

SCREENING-LEVEL HAZARD CHARACTERIZATION

Triglycidyl Isocyanurate

CASRN 2451-62-9

The High Production Volume (HPV) Challenge Program¹ 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^{1,2}) 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^{2,3} 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, EXTOKNET, 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 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

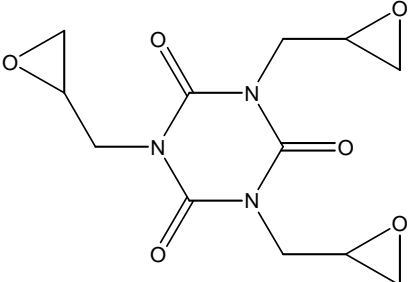
¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

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

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

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 information previously not readily available to the public.

<p>Chemical Abstract Service Registry Number (CASRN)</p>	<p>2451-62-9</p>
<p>Chemical Abstract Index Name</p>	<p>1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tris(oxiranylmethyl)-</p>
<p>Structural Formula</p>	

Summary

Commercial triglycidyl isocyanurate (TGIC) is a solid material consisting of approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer, with high water solubility and low vapor pressure. This chemical is expected to have high mobility in soil. Volatilization of this chemical is considered low based on the estimated Henry's Law constant. The rate of hydrolysis is considered moderate at neutral pH and rapid under acidic conditions. The rate of atmospheric photooxidation is considered moderate. This chemical is expected to have low persistence (P1) and low bioaccumulation potential (B1). The α - and β -isomers would be expected to have the same low persistence and low bioaccumulation potential but there are no data to substantiate this assumption.

The acute toxicity of triglycidyl isocyanurate is moderate in rats by the oral route, high in mice by the inhalation route, and low in rats by the dermal route. A repeated-dose toxicity study in male rats showed decreases in body weight gain at 4.36 mg/kg-bw/day; the NOAEL for systemic toxicity was 1.30 mg/kg-bw/day. No one- or two-generation reproductive or prenatal developmental toxicity studies are available. However, decreases in sperm counts were observed at 0.72 mg/kg-bw/day in another repeated-dose toxicity study in males, the lowest dose tested. This chemical did not induce dominant lethality. This chemical was slightly to moderately irritating to rabbit and guinea pig skin, severely irritating to rabbit eye, and a dermal sensitizer in guinea pigs. This chemical induced gene mutations *in vitro* but not *in vivo*; and induced chromosomal aberrations *in vivo* but was equivocal *in vitro*. There was no evidence of carcinogenicity in a two-year bioassay.

For acute hazard of CASRN 2451-62-9, the 96-hour LC₅₀ to fish is >77 mg/L, the measured 24-hour EC₅₀ to aquatic invertebrates is >90.6 mg/L, and the measured 72-hour EC₅₀ (biomass) to aquatic plants is 29 mg/L.

Reproductive and prenatal developmental toxicity studies were identified as data gaps under the

HPV Challenge Program.

The sponsor, Huntsman-Nissan-TGIC Consortium, submitted a Test Plan and Robust Summaries to EPA for triglycidyl isocyanurate (Araldite PT-810, CASRN 2451-62-9) on December 27, 2004. EPA posted the submission on the ChemRTK HPV Challenge website on January 19, 2005 (<http://www.epa.gov/chemrtk/pubs/summaries/triglyis/c15759tc.htm>). EPA comments on the original submission were posted to the website on April 28, 2006. Public comments were received and posted to the website. The sponsor submitted updated/revised documents on June 25, 2006, which were posted to the ChemRTK website on September 17, 2007.

1 **Chemical Identity**

1.1 **Identification and Purity**

Technical grade triglycidyl isocyanurate is a trifunctional epoxide resin containing approximately 76 – 80% of the alpha-isomer and approximately 20 – 24% of the beta-isomer. Excess epichlorohydrin reactant (oxirane, chloromethyl) may be present at concentrations up to 100 ppm.

1.2 **Physical-Chemical Properties**

The physical-chemical properties of commercial triglycidyl isocyanurate and the diastereomer racemates (α -triglycidyl isocyanurate and β -triglycidyl isocyanurate) are summarized in Table 1. Commercial triglycidyl isocyanurate (TGIC) is a solid material consisting of approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer, with high water solubility and low vapor pressure.

