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Provisional Peer-Reviewed Toxicity Values for

Acetone Cyanohydrin
(CASRN 75-86-5)

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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 National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

TABLE OF CONTENTS

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 ACETONE CYANOHYDRIN (CASRN 75-86-5)

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

Acetone cyanohydrin (C_4H_7NO; see Figure 1), CAS No. 75-86-5, is a colorless liquid with an odor of bitter almonds. It is used in the manufacturing of insecticides, as an intermediate for pharmaceuticals, and as a chemical intermediate for production of methyl methacrylate, methacrylic acid, and higher methacrylate esters (HSDB, 2011). A table of physicochemical properties is provided below (see Table 1).

Table 1. Physicochemical Properties of Acetone Cyanohydrin (CASRN 75-86-5)[a]

Property (Unit)	Value
Boiling point (ºC)	95
Melting point (ºC)	-19
Density (g/cm^3)	0.93
Vapor pressure (kPa at 20ºC)	3.0
pH (unitless)	No data
Solubility in water (g/100 mL at 25ºC)	Soluble in water (dissociates to form hydrogen cyanide and acetone)
Relative vapor density (air = 1)	2.93
Molecular weight (g/mol)	85.1

[a]WHO (2004).

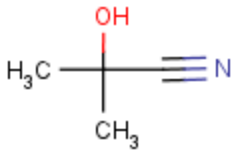

Figure 1. Acetone Cyanohydrin Structure

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment for acetone cyanohydrin is included in the United States Environmental Protection Agency (U.S. EPA) Integrated Risk Information System (IRIS; U.S. EPA, 2010b) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). No RfD or RfC values are reported in the Health Effects Assessment Summary Tables (HEAST; U.S. EPA 2010a). Provisional subchronic and chronic oral RfDs have been derived by U.S. EPA as a part of the Provisional Peer-Reviewed Toxicity Value program (PPRTV) (U.S. EPA, 2004). The RfDs are based on a subchronic gavage study in Sprague-Dawley rats (Ogrowsky, 1988—laboratory was Hazelton Laboratories America, Inc.) with a No-Observed-Adverse-Effect Level (NOAEL) of 8.75 mg/kg-day based on death at the Lowest-Observed-Adverse-Effect Level (LOAEL) 15 mg/kg-day, which is also considered a frank effect level (FEL). The subchronic p-RfD was 3×10^{-2} mg/kg-day. This value included a composite uncertainty factor (UF_C) of 300 (10 each for intraspecies variability, interspecies extrapolation, and 3 for a deficient database lacking a supporting chronic or subchronic study, a developmental toxicity study in a second species, and a

multi-generation reproduction study). The chronic p-RfD was 3×10^{-3} mg/kg-day with a UF_C of 3000 (10 each for intraspecies variability, interspecies extrapolation, extrapolation from a subchronic to chronic data, and 3 for a deficient database lacking a supporting chronic or subchronic study, a developmental toxicity study in a second species, and a multi-generation reproduction study) (U.S. EPA, 2004). A reevaluation of the Ogrowsky (1988) study for the current acetone cyanohydrin PPRTV identified 2.5 mg/kg-day as a FEL based on mortality in both male (2/20) and female rats (2/20).

The Chemical Assessments and Related Activities (CARA; U.S. EPA, 1994) list included a Health and Environmental Effects Profile (HEEP) for acetone cyanohydrin (U.S. EPA, 1985); however, the document is unavailable for review. The toxicity of acetone cyanohydrin has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2010). The World Health Organization (WHO, 2004) listed an occupational exposure limit (OEL) of 4.7 ppm or 5 mg/m^3 for acetone cyanohydrin as hydrogen cyanide (HCN) along with a skin notation based on a threshold limit value (TLV) derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2008). The National Institute of Occupational Safety and Health (NIOSH, 2010) listed 4 mg/m^3 (15-minute exposure) as a recommended exposure limit (REL) for acetone cyanohydrin. No OEL was adopted by the Occupational Safety and Health Administration (OSHA, 2006). The California Environmental Protection Agency (CalEPA, 2008, 2009) has not derived toxicity values for exposure to acetone cyanohydrin.

The HEAST (U.S. EPA, 2010a) does not report a cancer weight-of-evidence (WOE) classification, an oral slope factor, or an inhalation unit risk for acetone cyanohydrin. The International Agency for Research on Cancer (IARC, 2010) has not reviewed the carcinogenic potential of acetone cyanohydrin. Acetone cyanohydrin is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2009) has not derived a quantitative estimate of carcinogenic potential for acetone cyanohydrin.

Literature searches were conducted on sources published from 1900 through September 13, 2011 for studies relevant to the derivation of provisional toxicity values for acetone cyanohydrin, CAS No. 75-86-5. 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); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for health-related 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 toxicity database for acetone cyanohydrin and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. Principal studies are identified in bold and are labeled PS. The phrase "statistical significance" used throughout the document indicates a *p*-value of <0.05.

