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Provisional Peer-Reviewed Toxicity Values for

Ethylene Cyanohydrin
(CASRN 109-78-4)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR ETHYLENE CYANOHYDRIN (CASRN 109-78-4)

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 a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by 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.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

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.

Other U.S. Environmental Protection Agency (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.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Ethylene cyanohydrin (CAS No. 109-78-4), also known as β-hydroxypropionitrile, is a white/straw-colored liquid that is used as a solvent for certain cellulose esters and inorganic salts, as an organic intermediate for acrylates, and in the synthesis of acrylonitrile. The chemical structure of ethylene cyanohydrin is shown in Figure 1, and selected physicochemical properties of ethylene cyanohydrin are provided in Table 1.

$OH—CH_2—CH_2—CN$

Figure 1. Ethylene Cyanohydrin Structure

Table 1. Physicochemical Properties Table for Ethylene Cyanohydrin (CASRN 109-78-4)[a]

Property (unit)	Value
Boiling point (ºC)	221
Melting point (ºC)	−46
Density (g/cm^3)	1.04
Vapor pressure (mm Hg at 25ºC)	0.08
pH (unitless)	NA
Solubility in water (mg/L at 20ºC)	1.00×10^6
Relative vapor density (air = 1)	2.45
Molecular weight (g/mol)	71.08

[a]ACGIH (2011), ChemIDPlus (2011).

NA = not applicable.

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment for ethylene cyanohydrin is included in the U.S. EPA IRIS (U.S. EPA, 2011a) database, in the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009), or in the HEAST (U.S. EPA, 2011b). U.S. EPA (2005a) developed a PPRTV assessment for ethylene cyanohydrin, deriving a subchronic p-RfD of 1×10^{-1} mg/kg-day and a chronic p-RfD of 3×10^{-2} mg/kg-day. Subchronic and chronic p-RfC values were not determined. The Chemical Assessments and Related Activities (CARA) list does not include a Health and Environmental Effects Profile (HEEP) for ethylene cyanohydrin (U.S. EPA, 1994). The toxicity of ethylene cyanohydrin has not been reviewed by the ATSDR (2011) or the World Health Organization (WHO, 2011). CalEPA (2008, 2009a) has not derived toxicity values for exposure to ethylene cyanohydrin. No occupational exposure limits for ethylene cyanohydrin have been derived or recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2011), the National Institute of Occupational Safety and Health (NIOSH, 2011), or the Occupational Safety and Health Administration (OSHA, 2010).

The HEAST (U.S. EPA, 2011b) does not report a U.S. EPA (1986) cancer weight-of-evidence (WOE) classification or an oral slope factor (OSF) for ethylene cyanohydrin. The International Agency for Research on Cancer (IARC, 2011) has not reviewed the carcinogenic potential of ethylene cyanohydrin. Ethylene cyanohydrin is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2009b) has not derived a quantitative estimate of carcinogenic potential for ethylene cyanohydrin.

Literature searches were conducted on sources published from 1900 through May 2012 for studies relevant to the derivation of provisional toxicity values for ethylene cyanohydrin (CASRN 109-78-4). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); WHO; and Worldwide Science. The following databases outside of HERO were searched for health information: ACGIH, ATSDR, CalEPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for ethylene cyanohydrin and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. The phrase "statistical significance," used throughout the document, indicates a p-value of <0.05.

Table 2. Summary of Potentially Relevant Data for Ethylene Cyanohydrin (CASRN 109-78-4)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
			1. Oral (mg/kg-d)[a]					
Subchronic	ND							
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenic	ND							
			2. Inhalation (mg/m^3)[a]					
Subchronic	ND							
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenic	ND							
Animal								
			1. Oral (mg/kg-d)[a]					
Subchronic	**10/10 S-D rat, drinking water, 90 d**	**0, 10, 30, 90, or 270 (Adjusted)**	**Questionable effects on brain and heart weights**	**270**	**NDr**	**NDr**	**Sauerhoff et al. (1976a)**	**PS, PR**
	S-D rat, dietary, 52−64 d	0 or 301 (M), 343 (F) (Adjusted)	None	301/343	NDr	NDr	Bachhuber et al. (1955)	PR
Chronic Carcinogenic	**43/0 Wistar rat, dietary, 78 wk**	**0, 7, 74, or 221 (Adjusted)**	**Decreased body weight**	**74**	**NDr**	**221**	**Hirose et al. (1980a)**	**PS, PR**
	50/0 ICR mouse, dietary, 78 wk	0, 18, 180, or 539 (Adjusted)	Decreased body weight	180	NDr	539	Hirose et al. (1980b)	PR

Table 2. Summary of Potentially Relevant Data for Ethylene Cyanohydrin (CASRN 109-78-4)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Developmental	ND							
Reproductive	ND							
2. Inhalation (mg/m^3)[a]								
Subchronic	ND							
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenic	ND							

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects. All exposure values of long-term exposure (4 wk and longer) are converted from a discontinuous to a continuous (weekly) exposure.
HED = avg. mg test article ÷ avg. kg body weight ÷ Number daily dosed.
HED_n = (avg. mg test article ÷ avg. kg body weight ÷ Number daily dosed)$^{1/4}$.
[b]Notes: IRIS = utilized by IRIS, date of last update, PS = principal study, NPR = not peer reviewed, PR = peer reviewed, ND = no data, NDr = not determined, NR = not reported.