Property	Triglycidyl isocyanurate²
CASRN	2451-62-9
Molecular Weight	297.27
Physical State	Solid
Melting Point	95°C (measured; may decompose)
Boiling Point	Decomposes at >250°C (measured)
Vapor Pressure	5.4×10 ⁻⁸ mm Hg at 20°C (measured)
Water Solubility	10,000 mg/L at 25°C (measured)
Dissociation Constant (pK _a)	Not applicable
Henry's Law Constant	9.4×10 ⁻²¹ atm·m ³ /mole (estimated) ³
Log K _{ow}	-0.8 (measured)

¹Huntsman-Nissan-TGIC. November 2, 2006. Revised Robust Summaries and Test Plans for Triglycidyl Isocyanurate.

<http://www.epa.gov/chemrtk/pubs/summaries/triglyis/c15759tc.htm>.

²Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer and may also contain excess epichlorohydrin.

³U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. United States Environmental Protection Agency, Washington,

DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

2 General Information on Exposure

2.1 Production Volume and Use Pattern

This chemical has an aggregated production and/or import volume in the United States of 1 to 10 million pounds.

Non-confidential information in the IUR indicated that the industrial processing and uses of this chemical include adhesive and binding agents and intermediates. Non-confidential information in the IUR indicated that the commercial and consumer products containing this chemical include paints and coatings. The HSDB states this chemical is primarily used as a three-dimensional cross linking or curing agent in polyester powder coatings (paints); it is also used in solder “mask” inks in the printed circuit board industry. The HPV submission also states this chemical is primarily used as a hardener for polyester-based powder coatings.

2.2 Environmental Exposure and Fate

No quantitative information is available on environmental releases.

The environmental fate properties are provided in Table 2. Triglycidyl isocyanurate is expected to have high mobility in soil. A commercial mixture consisting of approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer was not readily biodegradable using a modified Sturm (OECD 301B) or MITI (OECD 301C) test. This preparation was also not inherently biodegradable using a modified Zahn-Wellens test (OECD 302B); however, these results likely measured the biodegradation of triglycidyl isocyanurate and its hydrolysis product, 1,3,5-tris(2,3-dihydroxypropyl)-1,3,5-triazine-2,4,6 (1H,3H,5H)-trione. Volatilization of triglycidyl isocyanurate is considered low based on the estimated Henry's Law constant. The rate of hydrolysis is considered moderate at neutral pH and rapid under acidic conditions. Triglycidyl isocyanurate is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Property	Triglycidyl isocyanurate
CASRN	2451-62-9
Photodegradation Half-life	No direct photolysis expected; 7 hours (estimated) ²
Hydrolysis Half-life	160 hours at pH 7 and 25°C (measured); 1 hour at pH 2 and 25°C (measured)
Biodegradation	0% after 28 days (not readily biodegradable); 9–48% after 28 days (not readily biodegradable); 44% after 28 days (not inherently biodegradable); 0–3% after 28 days (not readily biodegradable) ³

Bioconcentration	BCF = 3.2 (estimated) ²
Log K _{oc}	1 (estimated) ²
Fugacity (Level III Model)	
Air	0.665%
Water	47.8%
Soil	51.5%
Sediment	0.102%
Persistence ⁴	P1 (low)
Bioaccumulation ⁴	B1 (low)

¹Huntsman-Nissan-TGIC. November 2, 2006. Revised Robust Summaries and Test Plans for Triglycidyl Isocyanurate.

<http://www.epa.gov/chemrtk/pubs/summaries/triglyis/c15759tc.htm>.

²U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. United States Environmental Protection Agency, Washington, DC, USA.

<http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

³National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.

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

3 Human Health Hazard

A summary of the available health effects data submitted for SIDS endpoints is provided in Table 3.

Acute Oral Toxicity

(1) TIF:RAIF (SPF) rats (5/sex/dose) were administered triglycidyl isocyanurate (in 0.5% CMC, carboxymethyl cellulose) via gavage at 20 mg/kg-bw (females only), 100 mg/kg-bw (both sexes) or 500 mg/kg-bw (females only) and observed for 14 days. Mortality occurred in males at 100 mg/kg-bw and females at 500 mg/kg-bw.