Table 2. Summary of Potentially Relevant Data for Acetone Cyanohydrin (CASRN 75-86-5)

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							NA
Chronic	ND							NA
Developmental	ND							NA
Reproductive	ND							NA
Carcinogenicity	ND							NA
2. Inhalation (mg/m^3)[a]								
Subchronic	ND							NA
Chronic	ND							NA
Developmental	ND							NA
Reproductive	ND							NA
Carcinogenicity	ND							NA
Animal								
1. Oral (mg/kg-d)[a]								
Subchronic	20/20, Sprague-Dawley, Rat, gavage, 13 wk	0, 2.5, 8.75, 15	Mortality (≥10%) in males and females at all doses; increased absolute and relative liver weight in males	NA	NDr	2.5 (FEL)	Ogrowsky (1988)	NPR
Chronic	50 Albino Rat, Unspecified strain, sex, and route of administration; up to 8 mo	5 mg[c]	Effects not clearly reported	NDr	NDr	NDr	Motoc et al. (1971)	PR

Table 2. Summary of Potentially Relevant Data for Acetone Cyanohydrin (CASRN 75-86-5)

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]
Chronic	44 Albino Rat, 16 Rabbit, Unspecified strain, sex, dosing schedule, and route of administration; 6 mo	0.00005, 0.0005, 0.005, 1.33	Effects not clearly reported	NDr	NDr	NDr	Shkodich (1966, as reported in U.S. EPA, 1985)	NPR
Developmental	0/25, CD, Rat, gavage, GDs 6–15	0, 1, 3, 10	No treatment-related fetal malformations or developmental variations observed in any group	10 (maternal and developmental)	NDr	NA	International Research and Development Corporation (1986)	NPR
Reproductive	ND							NA
Carcinogenicity	ND							NA
2. Inhalation (mg/m^3)[a]								
Subchronic	**10/10, Sprague-Dawley, Rat, 6 hr/d, 5 d/wk, 28 d**	**0, 5.7, 18.6, 37.0 (extrarespiratory effects)**	**Breathing difficulties in males and females**	**5.7**	**NDr**	**18.6**	**Monsanto (1986b)**	**PS NPR**
	15/15, Sprague-Dawley, Rat, 6 hr/d, 5 d/wk, 14 wk	0, 6.3, 17.8, 35.9 (extrarespiratory effects)	No significant effects reported	35.9	NDr	NA	Monsanto (1986a)	NPR
Chronic	50 Albino Rat, Unspecified sex, strain; up to 8 mo	1 mL/84 L air[c]	Effects not clearly reported	NDr	NDr	NDr	Motoc et al. (1971)	PR
Developmental	ND							NA

Table 2. Summary of Potentially Relevant Data for Acetone Cyanohydrin (CASRN 75-86-5)

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]
Reproductive	0/24, Sprague-Dawley, Rat, inhalation, 6 hr/d, 7 d/wk, 21 d	0, 9.3, 26.5, 51.0 (extrarespiratory effects)	No significant effects reported	51.0	NDr	NA	Monsanto (1986c)	NPR
	15/0, Sprague-Dawley, Rat, inhalation, 6 hr/d, 5 d/wk, 10 wk	0, 6.2, 17.7, 35.6 (extrarespiratory effects)	No significant effects reported	35.6	NDr	NA	Monsanto (1986d)	NPR
Carcinogenicity	ND							NA

[a]Dosimetry: All exposure values of long-term exposure (4 weeks and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values for inhalation (cancer and noncancer), and oral (cancer only) are further converted to an HEC/HED. Values from animal developmental studies are not adjusted to a continuous exposure.

HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood:gas partition coefficient.

NA = not applicable, ND = No data, NDr = Not determined, hr = hour, d = day, wk = week.

[b]Notes: PS = principal study, PR = peer reviewed, NPR = not peer reviewed.

[c]Due to lack of clearly stated dosing methods and illegible data tables in the study report, an adjusted daily dose (oral) or HEC (inhalation) is not calculated for this study.

HUMAN STUDIES

Oral Exposures

The database of literature on the effects of oral exposure of humans to acetone cyanohydrin is limited to acute accidental exposures, coexposures with other chemicals, or combined exposure pathways (oral, dermal, and inhalation) (i.e., Sunderman and Kincaid, 1953; Krefft, 1955; Lang and Stintzy, 1960; Thiess and Hey, 1969; Winter et al., 1989; Sinitsyna, 1993). Because the specific duration and route of exposure are unclear, these studies are considered inappropriate for deriving a provisional oral reference dose.

Inhalation Exposures

Similarly, the literature database on effects of inhalation exposure of humans to acetone cyanohydrin are limited to acute accidental and multiple exposure pathways (i.e., Sunderman and Kincaid, 1953; Krefft, 1955; Lang and Stintzy, 1960; Thiess and Hey, 1969; Winter et al., 1989; Sinitsyna, 1993). These studies in humans are not considered appropriate for deriving a provisional inhalation reference concentration because details on the inhalation exposure to acetone cyanohydrin were not well reported, and the literature describes acute exposures.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to acetone cyanohydrin have been evaluated in one subchronic-duration study (i.e., Ogrowsky, 1988), one chronic-duration study (i.e., Motoc et al., 1971), and one developmental study (i.e., International Research and Development Corporation, 1986). No reproductive or carcinogenicity studies were identified in the literature.

Short-Term Studies

No information is available.

Subchronic-Duration Study

Ogrowsky (1988)

Ogrowsky (1988), from Hazelton Laboratories of America, Inc., conducted an unpublished, GLP-compliant subchronic oral toxicity study in Sprague-Dawley rats. Male and female rats (20/sex/dose; Charles River Breeding Laboratories, Inc., Raleigh, North Carolina) received 0, 2.5, 8.75, or 15 mg/kg-day acetone cyanohydrin in 0.01 N sulfuric acid via gavage for 13 weeks. The control group received vehicle only. The test material was stated to be >98% pure, and the stock and dosing solutions were stored in light-restrictive containers during the study. Animals were 43 days old at study initiation. Males weighed 174.9–231.7 g and females weighed 130.2–182.3 g at study initiation. The rats were provided Purina Certified Rodent Chow® and tap water ad libitum and were maintained on a 12-hour light/dark cycle.

