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United States
Environmental Protection
Agency

Provisional Peer-Reviewed Toxicity Values for

Glycidaldehyde
(CASRN 765-34-4)

U.S. EPA Office of Research and Development
Center for Public Health and Environmental Assessment

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Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

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Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's Center for Public Health and Environmental Assessment.

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPHEA	Center for Public Health and Environmental Assessment
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV document.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR GLYCIDALDEHYDE (CASRN 765-34-4)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by at least two Center for Public Health and Environmental Assessment (CPHEA) scientists and an independent external peer review by at least three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

Currently available PPRTV assessments can be accessed on the U.S. Environmental Protection Agency's (EPA's) PPRTV website at https://www.epa.gov/pprtv. PPRTV assessments are eligible to be updated on a 5-year cycle to incorporate new data or methodologies that might impact the toxicity values or characterization of potential for adverse human-health effects and are revised as appropriate. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA Superfund and Technology Liaison (https://www.epa.gov/research/fact-sheets-regional-science).

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

This work was conducted under the U.S. EPA Quality Assurance (QA) program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This work was conducted under the CPHEA Program Quality Assurance Project Plan (PQAPP) and the QAPP titled *Preparation of Provisional Toxicity Value (PTV) Documents (L-CPAD-0032718-QP)*. As part of the QA system, a quality product review is done prior to management clearance. A Technical Systems Audit may be performed at the discretion of QA staff.

All PPRTV assessments receive internal peer review by a panel of CPHEA scientists and an independent external peer review by at least three scientific experts. The reviews focus on whether all studies have been correctly selected, interpreted, and adequately described for the

purposes of deriving a provisional reference value. The reviews also cover quantitative and qualitative aspects of the provisional value development and address whether uncertainties associated with the assessment have been adequately characterized.

Other U.S. EPA programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVS

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development (ORD) CPHEA website at https://www.epa.gov/pprtv/forms/contact-us-about-pprtvs.

INTRODUCTION

Glycidaldehyde (CASRN 765-34-4) is an epoxy aldehyde compound. It is registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2018) but is not listed on the U.S. EPA's Toxic Substances Control Act (TSCA) public inventory (U.S. EPA, 2018c).

Glycidaldehyde is used as a research chemical and as medication for animals. Former uses of glycidaldehyde were as a cross-linking agent for textile treatment (i.e., finishing of wool), leather tanning, and fat liquoring (NLM, 2017). It is synthesized by hydrogen peroxide epoxidation of acrolein (NLM, 2017).

The empirical formula for glycidaldehyde is $C_3H_4O_2$ (see Figure 1). A list of physicochemical properties for glycidaldehyde is provided in Table 1. Glycidaldehyde is a reactive, colorless liquid with high water solubility. In the air, glycidaldehyde will exist in the vapor phase, based on its estimated vapor pressure of 32.7 mm Hg. It will be degraded in the atmosphere by reacting with photochemically produced hydroxyl radicals and have a half-life of 22.8 hours (0.95 days), calculated from an estimated reaction rate constant of 1.69×10^{-11} cm^3/molecule-second at 25°C (NLM, 2017). Based on its vapor pressure, glycidaldehyde is expected to volatilize from dry soil surfaces. Low volatilization, however, is expected from water or moist soil surfaces based on the compound's estimated Henry's law constant of 4.34×10^{-7} atm-m^3/mole. The estimated K_{oc} for glycidaldehyde indicates potential for mobility in soil but negligible potential to adsorb to suspended solids and sediment in aquatic environments; although glycidaldehyde may react with organic matter if it is released to the environment (NLM, 2017). There are no experimental hydrolysis data available for glycidaldehyde, but the chemical is expected to undergo hydrolysis based on analogy with the structurally similar compound glycidol (CASRN 556-52-5), which has a reported hydrolysis half-life at pH 7 of 12 hours to 4 days.

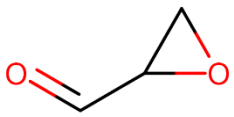

Figure 1. Glycidaldehyde (CASRN 765-34-4) Structure

Table 1. Physicochemical Properties of Glycidaldehyde (CASRN 765-34-4)

Property (unit)	Value
Physical state	Liquid
Boiling point (°C)	112.5[a]
Melting point (°C)	−62[a]
Density (g/cm^3 at 20°C)	1.140[b]
Vapor pressure (mm Hg)	32.7 (predicted average)[c]
pH (unitless)	NA
pKa (unitless)	NA
Solubility in water (mol/L)	9.28 (predicted average)[c]
Octanol-water partition constant (log K_{ow})	−0.664 (predicted average)[c]
Henry's law constant (atm-m^3/mol)	4.34×10^{-7} (predicted average)[c]
Soil adsorption coefficient log K_{oc} (L/kg)	6.32 (predicted average)[c]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	1.69×10^{-11} [a]
Atmospheric half-life (d)	0.95[a]
Relative vapor density (air = 1)	2.58[a]
Molecular weight (g/mol)	72.06[a]
Flash point (open cup in °C)	31[a]

[a]NLM (2017).
[b]Patnaik (2007).
[c]Data were extracted from the U.S. EPA CompTox Chemicals Dashboard (glycidaldehyde, CASRN 765-34-4. DTXSID 9020665; https://comptox.epa.gov/dashboard/DTXSID9020665. Accessed May 2, 2019).

NA = not applicable.

A summary of available toxicity values for glycidaldehyde from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Glycidaldehyde (CASRN 765-34-4)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference[c]
Noncancer			
IRIS (RfD)	4×10^{-4} mg/kg-d	Based on weight gain retardation, enlarged adrenals, hydropic renal pelvis, and hematopoietic effects in a subchronic inhalation study in rats using a route-to-route extrapolation.	U.S. EPA (2005)
HEAST (sRfD)	4×10^{-3} mg/kg-d	Based on decreased weight gain and kidney effects using route-to-route extrapolation and absorption factor of 0.5 from a subchronic inhalation study in rats.	U.S. EPA (2018b)
HEAST (RfC)	1×10^{-3} mg/m^3	Based on decreased weight gain and kidney effects in a subchronic inhalation study in rats.	U.S. EPA (2018b)
HEAST (sRfC)	1×10^{-2} mg/m^3	Based on decreased weight gain and kidney effects in a subchronic inhalation study in rats.	U.S. EPA (2018b)
DWSHA	NV	NA	U.S. EPA (2018a)
ATSDR	NV	NA	ATSDR (2019)
IPCS	NV	NA	IPCS (2018)
CalEPA	NV	NA	CalEPA (2011); CalEPA (2011); CalEPA (2017)
OSHA	NV	NA	OSHA (2017b); OSHA (2017a)
NIOSH	NV	NA	NIOSH (2016)
ACGIH	NV	NA	ACGIH (2018)
DOE (PAC)	PAC-1: 0.39 ppm PAC-2: 4.3 ppm PAC-3: 26 ppm	Based on TEELs.	DOE (2016)
USAPHC (air-MEG)	1-hr critical: 75 mg/m^3 1-hr marginal: 1.5 mg/m^3 1-hr negligible: 0.2 mg/m^3 1-yr negligible: 0.0068 mg/m^3	1-hr values based on TEELs; 1-yr value based on HEAST subchronic value.	U.S. APHC (2013)
Cancer			
IRIS (WOE)	Classification B2: *probable human carcinogen*	Based on an increased incidence of malignant tumors in rats and mice following subcutaneous injection of glycidaldehyde and of skin carcinomas following dermal application to mice. Supported by mechanistic data (mutagenicity, reactivity of epoxide and aldehyde groups) and carcinogenicity of structurally related epoxide compounds. No human data available.	U.S. EPA (2005)
HEAST	NV	NA	U.S. EPA (2018a)

Table 2. Summary of Available Toxicity Values for Glycidaldehyde (CASRN 765-34-4)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference[c]
DWSHA	NV	NA	U.S. EPA (2018a)
NTP	NV	NA	NTP (2016)
IARC (WOE)	Group 2B: *possibly carcinogenic to humans*	Based on sufficient evidence in experimental animals.	IARC (1999); IARC (2018)
CalEPA (WOE)	Listed as causing cancer under Proposition 65	NA	CalEPA (2018a); CalEPA (2018b)
ACGIH	NV	NA	ACGIH (2018)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DOE = U.S. Department of Energy; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; USAPHC = U.S. Army Public Health Command.
[b]Parameters: MEG = military exposure guideline; PAC = protective action criteria; RfC = reference concentration; RfD = reference dose; sRfC = subchronic reference concentration; sRfD = subchronic reference dose; TEEL = temporary emergency exposure limit; WOE = weight of evidence.
[c]Reference date for the HEAST data is the date the online source was accessed. All other reference dates are the publication date for the databases.

NA = not applicable; NV = not available.

METHODS

Literature Search

Four online scientific databases (PubMed, Web of Science [WOS], TOXLINE, and Toxic Substances Control Act Test Submissions [TSCATS] via TOXLINE) were searched by U.S. EPA's Health and Environmental Research Online (HERO) staff and stored in the HERO database.[1] The literature search focused on chemical name and synonyms (identified as "valid/validated" or "good" via the CompTox Chemicals Dashboard[2] and ChemSpider[3]) with no limitations on publication type, evidence stream (i.e., human, animal, in vitro, in silico), or health outcomes. Full details of the search strategy for each database are presented in Appendix A. The initial database searches were conducted in February 2018 and updated in May 2019 and March 2020.