LD₅₀ (male rats) < 100 mg/kg-bw

LD₅₀ (female rats) = 171 mg/kg-bw

(2) TIF:RAIF (SPF) rats (5/sex/dose) were administered triglycidyl isocyanurate (in arachis oil) via gavage at 100, 250, 500 or 1000 mg/kg-bw and observed for 14 days. Mortality occurred at and above 250 mg/kg-bw.

LD₅₀ = 305 mg/kg-bw

(3) TIF:RAIF (SPF) rats (5/sex/dose) were administered triglycidyl isocyanurate (in 0.5% CMC) via gavage at 20 mg/kg-bw (females), 100 mg/kg-bw (both sexes), 200 mg/kg-bw (both sexes) or 500 mg/kg-bw (females) and observed for 14 days. Mortality occurred in males at 100 and 200 mg/kg-bw and in females at 200 and 500 mg/kg-bw.

LD₅₀ (male rats) < 100 mg/kg-bw

LD₅₀ (female rats) = 255 mg/kg-bw

(4) TIF:RAIF (SPF) rats (5/sex/dose) were administered triglycidyl isocyanurate (in 2% CMC) via gavage at 100, 215, 317, 464, 600 or 1290 mg/kg-bw and observed for 14 days. Mortality occurred at and above 215 mg/kg-bw.

LD₅₀ = 431 mg/kg-bw

Acute Inhalation Toxicity

(1) CD-1 mice (5 males/concentration) were exposed to triglycidyl isocyanurate dust at concentrations of 1.05, 2.39 or 3.88 mg/L for 4 hours and observed for 14 days. Mortality occurred at 2.39 and 3.88 mg/L.

LC₅₀ = 2.0 mg/L

(2) Wistar rats (8 males/concentration) were exposed (whole-body) to triglycidyl isocyanurate at 4.16 mg/L for 4 hours and observed for 8 days. No deaths were observed.

LC₅₀ > 4.16 mg/L

(3) CD-1 mice (10 males/concentration) were exposed to triglycidyl isocyanurate dust at 100, 350 or 750 mg/m³ (corresponding to 0.100, 0.350 or 0.750 mg/L) for 5 days (duration per day not stated) and were observed for 14 days. Mortality occurred at all concentrations (5/10, 10/10 and 9/10 at 100, 300 and 750 mg/m³, respectively).

LC₅₀ = 0.100 mg/L

(4) TIF:RAIF (SPF) rats (10/sex/concentration) were exposed to triglycidyl isocyanurate aerosol at 0, 410 or 656 mg/m³ (0, 0.410 or 0.656 mg/L) for 4 hours and observed for 14 days. Mortality occurred in females at 656 mg/m³.

LC₅₀ (male) > 0.650 mg/L

LC₅₀ (female) = 0.650 mg/L

(5) TIF:RAIF (SPF) rats (10/sex/concentration) were exposed to triglycidyl isocyanurate dust at 309 mg/m³ (corresponding to 0.309 mg/L) for 4 hours and observed for 14 days. No deaths were observed.

LC₅₀ > 0.309 mg/L

Acute Dermal Toxicity

(1) TIF:RAIF rats (3/sex/dose) were administered triglycidyl isocyanurate dermally at 215, 1000, 2150 or 3170 mg/kg-bw on clipped, intact skin under occlusive conditions for 24 hours and were observed for 14 days. No mortality was observed.

LD₅₀ > 3100 mg/kg-bw

(2) Sprague-Dawley CFY rats (5/sex) were administered triglycidyl isocyanurate dermally at 2000 mg/kg-bw on clipped, intact skin under semi-occluded conditions for 24-hours and were observed for 14 days. No deaths were observed.

LD₅₀ > 2000 mg/kg-bw

(3) TIF:RAIF (SPF) rats (5/sex/dose) were administered triglycidyl isocyanurate dermally at 200 mg/kg-bw (males only) or 2000 mg/kg-bw (both sexes) dermally on shaved, intact skin under semi-occluded conditions for 24 hours and were observed for 14 days. No deaths were observed.
LD₅₀ > 2000 mg/kg-bw

Repeated-Dose Toxicity

(1) In a repeated-dose toxicity study, Sprague-Dawley rats (10 males/dose) were administered triglycidyl isocyanurate via the diet at 0, 10, 30 or 100 ppm (approximately 0.72, 2.08 and 7.32 mg/kg-bw/day, respectively) for up to 94 days. After treatment day 64, treated males were mated with untreated females (20/concentration) in order to assess male fertility. Slightly lower leukocyte and lymphocyte counts were noted in 2 out of 10 males at 100 ppm. Reddish coloration of mesenteric lymph nodes with hemosiderosis and congestion were seen in some animals at 100 ppm. The magnitude and significance of these changes were not provided. No mortalities were reported and no significant differences were noted for clinical signs, body weight/body weight gain, food consumption, blood chemistry or urinalysis parameters in the males.