The rats were observed for overt signs of toxicity 1 hour after daily dosing and were checked for mortality or moribundity twice daily. The rats were physically examined weekly beginning at the initiation of the study. Body weight and food consumption were also recorded weekly. Ophthalmological examinations were performed prior to study initiation and during the final week of dosing. Five untreated rats per sex were examined for clinical pathology prior to study initiation. On Weeks 4 and 13, the first 10 survivors/sex/dose group were also examined for clinical pathology. Blood samples were collected via the orbital sinus while rats were under carbon dioxide anesthesia. Clinical pathology included hematological and serum chemistry examinations. Hematological parameters examined included the following: leukocyte count

(total and differential), erythrocyte count, hemoglobin, hematocrit, platelet count, reticulocyte count, and cell morphology. Serum chemistry parameters examined included: sodium, potassium, chloride, total protein, albumin, calcium, phosphorous, total bilirubin, urea nitrogen, creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), globulin, alkaline phosphatase (ALP), cholesterol, albumin:globulin ratio, and lactate dehydrogenase. All surviving rats at Week 13 and all rats that died during the study were necropsied. The external surface, cranial cavity, carcass, external surface of the brain, thoracic, abdominal, and pelvic cavities and their viscera, tissues and organs of the neck region, and all orifices, were examined. The following organs were weighed: liver, kidneys, spleen, heart, adrenal glands, the brain with stem, and testes with epididymides or ovaries. The following tissues were excised and examined microscopically for histopathology in all rats: gross lesions, lungs, liver, and kidneys. For all control and high-dose rats and for all rats not surviving until study termination, the following organs were also examined: all gross lesions, brain with brainstem (medulla/pons, cerebellar cortex, and cerebral cortex), pituitary, thyroid with parathyroids, thymus, lungs, trachea, heart, mandibular salivary glands, liver, sternum with bone marrow, mammary gland, thigh musculature, eyes, skin, epididymides, prostate, seminal vesicles, kidneys, adrenals, pancreas, testes or ovaries, spleen, aorta, esophagus, stomach (forestomach and glandular), duodenum, jejunum, ileum, colon, cecum, rectum, urinary bladder, mesenteric lymph node, sciatic nerve, femur including articular surface, cervical spinal cord, mid-thoracic spinal cord, lumbar spinal cord, and exorbital lacrimal glands.

Cumulative survival data were analyzed using Life Table Analysis in the National Cancer Institute Package using Fisher's Exact Test to compare groups. Total body-weight gain, food consumption, clinical pathology, and organ-weight data were compared between treated and control rats of the same sex. Food consumption was assessed for Weeks 1–5, 5–9, and 9–13. These data were first analyzed using Levene's test for homogeneity of variance. Heterogeneous data were then transformed and retested for homogeneity of variance using the following transformations, in order, until the transformed data were homogeneous or until none of the transformations resulted in homogeneous data: log10, square, square root, reciprocal, angular (arcsine), or rank transformation. Homogeneous and/or transformed data were then analyzed using ANOVA. Where statistically significant results were indicated, Dunnett's t-test was used to assess difference between treated rats and controls, by sex.

The study author reported a statistically significant positive trend in mortality in males. Ten percent mortality (2/20) was observed in males receiving 2.5 and 8.75 mg/kg-day acetone cyanohydrin, and 25% mortality (5/20) was observed in males receiving 15 mg/kg-day acetone cyanohydrin. While there was no statistically significant positive trend in mortality observed in females, 10% mortality (2/20) was observed in all treated female groups. Importantly, no deaths were observed in the control group for either males or females. The study authors reported a statistically significant increase in absolute liver weight (19% increase compared to control) in males of the 15 mg/kg-day dose group (see Table B.1). The study author also observed a statistically significant increase in relative liver weight in males of the 8.75 and 15 mg/kg-day dose groups; however, these data are illegible and cannot be reported. No other treatment-related absolute or relative organ weight effects were observed. There were no significant differences in clinical observations, body-weight gain, food consumption, or the results of ophthalmological examinations between treated and control rats. For the clinical pathology parameters examined, the study author did not observe any treatment-related effects. Gross pathology and histopathology did not reveal any treatment-related effects. Due to frank effects

(≥10% mortality) observed in both male and females at all doses tested, identification of a NOAEL or LOAEL is precluded for this study.

Chronic-Duration Study

Motoc et al. (1971)

Motoc et al. (1971) conducted a peer-reviewed toxicity study originally published in French and translated to English. Both oral and inhalation exposures were investigated in this study. The study authors administered 5 mg acetone cyanohydrin (vehicle and purity not reported) to 6 groups of 50 albino rats of unspecified strain and sex via "digestive route" twice per week for 3, 5, or 8 months. The corresponding adjusted daily dose cannot be determined because the experimental design for the compound administration is not clearly reported. The study report provided data on the total amount of substance administered per kg/body weight; however, these data are illegible. Details regarding animal husbandry were not reported. The study authors did not report whether the study adhered to GLP standards. Based on information in the study data tables, rats were sacrificed at 3, 5, and 8 months, although this is not explicitly stated in the experimental methods. At necropsy, blood, stomach, liver, and kidneys were removed. Biochemical analysis of the blood serum was carried out to determine enzyme activity of leucine aminopeptidase (LAP), transaminases (ALT and AST), aldolase (Ald), glucose-6-phosphate dehydrogenase (G6P-D), total proteins, electrophoretic fractions, and glucoproteins. The study authors also used H&E and VG stains and a lipid histogram made on silica gel to detect proteins, lipids, mucopolysaccharides, nucleic acids, ATPase, G6P-D, β-glucuronidase, nonspecific esterase, and dehydrogenases (lactate, succinic, and malate).