Screening Process

Two screeners independently conducted a title and abstract screen of the search results using DistillerSR[4] to identify study records that met the Population, Exposure, Comparator, Outcome (PECO) eligibility criteria (see Appendix B for a more detailed summary):

- Population: Humans, laboratory mammals, and other animal models of established relevance to human health (e.g., *Xenopus* embryos); mammalian organs, tissues, and cell lines; and bacterial and eukaryote models of genetic toxicity.
- Exposure: In vivo (all routes), ex vivo, and in vitro exposure to the chemical of interest, including mixtures to which the chemical of interest may contribute significantly to exposure or observed effects.
- Comparator: Any comparison (across dose, duration, or route) or no comparison (e.g., case reports without controls).
- Outcome: Any endpoint suggestive of a toxic effect on any bodily system or mechanistic change associated with such effects. Any endpoint relating to disposition of the chemical within the body.

Records that were not excluded based on title and abstract screening advanced to full-text review using the same PECO eligibility criteria. Studies that have not undergone peer review were included if the information could be made public and sufficient details of study methods and findings were included in the report. Full-text copies of potentially relevant records identified from title and abstract screening were retrieved, stored in the HERO database, and independently assessed by two screeners using DistillerSR to confirm eligibility. At both title/abstract and full-text review levels, screening conflicts were resolved by discussion between the primary screeners with consultation by a third reviewer to resolve any remaining disagreements. Studies that were unclear at the title/abstract level advanced to full-text review. During title/abstract or full-text level screening, studies that were not directly relevant to the PECO, but could provide supplemental information, were categorized (or "tagged") relative to

[1]U.S. EPA's HERO database provides access to the scientific literature behind U.S. EPA science assessments. The database includes more than 2,500,000 scientific references and data from the peer-reviewed literature used by U.S. EPA to develop its regulations.
[2]CompTox Chemicals Dashboard: https://comptox.epa.gov/dashboard/DTXSID9020665.
[3]ChemSpider: http://www.chemspider.com/Chemical-Structure.12461.html?rid=565c63c9-aa2f-44cb-b979-9cc783134953.
[4]DistillerSR is a web-based systematic review software used to screen studies available at https://www.evidencepartners.com/products/distillersr-systematic-review-software.

the type of supplemental information they provided (e.g., review, commentary, or letter with no original data; conference abstract; toxicokinetics; mechanistic information aside from in vitro genotoxicity studies, studies on routes of exposure other than oral and inhalation; studies of acute exposure only, etc.). Conflict resolution was not required during the screening process to identify supplemental information (i.e., tagging by a single screener was sufficient to identify the study as potential supplemental information).

LITERATURE SEARCH AND SCREENING RESULTS

The database searches yielded 177 unique records. Of the 177 studies identified, 40 were excluded during title and abstract screening, 137 were reviewed at the full-text level, and 75 were considered relevant to the PECO eligibility criteria (see Figure 2). This included 1 in vivo animal study and 74 in vitro genotoxicity studies. The detailed search approach, including the query strings and PECO criteria, are provided in Appendix A and Appendix B, respectively.

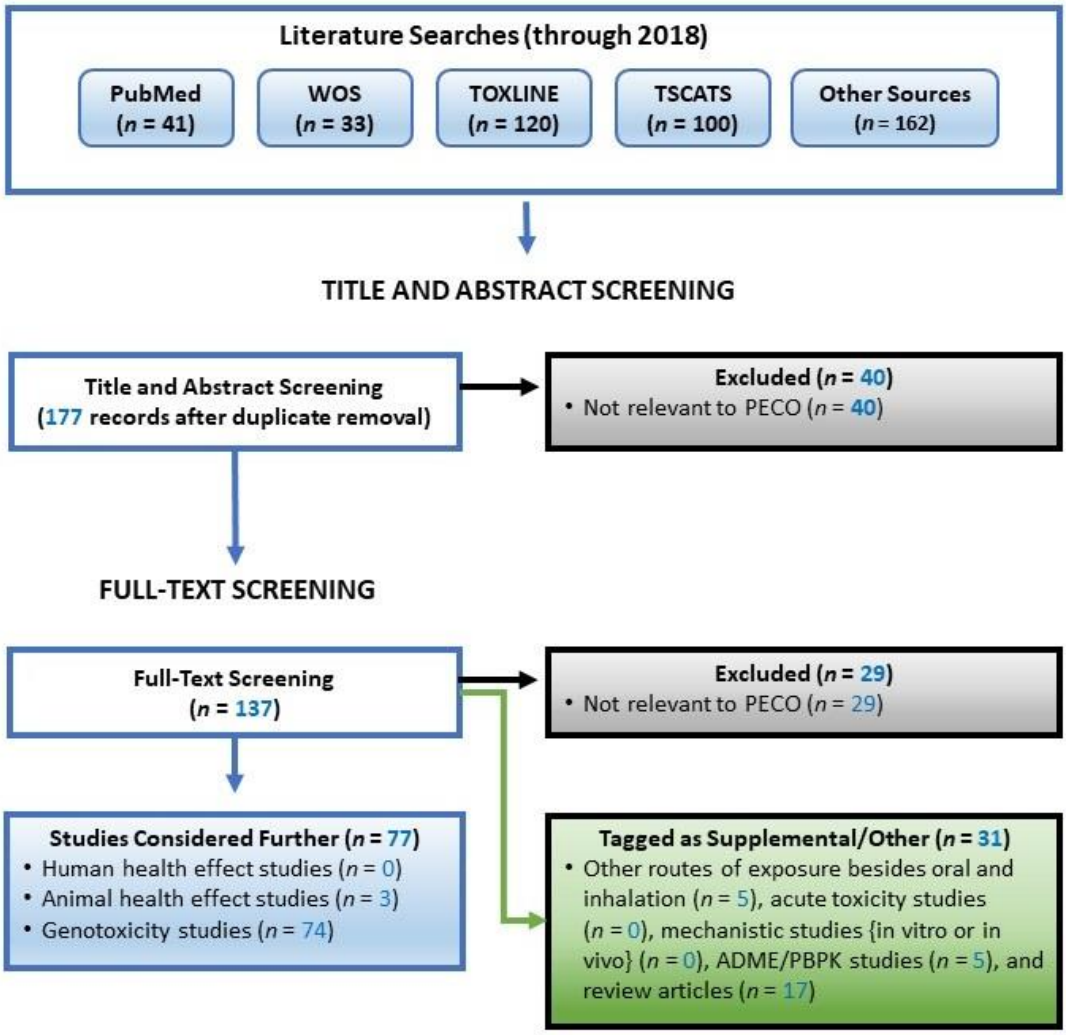

Figure 2. Literature Search and Screening Flow Diagram for Glycidaldehyde (CASRN 765-34-4)

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the relevant noncancer and cancer evidence bases, respectively, for glycidaldehyde and include all potentially relevant acute, repeated short-term, subchronic, and chronic studies, as well as reproductive and developmental toxicity studies identified from the literature screening results. Principal studies are identified in bold. The phrase "statistical significance" and the term "significant," used throughout the document, indicates a *p*-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for Glycidaldehyde (CASRN 765-34-4)							
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
No adequate studies identified.							
Animal							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
Subchronic	**10 M, Long-Evans rat; 4 hr/d, 5 d/wk, 12 wk** **Reported nominal concentrations: 0, 10, 20, 40, 80 ppm**	**0, 3.5, 7.0, 14, 28**	**Hematological changes in the bone marrow**	**3.5**	**7.0**	**Hine et al. (1961)**	**PS, PR, IRIS**

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: Doses are presented as ADDs (mg/kg-day) for oral noncancer effects and as HECs (mg/m^3) for inhalation noncancer effects. The HEC from animal studies was calculated using the equation for ER effects from a Category 3 gas (U.S. EPA, 1994): HEC_{ER} = (ppm × molecular weight ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × ratio of animal:human blood-gas partition coefficients (default of 1 applied).
[c]Notes: IRIS = study used for Integrated Risk Information System RfD value U.S. EPA (2005); PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; ER = extrarespiratory; HEC = human equivalent concentration; IRIS = Integrated Risk Information System; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NOAEL = no-observed-adverse-effect level.

Table 3B. Summary of Potentially Relevant Cancer Data for Glycidaldehyde (CASRN 765-34-4)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**Reference (comments)**	**Notes**
Human					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					
Animal					
1. Oral (mg/kg-d)					
No adequate studies identified.					
2. Inhalation (mg/m^3)					
ND					

ND = no data.

HUMAN STUDIES

Oral Exposures

No oral studies in humans have been identified.

Inhalation Exposures

Hine et al. (1961)

In a sensory threshold study, student and staff member volunteers (8−12/group) were exposed to glycidaldehyde vapor at nominal concentrations of 1, 2.5, 5, 10, or 20 ppm (2.9, 7.4, 15, 29, or 59 mg/m^3)[5] for 5 minutes in a whole-body chamber designed for human exposures. Subjects scored clinical signs of irritation on a scale of 0−4 every minute during exposure, including olfactory cognition, eye irritation, nose irritation, pulmonary discomfort, and central nervous system (CNS) effects.

Glycidaldehyde was irritating to the eyes and mucous membranes in exposed subjects. Olfactory cognition was reported in all subjects except one volunteer exposed to 29 mg/m^3. Nose irritation was reported in all subjects at ≥7.4 mg/m^3 and 7/9 subjects at 2.9 mg/m^3. Eye irritation was reported in 3/9, 4/11, 7/8, 10/10, and 11/12 subjects at 2.9, 7.4, 15, 29, and 59 mg/m^3, respectively. Average eye irritation score increased with increasing concentration, and profuse tearing was observed in 7/12 subjects at 59 mg/m^3. Similarly, pulmonary discomfort scores increased with increasing concentration, with discomfort reported in 2/9, 3/11, 2/8, 7/10, and 9/12 subjects at 2.9, 7.4, 15, 29, and 59 mg/m^3, respectively. Seven subjects complained of a sore throat at the highest concentration. CNS effects were infrequent and limited to mild to moderate headache in one or two subjects at 2.9, 29, and 59 mg/m^3.