LOAEL (systemic toxicity; males only) = not established

NOAEL (systemic toxicity; males only) = 7.32mg/kg/day (based on no adverse effects at the highest dose tested)

(2) In a repeated-dose toxicity study, Sprague-Dawley rats (50 males/concentration) were administered triglycidyl isocyanurate via the diet at 0, 10, 30, 100 or 300 ppm (approximately 0, 0.43, 1.30, 4.36 or 13.6 mg/kg-bw/day, respectively) for 104 weeks. However, due to a high rate of mortality, dosing was discontinued in the 300 ppm group at week 63 (44% mortality), and for the remaining doses at weeks 98/99 (60% mortality at 10 ppm). At the end of the treatment period, all surviving animals were killed and underwent a macro- and microscopic evaluation. Decreased food consumption and body weight gain were noted at 100 and 300 ppm. Signs of poor clinical condition were noted in the 300 ppm group. An increase in neutrophil percentage and a decrease in lymphocyte percentage were noted at 300 ppm. At 300 ppm, a high incidence of mastocytosis, hemosiderosis and sinusoidal hemorrhage in mesenteric lymph nodes, high incidence of lymphoid depletion in the spleen, moderate to marked dilation of some intestinal segments and hypo-secretion with small tubulo-alveolar units in the prostate were reported. No treatment-related differences were seen at 10, 30 and 100 ppm. The study authors concluded that the mortality observed in the 300 ppm dose group was possibly due to a histamine-related hypotension, but the mortality in the remaining dose groups was not treatment-related because it was similar in the control group and is commonly recorded in this strain and age of rats.

LOAEL (systemic toxicity; males only) = 4.36 mg/kg-bw/day (based on decreased body weight gain)

NOAEL (systemic toxicity; males only) = 1.30 mg/kg-bw/day

Reproductive/Developmental Toxicity

There are no standard one- or two-generation reproductive or prenatal developmental toxicity studies with triglycidyl isocyanurate. However, a repeated-dose toxicity study in Sprague-

Dawley rats addressed fertility (males only; previously described in #1 above) and several dominant lethal assays are available.

There was a slight, but dose-related decrease in the mean number of spermatozoa in all treated groups (5, 13 and 23% for 10, 30 and 100 ppm, respectively; statistical significance not provided). The mean spermatozoa viability was similar compared to controls, the mating index was 100% in all groups, and no treatment-related infertility was reported. Longer-term exposures (98/99 weeks) did not reveal any effect on male reproductive organs. Although the decrease in sperm number in this study did not appear have an adverse affect on fertility, human male fertility is generally lower than that of test species and therefore, statistically significant changes in sperm count would be considered adverse.

In this same study, treated males were mated with untreated females and a variety of observations were made on the dams and fetuses. For the dams, no clinical signs and no unscheduled mortalities occurred. The gestation index was 100% in all groups, and no significant differences were noted for the mean number of corpora lutea, implantation sites, and pre-implantation losses. For the fetuses, no dead fetuses were reported, no external anomalies or malformations were observed, and no significant differences were noted for the following: number of fetuses, mean fetal body weight, sex-ratio of live fetuses, mean number of live born pups, viability index of pups on days 4 and 21 postpartum, lactation index, mean pup body weight, pinna unfolding, hair growth, tooth eruption, eye opening, auditory canal opening, reflex development, surface righting, cliff avoidance, and air righting.