The biochemical results were reported in graphs not included in the study document. Several of these results were mentioned in the discussion, including decreased albumin/globulin ratio and albumin; changes AST and ALT (direction of change not specified); and increased γ-globulins, serum glucoproteins, β-glucuronidase, LAP, G6P-D, and Ald activity compared to control; however, the study authors do not clearly specify whether these effects occurred as a result of oral or inhalation exposure. Furthermore, the timepoint at which the biochemical parameters were measured is not specified. The study authors concluded that rats in the exposed group exhibited varying degenerative lesions in the stomach as well as reversible and irreversible degenerative lesions in the liver and kidney. The study authors did not delineate the meaning of reversible versus irreversible lesions. Stomach lesions were reported to increase in severity over the study period whereas liver lesions decreased in reversibility in the last two stages of the study. Lesions in the kidney were reported to be less severe and irreversible in the last study stage. The study authors did not specify the number of rats in the treatment groups displaying any of the noted effects or at which exposure duration the effects occurred. No other effects were reported. Due to lack of dosing information and poor reporting of methods and results, identification of a NOAEL or LOAEL is precluded for this study.

Shkodich (1966, as reported in U.S. EPA, 1985)

In an oral toxicity study originally published in Russian, Shkodich (1966) studied the chronic toxicity of acetone cyanohydrin in 44 albino rats and 16 rabbits given 0.00005, 0.0005, 0.005, and 1.33 mg/kg-day for 6 months (as reported in U.S. EPA, 1985). Details on the sex and strain of the rats and rabbits used, as well as the route of dose administration and dosing schedule were not provided. The U.S. EPA (1985) report states that in rats, there were increases in erythrocytes, reticulocytes and hemoglobin, as well as increased liver and adrenal vitamin C at 1.33 mg/kg-day. Decreased brain sulfhydryl content and decreased serum catalase and

cholinesterase were also observed at 1.33 mg/kg-day. Changes in serum catalase and cholinesterase were also reported at 0.0005 mg/kg-day, but the directionality is unknown. Nervous system effects qualitatively described as "attenuation of the processes of internal inhibition and certain intensification of the excitatory process" were reported at 0.0005 and 1.33 mg/kg-day. It was not clear if the changes observed at 0.0005 and 1.33 mg/kg-day were also observed at 0.005 mg/kg-day. In rabbits, a reduced rate of galactose utilization and decreased serum sulfhydryl concentration was observed at 1.33 mg/kg-day. The study author did not specify the number of rats or rabbits in the treatment groups displaying any of the noted effects. Due to lack of dosing information and poor reporting of methods and results, identification of a NOAEL or LOAEL is precluded for this study.

Developmental Study

International Research and Development Corporation (1986)

In an unpublished, non-peer-reviewed developmental study, International Research and Development Corporation (1986) investigated the potential teratogenic effects of acetone cyanohydrin in rats. Seventy-five pregnant Charles River COBS CD rats (25/dose) were administered single daily gavage doses of 1, 3, or 10 mg/kg-day (5.0 mL/kg volume) of acetone cyanohydrin (purity not reported) in deionized water vehicle on gestation days (GDs) 6–15. Doses were calculated using body-weight measurements taken on GDs 6, 9, and 12. A control group of 25 female rats received deionized water over the same test conditions and period. Rat body weights were recorded on GDs 0, 6, 9, 12, 16, and 20. Prior to treatment, rats were observed for mortality and changes in appearance and behavior twice daily and once daily for clinical signs on GDs 6–20. On GD 20, surviving females were sacrificed, and fetuses were removed via Cesarean section for teratologic evaluation. Maternal tissues were preserved for examination of gross findings. The study was reported to adhere to GLP guidelines.

Rats were provided with Purina Certified Rodent Chow #5002 and tap water ad libitum throughout the study period. Animal rooms were environmentally controlled at approximately 21–23°C and 25–78% humidity. Prior to mating, 131 virgin female Charles River COBS CD rats were acclimated and observed for changes in appearance and behavior for 29 days. During acclimation, rats were housed in individual hanging wire-mesh cages. After the acclimation period, rats were weighed and physically examined for suitability to mate. One male and one female rat of the same strain and source were housed together for mating. Successfully mated females were returned to individual cages and assigned to control or treated groups using a block design.

Mated females were sacrificed on GD 20 to determine the number and location of viable and nonviable fetuses, early and late resorptions, and total number of implantations and corpora lutea. Gross necropsies on females included examinations of abdominal and thoracic cavities, organs, and morphological changes. One hundred litters were weighed, sexed, and examined for malformations and developmental variations including the palate and eyes. Fetuses were examined externally, viscerally, and skeletally using the Wilson razor-blade sectioning technique and Dawson method.

All comparisons of the treatment groups to the control groups were performed at significance levels of $p < 0.05$ and $p < 0.01$. The study authors used χ^2 tests with Yates's correction and Fisher's exact tests for identifying statistically significant differences in male to female fetal sex ratios and proportions of litter malformations. Mann-Whitney U-test was used

to compare the proportion of resorbed and dead fetuses and postimplantation losses. Bartlett's test was used to determine homogeneity of variances. T-tests were used to calculate equal or unequal variances.

The study authors reported no maternal deaths in treated and control groups. Differences in antemortem and necropsy observations were found to be statistically nonsignificant between dams in the control and treated groups. Clinical observations included hair loss, soft stool, and scabbing on the nose. Instances of red, swollen hindlimbs were reported in the 1 mg/kg-day dose group, and lower lip nodules were reported in the 10 mg/kg-day dose group. Control-group necropsy observations include single instances of hydronephrosis, intestinal worms, and subcutaneous abdominal mass. Gross lesions were not identified in the treated animals. The study authors concluded that the decrease in body-weight gain during treatment and GDs 12–16 and 16–20 in the 3 and 10 mg/kg-day dose groups were not treatment related. Body-weight changes observed in the 1 mg/kg-day dose group during treatment Days 6–15 (GDs 0–20) were not considered treatment related.