HUMAN STUDIES

Oral Exposures

No oral studies on the subchronic, chronic, developmental, or reproductive toxicity or on the carcinogenicity of ethylene cyanohydrin in humans were identified.

Inhalation Exposures

No inhalation studies on the acute, subchronic-duration, chronic-duration, developmental, or reproductive toxicity or on the carcinogenicity of ethylene cyanohydrin in humans were identified.

ANIMAL STUDIES

Oral Exposure

The effects of oral exposure of animals to ethylene cyanohydrin were evaluated in two subchronic-duration studies (i.e., Sauerhoff et al., 1976a; Bachhuber et al., 1955) and one combined chronic-duration toxicity and carcinogenicity study (i.e., Hirose et al., 1980a,b).

Subchronic Studies

Sauerhoff et al., 1976a

The study by Sauerhoff et al. (1976a) is selected as the principal study for derivation of the subchronic p-RfD value. In this peer-reviewed study, ethylene cyanohydrin (>99% purity) was administered in the drinking water to 10 S-D rats/sex/dose of 0, 10, 30, 90, or 270 mg/kg-day for 90 days. Weekly adjustments were made to the dose formulations based on water consumption and body weight. The rats were obtained from Spartan Research Animals Inc. (Haslett, MI) and were housed individually in wire-bottomed cages with water and commercial laboratory animal chow available ad libitum. No further details of animal husbandry were provided. The study authors stated that the stability and concentration of ethylene cyanohydrin were confirmed in the drinking water. The rats were weighed and food consumption determined weekly. All rats were observed frequently for clinical signs of toxicity (schedule not reported). On Day 85, hematologic evaluations (i.e., packed cell volume, erythrocyte count, leukocyte count, hemoglobin [Hb], percentage neutrophils, and percentage lymphocytes) and urinalyses (i.e., specific gravity, pH, sugar, protein, ketones, occult blood, and bilirubin) were conducted on five rats/sex from the control and 270-mg/kg-day groups. At necropsy on Days 91 and 92, blood samples were collected from five rats/sex/dose for the determination of the serum levels of urea nitrogen, alkaline phosphatase activity, and glutamic pyruvic transaminase activity. A gross pathologic examination was conducted on all rats, and the weights of brain, heart, liver, kidney, and testes were determined. Samples of the following tissues were obtained and fixed in 10% buffered formalin: heart, liver, kidney, gonads, uterus, thyroid, trachea, parathyroid, lung, adrenal gland, spleen, pancreas, stomach, small intestine, large intestine, urinary bladder, accessory sex glands, skeletal muscle, peripheral nerve, spinal cord, brain, eye, pituitary gland, thymus, and aorta. Following routine processing and staining with hematoxylin and eosin, all of the aforementioned tissues from the control and 270-mg/kg-day groups were examined microscopically (five rats/sex). Analysis of variance and Dunnett's test ($p < 0.05$) were used to determine whether ethylene cyanohydrin induced significant alterations in body weights, food consumption, water consumption, hematological values, clinical chemical parameters, organ weights, and organ-to-body-weight ratios. The statistical analyses are considered adequate; parametric testing is only appropriate when the assumptions of normality of distribution and homogeneity of variances are met. This study was

conducted prior to the adoption of Good Laboratory Practice (GLP) standards as described in 40 CFR Part 160.

No treatment-related effects were noted on mortality, clinical signs, body weights, food or water consumption, clinical chemistry, hematology, or gross or microscopic pathology (Sauerhoff et al., 1976a). The study authors concluded that the NOAEL was 270 mg/kg-day, the highest dose tested. A LOAEL was not identified.

A PPRTV document for ethylene cyanohydrin was previously published by U.S. EPA (2005a). The 2005 document used the study by Sauerhoff et al. (1976a) to derive a subchronic p-RfD of 1×10^{-1} mg/kg-day, based on a NOAEL of 30 mg/kg-day. It was stated that the decreases in absolute brain and heart weights represented a treatment-related and toxicologically significant effect due to the mechanism of toxicity for the cyanohydrin compounds as a class. U.S. EPA (2005a) further stated that the heart and brain are especially sensitive to alterations in cellular energy status, and would be expected to be sensitive to compounds that interfere with energy metabolism. In this regard, Sauerhoff et al. (1976a) stated the following:

> *"No significant differences occurred between the mean organ weights or organ to body weight ratios of male rats receiving (ethylene cyanohydrin) and controls. Brain and heart weights of females receiving 270 and 90 mg/kg-day were slightly but significantly ($p<0.05$) lower than controls. The weight differences of these tissues were not accompanied by pathologic alteration."*