Sensory irritation was evident in subjects at all concentrations tested; however, because all reported data are subjective, this study is not considered adequate to identify a no-observed adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) value in humans. Furthermore, the volunteers were only exposed for 5 minutes, thus using these data to derive provisional reference concentrations (p-RfCs) would require extrapolation from a 5-minute exposure to subchronic and/or chronic exposure. Therefore, this study is not included in Table 3A.

ANIMAL STUDIES

Oral Exposures

No adequate repeated-dose oral studies have been identified.

Inhalation Exposures

Subchronic Studies

Hine et al. (1961)

Male Long-Evans rats (10/group) were exposed to glycidaldehyde vapor (purity not reported) at nominal concentrations of 0, 10, 20, 40, or 80 ppm (0, 29, 59, 120, or 240 mg/m^3)[5] for 4 hours/day, 5 days/week, for 12 weeks (whole-body exposure is assumed). Analytical concentrations were not reported. The animals were observed for mortality and their weights were monitored; however, the frequency of observations and body-weight measurements were not reported. Blood samples for hematology (total leukocytes, percent polymorphonuclear leukocytes [% PMNs], total erythrocytes, and hemoglobin) were collected before exposure, after

[5]Concentration in mg/m^3 = concentration in ppm × molecular weight (72.06 g/mol) ÷ 24.45.

17 exposures (3.5 weeks), and at study termination. At necropsy, the animals were examined for gross abnormalities, and the following organs were collected and weighed: thymus, spleen, testis, liver, kidney, and lung. Bone marrow was extracted from each femur (one sample was used for nucleated cell count and the other was used to determine the M:E ratio [undefined by study authors but presumed to be the myeloid-to-erythroid (M:E) ratio]). Histopathology was performed on the spleen, liver, kidney, and lung. Statistical analysis of body weight, relative organ weight, and hematological data was performed, but the statistical test used was not specified.

The incidence of mortality was 1/10, 0/10, 1/10, 2/10, and 8/10 in the 0-, 29-, 59-, 120-, and 240-mg/m^3 groups, respectively. Pneumonia was described as the cause of death for rats in the 0-, 59-, and 120-mg/m^3 groups. At 240 mg/m^3, 8/10 rats died after only four exposures and the remaining 2 animals were euthanized after the fifth exposure. Body-weight gain over the course of the study was significantly decreased by 27 and 23% at 59 and 120 mg/m^3, respectively, compared with controls (see Table D-1). No exposure-related changes in hematological endpoints were observed in the surviving animals at 3.5 or 12 weeks. The two surviving rats exposed to 240 mg/m^3 for 5 days, however, showed low leukocyte counts and a significant increase in % PMNs, although the study authors did not specify which control data were used for comparison. Nucleated bone marrow cells were significantly decreased by 44−48% at exposure concentrations $\geq$59 mg/m^3 (see Table D-1). The M:E ratio was variable across groups, and no significant treatment-related changes were noted (see Table D-1).

Statistically significant changes observed in relative organ weights at 12 weeks were increased relative testes weight and decreased relative thymus and spleen weights (see Table D-1). Absolute organ-weight data were not reported. The significant increases in relative testes weight at 59 and 120 mg/m^3 (and the statistically nonsignificant 15% increase in relative liver weight at 59 mg/m^3) may reflect reduced body weight in these exposure groups. Therefore, the biological relevance of increased relative testes and liver weights is unclear. The significant decreases in relative spleen and thymus weight at 120 mg/m^3, however, indicate that those organs lost weight (relative to controls) to a larger degree than the body overall. These changes likely reflect a target organ effect of glycidaldehyde, although the study authors noted a potential for large experimental error due to the small size of the thymus which can make it difficult to get precise weight measurements.

Gross necropsy findings were a "striking reduction in body fat" in animals that died or were sacrificed by Day 5 at 240 mg/m^3, reduced body fat and small spleens at 120 mg/m^3, and single rats with enlarged adrenals or hydropic renal pelvis at 59 mg/m^3. No histopathological lesions were observed in the spleen, liver, kidney, or lungs of rats exposed to $\leq$120 mg/m^3. Splenic abscess, focal hepatic necrosis, and tubular degeneration of kidneys were "usually" observed in rats that died or were sacrificed following exposure to 240 mg/m^3 for up to 5 days (incidence data not reported).

A NOAEL of 29 mg/m^3 and a LOAEL of 59 mg/m^3 are identified for this study based on hematological changes in the bone marrow. Decreased body-weight gain at 59 mg/m^3 was not used as the basis for the LOAEL because the response at which this effect is considered to be biologically relevant is unknown. Decreased thymus weight at 29 mg/m^3 was not used as the basis for the LOAEL due to the lack of supporting dose-response (small, statistically nonsignificant decrease at 59 mg/m^3), lack of reported variance data, lack of absolute

organ-weight data, and the considerable potential for experimental error acknowledged by the study authors. The high concentration of 240 mg/m^3 is a frank effect level (FEL) based on rapid mortality of exposed rats. The nominal concentrations of 0, 29, 59, 120, and 240 mg/m^3 correspond to human equivalent concentration (HEC) values of 0, 3.5, 7.0, 14, and 28 mg/m^3 for extrarespiratory (ER) effects.[6]

Chronic/Carcinogenicity Studies

No adequate studies have been identified.

Reproductive/Developmental Studies

No studies have been identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Table 4A provides an overview of genotoxicity studies of glycidaldehyde and Table 4B provides an overview of other supporting animal studies on glycidaldehyde.

Genotoxicity

The genotoxicity of glycidaldehyde has been studied in a variety of assays both in vitro and in vivo. The available studies are summarized below (see Table 4A for more details). Data indicate that glycidaldehyde is mutagenic and directly interacts with deoxyribonucleic acid (DNA), forming DNA adducts and causing DNA damage. There is also some evidence that glycidaldehyde is clastogenic and induces cell transformation.

Glycidaldehyde is mutagenic in *Salmonella typhimurium* both in the presence and absence of metabolic activation (Dunkel et al., 1984; Bartsch et al., 1983; Bartsch et al., 1980; Rosenkranz et al., 1980; Shell Oil, 1980; Dunkel, 1979; Rosenkranz and Poirier, 1979; Simmon, 1979b; Wade et al., 1979). In all studies that specified results by tester strain, mutagenicity was observed in *S. typhimurium* strains evaluating base-pair mutations (TA100, TA1530, TA1535), but not strains evaluating frame-shift mutations (TA98, TA1536, TA1537, TA1538, TA1531, TA1532, TA1533) (Dunkel et al., 1984; Bartsch et al., 1983; Bartsch et al., 1980; Rosenkranz et al., 1980; Shell Oil, 1980; Rosenkranz and Poirier, 1979; Simmon, 1979b; Wade et al., 1979). Similarly, in the intraperitoneal (i.p.) host-mediated assay, mutations were induced in *S. typhimurium* strain TA1530, but not TA1538 (Simmon et al., 1979). Glycidaldehyde was also mutagenic in *Escherichia coli* WP-2 strain (Dunkel et al., 1984), bacteriophage T4-infected *E. coli* (Corbett et al., 1970), and *Klebsiella pneumoniae* (Knaap et al., 1982; Voogd et al., 1981). Mutations were not induced in *Saccharomyces cerevisiae* in vitro or in the host-mediated assay [Izard (1983) as cited in IARC (1999); Simmon et al. (1979)].

Glycidaldehyde is mutagenic in the mouse lymphoma thymidine kinase assay (TK+/– → TK–/–) (Amacher and Turner, 1982) but did not induce forward mutations in the mouse lymphoma hypoxanthine-guanine phosphoribosyltransferase (HGPRT) mutation assay (Knaap et al., 1982). Dominant lethal mutations were not induced in mice exposed via i.p. injection (Shell Oil, 1980).

[6]HEC calculated by treating glycidaldehyde as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because blood-gas partition coefficients for glycidaldehyde were not located for rats or humans.

Glycidaldehyde induced sex-linked recessive lethals and chromosome loss in *Drosophila melanogaster* following exposure via injection (Vogel et al., 1993; Vogel, 1989; Vogel et al., 1986; Knaap et al., 1982). Vogel et al. (1993; 1990) led to a prediction that glycidaldehyde is a DNA cross-linking agent based on ratio >2 for chromosomal loss:sex-linked recessive lethals in *D. melanogaster*. When *D. melanogaster* mutants with deficiencies in DNA repair (unscheduled DNA synthesis) were used, the number of sex-linked recessive lethals increased 9−12-fold. Glycidaldehyde also caused increased cytotoxicity in the repair-deficient PolA- *E. coli* strain with and without metabolic activation (Rosenkranz and Poirier, 1979; Fluck et al., 1976). Evidence of DNA repair was also observed in human lung fibroblast cells exposed to glycidaldehyde in vitro (Mitchell, 1976).

Glycidaldehyde is a reactive DNA alkylating agent that readily forms DNA adducts. Stable cyclic deoxyadenosine DNA adduct formation has been observed in skin DNA of mice following dermal exposure to glycidaldehyde (Steiner et al., 1992a). The major adduct was identified as 3-β-D-deoxyribofuranosyl-7(hydroxymethyl)-3*H*-imidazo[2,1-*i*]purine-3′-monophosphate. In isolated calf thymus DNA, the same major DNA adduct was identified when DNA was incubated at a pH of 7.0. However, when the pH was increased to 10.0, the major DNA adduct was 5,9-dihydro-7-(hydroxymethyl)-9-oxo-3-β-D-deoxyribofuranosyl-3*H*-imidazo[1,2-*a*]purine-3′-monophosphate (Steiner et al., 1992a). In other studies with isolated DNA, deoxyadenosine, deoxycytosine, and deoxyguanosine adducts were identified at varying levels depending on the pH of the test system (Kohwi, 1989; Van Duuren and Loewengart, 1977). Adduct formation and structures have been extensively characterized in isolated nucleotides and nucleosides. These studies, along with those summarized in Table 4A, indicate that glycidaldehyde forms exocyclic etheno ring adducts, with guanine adducts formed preferentially at basic pH levels and adenine and cytosine adducts formed preferentially at acidic pH levels (Hang et al., 2002; Chenna et al., 2000; Golding et al., 1996; Steiner et al., 1992b; Golding et al., 1990; Golding et al., 1986a, b; Nair and Turner, 1984; Goldschmidt et al., 1968).

