

No adequate data were available concerning CASRN 68609-97-2 for aquatic invertebrates.

*Toxicity to Aquatic Plants*

No adequate data were available concerning CASRN 68609-97-2 for aquatic plants.

**Conclusion:** There is no adequate toxicity data for CASRN 68609-97-2 in fish, aquatic invertebrates, or aquatic plants.

<b>Table 5. Summary of the Screening Information Dataset as Submitted under the U.S. HPV Challenge Program – Aquatic Toxicity Data</b>	
<b>Endpoints</b>	<b>Alkyl (C<sub>12</sub> – C<sub>14</sub>) Glycidyl Ether (CASRN 68609-97-2)</b>
<b>Fish 96-h LC<sub>50</sub> (mg/L)</b>	No Data
<b>Aquatic Invertebrates 48-h EC<sub>50</sub> (mg/L)</b>	No Data
<b>Aquatic Plants 72-h EC<sub>50</sub> (mg/L)</b>	No Data
<b>Chronic Toxicity to Aquatic Invertebrates 21-d EC<sub>50</sub></b>	No Data