The effects on brain and heart weights in the females were statistically significant at 270 and 90 mg/kg-day. It was not indicated whether the decreases in absolute brain and heart weights were dose-related. Furthermore, the decreases in absolute weights were not accompanied by corresponding organ-to-body-weight differences; the magnitudes of the "slightly but significantly lower" organ weights were not provided; the organ-weight decreases were not associated with adverse gross or microscopic pathology; and no other additional evidence of toxicity was observed in these animals systemically or in specific organs. The decreases in absolute weights were observed only in females; however, in a concurrent metabolism study (Sauerhoff et al., 1976b), no sex-related differences were observed in the pharmacokinetics (plasma concentrations) of the compound following oral administration, and only 0.44% of the administered radioactive dose was isolated in the expired air as [^{14}C]-HCN. The study authors also reported rapid elimination of the compound in the urine ($t_{1/2}$ = 6.13 hours). Additionally, there was no evidence of toxicity in the rat following treatment for 52−64 days at a dietary dose of approximately 340 mg/kg-day (Bachhuber et al., 1955), and there was only evidence for slight toxicity in studies of longer duration at equivalent or higher doses. In the chronic-duration studies, discussed below, there was evidence of only minimal toxicity (i.e., decreased terminal body weights) in rats and mice dosed orally at up to 221 and 539 mg/kg-day, respectively, for up to 78 weeks (Hirose et al., 1980a,b). In addition, the oral LD_{50} is 3200 mg/kg for the rat and 1800 mg/kg for the mouse (HSDB, 2003). Taken together, these data suggest that cyanide toxicity is a minor concern for ethylene cyanohydrin. Therefore, the NOAEL is considered to be 270 mg/kg-day, the highest dose tested, for derivation of the subchronic p-RfD value.

Bachhuber et al., 1955

In a peer-reviewed study by Bachhuber et al. (1955), 5−6 S-D rats (number/sex not specified) were fed diets containing either 0 or 0.35% (equivalent to 301/343 mg/kg-day in males/females) ethylene cyanohydrin for 52−64 days. Body-weight gains, skeletal alterations, clinical signs, and gross abnormalities were recorded (a detailed list of the parameters evaluated was not provided). No adverse effects were reported. The NOAEL was 0.35% (equivalent to 301 mg/kg-day in males and 343 mg/kg-day in females); a LOAEL was not identified. This study is considered unsuitable for use as a principal study due to the fact that the only data presented are a single entry of weight gain/day.

Chronic-duration Studies

Hirose et al., 1980a

The study by Hirose et al. (1980a) is selected as the principal study for derivation of the chronic p-RfD value. In this peer-reviewed study, ethylene cyanohydrin (purity not reported) was administered in commercial Oriental M diet to 43 male Wistar rats/dose of 0 (n = 31), 100, 1000, or 3000 ppm (equivalent to 0, 7, 74, or 221 mg/kg-day based on U.S. EPA [1988] species default values) for 78 weeks. The rats were obtained from Nihon Rat Co. (Saitama, Japan) and were housed six/cage in a room at 24 ± 2°C with alternate 12-hour periods of light. Diet and water were available ad libitum. The study was terminated after 78 weeks. Necropsies were performed at termination and for animals that died while on the study. The liver, kidneys, and spleen were weighed. Organs and tissues (detailed list not provided) were fixed, routinely prepared, and examined microscopically. For hematological and blood biochemical analyses, blood was collected from all rats before sacrifice, and the white blood cells (WBCs), red blood cells (RBCs), Hb, hematocrit (Ht), serum total protein (TP), alkaline phosphatase (SAP), glucose, blood urea nitrogen (BUN), serum glutamic-oxaloacetic transaminase (SGOT), and serum glutamic-pyruvic transaminase (SGPT) were measured. Statistical analyses were not reported. This study was conducted prior to the adoption of GLP standards as described in 40 CFR Part 160.

Final body weight was decreased by 10% at 100 and 1000 ppm and by 13% at 3000 ppm compared to the controls (Hirose et al., 1980a; see Table B.1). The effect on body weight at 1000 ppm was similar to that at 100 ppm, and no other evidence of toxicity was noted in these dose groups. Therefore, the effects observed at 100 and 1000 ppm are considered incidental. At 3000 ppm, the study authors reported that, RBCs, Hb, and Ht were decreased by 14−16% compared to the controls, possibly indicative of mild anemia, and that WBCs were decreased by 24% (see Table B.2). Due to the slight magnitude of change from the controls, these effects are considered to be treatment-related, but not adverse. Although statistical significance and standard deviations were not reported, the possibility of a dose-related trend could not be dismissed, and the 13% decrease in body weight at the high dose is considered adverse. No increased incidence of tumors was reported at any dose. Although not stated by the study authors, a LOAEL of 221 mg/kg-day based on a biologically significant decrease in body weight (>10%) is identified, with a corresponding NOAEL of 74 mg/kg-day.

The 2005 PPRTV assessment for ethylene cyanohydrin (U.S. EPA, 2005a) cited Hirose et al. (1980a) and stated the following regarding decreased terminal body weights.*"...data showing growth throughout the study were not presented, statistical analysis was not performed, and group means were reported without any measure of within group*

variability (standard deviation), making it difficult to evaluate the data and precluding independent statistical analysis."