The study authors reported no differences in Cesarean section observations between the control group and the 1 or 3 mg/kg-day dose groups. Similarly, the number of viable fetuses per dam, mean postimplantation losses per dam, fetal body weights, and fetal sex distribution were comparable between the control group and dosed groups. The study authors reported significantly fewer corpora lutea ($p < 0.05$) and total implantations ($p < 0.01$) per dam in the 10 mg/kg-day dose group compared to the control group; however, the study authors did not consider this effect related to treatment because the values were established prior to compound administration. Table B.2 shows the mean maternal and fetal observations at Cesarean section.

The study authors reported no significant differences between the control and treated groups for incidence of fetal malformations and developmental variations. Two to three incidences of microphthalmia were reported within the control and all three treated groups. The study authors concluded that the following malformations were not "biologically relevant:" transposition of great vessels with right-sided aortic arch, interventricular septal defect, malpositioned heart, malformed lungs, diaphragmatic hernia, vestigial uterine horn, and bent ribs.

The study authors concluded that orally administered acetone cyanohydrin at dose levels up to 10 mg/kg-day did not produce a teratogenic response in Charles River COBS CD rats. Thus, a NOAEL of 10 mg/kg-day (the highest dose tested) is identified from the study.

Reproductive Studies
No information is available.

Carcinogenicity Studies
No information is available.

Inhalation Exposures

The effects of inhalation exposure of animals to acetone cyanohydrin have been evaluated in two subchronic-duration studies (i.e., Monsanto 1986a,b), one chronic-duration study (i.e., Motoc et al., 1971), and two reproductive toxicity studies examining the effect of

acetone cyanohydrin on fertility (i.e., Monsanto, 1986c,d). No carcinogenicity studies were identified in the literature.

Short-Term Study

Sunderman and Kinkaid (1953)

Sunderman and Kinkaid (1953) conducted a published acute-duration toxicity study. The study authors exposed 125 Wistar albino rats of unspecified sex and origin to 250 mL (~95% purity) of acetone cyanohydrin by placing the material in a saturator comprised of a glass vessel with a glass disperser immersed to a depth of 13 cm. Air was passed through a calcium chloride drying tower, through the saturator, and, finally, through a dessicator (total void 8 L) at 23°C. The corresponding adjusted daily dose cannot be determined since the study does not involve a standard exposure duration or number of days, and the study authors do not report the total exposure time. Details regarding animal husbandry and handling were not reported. The study compliance with GLP standards was not reported. The study authors reported animal collapse after 4 minutes and death after 11 minutes following exposure to air saturated with acetone cyanohydrin. At approximately 10 minutes, 50% mortality occurred.

Of the 125 animals used in the study, only 15 were deemed to be employed under sufficiently controlled conditions. These 15 were included in the determination of the average exposure time required for death by the study authors. No other results were reported. Identification of a NOAEL or LOAEL is precluded for this study.

Subchronic Studies

Monsanto (1986b)

The study by Monsanto (1986b) is selected as the principal study for derivation of both the screening subchronic and chronic provisional RfC. In an unpublished, subchronic inhalation toxicity study conducted by Monsanto (1986b), the study authors exposed groups of 10 male and 10 female Sprague-Dawley rats (Crl:CD®[S-D]BR) to mean analytical concentrations of 0, 9.2, 29.9, or 59.6 ppm acetone cyanohydrin vapor (purity 99.21%) via whole-body inhalation exposure for 6 hours/day, 5 days/week, for 28 days. The corresponding concentrations adjusted for continuous exposure over 24 hours/day, 7 days/week are 5.7, 18.6, and 37.0 mg/m^3, respectively. The study authors did not state whether the experiment adhered to GLP standards. Animals were obtained from the Charles River Breeding Laboratories (Portage, MI). After a quarantine period (8 days), animals were randomly assigned on the basis of body weight to each of the four exposure concentrations and housed individually in suspended stainless steel wire mesh cages in rooms routinely maintained at 70–74ºF, 30–65% relative humidity, with a 12-hour light/dark cycle. Ralston-Purina Certified Rodent Chow® and tap water were available ad libitum except during the exposure period. During exposure, the rats were individually housed in suspended wire mesh cages within Rochester-type stainless steel and glass exposure chambers (10 m^3 volume).

Animals were examined for gross signs of toxicity prior to and following each exposure. During exposure, animals were observed between the second and fifth hours to estimate the percentage of subjects exhibiting signs of toxicity (hypoactivity, hyperactivity, tremors and/or convulsions, irritation of the eyes and/or nose, and breathing difficulties). Animals were weighed and examined weekly for gross signs of toxicity. Mortality was checked and recorded on nonexposure days. Five animals per sex per group (with the exception of high-dose males in which mortality occurred prior to sacrifice) were randomly selected for each of the two

scheduled necropsy days. Urine was collected overnight from each animal prior to sacrifice. At necropsy, blood samples were taken for hematology assays (red blood cell count [RBC], white blood cell count [WBC], hemoglobin [HGB], hematocrit [HCT], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]) and serum chemistry analysis (alkaline phosphatase [ALP], alanine aminotransferase [ALT], blood urea nitrogen [BUN], glucose, total protein, lactic dehydrogenase [LDH], LDH isoenzymes, bilirubin, thiocyanate, T_3, T_4). Serum proteins were analyzed by electrophoresis. Urine samples were analyzed for thiocyanate. The study authors conducted gross pathology on the following tissues: abdominal aorta, adrenals, bone and bone marrow from the femur, brain, esophagus, eyes with optic nerve, ovaries, testes with epididymides, heart, kidneys, liver, lung (with mainstem bronchi), lymph nodes, mammary gland (if present), nasal turbinates, pancreas, pituitary, prostate, salivary gland, sciatic nerve, skeletal muscle, skin, spleen, stomach, thymus, trachea, thyroid/parathyroid, urinary bladder, uterus, and any gross lesions. Additionally, the following organs were weighed: adrenals, brain, testes (with epididymides), heart, kidneys, liver, pituitary, and spleen. The following select tissues from the control and high level exposure animals were examined microscopically: adrenals, bone and bone marrow, brain, eyes with optic nerves, intestine (duodenum), liver, lung, trachea, stomach, spleen, kidneys, heart, testes, skeletal muscle, thyroid, and nasal turbinates. The study authors analyzed differences in body weight, absolute organ weight, and clinical chemistry data using Dunnett's two-tailed test. Significant differences in organ-to-body-weight ratios were analyzed using the Mann-Whitney test with Bonferroni's inequality. Frequency of lesions was compared using Fisher's exact test with Bonferroni's inequality.