In vivo Dominant Lethal Assays

1) In a dominant lethal assay, male ICR mice (20/dose) were administered triglycidyl isocyanurate via gavage at 137.5, 275 or 550 mg/kg-bw and were mated with untreated female mice (40/dose) for 3 weeks. Positive controls were also tested and responded appropriately. No toxic effects were noted in any of the animals after dosing. Three males in the high-dose group and one male of the vehicle control group died during the first week of mating. Several animals in the low- and high-dose groups were observed to have scruffy coats during the first week of mating. There were no treatment-related effects on any of the measured implantation indices. **Triglycidyl isocyanurate did not induce dominant lethal effects in this assay.**

(2) In dominant lethal assay, male albino mice (Tif: MAG f (SPF)) were administered triglycidyl isocyanurate via gavage at 0, 160 and 480 mg/kg-bw and were mated with untreated females. At 160 mg/kg-bw, there was no difference in mating ratio, the number of implantations and resorptions between the treated and the control groups. At 480 mg/kg-bw, there was a significant increase in the number of resorptions compared with the control group. **Triglycidyl isocyanurate induced dominant lethal effects in this assay.**

(3) In a dominant lethal assay, CD-1 mice (30 males/dose) were exposed to triglycidyl isocyanurate via whole-body inhalation at 0, 2.5, 10 or 50 mg/m³ (measured concentrations 1.79, 10.3 or 49.6 mg/m³) for 6 hours/day for 5 days. Positive controls were tested concurrently and responded accordingly. There was 10% mortality, reduced body weight gain and ocular discharge and swelling in the high-dose group. Effects on male fertility were observed at

50 mg/m³ as evidenced by reduced number of males impregnating females, reduced number of pregnant females and females with copulation plugs for the first 3 mating weeks, indicative of effects on mature sperm and maturing spermatids. No effects on male fertility were observed for the spermatocyte stages.

Triglycidyl isocyanurate did not induce dominant lethal effects in this assay.

(4) CD-1 (ICR) mice (10 males/concentration) were exposed to triglycidyl isocyanurate dust via whole-body inhalation at target concentrations of 0 (air), 100, 1000 and 1700 mg/m³ (115, 975, 1575 mg/m³, measured-gravimetric) 6 hours/day for 5 consecutive days and mated with untreated females of the same strain approximately 24 hours after the last exposure. On gestation day 15, females were sacrificed and the number of implantation sites counted. A positive control was included in the test. There was a marked decrease in body weight of the treated mice. No effects on male fertility were evident at any exposure concentration. There was no effect on the numbers of resorptions per litter, total number of implants, number of viable implants or percent post-implantation loss.

Triglycidyl isocyanurate did not induce dominant lethal effects in this assay.

Genetic Toxicity – Gene Mutation

In vitro

(1) In five bacterial reverse mutation assays, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and *Escherichia coli*, WP2uvrA were exposed to triglycidyl isocyanurate at concentrations ranging from 1.0 to 10,000 µg/plate in the presence and absence of metabolic activation. Positive controls were tested concurrently and responded appropriately. Concentrations exhibiting cytotoxicity or precipitation were not identified.

Triglycidyl isocyanurate was mutagenic in these assays.

(2) Mouse lymphoma cells (L5178Y) were exposed to triglycidyl isocyanurate at 0.375, 0.75, 1.50, 3.00 and 6.00 µg/mL with metabolic activation and at 0.175, 0.35, 0.70 1.40 and 2.80 µg/mL without metabolic activation. In the absence of metabolic activation, at 1.40 and 2.80 µg/mL a markedly elevated mutation frequency was noted. Similarly, in the presence of metabolic activation, the highest concentration, 6.0 µg/mL led to the markedly elevated mutant frequency when compared with the solvent control. The negative and positive controls responded appropriately.

Triglycidyl isocyanurate was mutagenic in this assay.

(3) In two NTP studies, *Salmonella typhimurium* strains TA98 and TA100 were exposed to triglycidyl isocyanurate at concentrations ranging from 10 to 2000 µg/plate in the presence and absence of metabolic activation. Positive controls were tested concurrently and responded appropriately.

Triglycidyl isocyanurate was mutagenic in these assays.

Genetic Toxicity – Chromosomal Aberrations

In vitro

(1) Primary human lymphocytes were exposed to triglycidyl isocyanurate at 0.0625, 0.125, 0.25, 0.5 or 1.0 µg/mL in the absence of metabolic activation or 0.625, 1.25, 2.5, 5.0 or 10 µg/mL in

the presence of metabolic activation. Positive controls were tested concurrently and responded appropriately. Cytotoxic concentration was 10 µg/mL in the presence of metabolic activation and 1.0 µg/mL in the absence of activation.