However, after reevaluation of the rat study by Hirose et al. (1980a), the critical effect is decreased body weight (>10%) at 221 mg/kg-day based on a WOE approach. In addition to the decreased body weights, findings suggestive of a treatment-related, nonadverse anemia were noted in the 221 mg/kg-day rats. Decreased terminal body weights (decreased 10% at 539 mg/kg-day) were also present in the concurrently performed mouse study (Hirose et al., 1980b; see below) and were observed in a dose-dependent manner. Because decreases in body weight were noted in two species, the 13% decrease in body weights in the rat is considered biologically significant effect.

Hirose et al., 1980b

In a concurrently performed, peer-reviewed study by Hirose et al. (1980b), ethylene cyanohydrin (purity not reported) was administered in commercial Oriental M diet to 50 male ICR mice/dose of 0 (n = 30), 100, 1000, or 3000 ppm (determined by the reviewers to be equivalent to 0, 18, 180, or 539 mg/kg-day based on U.S. EPA [1988] species default values) for 78 weeks. Mice were housed 10/cage in a room at 24 ± 2°C with alternate 12-hour periods of light. Diet and water were available ad libitum. After 78 weeks of treatment, animals were maintained on the control diet for 7 weeks and then terminated. The same parameters were examined in the mouse as in the previously described rat study (Hirose et al., 1980a).

Although statistical significance and standard deviations were not reported, final body weights were decreased by 10% at 539 mg/kg-day, and a dose-related effect was observed (Hirose et al., 1980b; see Table B.1). No other toxicological effect was reported, and no increased incidence of tumors was reported at any dose. Although not stated by the study authors, the LOAEL is 539 mg/kg-day, based on a decrease in body weight that was also observed in Hirose et al. (1980a), with a corresponding NOAEL of 180 mg/kg-day.

Developmental Studies

No developmental toxicity studies on ethylene cyanohydrin were identified.

Reproduction Studies

No reproductive toxicity studies on ethylene cyanohydrin were identified.

Carcinogenic Studies

Carcinogenic potential was evaluated in the combined chronic-duration toxicity and carcinogenicity studies by Hirose et al. (1980a,b) as previously described. No increased incidence of tumors was reported in any tissue at any dose.

Inhalation Exposure

No inhalation studies on the subchronic, chronic, developmental, or reproductive toxicity or on the carcinogenicity of ethylene cyanohydrin in animals were identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Other studies that are not appropriate for selection of a POD for ethylene cyanohydrin and the determination of p-RfD, p-RfC, p-OSF, or p-IUR values can, however, provide

supportive data that supplement a WOE approach to risk assessment. These studies may include genotoxicity (see Table 3a) and short-term, metabolic, and toxicokinetic studies (see Table 3b).

Table 3A. Summary of Ethylene Cyanohydrin Genotoxicity Studies

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	Ethylene cyanohydrin was evaluated in the Ames assay with preincubation. The chemical was tested in the presence and absence of Arochlor 1254-induced male S-D rat and male Syrian hamster liver homogenate S9. *Salmonella typhimurium* TA98, TA100, TA1535, and TA97 and/or TA1537 were used.	10 mg/plate	–	–	Ethylene cyanohydrin is not mutagenic in *Salmonella typhimurium* TA98, TA100, TA1535, and TA97 and/or TA1537.	Zeiger et al. (1992)
Mutation	Ethylene cyanohydrin was evaluated in a fluctuation test. *Klebsiella pneumoniae* was tested with the chemical, and mutagenicity was determined on the basis of the proportion of streptomycin-resistant or dependent mutants.	0.015 M	–	ND	Ethylene cyanohydrin is not mutagenic in *Klebsiella pneumonia*e under the study's test conditions.	Voogd and Vet (1969)
SOS repair induction	ND					
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	ND					
Recombination induction	ND					
Chromosomal aberration	ND					
Chromosomal malsegregation	ND					
Mitotic arrest	ND					
Genotoxicity studies in mammalian cells—in vitro						
Forward mutation	ND					
Chromosomal aberrations	ND					
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					

Table 3A. Summary of Ethylene Cyanohydrin Genotoxicity Studies

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in mammals—in vivo						
Chromosomal aberrations	ND					
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adducts	ND					
Mouse biochemical or visible specific locus test	ND					
Dominant lethal	ND					
Genotoxicity studies in subcellular systems						
DNA binding	ND					

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive, ± = equivocal or weakly positive, – = negative, T = cytotoxicity, ND = no data.