During exposure, irritation of the eyes and/or nose and breathing difficulties were noted in all animals in the mid- and high-exposure groups, and hypoactivity was observed in all animals in the high-exposure group. Respiratory distress (4/10), tremors and/or convulsions (3/10), foaming at the mouth (2/10), and prostrate posture (4/10) were observed in high-exposure males after the first exposure. Signs of acute toxicity were followed by death in 3/10 high-exposure males. Chromorhinorrhea (5/10 mid-exposure males, 1/10 mid-exposure females, 8/10 high-exposure males, 1/10 high-exposure females) and irritation around the ear (all males and females in mid and high-exposure groups) were noted during exposure, as well as during weekly weigh periods. Mean body weights of high-dose males were lower than controls; however, these changes were not significant and were within 10% of control values. RBC, HGB, and MCHC were significantly decreased in high-exposure females (see Table B.3). Urine thiocyanate levels were statistically significantly elevated in all animals in the mid and high-exposure groups. Serum thiocyanate levels were also statistically significantly elevated in all animals in the low- and mid-exposure groups. These markers serve as indicators that acetone cyanohydrin was absorbed in the animals. The study authors reported that total serum protein was statistically significantly decreased in the mid- and high-exposure males, and nonsignificantly decreased at the lowest concentration. Serum T_3 levels were elevated, and LDH levels were decreased significantly in the mid-exposure males. BUN levels were significantly elevated in the high exposure females. No biologically significant changes were reported in the serum protein fraction or LDH isoenzyme levels. No gross or microscopic exposure-related lesions were observed. No significant changes in absolute organ weights or terminal body weights were observed. The mean liver-to-terminal-body-weight ratio was significantly increased in mid-exposure males (6% increase compared to control), although this change is <10% and not considered to be biologically significant (see Table B.4). Based on increased incidence of clinical signs of breathing difficulties observed in mid-dose males and females, the

study authors identified a NOAEL of 5.7 mg/m^3 (5.7 mg/m^3 HEC for extrarespiratory effects). The corresponding LOAEL is 18.6 mg/m^3 (18.6 mg/m^3 HEC for extrarespiratory effects) (see Table B.3).

Monsanto (1986a)

Monsanto (1986a) conducted an unpublished, 14-week subchronic toxicity study. The study authors exposed groups of 15 male and 15 female Sprague-Dawley rats (Crl:CD®[S-D]BR) to mean analytical concentrations of 0, 10.1, 28.6, or 57.7 ppm acetone cyanohydrin (purity 97.79–98.13 %), 6 hours/day, 5 days/week, for 14 weeks, with a minimum of 69 exposure days. The corresponding concentrations adjusted for continuous exposure over 24 hours/day, 7 days/week are 0, 6.3, 17.8, and 35.9 mg/m^3, respectively. The study authors did not state whether the experiment adhered to GLP standards. Animals were obtained from the Charles River Breeding Laboratories (Portage, MI). After a quarantine period (10 days), animals were randomly assigned on the basis of body weight to each of the four exposure groups and housed individually in suspended stainless steel wire mesh cages in rooms routinely maintained at 70–74ºF, 35–60% relative humidity, with a 12-hour light/dark cycle. Purina Laboratory Certified Rodent Chow® and tap water were available ad libitum except during the exposure period.

Animals were examined for gross signs of toxicity prior to and following each exposure. During exposure, animals were observed between the second and fifth hours to estimate the percentage of subjects exhibiting signs of toxicity (hypoactivity, hyperactivity, tremors and/or convulsions, irritation of the eyes and/or nose, and breathing difficulties). Animals were weighed and examined weekly for gross signs of toxicity. Five animals per sex per group were randomly selected for each of the three scheduled necropsy days. Urine was collected overnight from each animal prior to sacrifice. At necropsy, blood samples were taken for hematology (RBC, WBC [total and differential], HGB, HCT, MCV, MCH, MCHC, platelets, reticulocyte count) and serum chemistry analysis (ALP, AST, ALT, BUN, glucose, total protein, globulin, albumin, LDH, total bilirubin, thiocyanate, T_3, T_4, and serum protein electrophoresis). Urine and serum samples were also analyzed for thiocyanate. The study authors also examined the following tissues microscopically: abdominal aorta, adrenals, bone and bone marrow from the femur, brain, esophagus, eyes with optic nerve, ovaries, testes with epididymides, heart, colon, ileum, kidneys, liver, lung (with mainstem bronchi), lymph nodes, mammary gland (if present), nasal turbinates, pancreas, pituitary, prostate, salivary gland, sciatic nerve, skeletal muscle, skin, spinal cord, spleen, stomach, thymus, trachea, thyroid/parathyroid, urinary bladder, uterus (including cervix). Additionally, the following organs were weighed: adrenals, testes (with epididymides), heart, kidneys, liver, and spleen. Body weight, absolute organ weight, and clinical chemistry were analyzed using Dunnett's test. Organ-to-body-weight ratios were compared to controls using the Mann-Whitney U test with Bonferroni's correction, and incidence of lesions were compared between treated groups and the control with Fisher's exact test with Bonferroni's inequality procedure.