A single study in Syrian hamster embryo (SHE) cells showed increased micronuclei (MN) following in vitro exposure to glycidaldehyde (Fritzenschaf et al., 1993). Glycidaldehyde also induced cell transformation in SHE cells and mouse Balb/3T3 cells (Dunkel et al., 1981; Pienta, 1980a, b). Mitotic recombination was induced in *S. cerevisiae* D3 cells exposed to glycidaldehyde with or without metabolic activation (Simmon, 1979a).

Supporting Animal Studies

Supporting animal studies include acute lethality studies, an oral carcinogenicity study that is considered inadequate based on inadequate frequency of exposure (1 day per week during course of study) and small size of animal groups (five per group), and dermal and subcutaneous (s.c.) injection carcinogenicity studies. These studies are summarized below (see Table 4B for additional details).

Acute Lethality Studies

Acute lethality studies reported oral median lethal dose (LD_{50}) values of 232 and 200 mg/kg in rats and mice, respectively, an inhalation median lethal concentration (LC_{50}) value of 252 ppm in rats, and a dermal LD_{50} value of 249 mg/kg in rabbits (Simmon et al., 1979; Hine et al., 1961). Glycidaldehyde was reported to be moderately irritating to the skin of rabbits (Hine et al., 1961).

Supporting Studies for Carcinogenic Effects in Animals

An oral carcinogenicity study by Van Duuren et al. (1966) found no gastric or other tumors in five mice treated with 33 mg/animal glycidaldehyde via gavage in tricaprylin once weekly. However, the study design is considered inadequate for tumor assessment because of inadequate exposure regimen and the small number of animals tested per group.

The incidences of skin papillomas and malignant skin tumors were increased in mice dermally exposed to ~100 mg glycidaldehyde in acetone or benzene 3 times/week for life (Van Duuren et al., 1967a; Van Duuren et al., 1965). Based on statistics conducted by the U.S. EPA for the purposes of this PPRTV assessment, the incidences of both tumor types were significantly increased in both studies, compared with respective controls. Glycidaldehyde was a weak skin tumor initiator relative to 7,12-dimethylbenz[a]anthracene (DMBA) in mice in studies conducted using croton resin/oil as a promotor (Shamberger et al., 1974; Van Duuren et al., 1965).

In injection assays, weekly lifetime s.c. injections of glycidaldehyde produced statistically significant increases in malignant injection-site tumors in rats and mice (Van Duuren et al., 1967b; Van Duuren et al., 1966). Based on statistics conducted by the U.S. EPA for the purposes of this PPRTV assessment, the incidence of malignant tumors at the injection site was significantly increased in mice exposed to 3.3 mg/animal-week and rats exposed to 33 mg/animal-week, compared with respective controls. No statistically significant increases were seen in mice at 0.1 mg/animal-week or rats at 1 mg/animal-week. However, injection assays like dermal studies cannot be used for quantitative tumor assessment given the route of exposure.

Metabolism/Toxicokinetic Studies

No studies were found regarding absorption, distribution, or excretion of glycidaldehyde. Based on toxicity and mortality following oral, inhalation, and dermal exposure in animals (Hine et al., 1961), absorption of glycidaldehyde can occur through all three routes.

Metabolism data for glycidaldehyde are limited to in vitro data. Glycidaldehyde is converted into glyceraldehyde by epoxide hydrase in rat liver and lung preparations (Patel et al., 1980). Glycidaldehyde is also a substrate for rat lung and liver cytosolic glutathione *S*-transferases (GST), with the rate of glutathione conjugation observed in liver cytosol twice the rate observed in lung cytosol (Patel et al., 1980). Fjellstedt et al. (1973) also reported that glycidaldehyde is a substrate for purified rat liver glutathione epoxide transferase. Based on the reactivity of glycidaldehyde (due to one epoxide and one aldehyde group), Van Duuren et al. (1966) predicted rapid hydrolysis in the acidic pH of the stomach.

Mode-of-Action/Mechanistic Studies

As discussed in the "Genotoxicity" section and Table 4A, glycidaldehyde is a DNA-alkylating agent that shows mutagenic activity in many assay systems. Because a cancer assessment is not provided in this document, a detailed discussion of the carcinogenic mode of action (MOA) for glycidaldehyde was not conducted.

Table 4A. Summary of Glycidaldehyde (CASRN 765-34-4) Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**References**
Genotoxicity studies in prokaryotic organisms						
Mutation (reverse)	*Salmonella typhimurium* TA1535, TA100	0−0.6 µM/plate	+	NDr	Plate incorporation assay. Dose-related increase in revertants/plate. The concentration needed to produce 500 revertants/plate was reported as 19 and 15 µM for TA1535 and TA100, respectively.	Bartsch et al. (1983); Bartsch et al. (1980)
Mutation (reverse)	*S. typhimurium* TA1535, TA100	0, 0.24, 0.3, 0.61, 1.22 mM	+	NDr	Liquid incubation assay. The number of mutants/mM-min incubation was reported as 2.56 and 4.15 for TA1535 and TA100, respectively.	Bartsch et al. (1983)
Mutation (reverse)	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	0.3, 1.0, 3.3, 10, 33.3, 100, 333.3 µg/plate	+ (TA1535, TA100) ± (TA1537, TA98) – (TA1538)	NDr	Plate incorporation and/or preincubation assays performed in 4 different laboratories. Glycidaldehyde induced mutations in TA100 and TA1535 without metabolic activation. Findings were mixed or equivocal for TA1537 and TA98, and negative for TA1538.	Dunkel et al. (1984)
Mutation (reverse)	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	0.3, 1.0, 3.3, 10, 33.3, 100, 333.3 µg/plate	+ (strains NS)	+ (strains NS)	Plate incorporation assay. Glycidaldehyde induced mutations with and without metabolic activation with liver S9 from uninduced and Aroclor 1254-induced rat, mouse, and hamster in three separate laboratories. Magnitude of induction and strain-specific results were not reported.	Dunkel (1979)
Mutation (reverse)	*S. typhimurium* TA1535	0, 0.5, 1, 5, 10, 50, 100 µg/plate	+	NDr	Preincubation assay. Dose-related increase in revertants/plate in 4 separate experiments from a single laboratory.	Rosenkranz et al. (1980)
Mutation (reverse)	*S. typhimurium* TA1535, TA1538	0, 0.01, 0.1 µL/plate	+ (TA1535) – (TA1538)	+ (TA1535) – (TA1538)	Plate incorporation assay. Revertants increased >35−200-fold without metabolic activation and 7−100-fold with metabolic activation in TA1535 (base-substitution mutant). Negative in TA1538 (frame-shift mutant).	Rosenkranz and Poirier (1979)

Table 4A. Summary of Glycidaldehyde (CASRN 765-34-4) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Mutation (reverse)	*S. typhimurium* TA1530, TA1531, TA1532, TA1533	NS	+ (TA1530) – (TA1531, TA1532, TA1533)	NDr	Plate incorporation assay. Revertants increased 16-fold in TA1530 (base-substitution mutant); no increased observed in other mutants (frame-shift mutants).	Shell Oil (1980)
Mutation (reverse)	*S. typhimurium* TA100, TA98	0, 50, 1,000 µg/plate	+ (TA100) – (TA98)	+ (TA100) – (TA98)	Plate incorporation assay. Revertants increased >13-fold in TA100 (base-substitution mutant) with or without metabolic activation; no increase observed in TA98 (frame-shift mutant). Cytotoxic without metabolic activation at 1,000 µg/plate in both strains.	Shell Oil (1980)
Mutation (reverse)	*S. typhimurium* TA100, TA98	0, 0.5, 1, 2, 5, 10, 20 µg/plate	+ (TA100) – (TA98)	+ (TA100) – (TA98)	Plate incorporation assay. Revertants increased in a dose-related manner in TA100 (base-substitution mutant) with or without metabolic activation (>twofold increase at all tested concentrations); no increase observed in TA98 (frame-shift mutant).	Shell Oil (1980)
Mutation (reverse)	*S. typhimurium* TA1535, TA1536, TA1537, TA1538, TA98, TA100	10 µg/plate	+ (TA1535, TA100) – (TA1536, TA1537, TA1538, TA98)	NDr	Plate incorporation assay. The number of revertants/place increased >30-fold and >20-fold in TA1535 and TA100, respectively, with exposure.	Simmon (1979b)
Mutation (reverse)	*S. typhimurium* TA100 and TA98	0.01, 0.05, 0.20, 10 mg/plate	+ (TA100) – (TA98)	+ (TA100) – (TA98)	Plate incorporation assay. Revertants increased in dose-related manner in TA100 (base-substitution mutant) with or without metabolic activation (>twofold increase at all tested concentrations); no increase observed in TA98 (frame-shift mutant). Cytotoxic at 10 mg/plate in both strains.	Wade et al. (1979)