Table 3B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Carcinogenicity other than oral/inhalation	ND			
Other toxicity studies (exposures other than oral or inhalation)	ND			
Short-term studies	Albino guinea pigs were treated with cheese cloth patches containing either 0, 0.1, 0.2, or 0.5 mL ethylene cyanohydrin for 24 hr and observed for signs of toxicity until recovery was complete. Two Wistar albino rats and albino guinea pigs (number not stated) received whole body exposure to ethylene cyanohydrin by passing a known volume of air thru sintered glass immersed in the liquid for 1 hr followed by observation (duration not stated) for signs of toxicity. No estimate of concentration was provided.	Dermal toxicity: There was an appearance of pain upon administration and little if any evidence of irritation at the site. There was no quantitative evidence of systemic toxicity via the dermal route. Inhalation: No signs of toxicity observed, either intermediate or delayed, in rats and guinea pigs. Results were not quantified.	Low toxicity to rats or guinea pigs by skin penetration or inhalation.	Sunderman and Kincaid (1953a) Sunderman and Kincaid (1953b)
Metabolism/ toxicokinetics	S-D rats (3/sex) were used in excretion studies for the separate collection of urine, feces, and expired air. Additional groups of three rats of each sex were used to characterize the concentration of ^{14}C-activity in plasma as a function of time. Rats were dosed with approximately 3.0 mL/kg of isotopically-diluted ^{14}C-ethylene cyanohydrin in water via gavage at a dose of 20 mg/kg and 19 μCi/kg specific activity. Samples of blood were collected at various intervals up to 116 hr postdose. After animal termination, the carcasses were skinned, and muscle, fat, kidney, skin, spleen, liver, and carcass were collected and prepared for radioanalysis by liquid scintillation counting. Metabolites were isolated and identified in urine samples and hydrolyzed urine samples (acid and heat treated) using thin layer chromatography.	^{14}C-activity was found in urine (53.2% dose), including urinary SCN, feces (7.39%), and expired air as HCN (0.44%) and carbon dioxide (25.6%). Absorption was a first-order process with a rate constant of 1.0 hr^{-1} corresponding to a half-life of 0.69 hr. The half-life values for the α and β phase of plasma clearance are 4.41 and 53.3 hr, respectively. Two components in urine were found to contain ^{14}C activity in addition to urinary thiocyanate.	The pharmacokinetics of absorption and excretion were determined, and urinary metabolites were characterized.	Sauerhoff et al. (1976b)
Mode of action/ mechanistic	ND			
Immunotoxicity	ND			
Neurotoxicity	ND			

ND = no data.

Tests Evaluating Genotoxicity

Two mutagenicity studies are presented below indicating that ethylene cyanohydrin has limited mutagenic potential (Zeiger et al., 1992; Voogd and Vet, 1969).

Zeiger et al. (1992) evaluated the potential of ethylene cyanohydrin and other test compounds to cause mutagenesis in the Ames assay with preincubation. The chemicals were tested in the presence and absence of Arochlor 1254-induced male S-D rat and male Syrian hamster liver homogenate S9. All chemicals were initially evaluated in a toxicity assay to determine the appropriate dose range for the mutagenicity assay. Chemicals were tested to a toxic dose (as indicated by decreased his+ colonies and/or bacterial lawn), a dose immediately below the toxic dose, to the limit of solubility, or to a maximum of 10 mg/plate. Concurrent solvent and positive controls were run with each trial. A chemical was designated nonmutagenic only after it had been tested in *Salmonella typhimurium* TA98, TA100, TA1535, and TA97 and/or TA1537, without activation and with 10% and 30% rat and hamster S9. Ethylene cyanohydrin was determined to be nonmutagenic at concentrations up to 10 mg/plate.

Voogd and Vet (1969) evaluated the potential of ethylene cyanohydrin and other test compounds to cause mutagenesis in the fluctuation test, using a mutant of *Klebsiella pneumoniae* that requires uracil and proline for growth. Nutrient broth containing the test substance at 0.015 M was seeded with 100 bacteria/mL and subdivided in 105 portions of 3 mL each. After overnight incubation at 37°C, the total number of streptomycin-resistant and streptomycin-dependent bacteria was determined in 100 subsamples by a pour-plate technique using nutrient agar supplemented with 100 µg/mL of dihydrostreptomycin. After 3 days incubation at 37°C, the colonies in the dihydrostreptomycin-containing agar were counted. The number of bacteria present in the five remaining subsamples was determined using nutrient-agar without dihydrostreptomycin. The mutation rate was calculated based on the number of subsamples without streptomycin-resistant or dependent mutants using a Poisson distribution. If mutants were present in all subsamples, the mutation rate was estimated by the number of mutants in the median portion.

Ethylene cyanohydrin was determined to be nonmutagenic at 0.015 M. The negative control produced the appropriate response, and other evaluated test compounds were found to be mutagenic in this study.

Short-term Studies

Sunderman and Kincaid (1953a,b) conducted short-term studies of dermal and inhalation toxicity of ethylene cyanohydrin. In the dermal study, albino guinea pigs were treated with cheese cloth patches containing either 0, 0.1, 0.2, or 0.5 mL ethylene cyanohydrin (purity = 92.5%) taped to shaved skin for 24 hours and observed (duration not stated) for signs of toxicity until recovery was complete. There appeared to be some pain in the exposed animals immediately after treatment but no other signs of toxicity. There was "little if any skin irritation" after 24 hours of exposure. The study authors provided no indication of what observations were conducted but concluded that ethylene cyanohydrin has a low toxicity via the dermal route of exposure.