The study authors reported no signs of toxicity during the exposure period. Pre and postexposure observations of swaying movement, ocular and integument conditions, salivation, and discharges about the nose were not considered exposure related by the study authors. With the exception of the highest exposure group of males on exposure Day 7, no significant decreases in mean body weight were observed throughout the study. No animals died during the course of exposure. Statistically significant changes in hematological parameters (MCHC and MCH for

males; RBC, HCT, MCV, MCH, MCHC for females) were observed in low- and mid-exposure animals; however, the study authors did not consider these values to be biologically significant because the values remained within the normal variation for rats, and no dose-response was observed. In the mid- and high-exposure groups of females, a dose-related decrease in glucose levels was observed as well as a significant decrease of globulin and total protein ($p = 0.01$) in the low- and mid-exposure females; however, the study authors did not consider these changes to be biologically significant because the values remained within the normal variation for rats. There were no significant differences in urinary output. There were no changes in serum protein fractions or in serum T_3 and T_4 levels. Urine thiocyanate levels were elevated significantly in the mid- and high-exposure animals ($p = 0.01$). Serum thiocyanate levels were increased significantly in the low- and mid-exposure females ($p = 0.01$). The presence of thiocyanate indicated that animals absorbed the test substance. No exposure-related lesions or microscopic lesions were observed. No changes in mean body weights, fasted body weights, absolute organ weights, or organ-to-body-weight ratios were observed in any exposure group. Based on the lack of toxic effects observed at the exposure concentrations tested, the study authors identified a NOAEL of 35.9 mg/m^3 (35.9 mg/m^3 HEC for extrarespiratory effects). This NOAEL represents the highest exposure concentration tested. A LOAEL is not identified from the study.

Chronic-Duration Studies

Motoc et al. (1971)

Motoc et al. (1971) conducted a chronic toxicity study originally published in French and translated to English. The study authors exposed groups of 50 albino rats of unspecified sex to acetone cyanohydrin (1 mL/84 L air) via inhalation twice per week (exposure length not specified) for the duration of the study (up to 8 months). The corresponding human equivalent concentrations (HECs) cannot be determined because the study does not specify the number of exposure hours per day and does not clearly indicate the study duration. Details regarding animal husbandry, animal handling, and the exposure chamber were not reported. Study authors did not report whether the experiment adhered to GLP standards. Based on information in a study table, the study authors appear to have sacrificed animals at 3, 5, and 8 months, although this is not explicitly stated in the experimental methods section. At sacrifice, blood, lungs, liver, and kidneys were removed. Biochemical analysis was carried out to determine enzyme activity of leucine aminopeptidase (LAP), transaminases (ALT and AST), aldolase (Ald), glucose-6-phosphate dehydrogenase (G6P-D), total proteins, electrophoretic fractions, and glucoproteins. The study authors also used H&E and V.G. stains and a lipid histogram made on silica gel to detect proteins, lipids, mucopolysaccharides, nucleic acids, ATPase, G6P-D, β-glucuronidase, nonspecific esterase, and dehydrogenases (lactate, succinic, and malate).

The biochemical results were reported in graphs not included in the study document. Several of these results are mentioned in the discussion, including decreased albumin/globulin ratio and albumin; changes AST and ALT (direction of change not specified); and increased γ-globulins, serum glucoproteins, β-glucuronidase, LAP, G6P-D, and Ald activity compared to control; however it is unclear at which exposure duration, substance, or route of administration pertains to these results. The study authors concluded that rats in the exposed group exhibited degenerative lesions in the lung with desquamation of the bronchial epithelium, irreversible degenerative lesions in the liver, and irreversible lesions in the kidney. The study authors did not elaborate on the type of pathology that they considered to be irreversible. The study authors did not specify the number of animals in the exposed group displaying any of the noted effects or at which exposure lengths the effects occurred. No other effects were reported. Due to lack of

dosing information and poor reporting of methods and results, a NOAEL or LOAEL are not determined from this study.

Developmental Studies
No information is available.

Reproductive Studies
Monsanto (1986c)
Monsanto (1986c) conducted an unpublished study that investigated the effects of inhaled acetone cyanohydrin to female fertility. The study authors exposed groups of 24 female Sprague-Dawley rats (Crl:CD®[S-D]BR) to mean analytical concentrations of 0, 10.7, 30.4, or 58.6 ppm acetone cyanohydrin vapor (purity 97.79–98.5%) via whole-body inhalation for 6 hours/day, 7 days/week, for 21 days (constant airflow of 1699 L/min in chamber). The corresponding concentrations adjusted for continuous exposure over 24 hours/day, 7 days/week are 0, 9.3, 26.5, or 51.0 mg/m^3. The study's compliance with GLP standards was not reported. Animals were obtained from the Charles River Breeding Laboratories (Portage, MI). After a quarantine period (7 days), animals were randomly assigned on the basis of body weight to each of the four groups, and housed individually in suspended stainless steel wire mesh cages in rooms routinely maintained at ~72ºF, 40–60% relative humidity, with a 12-hour light/dark cycle. Tap water treated with ion exchange water softener was available ad libitum. Purina Certified Rodent Chow® No. 5002 was also available ad libitum except during the exposure periods.