Table 4A. Summary of Glycidaldehyde (CASRN 765-34-4) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Mutation (reverse)	*Escherichia coli* WP-2 *uvrA*	0.3, 1.0, 3.3, 10, 33.3, 100, 333.3 µg/plate	+	NDr	Repeated twice in each of 4 labs. Glycidaldehyde consistently induced mutations without metabolic activation.	Dunkel et al. (1984)
Mutation (forward)	Bacteriophage T4-infected *E. coli*	NS	+	NDr	Glycidaldehyde induced A/T- and G/C-based pair transitions and phase shift mutations. No cytotoxicity observed.	Corbett et al. (1970) [abstract]
Mutation (forward)	*Klebsiella pneumoniae*	0, 0.01, 0.02, 0.1, 0.2, 1 mM	+	NDr	Fluctuation test. Dose-related increase in mutations at all concentrations tested. Mutation frequency increased 2−64-fold. No cytotoxicity observed.	Knaap et al. (1982)
Mutation (forward)	*K. pneumoniae*	0, 0.005, 0.01, 0.02, 0.1, 0.2, 1 mM/L	+	NDr	Fluctuation test. Dose-related increase in mutations at all concentrations tested (1.7- to 69-fold).	Voogd et al. (1981)
DNA repair	*E. coli* PolA+ and PolA− (DNA polymerase-deficient)	5, 10, 25 µL/well	+	+	Disc diffusion assay. Preferential inhibition of DNA-repair deficient PolA− strain at 5 and 25 µL/well. Metabolic activation did not increase inhibition.	Fluck et al. (1976)
DNA repair	*E. coli* PolA+ and PolA− (DNA polymerase-deficient)	1 µL	+	NDr	Disc diffusion assay. Preferential inhibition of DNA-repair deficient PolA− strain.	Rosenkranz and Poirier (1979)
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation (reverse)	*Saccharomyces cerevisiae* S211, S138	Up to 11,000 µg/mL	−	NDr	Glycidaldehyde did not induce revertants.	Izard (1973) as cited in IARC (1999)
Mitotic recombination	*S. cerevisiae* D3	0.05% (weight/vol or vol/vol)	+	+	Mitotic recombination induced with or without metabolic activation. Induction greater with metabolic activation.	Simmon (1979a)
Genotoxicity studies in mammalian cells—in vitro						
Mutation (TK+/− → TK−/−)	Mouse lymphoma L51788Y cells	0, 8.9, 11.9, 15.8, 21.1, 28.2, 37.6, 50.1 µg/mL	NDr	+	TK mutation assay. Mutations increased ≥twofold at all tested concentrations. Cell survival was <60% of control at ≥21.1 µg/mL.	Amacher and Turner (1982)

Table 4A. Summary of Glycidaldehyde (CASRN 765-34-4) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Mutation (forward)	Mouse lymphoma L51788Y cells	0, 0.01, 0.03, 0.1 mM	−	NDr	HGPRT mutation assay. Cell survival was decreased >25% at ≥0.03 mM.	Knaap et al. (1982)
MN	SHE cells	NS	+	NDr	Assay run in triplicate. Reproducible, dose-dependent, and statistically significant increase in MN observed with exposure.	Fritzenschaf et al. (1993)
UDS	Diploid human lung fibroblasts (WI38 cells)	0–10^{-2} M	+	NDr	Increased UDS (>twofold) detected at 10^{-3} M.	Mitchell (1976)
Cell transformation	Mouse Balb/3T3 cells	0, 0.008, 0.04, 0.2, 1.0 µg/mL	+	NDr	Each concentration tested in 15−20 plates. A >twofold increase in the mean number of transformed foci/plate was observed at 1.0 µg/mL. No cytotoxicity reported.	Dunkel et al. (1981)
Cell transformation	SHE cells	0, 0.1, 1.0, 10, 100 µg/mL	+	NDr	Each concentration tested in 6−12 plates. The number of transformed colonies was increased at 1.0 µg/mL. Cytotoxic at ≥10 µg/mL.	Dunkel et al. (1981)
Cell transformation	SHE cells	0.1–100 µg/mL	+	NDr	Cell transformation was observed at 0.1 and 1 µg/mL.	Pienta (1980a); Pienta (1980b)
Genotoxicity studies—in vivo						
Dominant lethal	Male mice (5/group) were exposed once to glycidaldehyde in corn oil via i.p. injection. Males were mated to unexposed females 2 and 3 wk postexposure. Females sacrificed 15 d after first day of mating.	0, 1.0 mM/kg	−	NA	No increases in frequency of dominant lethal mutations.	Shell Oil (1980)

Table 4A. Summary of Glycidaldehyde (CASRN 765-34-4) Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**References**
Mutation (host-mediated assay)	Mice were exposed once to glycidaldehyde via i.m. injection. *S. typhimurium* TA1530 or TA1538 was injected i.p. into mouse, and animals were sacrificed 4 hr later. *S. typhimurium* were removed, cultured, and evaluated for mutants after 2 d.	456 mg/kg	+ (TA1530) – (TA1538)	NA	Mutation frequency was significantly increased 2.5-fold in exposed group with TA1530. No change in mutation frequency was observed in TA1538.	Simmon et al. (1979)
Mutation (host-mediated assay)	Mice were exposed once to glycidaldehyde via gavage. *S. cerevisiae* was injected i.p. into mouse, and animals were sacrificed 4 hr later. *S. cerevisiae* were removed, cultured, and evaluated for mutants after 2−3 d.	200 mg/kg	–	NA	Mutation frequency was increased 0.7-fold in exposed group.	Simmon et al. (1979)
DNA adduct	CH3 mice were dermally exposed to glycidaldehyde in acetone for 24 hr. Exposed skin was evaluated for DNA adducts.	0, 2, 10 mg/animal	+	NA	Stable cyclic dA adducts formed in a dose-related manner in skin DNA of treated animals. Adducts were identified as 3-β-D-deoxyribofuranosyl-7-(hydroxymethyl)-3*H*-imidazo[2,1-*i*]purine-3′-monophosphate. No dG adducts were detected in epidermal DNA.	Steiner et al. (1992a)
Genotoxicity studies in invertebrates in vivo						
SLRL	*Drosophila melanogaster* males were exposed via injection and mated to five consecutive batches of unexposed females. Flies were evaluated for SLRL.	0, 1, 10, 25, 42, 50 mM	+	NA	% SLRL was increased at ≥25 mM. Survival was not affected.	Knaap et al. (1982)

Table 4A. Summary of Glycidaldehyde (CASRN 765-34-4) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
SLRL	Excision repair-proficient *D. melanogaster* males were exposed via injection and mated to unexposed excision repair-deficient (*Basc*) females for 2−3 d/brood. Flies were evaluated for SLRL.	10 mM	+	NA	% SLRL was significantly increased in treated flies; % SLRL was 0.87−0.96%, after correction for 0.10% spontaneous SLRLs.	Vogel et al. (1993)
SLRL	Excision repair-deficient *D. melanogaster* (*Basc*) males were exposed via injection and mated with untreated excision repair-proficient (*exr*$^{+}$) or excision repair-deficient (*mei-*^{9L1}) females 24 hr after injection. Flies were evaluated for SLRL.	10 mM	+	NA	The number of SLRLs was increased 12-fold in *mei-*^{9L1} females, compared with *exr*$^{+}$. 20 mM was noted as a lethal dose for *mei-*^{9L1} females.	Vogel (1989)
SLRL	Excision repair-proficient *D. melanogaster* (*exr*$^{+}$) males were exposed (method NS) and mated with untreated excision repair-proficient (*exr*$^{+}$) or excision repair deficient (*mei-*^{9L1}) females.	NS	+	NA	The number of SLRLs was increased 9.7-fold in *mei-*^{9L1} females, compared with *exr*$^{+}$.	Vogel et al. (1986)
Chromosome loss	*D. melanogaster* males (*R1[2] y B; B*^{S} *Y y*+) were exposed via injection and mated to unexposed females (*y w spl sn*^{3}) to produce 2 broods. Flies were evaluated for ring-X loss.	0, 10 mM	+	NA	Significant induction of chromosome loss in treated flies (~2−3% induction compared with controls).	Vogel et al. (1993)

Table 4A. Summary of Glycidaldehyde (CASRN 765-34-4) Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**References**
Genotoxicity studies in subcellular systems						
DNA adduct	Calf thymus DNA, tested at pH 7 or 10	9.5 µM	+	NDr	At pH 7: stable cyclic dA adducts were formed. Major adduct identified as 3-β-D-deoxyribofuranosyl-7-(hydroxymethyl)-3*H*-imidazo[2,1-*i*]purine-3′-monophosphate. At pH 10: stable cyclic dA adducts were formed. Major adduct identified as 5,9-dihydro-7-(hydroxymethyl)-9-oxo-3-β-D-deoxyribofuranosyl-3*H*-imidazo[1,2-*a*]purine-3′-monophosphate. Small amounts of the major adduct formed at pH 7.0 were also observed.	Steiner et al. (1992a)
DNA adduct	Calf thymus DNA, tested at pH 10	1.25 mM	+	NDr	dG adducts detected.	Van Duuren and Loewengart (1977)
DNA adduct	Linear or supercoiled plasmid DNA, tested at pH 4−8	0, 0.1, 0.5, 1, 2 µL	+	NDr	Linear: dG adducts detected at pH 5−8; dA adducts detected at pH 4. Supercoiled: dA and dC adducts detected at pH 5−8; dA and dG detected at pH 4.	Kohwi (1989)

[a]+ = positive; ± = equivocal; – = negative.

dA = deoxyadenosine; dC = deoxycytosine; dG = deoxyguanosine; DNA = deoxyribonucleic acid; HGPRT = hypoxanthine-guanine phosphoribosyltransferase; i.m. = intramuscular; i.p. = intraperitoneal; MN = micronuclei; NA = not applicable; NDr = not determined; NS = not specified; SHE = Syrian hamster embryo; SLRL = sex-linked recessive lethal; TK = thymidine kinase; UDS = unscheduled DNA synthesis.