In the same study, two Wistar albino rats and albino guinea pigs (number not stated) received 1 hour of whole-body exposure to ethylene cyanohydrin by passing a known volume of air through sintered glass immersed in the liquid for 1 hour followed by observation (duration not stated) for signs of toxicity. No estimate of the exposure concentration was provided. No immediate or delayed signs were observed in either rats or guinea pigs, but the study authors provided no indication of the nature or extent of the observations. The study authors concluded that ethylene cyanohydrin exhibited no toxicity in small experimental animals via the inhalation route and low toxicity via dermal route of exposure.

Metabolism Studies

In a study conducted by Sauerhoff et al. (1976b) performed concurrently with the subchronic-duration toxicity study previously described (Sauerhoff et al., 1976a), three S-D rats/sex were housed individually in modified glass Roth-type metabolism cages designed for the separate collection of urine, feces, and expired air for excretion studies. Additional groups of three rats/sex were used to characterize the concentration of ^{14}C-activity in plasma as a function of time. These rats were housed individually in stainless steel metabolism cages. Approximately 3.0 mL/kg of isotopically-diluted ^{14}C-ethylene cyanohydrin ([^{14}C]-CN) in water were administered by gavage to provide a dose of 20 mg/kg of the test compound at a specific activity of 19 μCi/kg. Urine, feces, and expired air (carbon dioxide and hydrogen cyanide [HCN] trapping solutions) were collected up to 120 hours postdose and prepared for radioanalysis. Samples of blood were collected from a freshly cut section of tail at 1, 2, 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, 76, 80, 92, 104, and 116 hours postdose. Plasma samples were prepared and radioassayed. All rats were euthanized by decapitation at 120 hours post dosing with cyanohydrin. The carcasses were skinned, and muscle, fat, kidney, skin, spleen, liver, and carcass were collected and prepared for radioanalysis. Liquid scintillation counting was used to determine the concentration of radioactivity in prepared samples. Metabolites were isolated and characterized in urine samples and hydrolyzed urine samples (acid and heat treated) using thin layer chromatography.

The overall recovery of the ethylene cyanohydrin administered dose from urine, feces, expired air, tissues, carcass, and cage washings of all rats was 95.6 ± 5.8% (mean ± SD; Sauerhoff et al., 1976b). ^{14}C-Activity was found in urine (53.2% dose), including urinary thiocyanate (SCN), feces (7.39% dose), and expired air as HCN (0.44% dose) and carbon dioxide (25.6% dose). The plasma concentration of the ^{14}C-activity over time was not sex-dependent. Absorption was a first-order process with a rate constant of 1.0 hour^{-1} corresponding to a half-life of 0.69 hour. Peak plasma levels of 47 μg parent equivalents/g plasma were observed 4 hours postdose. The clearance of ^{14}C-activity from plasma was biphasic with half-life values for the α and β phases of plasma clearance of 4.41 and 53.3 hours, respectively. Tissue distribution was not reported. Two unidentified components in urine were found to contain ^{14}C-activity along with the thiocyanate. The major unknown component in urine was hydrolyzable to a compound that exhibited the same retention factor (R_f) as the parent. One minor component was found in unhydrolyzed urine that exhibited the same R_f as the parent. The study authors concluded that the low toxicity of ethylene cyanohydrin was due to the rapid elimination in the urine and low rate of conversion to cyanide.

DERIVATION OF PROVISIONAL VALUES

Table 4 presents a summary of noncancer reference values. Table 5 presents a summary of cancer values. No cancer values could be derived.

Table 4. Summary of Noncancer Reference Values for Ethylene Cyanohydrin (CASRN 109-78-4)

Toxicity Type (Units)[a]	Species/ Sex	Critical Effect	Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Rat/M/F	Questionable effects on brain and heart weights	3×10^{-1}	NOAEL	270	1000	Sauerhoff et al. (1976a)
Chronic RfD (mg/kg-d)	Rat/M	Biologically significant decrease in body weight	7×10^{-2}	NOAEL	74	1000	Hirose et al. (1980a)
Subchronic p-RfC (mg/m^3)	ND						
Chronic p-RfC (mg/m^3)	ND						

ND = no data.

Table 5. Summary of Cancer Values for Ethylene Cyanohydrin (CASRN 109-78-4)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	ND			
p-IUR	ND			

ND = no data

DERIVATION OF ORAL REFERENCE DOSE

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

Two subchronic-duration oral studies were located: Sauerhoff et al. (1976a) and Bachhuber et al. (1955). The highest doses tested were similar in these studies; however, the parameters examined and reported were very limited in the study by Bachhuber et al. (1955). The point of departure (POD) is the NOAEL identified at the highest dose tested (Sauerhoff et al., 1976a). Therefore, the study by Sauerhoff et al. (1976a) serves as the principal study for derivation of the subchronic p-RfD. It should be emphasized that the subchronic p-RfD is based on a free standing NOAEL with questionable effects on brain and heart weights.