Triglycidyl isocyanurate did not induce chromosomal aberrations in this assay.

(2) In a National Toxicology Program (NTP) study, Chinese hamster ovary (CHO) cells were exposed to triglycidyl isocyanurate in the absence of metabolic activation at 3, 10, 30 or 50 µg/mL in one trial and at 9.95, 19.9 or 29.9 µg/mL in a second trial. CHO cells were also exposed to 10, 30 or 100 µg/mL in the presence of metabolic activation. Positive and negative controls were tested concurrently and responded appropriately.

Triglycidyl isocyanurate induced chromosomal aberrations in this assay.

In vivo

(1) ICR mice (10 males/dose) were administered triglycidyl isocyanurate in peanut oil via gavage at 30, 125 and 350 mg/kg-bw daily for 5 days and were sacrificed 6 hours after the final dosing. Spermatogonial metaphase cells were analyzed for chromosomal aberrations. The test substance induced significant frequencies of aberrant cells in spermatogonial cells of mice at 125 and 350 mg/kg-bw. Positive and negative controls responded appropriately.

Triglycidyl isocyanurate induced chromosomal aberrations in these assays.

(2) TIF:MAGF (SPF) mice (15 males/dose) were administered triglycidyl isocyanurate via gavage at 42.7 or 128 mg/kg-bw/day for 5 days. Cytotoxicity was seen at the high-dose. Spermatogonial metaphase cells were analyzed for chromosomal aberrations. The results indicated that triglycidyl isocyanurate induced chromosomal aberrations in mouse spermatogonial cells.

Triglycidyl isocyanurate induced chromosomal aberrations in these assays.

(3) TIF:MAGF (SPF) mice (15 males/dose) were administered triglycidyl isocyanurate (in Arachis oil) via gavage at 32 or 96 mg/kg-bw/day on days 0, 2, 3, 5 and 9. The results indicated that triglycidyl isocyanurate induced chromosomal aberrations in mouse spermatocytes. Negative control (solvent) responded appropriately. Positive control was not included in the test.

Triglycidyl isocyanurate induced chromosomal aberrations in these assays.

(4) Mice (5 males/dose, strain not specified) were administered triglycidyl isocyanurate via gavage at 185.2, 555.6, 1667 and 5000 mg/kg-bw daily for 5 days and were sacrificed 6 hours after the final dose. Spermatogonial metaphase cells were analyzed for chromosomal aberrations. Negative and positive controls responded appropriately. The number of aberrant spermatogonial cells in treated mice was not significantly different from those in the negative control and was within the accepted normal control range.

Triglycidyl isocyanurate did not induce chromosomal aberrations in this assay.

Genetic Toxicity – Other

In vitro

(1) In an unscheduled DNA synthesis assay, human fibroblasts were exposed to triglycidyl isocyanurate at 2.7, 9, 30, 100, 250 or 400 µg/mL in the absence of metabolic activation.

Cytotoxic concentration was greater than 400 µg/mL. Positive controls were tested concurrently and responded appropriately.

Triglycidyl isocyanurate did not induce unscheduled DNA synthesis in this assay.

(2) In an NTP, sister chromatid exchange assay, Chinese hamster ovary (CHO) cells were exposed to triglycidyl isocyanurate at 0.066, 0.198, 0.66 or 1.98 µg/mL in the absence of metabolic activation in one trial and at 0.101, 0.303, 0.505 or 0.76 µg/mL in the second trial. CHO cells were also exposed to triglycidyl isocyanurate at 1.98, 6.6, 19.8 or 66 µg/mL in the presence of metabolic activation. Positive and negative controls were tested concurrently and responded appropriately.

Triglycidyl isocyanurate induced sister chromatid exchange in this assay.

In vivo

Several dominant lethal assays (previously described) are available.

Additional Information

Skin Irritation

(1) New Zealand white rabbits (3/sex) were administered 0.5 g of triglycidyl isocyanurate (in propylene glycol and saline, 70:30) dermally on intact and abraded skin under occluded conditions for 24 hours. Skin reactions were assessed upon removal of the patches and during the 7-day observation period.