Table 4B. Other Glycidaldehyde (CASRN 765-34-4) Studies				
Test[a]	**Materials and Methods**	**Results**	**Conclusions**	**References**
Supporting evidence—noncancer effects in animals following exposure via any route				
Acute (oral)	Rats (6/group; sex and strain NS) were exposed to glycidaldehyde once via gavage at 1, 50, 500, 5,000, or 15,000 mg/kg.	Mortality incidence was 0/6, 0/6, 5/6, 6/6, and 6/6 at 1, 50, 500, 5,000, and 15,000 mg/kg, respectively. Death occurred within 10−15 min at 15,000 mg/kg, 45 min−6 hr at 5,000 mg/kg, and 6 hr−4 d at 500 mg/kg.	Rat oral LD_{50} (95% CI) = 232 (108−500) mg/kg.	Hine et al. (1961)
Acute (oral)	The oral LD_{50} was determined in adult male Swiss-Webster mice using a 24-hr observation period. Additional study details were not provided.	Mouse oral LD_{50} = 200 mg/kg.	Mouse oral LD_{50} = 200 mg/kg.	Simmon et al. (1979)
Acute (inhalation)	Rats (6/group; sex and strain NS) were acutely exposed to glycidaldehyde via inhalation at 127, 174, 275, or 430 ppm. An additional group was exposed to saturated air. Duration of exposure was not reported.	Mortality incidence was 0/6, 0/6, 5/6, and 5/6 at 127, 174, 275, and 430 ppm, respectively, and 6/6 at saturated air concentrations. Death occurred within 65−85 min at saturation and between 7 and 48 hr at 275−430 ppm.	Rat inhalation LC_{50} (95% CI) = 252 (200−316) ppm.	Hine et al. (1961)
Acute (dermal)	Rabbits (3/group; sex and strain NS) were acutely exposed to glycidaldehyde via dermal exposure at 44, 350, or 2,820 mg/kg. Duration of exposure was not reported.	Incidence of mortality was 0/3, 2/3, and 3/3 for 44, 350, and 2,820 mg/kg, respectively. Time of death was 10−24 hr for 350 mg/kg and 2−4 hr for 2,820 mg/kg. Moderate skin irritation was reported.	Rabbit dermal LD_{50} = 249 (195−318) mg/kg. Glycidaldehyde is a moderate skin irritant.	Hine et al. (1961)
Supporting evidence—cancer effects in animals following exposure via any route				
Cancer assay (oral)	S-D rats (5 F/group) were administered 0 or 33 mg/animal glycidaldehyde in 0.5 mL tricaprylin via gavage 1 d/wk for life. Animals were examined for palpable tumors during exposure and underwent gross necropsy at death.	Median survival was 329 d in treated rats and 525 d in vehicle controls. No tumors were observed in control or exposed rats in the gastric tract nor distant sites.	Glycidaldehyde was not carcinogenic under the conditions of this assay. However, the study design is considered inadequate for tumor assessment due to inadequate animal numbers (5/group).	Van Duuren et al. (1966)

Table 4B. Other Glycidaldehyde (CASRN 765-34-4) Studies				
Test[a]	**Materials and Methods**	**Results**	**Conclusions**	**References**
Cancer assay (dermal)	ICR/Ha Swiss mice (41 F) were administered ~100 mg glycidaldehyde (10% solution in acetone) to clipped dorsal skin 3 d/wk for life. Additional groups (100 F/group) served as untreated and acetone controls. Endpoints evaluated included survival, skin condition, and tumor incidence.	Median survival was 419 to >526 d in untreated and acetone control mice and 445 d in treated mice. Mild skin irritation (slight hair loss and crusting) was reported in glycidaldehyde treated mice. Skin papillomas were observed in 6/41 treated rats; no papillomas were observed in the control groups. Observed papillomas progressed into malignant skin tumors in 3/6 mice with papillomas.	Glycidaldehyde was carcinogenic under the conditions of this assay. Based on statistics conducted for this review, both the incidences of skin papillomas and malignant skin tumors were significantly increased in treated mice, compared with vehicle and untreated controls.	Van Duuren et al. (1967a)
Cancer assay (dermal)	Swiss mice (30 F) were administered ~100 mg glycidaldehyde (3% solution in benzene) to clipped dorsal skin 3 d/wk for life. Additional groups (60 F/group) served as untreated and benzene controls. Endpoints evaluated included survival, skin condition, and skin tumor incidence.	Median survival was 441 d in untreated controls, 498 d in benzene controls, and 496 d in treated mice. Moderate skin irritation (persistent hair loss and crusting) was reported in glycidaldehyde-treated mice. Skin papillomas were observed in 8/30 treated mice. Skin carcinomas were also observed in 8/30 treated mice. No papillomas or carcinomas were observed in the control groups.	Glycidaldehyde was carcinogenic under the conditions of this assay. Based on statistics conducted for this review, both the incidences of skin papillomas and carcinomas were significantly increased in treated mice, compared with vehicle and untreated controls.	Van Duuren et al. (1965)
Initiation-promotion assay (dermal)	5 groups of Swiss mice (30 F/group) were used in this assay. Group 1 (G + C) was dermally exposed once to 2.5 mg glycidaldehyde in 0.25 mL acetone, unexposed for 3 wk, then dermally exposed to 0.1% croton oil 5 d/wk for 27 wk. Group 2 (C only) was dermally exposed to 0.1% croton oil 5 d/wk for 27 wk only. Groups 3 and 4 were acetone and unexposed controls, respectively. Group 5 (DMBA + C) was a DMBA-positive initiation control. Endpoints evaluated included skin tumor incidence.	Skin tumor (keratoacanthoma) incidence was 40% at Wk 30 in the G + C group (first tumor at 16 wk) and 95% in the DMBA + C group (first tumor at 5 wk). Tumor incidences in C-only and acetone and untreated control groups were not reported.	Glycidaldehyde was a weak tumor initiator compared with DMBA under the conditions of this assay.	Shamberger et al. (1974)

Table 4B. Other Glycidaldehyde (CASRN 765-34-4) Studies

Test[a]	Materials and Methods	Results	Conclusions	References
Initiation-promotion assay (dermal)	4 groups of Swiss mice (20 F/group) were used in this assay. Group 1 (G + C) was dermally exposed once to 1 mg glycidaldehyde, unexposed for 2 wk, then dermally exposed to 1 mg croton resin 3 d/wk for life. Group 2 (G only) was exposed once to 1 mg glycidaldehyde and observed for life. Group 3 (C only) was dermally exposed to 1 mg croton resin 3 d/wk for life. Group 4 (DMBA + C) was a DMBA-positive initiation control. Endpoints evaluated included survival and skin tumor incidence.	Median survival was 348 d in the G-only group, 439 d in the C-only group, 386 d in the G + C group, and 276 d in the DMBA + C group. Skin papilloma incidence was 0/20, 1/20, and 2/20 in the G-only, C-only, and G + C groups, respectively. The days to first tumor were 426 d in the C-only group and 264 d in the G + C group. No skin carcinomas were observed in any of these groups. In the DMBA + C group, 9/20 mice had skin papillomas and 8/20 mice had skin carcinomas. Time to first papilloma and carcinoma was 51 and 110 d, respectively.	Glycidaldehyde was a weak tumor initiator compared with DMBA under the conditions of this assay.	Van Duuren et al. (1965)
Cancer assay (s.c.)	S-D rats (20 F/group) were administered 0 (2 groups) or 33 mg/animal glycidaldehyde via s.c. injection in 0.1 mL tricaprylin 1 d/wk for life. Injections were given in the left axillary area. An untreated control group of 30 F rats was included as well. Endpoints evaluated included survival and tumor incidence.	Median survival time was 483−537 d in control rats and 425 d in treated rats. Subcutaneous sarcomas were observed at the injection site in 5 (25%) treated rats. No tumors were observed at the injection site in any of the control groups.	Glycidaldehyde was carcinogenic under the conditions of this assay. Based on statistics conducted for this review, the incidence of s.c. sarcomas at the injection site was significantly increased in treated rats, compared with vehicle and untreated controls.	Van Duuren et al. (1967b)
Cancer assay (s.c.)	S-D rats (50 F/group) were administered 0 or 1 mg/animal glycidaldehyde via s.c. injection in 0.1 mL tricaprylin 1 d/wk for life. Injections were given in the left axillary area. An untreated control group of 50 F rats was included as well. Endpoints evaluated included survival and tumor incidence.	Median survival was 554 d in untreated controls, >565 d in vehicle controls, and 545 d in treated rats. A malignant fibrosarcoma was observed at the injection site in one treated rat and benign injection site fibroadenomas were observed in three additional treated rats. An injection-site adenocarcinoma was recorded in one vehicle control animal.	Glycidaldehyde was not carcinogenic under the conditions of this assay.	Van Duuren et al. (1966)

Table 4B. Other Glycidaldehyde (CASRN 765-34-4) Studies

Test[a]	Materials and Methods	Results	Conclusions	References
Cancer assay (s.c.)	ICR/Ha Swiss mice (30−50 F/group) were administered 0, 0.1, or 3.3 mg/animal glycidaldehyde via s.c. injection in 0.05 mL tricaprylin 1 d/wk for life. Injections were given in the left axillary area. Each exposure group had concurrent vehicle and untreated control groups (30−50 F/group). Endpoints evaluated included survival and tumor incidence.	Median survival was 415−431 d in untreated controls, 368−535 d in vehicle controls, 593 d at 0.1 mg/animal, and 472 d at 3.3 mg/animal. Malignant tumors (fibrosarcoma, squamous cell carcinomas, adenocarcinomas) were observed at the injection site in 6 and 23% of mice at 0.1 and 3.3 mg/animal, respectively. One animal with benign papillary tumor was also observed at 3.3 mg. No malignant tumors were observed at the injection site in any of the vehicle or untreated control groups.	Glycidaldehyde was carcinogenic under the conditions of this assay. Based on statistics conducted for this review, the incidence of malignant tumors at the injection site was significantly increased at 3.3 mg/animal, compared with vehicle and untreated controls.	Van Duuren et al. (1966)

[a]Acute = exposure for ≤24 hours (U.S. EPA, 2002).