Sauerhoff et al. (1976a) was conducted prior to the adoption of GLP standards. However, this peer-reviewed study generally meets the standards of study design and performance with regard to numbers of animals, examination of potential toxicity endpoints, and presentation of information.

Adjusted for daily exposure:

The following dosimetric adjustments were made for each dose in the principal study for dietary treatment.

$$\begin{aligned} NOAEL_{ADJ} &= NOAEL \times [\text{conversion to daily dose}] \\ &= 270 \text{ mg/kg-day} \times (\text{days of week dosed} \div 7 \text{ days in week}) \\ &= 270 \text{ mg/kg-day} \times (7 \div 7) \\ &= 270 \text{ mg/kg-day} \end{aligned}$$

$$\begin{aligned} \textbf{Subchronic p-RfD} &= \textbf{NOAEL}_{\textbf{ADJ}} \div \textbf{UF}_{\textbf{C}} \\ &= 270 \text{ mg/kg-day} \div 1000 \\ &= \mathbf{3 \times 10^{-1} \text{ mg/kg-day}} \end{aligned}$$

Table 6 summarizes the uncertainty factors (UFs) for the subchronic p-RfD for ethylene cyanohydrin, and the confidence descriptors for the subchronic p-RfD are provided in Table 7.

Table 6. UFs for Subchronic p-RfD of Ethylene Cyanohydrin

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans.
UF_D	10	A UF_D of 10 is selected because there are no acceptable two-generation reproductive or developmental toxicity studies.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied for using a POD based on a NOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study was utilized as the critical study.
UF_C	1000	

Table 7. Confidence Descriptor for Subchronic p-RfD for Ethylene Cyanohydrin		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in Study	M	The study was given a medium confidence level because the peer-reviewed study examined a wide range of doses on growth, food consumption, and hematological effects in male and female rats, but only limited data were available for independent verification of conclusions.
Confidence in Database	L	The database was given a low confidence level because only two subchronic-duration studies were located; no reproductive or developmental studies were located.
Confidence in Subchronic p-RfD[b]	L	The overall confidence in the subchronic p-RfD is low due to a lack of confidence in the database and the questionable effects on brain and heart weights that were observed.

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than the lowest entry in table.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

One combined chronic-duration toxicity-carcinogenicity report was located that addressed chronic-duration toxicity of ethylene cyanohydrin and is identified as the principal study for derivation of a chronic p-RfD (Hirose et al., 1980a,b). This single report details studies conducted in both the male rat and the male mouse. The critical effect for both species was decreased body weight at the high dose of 221 mg/kg-day for the rat and 539 mg/kg-day for the mouse. The body-weight decrease in mice was about 10% (36.9 g control vs. 36.8 g high-dose group) and is supported by decreased body weight in rats (562 g control vs. 486 g high-dose group). The rats showed decreased terminal body-weight in the two lower dosage groups (504 and 507 g); however, in the absence of standard deviation data, the magnitude of body-weight decrease in these two groups raises concern for the biological relevance in these two groups. Although the importance of this effect in the rat was dismissed in a previously published PPRTV document (U.S. EPA, 2005a) because statistical analyses and standard deviations were not reported, upon further consideration, the 13% decrease in body weights in rats exposed to the high dose is considered a potentially biologically significant effect as it was corroborated in another species. Furthermore, rats showed decreased hematological parameters in exposed groups; and in the absence of standard deviation values, the decreased Hb values in the high-dose groups (14–16% versus control) are considered potentially biologically relevant. The NOAEL (74 mg/kg-day) identified in male rats based on decreased body weights and supported by decreased hematological parameters (reduced Hb values) is selected as the POD.

Hirose et al. (1980) was conducted prior to the adoption of GLP standards. This peer-reviewed study generally meets the standards of study design and performance with regard to numbers of animals, examination of potential toxicity endpoints, and presentation of information. However, test chemical purity was not reported.

Adjusted for daily exposure:

The following dosimetric adjustments were made for each dose in the principal study for dietary treatment.

$NOAEL_{ADJ}$ = NOAEL × [conversion to daily dose]
= 74 mg/kg-day × (days of week dosed ÷ 7 days in week)
= 74 mg/kg-day × 7 ÷ 7
= 74 mg/kg-day

Chronic p-RfD = $NOAEL_{ADJ} \div UF_C$
= 74 mg/kg-day ÷ 1000
= **7×10^{-2} mg/kg-day**

Table 8 summarizes the UFs for the chronic p-RfD for ethylene cyanohydrin, and the confidence descriptors for the chronic p-RfD are provided in Table 9.