Triglycidyl isocyanurate was minimally irritating in this study.

(2) New Zealand white rabbits (5/sex) were administered 0.5 g of triglycidyl isocyanurate (in arachis oil) dermally on intact skin under semi-occluded conditions for 24 hours. Skin reactions were assessed upon removal of the patches and during the 7-day observation period. Very slight erythema was noted at the application sites at one and 24-hour observation. All treated sites were normal at the 72-hour observation.

Triglycidyl isocyanurate was mildly irritating in this study.

(3) New Zealand white rabbits (3/sex) were administered 0.5 g of neat triglycidyl isocyanurate dermally on intact and abraded skin under occluded conditions for 24 hours. Skin reactions were assessed upon removal of the patches and during the 7-day observation period.

Triglycidyl isocyanurate was slightly irritating in this study.

(4) New Zealand white rabbits (3 males) were administered 0.5 g of triglycidyl isocyanurate (in distilled water) dermally on intact skin under occluded conditions for 24 hours. Skin reactions were assessed upon removal of the patches and up to 72-hours observation period. Very slight erythema was noted at the application sites at one and 24-hour observation. All treated sites were normal at the 72-hour observation.

Triglycidyl isocyanurate was mildly irritating in this study.

(5) New Zealand white rabbits (1/sex) were administered 1 g of neat triglycidyl isocyanurate or 1 mL of a 4% solution of triglycidyl isocyanurate dermally on shaved skin for 6 hours under

occluded conditions for 3 consecutive days. One pair of male and female rabbits was treated in a similar manner, but the application sites were not covered during the exposure. Irritation was assessed on day 7.

Triglycidyl isocyanurate was moderately irritating in these studies.

(6) Guinea pigs (5/sex) were administered dermally 0.5 mL of triglycidyl isocyanurate on shaved skin. The application sites remained uncovered.

Triglycidyl isocyanurate was moderately irritating in this study.

Eye Irritation

(1) CFE rabbits (sex distribution and number not stated) were instilled 100 mg of solid triglycidyl isocyanurate into one eye; the other eye served as control. The test substance showed severe irritation with temporary blindness.

Triglycidyl isocyanurate was severely irritating in this assay.

(2) New Zealand white rabbit (1 male) was instilled 0.1 mL of triglycidyl isocyanurate into the right eye; the left eye served as control. Severe ocular reactions including diffuse corneal opacity and iridial inflammation were noted.

Triglycidyl isocyanurate was severely irritating in this assay.

(3) New Zealand White rabbits (3/sex) were instilled 0.5 g triglycidyl isocyanurate into one eye; the other eye served as control. An additional group of six rabbits was instilled 0.1 g triglycidyl isocyanurate and after 30 seconds, the eyes of three animals were rinsed. Marked eye irritation was observed.

Triglycidyl isocyanurate was severely irritating in this assay.

Sensitization

(1) In four guinea pig maximization tests, triglycidyl isocyanurate was sensitizing with rates of sensitization varied from 20 to 90% (weak to extreme sensitizing) in the studies.

Triglycidyl isocyanurate was a dermal sensitizer in these four assays.

(2) Guinea pigs (30 males: 20 test and 10 control) were administered triglycidyl isocyanurate in four intradermal injections at 0, 1.0, 3.0 and 5.0% to the neck area. One week later, 0.1 mL of the test substance in corn oil was applied to the shaved backs of guinea pigs at 10, 15, 25 or 30%. While a response (erythema) was noted during the challenge period, the study concluded that triglycidyl isocyanurate was not sensitizing because the skin reactions faded between the 24- and 48-hour readings and were not reproducible during a second challenge. The summary concluded that skin reactions were a response to a state of hyperactivity.

Triglycidyl isocyanurate in corn oil was not a dermal sensitizer in this assay.

Carcinogenicity

In the repeated-dose toxicity study in rats previously described (#2), no statistical difference in tumor formation or latency period of tumor formation between treated and control groups was observed.

Triglycidyl isocyanurate did not show evidence of carcinogenicity in this study.