CI = confidence interval; DMBA = 7,12-dimethylbenz(a)anthracene; F = female(s); LC_{50} = median lethal concentration; LD_{50} = median lethal dose; NS = not specified; s.c. = subcutaneous; S-D = Sprague-Dawley.

DERIVATION OF PROVISIONAL VALUES

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional Reference Dose

The database for oral toxicity of glycidaldehyde is limited to acute lethality studies (Simmon et al., 1979; Hine et al., 1961) and an inadequate cancer study (Van Duuren et al., 1966), precluding derivation of a subchronic provisional reference dose (p-RfD).

Derivation of Chronic Provisional Reference Dose

A chronic p-RfD value was not derived because an oral RfD is available on U.S. EPA's Integrated Risk Information System (IRIS) database (U.S. EPA, 2005). The IRIS oral RfD is based on the subchronic inhalation study by Hine et al. (1961) via route-to-route extrapolation.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional Reference Concentration

The database of potentially relevant studies for deriving a subchronic p-RfC for glycidaldehyde is limited to a single 12-week inhalation study in male rats (Hine et al., 1961). The study examined a variety of endpoints in rats after 12 weeks of exposure and included a control plus four concentration groups. However, study limitations included lack of analytical concentrations, use of one sex (male), histopathology on a limited set of organs, inadequate data reporting for several endpoints (lack of variance data, lack of absolute organ weights, lack of incidence data), and lack of study design and methods description (e.g., exposure chamber conditions, generation of atmospheres). Based on these limitations, the study was not considered appropriate to use as the basis of a provisional toxicity value. However, this study was used for the derivation of "screening-level" values for subchronic and chronic inhalation exposure to glycidaldehyde (see Appendix C).

A summary of noncancer provisional reference values for glycidaldehyde is shown in Table 5.

Table 5. Summary of Noncancer Reference Values for Glycidaldehyde (CASRN 765-34-4)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED/HEC)	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	NDr						
Chronic p-RfD (mg/kg-d)	Oral RfD value of 4×10^{-4} mg/kg-d is available on IRIS (U.S. EPA, 2005).						
Screening subchronic p-RfC (mg/m^3)	Rat/M	Hematological changes in bone marrow	1×10^{-2}	NOAEL	3.5	300	Hine et al. (1961)
Screening chronic p-RfC (mg/m^3)	Rat/M	Hematological changes in bone marrow	1×10^{-3}	NOAEL	3.5	3,000	Hine et al. (1961)

HEC = human equivalent concentration; HED = human equivalent dose; IRIS = Integrated Risk Information System; M = male(s); NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; RfD = reference dose
UF_C = composite uncertainty factor.

PROVISIONAL CARCINOGENICITY ASSESSMENT

A provisional cancer assessment was not prepared for glycidaldehyde because IRIS (U.S. EPA, 2005) includes a cancer assessment for this compound. Based on the weight of evidence (WOE), IRIS classified glycidaldehyde as a B2 *probable human carcinogen*, although data were not adequate for deriving quantitative estimates of carcinogenic risk by oral or inhalation exposure (see Table 6).

Table 6. Summary of Cancer Risk Estimates for Glycidaldehyde (CASRN 765-34-4)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Risk Estimate	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

APPENDIX A. LITERATURE SEARCH STRATEGY

Non-date-limited literature searches were conducted in February 2018 and updated in May 2019 for studies relevant to the derivation of provisional toxicity values for glycidaldehyde (CASRN 765-34-4). Synonyms included in the search were oxirane-2-carbaldehyde, 2-oxiranecarboxaldehyde, oxirane-carboxaldehyde, 2,3-epoxypropionaldehyde, 2,3-epoxy-1-propanal, 2,3-epoxypropanal, and epoxypropanal. Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE (including the Toxic Substances Control Act Test Submissions [TSCATS] database), and Web of Science (WOS). In addition, the following databases were searched outside of HERO: U.S. EPA Chemical Data Access Tool (CDAT), U.S. EPA ChemView, Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), U.S. EPA Health Effects Assessment Summary Tables (HEAST), International Programme on Chemical Safety (IPCS) INCHEM, U.S. EPA Integrated Risk Information System (IRIS), Japan Existing Chemical Data Base (JECDB), National Toxicology Program (NTP), and Organisation for Economic Co-operation and Development (OECD), including eChemPortal. The following additional sources were checked for regulatory values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

LITERATURE SEARCH STRINGS

PubMed

"Glycidaldehyde" OR "2-Oxiranecarboxaldehyde" OR "2, 3-Epoxypropionaldehyde" OR "2,3-Epoxy-1-propanal" OR "2,3-Epoxypropanal" OR "2,3-Epoxypropionaldehyde" OR "Epoxypropanal" OR "Oxirane-carboxaldehyde"

WOS

TS=("Glycidaldehyde" OR "2-Oxiranecarboxaldehyde" OR "2, 3-Epoxypropionaldehyde" OR "2,3-Epoxy-1-propanal" OR "2,3-Epoxypropanal" OR "2,3-Epoxypropionaldehyde" OR "Epoxypropanal" OR "Oxirane-carboxaldehyde" OR "765-34-4") AND ((WC=("Toxicology" OR "Endocrinology & Metabolism" OR "Gastroenterology & Hepatology" OR "Gastroenterology & Hepatology" OR "Hematology" OR "Neurosciences" OR "Obstetrics & Gynecology" OR "Pharmacology & Pharmacy" OR "Physiology" OR "Respiratory System" OR "Urology & Nephrology" OR "Anatomy & Morphology" OR "Andrology" OR "Pathology" OR "Otorhinolaryngology" OR "Ophthalmology" OR "Pediatrics" OR "Oncology" OR "Reproductive Biology" OR "Developmental Biology" OR "Biology" OR "Dermatology" OR "Allergy" OR "Public, Environmental & Occupational Health") OR SU=("Anatomy & Morphology" OR "Cardiovascular System & Cardiology" OR "Developmental Biology" OR "Endocrinology & Metabolism" OR "Gastroenterology & Hepatology" OR "Hematology" OR "Immunology" OR "Neurosciences & Neurology" OR "Obstetrics & Gynecology" OR "Oncology" OR "Ophthalmology" OR "Pathology" OR "Pediatrics" OR "Pharmacology & Pharmacy" OR "Physiology" OR "Public, Environmental & Occupational Health" OR "Respiratory System" OR "Toxicology" OR "Urology & Nephrology" OR "Reproductive Biology" OR "Dermatology" OR "Allergy")) OR (TS="rat" OR TS="rats" OR TS="mouse" OR

TS="murine" OR TS="mice" OR TS="guinea" OR TS="muridae" OR TS=rabbit* OR TS=lagomorph* OR TS=hamster* OR TS=ferret* OR TS=gerbil* OR TS=rodent* OR TS="dog" OR TS="dogs" OR TS=beagle* OR TS="canine" OR TS="cats" OR TS="feline" OR TS="pig" OR TS="pigs" OR TS="swine" OR TS="porcine" OR TS=monkey* OR TS=macaque* OR TS=baboon* OR TS=marmoset* OR TS="child" OR TS="children" OR TS=adolescen* OR TS=infant* OR TS="WORKER" OR TS="WORKERS" OR TS="HUMAN" OR TS=patient* OR TS=mother OR TS=fetal OR TS=fetus OR TS=citizens OR TS=milk OR TS=formula OR TS=epidemio* OR TS=population* OR TS=exposure* OR TS=questionnaire OR SO=epidemio*) OR TI=toxic*)A.1.3 TOXLINE

TOXLINE
@AND+@OR+(Glycidaldehyde+"2-Oxiranecarboxaldehyde"+"2,
3-Epoxypropionaldehyde"+"2,3-Epoxy-1-propanal"+"2,3-Epoxypropanal"+"2,3-Epoxypropionaldehyde"+Epoxypropanal+"Oxirane-carboxaldehyde"+@TERM+@rn+765-34-4)+@org+(ANEUPL+BIOSIS+CIS+DART+EMIC+EPIDEM+HEEP+HMTC+IPA+RISKLINE+MTGABS+NIOSH+NTIS+PESTAB+PPBIB)+@AND+not+@org+p(ubmed+pubdart)

TSCATS
@TERM+@rn+"765-34-4"+@org+TSCATS

APPENDIX B. DETAILED PECO CRITERIA

Table B-1. Population, Exposure, Comparator, and Outcome (PECO) Criteria

PECO Element	Evidence
Population	Humans, laboratory mammals, and other animal models of established relevance to human health (e.g., *Xenopus* embryos); mammalian organs, tissues, and cell lines; and bacterial and eukaryote models of genetic toxicity.
Exposure	In vivo (all routes), ex vivo, and in vitro exposure to the chemical of interest, including mixtures to which the chemical of interest may contribute significantly to exposure or observed effects.
Comparator	Any comparison (across dose, duration, or route) or no comparison (e.g., case reports without controls).
Outcome	Any endpoint suggestive of a toxic effect on any bodily system, or mechanistic change associated with such effects. Any endpoint relating to disposition of the chemical within the body.

APPENDIX C. SCREENING PROVISIONAL VALUES

For reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional toxicity values for glycidaldehyde. However, information is available for this chemical, which although insufficient to support deriving a provisional toxicity value under current guidelines, may be of use to risk assessors. In such cases, the Center for Public Health and Environmental Assessment (CPHEA) summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the provisional reference values to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there could be more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment.