Table 8. UFs for Chronic p-RfD of Ethylene Cyanohydrin

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans.
UF_D	10	A UF_D of 10 is selected because there are no acceptable two-generation reproduction studies or developmental studies.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied for using a POD based on a NOAEL.
UF_S	1	A UF_S of 1 is applied because a chronic-duration study was utilized as the critical study.
UF_C	1000	

Table 9. Confidence Descriptor for Chronic p-RfD for Ethylene Cyanohydrin		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in Study	M	The study was given a medium confidence level because the peer-reviewed study examined a variety of hematological effects and organ weight changes, but only limited data were available for independent verification of conclusions.
Confidence in Database	L	The database was given a low confidence level because only two subchronic-duration studies were located; no reproductive or developmental studies were located.
Confidence in Subchronic p-RfD[b]	L	The overall confidence in the subchronic p-RfD is low due to a lack of confidence in the database and the level of response in the endpoint that was selected for the POD.

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than the lowest entry in table.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No published studies investigating the effects of subchronic- or chronic-duration inhalation toxicity of ethylene cyanohydrin in humans or animals were identified that were acceptable for use for dose response assessment.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

IRIS (U.S. EPA, 2011a) does not provide a cancer WOE descriptor for the oral or inhalation routes. A combined chronic-duration toxicity-carcinogenicity report detailing studies performed both in the rat and the mouse was located that addressed the carcinogenic potential of ethylene cyanohydrin (Hirose et al., 1980a,b). There was no evidence of carcinogenicity. The cancer WOE descriptor (see Table 10) is considered to be "Inadequate Information to Assess Carcinogenic Potential."

Table 10. Cancer WOE Descriptor for Ethylene Cyanohydrin (CASRN 109-78-4)			
Possible WOE Descriptor	**Designation**	**Route of Entry (oral, inhalation, or both)**	**Comments**
"Carcinogenic to Humans"	NS	NA	There are no human data available.
"Likely to be Carcinogenic to Humans"	NS	NA	There is not enough evidence to support this statement.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	There is not enough evidence to support this statement.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**One study was conducted in rats and mice for 78 wk at doses resulting in decreased body weights without any increase in the incidence of neoplastic lesions (Hirose et al., 1980a,b). The duration of this study is shorter than the preferred lifetime exposure, which may have prevented identifying carcinogenicity later in life. There are no studies describing carcinogenicity following an inhalation exposure.**
"Not Likely to be Carcinogenic to Humans"	NS	NA	There is not enough evidence to support this statement.

NS = not selected; NA = not applicable.

MODE-OF-ACTION (MOA) DISCUSSION

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b) define MOA "… as a sequence of key events and processes starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation" (p. 1−10). Examples of possible modes of carcinogenic action for any given chemical include "… mutagenicity, mitogenesis, programmed cell death, cytotoxicity with reparative cell proliferation, and immune suppression" (p. 1−10). No carcinogenicity studies in human or animals demonstrating carcinogenic potential of cyanohydrin were located (see the "Cancer Weight-of-Evidence Descriptor" above).

MUTAGENIC MOA

Ethylene cyanohydrin was not mutagenic in *Salmonella typhimurium* TA97, TA98, TA100, TA1535, or TA1537 (with or without activation) or *Klebsiella pneumoniae* (without activation). There is no evidence of carcinogenic potential in humans or animals.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of data on the carcinogenicity of ethylene cyanohydrin precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

APPENDIX A. PROVISIONAL SCREENING VALUES

There are no provisional screening values for ethylene cyanohydrin.

APPENDIX B. DATA TABLES

Table B.1. Body Weights (g) in Male Rodents Treated with Ethylene Cyanohydrin in the Diet for 78 Weeks[a]

	Dose ppm (HED_{ADJ} mg/kg-day)			
	Rat			
Body weights	**0 (0)**	**100 (7)**	**1000 (74)**	**3000 (221)**
Initial	148.0	148.6	148.7	150.4
Final	562.0	504.0 (↓10)	507.5 (↓10)	486.3 (↓13)
	Mouse			
Body weights	**0 (0)**	**100 (18)**	**1000 (180)**	**3000 (539)**
Initial	36.9	37.1	36.6	36.8
Final	46.7	46.2 (↓1%)	43.2 (↓7%)	42.0 (↓10)

[a]Data were obtained from Table 1 on page 3 of the study by Hirose et al. (1980). Percent difference from controls is included in parentheses and was calculated by the reviewers.

Table B.2. Mean Hematological and Blood Biochemical Values of Male Rats Treated with Ethylene Cyanohydrin for 78 Weeks[a]

Group	Dose (ppm)	No. of Rats	RBC ($\times 10^4$/mm^3)	WBC ($\times 10^2$/mm^3)	Hb (mg/dL)	Ht (%)	SGOP (K units)	SGPT (K units)	SAP (KA units)	Glucose (mg/dL)	TP (g/dL)	BUN (mg/dL)
1	3000	19	624	78	11.8	41.0	130	30	14.5	68	6.9	20
2	1000	24	713	86	13.8	43.6	128	30	14.3	73	6.5	13
3	100	20	701	98	13.8	45.5	130	22	14.8	75	6.9	18
4	0	13	727	103	14.0	49.0	127	23	11.7	74	6.4	19

[a]Hirose et al. (1980a).

APPENDIX C. BMD MODELING OUTPUTS FOR ETHYLENE CYANOHYDRIN

No data supported BMD modeling.

APPENDIX D. REFERENCES

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