Conclusion: The acute toxicity of triglycidyl isocyanurate is moderate in rats by the oral route, high in mice by the inhalation route, and low in rats by the dermal route. A repeated-dose toxicity study in male rats showed decreases in body weight gain at 4.36 mg/kg-bw/day; the NOAEL for systemic toxicity was 1.30 mg/kg-bw/day. No one- or two-generation reproductive or prenatal developmental toxicity studies are available. However, decreases in sperm counts were observed at 0.72 mg/kg-bw/day in another repeated-dose toxicity study in males, the lowest dose tested. This chemical did not induce dominant lethality. This chemical was slightly to moderately irritating to rabbit and guinea pig skin, severely irritating to rabbit eye, and a dermal sensitizer in guinea pigs. This chemical induced gene mutations *in vitro* but not *in vivo*; and induced chromosomal aberrations *in vivo* but was equivocal *in vitro*. There was no evidence of carcinogenicity in a two-year bioassay.

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Summary of Human Health Data	
Endpoints	Triglycidyl isocyanurate (2451-62-9)
Acute Oral Toxicity LD₅₀ (mg/kg-bw)	< 100
Acute Inhalation Toxicity LC₅₀ (mg/L)	0.65 0.1 (5-d)
Acute Dermal Toxicity LD₅₀ (mg/kg-bw)	> 2000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = 1.30 LOAEL = 4.36
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	Reproductive toxicity = Data gap
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	Data gap
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Positive
Genetic Toxicity – Gene Mutation <i>In vivo</i>	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	Positive

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Summary of Human Health Data	
Endpoints	Triglycidyl isocyanurate (2451-62-9)
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	Positive
Genetic Toxicity – Other <i>In vitro</i> Unscheduled DNA Synthesis	Negative
Genetic Toxicity – Other <i>In vivo</i> Dominant Lethal Effects DNA Binding Effects	Negative Positive
Additional Information Dermal Irritation	Slightly to moderately irritating
Eye Irritation	Markedly to severely irritating
Dermal Sensitization	Positive Negative evidence
Carcinogenicity	

4. Environmental Effects Aquatic Toxicity

A summary of the available ecological effects data submitted for SIDS endpoints is provided in Table 4.

Acute Toxicity to Fish

Zebrafish (*Brachydanio rerio*, 10/concentration) were exposed to triglycidyl isocyanurate at a nominal concentration of 100 mg/L (average measured concentration approximately 77 mg/L) under static conditions for 96 hours in a limit test. No mortality occurred and no adverse effects were noted in any of the fish. DMSO was used as a solvent in this test.

96-h LC₅₀ = > 77 mg/L

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*, 20/concentration) were exposed to triglycidyl isocyanurate at nominal concentrations of 10, 18, 32, 58 or 100 mg/L under static conditions for 24 hours. Measured concentrations were 9.8, 17.1, 30.5, 54.5 or 90.6 mg/L. Immobilization (20%) occurred at 100 mg/L. The reported 24-hour EC₅₀ was greater than 90.6 mg/L. DMSO was used as a solvent in this test. EPA used a 48-hour EC₅₀ value estimated using ECOSAR v1.00a to support the evaluation of acute toxicity of this chemical.

24-h EC₅₀ = >90.6 mg/L

48-h EC₅₀ = 49 mg/L (estimated)

Toxicity to Aquatic Plants

Green algae (*Scenedesmus subspicatus*) were exposed to triglycidyl isocyanurate at nominal concentrations of 0.41, 1.23, 3.7, 11, 33 or 100 mg/L under static conditions for 72 hours. Measured concentrations were .21, 0.72, 2.1, 6.3, 19.4 or 63.4 mg/L. Control response was satisfactory.

72-h EC₅₀ (biomass) = 29 mg/L

Conclusion: For acute hazard of CASRN 2451-62-9, the 96-hour LC₅₀ to fish is >77 mg/L, the measured 24-hour EC₅₀ to aquatic invertebrates is >90.6 mg/L, and the measured 72-hour EC₅₀ (biomass) to aquatic plants is 29 mg/L.

No data gaps were identified under the HPV Challenge Program.

Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Summary of Environmental Effects – Aquatic Toxicity Data	
Endpoints	Triglycidyl isocyanurate (2451-62-9)
Fish 96-h LC₅₀ (mg/L)	> 77
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	> 90.6 (24-h) 49 (e)
Aquatic Plants 72-h EC₅₀ (mg/L) (growth) (biomass)	– 29

Bold= measured data; e= estimated data; –Indicates that endpoint was not addressed.