Derivation of a Screening Subchronic Provisional Reference Concentration

The database of potentially relevant studies for deriving a subchronic p-RfC for glycidaldehyde is limited to a single 12-week inhalation study in male rats (Hine et al., 1961). The critical effect identified in this study was decreased hematological changes in the bone marrow at ≥59 mg/m^3 (human equivalent concentration [HEC] = 7.0 mg/m^3). Hematological changes (e.g., changes in leukocytes) were also observed in rabbits that were exposed to glycidaldehyde via the intravenous (i.v.) route (Hine et al., 1961); these data support the selection of hematological changes in the bone marrow of rats as the critical effect for deriving the subchronic p-RfC. No effects were observed at 29 mg/m^3 (HEC = 3.5 mg/m^3).

The no-observed-adverse-effect level (NOAEL) (HEC) of 3.5 mg/m^3 for male rats was calculated by using U.S. EPA (1994) methodology for an extrarespiratory effect as follows:

Exposure concentration adjustment for continuous exposure:

$$\begin{aligned} NOAEL_{ADJ} &= \text{NOAEL (ppm)} \times (\text{MW} \div 24.45) \times (\text{hours per day exposed} \div 24 \text{ hours}) \times (\text{days per week exposed} \div 7 \text{ days}) \\ &= 10 \text{ ppm} \times (72.06 \text{ g/mol} \div 24.45) \times (4 \text{ hours} \div 24 \text{ hours}) \times (5 \text{ days} \div 7 \text{ days}) \\ &= 29 \text{ mg/m}^3 \times (4 \text{ hours} \div 24 \text{ hours}) \times (5 \text{ days} \div 7 \text{ days}) \\ &= 3.5 \text{ mg/m}^3 \end{aligned}$$

HEC conversion for extrarespiratory effects:

$$\begin{aligned} \text{NOAEL (HEC)} &= NOAEL_{ADJ} \times \text{Hb/g-A} \div \text{Hb/g-H} \\ &= 3.5 \text{ mg/m}^3 \times 1 \\ &= 3.5 \text{ mg/m}^3 \end{aligned}$$

where

Hb/g-A ÷ Hb/g-H = the ratio of the blood-gas (air) partition coefficient of the chemical for the laboratory animal species to the human value.

In the absence of data for glycidaldehyde for male rats, the default value of 1 was used, as specified in U.S. EPA (1994) guidance.

Data reporting for the Hine et al. (1961) study is inadequate for benchmark dose (BMD) modeling because variance data were not reported for the critical endpoint. Therefore, the NOAEL (HEC) of 3.5 mg/m^3 is selected as the point of departure (POD) for deriving the screening subchronic p-RfC.

The screening subchronic p-RfC of 1×10^{-2} mg/m^3 is derived by applying a composite uncertainty factor (UF_C) of 300 (reflecting an interspecies uncertainty factor [UF_A] of 3, an intraspecies uncertainty factor [UF_H] of 10, and a database uncertainty factor [UF_D] of 10) to the selected POD of 3.5 mg/m^3, as follows:

$$\begin{aligned} \textbf{Screening Subchronic p-RfC} &= \text{POD (HEC)} \div UF_C \\ &= 3.5 \text{ mg/m}^3 \div 300 \\ &= \mathbf{1 \times 10^{-2} \text{ mg/m}^3} \end{aligned}$$

Table C-1 summarizes the uncertainty factors for the screening subchronic p-RfC for glycidaldehyde.

Table C-1. Uncertainty Factors for the Screening Subchronic p-RfC for Glycidaldehyde (CASRN 765-34-4)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans using toxicokinetic cross-species dosimetric adjustment for systemic effects from a Category 3 gas, as specified in U.S. EPA (1994) guidelines for deriving RfCs.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The inhalation database for glycidaldehyde is limited to an acute lethality study and a subchronic inhalation study in rats. There are no reproductive or developmental toxicity studies available by inhalation or oral exposure. Furthermore, the principal study did not examine nasal effects, which could be a target organ for glycidaldehyde-induced toxicity given that it is a water-soluble reactive aldehyde; compounds of this nature (e.g., acrolein) have been shown to cause nasal effects in toxicity studies.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of glycidaldehyde in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because the subchronic POD was derived from subchronic data.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; RfC = reference concentration; UF = uncertainty factor(s); UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of a Screening Chronic Provisional Reference Concentration

No chronic inhalation studies were identified for glycidaldehyde. Therefore, the 12-week inhalation study in male rats (Hine et al., 1961) used as the basis for the screening subchronic p-RfC is selected as the basis for the screening chronic p-RfC. As discussed above, the POD from this study is a NOAEL (HEC) of 3.5 mg/m^3 for hematological changes in the bone marrow.

The screening chronic p-RfC of 1×10^{-3} mg/m^3 is derived by applying a UF_C of 3,000 (reflecting a UF_A of 3, a UF_H of 10, a UF_D of 10, and a subchronic-to-chronic uncertainty factor [UF_S] of 10) to the selected POD of 3.5 mg/m^3.

Screening Chronic p-RfC = POD (HEC) ÷ UF_C
= 3.5 mg/m^3 ÷ 3,000
= **1×10^{-3} mg/m^3**

Table C-2 summarizes the uncertainty factors for the screening chronic p-RfC for glycidaldehyde.

Table C-2. Uncertainty Factors for the Screening Chronic p-RfC for Glycidaldehyde (CASRN 765-34-4)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans using toxicokinetic cross-species dosimetric adjustment for systemic effects from a Category 3 gas, as specified in U.S. EPA (1994) guidelines for deriving RfCs.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The inhalation database for glycidaldehyde is limited to an acute lethality study and a subchronic inhalation study in rats. There are no chronic inhalation studies. There are no reproductive or developmental toxicity studies available by inhalation or oral exposure. Furthermore, the principal study did not examine nasal effects, which could be a target organ for glycidaldehyde-induced toxicity given that it is a water-soluble reactive aldehyde; compounds of this nature (e.g., acrolein) have been shown to cause nasal effects in toxicity studies.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of glycidaldehyde in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	10	A UF_S of 10 is applied because the chronic POD was derived from subchronic data.
UF_C	3,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; RfC = reference concentration; UF = uncertainty factor(s); UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

APPENDIX D. DATA TABLES

Table D-1. Selected Data for Male Long-Evans Rats Exposed to Glycidaldehyde (CASRN 765-34-4) via Inhalation for 12 Weeks (4 Hours/Days, 5 Days/Week)[a]

Endpoint	Nominal Concentration in mg/m^3 (HEC_{ER})				
	0	**29 (3.5)**	**59 (7.0)**	**120 (14)**	**240 (28)**
Survival[b]	9/10 (90%)	10/10 (100%)	9/10 (90%)	8/10 (80%)	0/10[c] (0%)
Body-weight gain[d, e] (%)	109	107 (−2%)	80* (−27%)	84* (−23%)	NA
Relative organ weights[d, e]					
Thymus (%)	0.0587	0.0364* (−38%)	0.0501 (−15%)	0.0415* (−29%)	NA
Spleen (%)	0.335	0.338 (+0.9%)	0.364 (+9%)	0.217* (−35%)	NA
Testes (%)	0.904	0.991 (+10%)	1.088* (+20%)	1.001* (+11%)	NA
Liver (%)	3.34	3.25 (−3%)	3.85 (+15%)	3.45 (+3%)	NA
Kidney (%)	0.665	0.654 (−2%)	0.684 (+3%)	0.700 (+5%)	NA
Lung (%)	0.405	0.494 (+22%)	0.487 (+20%)	0.434 (+7%)	NA
Bone marrow[e, f]					
Nucleated cells (× 10^8)	2.27	1.86 (−18%)	1.19* (−48%)	1.24* (−45%)	0.62† (−44%)
M:E ratio	2.7	3.6 (+33%)	5.1 (+89%)	4.3 (+59%)	2.4 (−11%)
Total Leukocytes					
0 Exposures	14,000	13,000	13,000	12,400	9,900
17 Exposures	15,600	13,600	15,200	12,000	7,300 (5 exposures)
60 Exposures	15,000	13,700	15,800	12,000	
Leukocytes (% Polymorphonuclear)					
0 Exposures	13	25	22	17	10
17 Exposures	21	20	18	11	54* (5 exposures)
60 Exposures	27	29	19	23	
Erythrocytes (× 10^6)					
0 Exposures	7.1	7.4	7.5	7.4	6.9
17 Exposures	7.2	8.7	9.5	8.5	8.7 (5 exposures)
60 Exposures	8.7	8.9	9.2	9.8	
Hemoglobin (%)					
0 Exposures	16.3	16.0	16.3	16.0	16.0
17 Exposures	17.0	17.2	18.4	16.9	17.3 (5 exposures)
60 Exposures	19.8	19.8	19.4	20.1	

[a]Hine et al. (1961).
[b]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
[c]8/10 animals died after 4 exposures; the 2 surviving animals were sacrificed after the fifth exposure.
[d]Data are means (no variance data reported); n = 8−10/group (see "survival" row).
[e]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[f]Data are means (no variance data were reported); n = 8−10/group at 12 weeks for groups exposed to ≤120 mg/m^3; n = 2 surviving rats at 5 days for the 240-mg/m^3 group.
*Significantly different from control ($p < 0.05$), as reported by the study authors.
†Significantly different from reference value of 1.10 × 10^8 for a 100-g rat, as reported by the study authors (the average body weight of these two rats was 122 g).

ER = extrarespiratory; HEC = human equivalent concentration: M:E = myeloid to erythroid; NA = not applicable.

APPENDIX E. REFERENCES

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