Female animals were treated for 21 exposure days and mated to untreated males. Exposure was then continued until copulation was confirmed or for a maximum of five nights cohoused with a male without signs of copulation. Females were given a thorough physical examination and weighed once per week and on GDs 0 and 13. Vaginal smears were performed on females without confirmed copulation on five consecutive days to evaluate the estrus cycle. Males were weighed prior to assignment in the study and the week prior to mating. Females were observed for clinical signs before and after exposures, and all animals were checked twice daily for gross abnormalities and mortality. Successfully mated females were sacrificed at GD 13; females without confirmed copulation were sacrificed in the second week after the last day of cohousing. Gross necropsies on females included examination of the external surface, tissues and organs of the thoracic and abdominal cavities for lesions, and pregnancy status. Nidations were classified and counted, and numbers of corpora lutea were recorded for pregnant females. The ovaries and uteri (including corpus and cervix) were preserved. No necropsies were performed on males. Body weights were analyzed using Dunnett's test, and counted and proportional data were evaluated with the Mann-Whitney U-test and Fisher's exact test, respectively, using Bonferroni's correctional inequality.

No mortalities were reported. The study authors did not report any treatment-related effects on body weight during exposure or during gestation for pregnant females. Red nasal discharge or encrustation was observed postexposure and appeared to be concentration-related in the third week of exposure. No significant clinical signs or treatment-related effects were reported during the weekly physical examinations or preexposure. No clinical signs of toxicity were observed during exposure. No significant difference was observed for terminal body weights, and no treatment-related lesions were reported. No treatment-related fertility effects were observed at any of the exposure concentrations. Efficiency in mating and pregnancy rates were similar in all exposure groups and in the control group. No significant differences were

observed in the pre or postimplantation loss for any of the exposure groups compared to controls. Five females did not exhibit confirmed copulation. Four of these five females exhibited signs of estrus during the five-day observation period, while the final female did not exhibit signs of estrus and was subsequently determined to be pregnant. No other significant effects were reported. Based on lack of treatment-related effects observed at any exposure concentration, the study authors identified a NOAEL of 51.0 mg/m^3 (51.0 mg/m^3 HEC for extrarespiratory effects). This NOAEL represents the highest exposure concentration tested in the study.

Monsanto (1986d)

Monsanto (1986d) conducted an unpublished study that investigated the effects of inhaled acetone cyanohydrin to fertility in male rats. The study authors exposed groups of 15 male Sprague-Dawley rats (Crl:CD®[S-D]BR) to mean analytical concentrations of 0, 10, 28.5, or 57.2 ppm acetone cyanohydrin vapor (purity 97.79–98.5%), 6 hours/day, 5 days/week for 10 weeks. The corresponding HECs are 0, 6.2, 17.7, and 35.6 mg/m^3 for extra-respiratory effects. The study compliance with GLP standards was not reported. Animals were obtained from the Charles River Breeding Laboratories (Portage, MI). After a quarantine period (7–10 days), animals were randomly assigned on the basis of body weight to each of the 4 groups, and housed individually in suspended stainless steel wire mesh cages in rooms routinely maintained at ~72ºF, 40–60% relative humidity, with a 12-hour light/dark cycle. Tap water treated with ion exchange water softener was available ad libitum. Purina Certified Rodent Chow® No. 5002 was also available ad libitum except during the exposure periods.

Male animals were treated for 48 days and then mated to untreated virgin females. Exposure was then continued for an additional 10 days. Males were weighed and given a thorough physical examination once per week. Females were weighed the week prior to mating and on GDs 0 and 13. Males were observed for clinical signs before, during, and after exposures, and all animals were checked twice each day for gross abnormalities and mortality. Mated females were sacrificed on GD 13 to determine pregnancy status, number of implantations, and pre and postimplantation loss. At necropsy for females, gross examination of the external surface and tissues and organs of the thoracic and abdominal cavities was performed. Total nidations, numbers of resorptions, live implantations, and corpora lutea were recorded for pregnant females. Males were also sacrificed three weeks after treatment, and gross necropsies were performed to determine if treatment-related lesions were present. The following tissues and organs were examined: thoracic, abdominal, and scrotal cavities; testes, epididymides, prostate glands, and seminal vesicles. The study authors used Dunnett's test, the Mann-Whitney U test, and Fisher's exact test to analyze body weights, counted data, and proportional data, respectively. Bonferroni's correction was used to compare multiple groups to the control where appropriate.

No treatment-related effects were reported for any of the male exposure groups. No mortality was reported prior to sacrifice. No treatment-related clinical effects were reported for any of the exposure groups. At necropsy, no significant differences in mean body weight were reported. No treatment-related lesions were reported in any of the exposure group males. There was no evidence of treatment-related effects on fertility in any exposure group. Efficiency in mating and effecting pregnancy in treated groups was not significantly different from controls. The numbers of live implantations and pre or postimplantation loss were not significantly different in females mated to exposed males compared to females mated to control males. Based on the lack of observed toxic effects, the study authors identified a NOAEL of 35.6 mg/m^3

(35.6 mg/m^3 HEC for extrarespiratory effects). This NOAEL represents the highest exposure concentration tested in the study.

Carcinogenicity Studies

No carcinogenicity studies on exposure of animals to acetone cyanohydrin via the inhalation route were identified in the literature.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

There are some in vitro and in vivo genotoxicity studies for acetone cyanohydrin available. The results of these studies are negative for mutagenicity (see Table 3A).

Table 3A. Summary of Acetone Cyanohydrin Genotoxicity

Endpoint	Test System	Dose/Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA100, TA98 with or without S9 activation	6.1, 18.3, 55.0, 165, 495 µg/plate	–	–	Not mutagenic to *Salmonella typhimurium*	Hazleton Laboratories (1986)
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						
Mutation	Chinese Hamster Ovarian (CHO-K1-BH4) cells	100, 500, 700, 850, 950 µg/mL	–	–	No significant occurrence of mutants compared to control	Pharmakon Research International (1986)
Chromosomal aberrations	ND					

Table 3A. Summary of Acetone Cyanohydrin Genotoxicity

Endpoint	Test System	Dose/Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adducts	ND					
Genotoxicity studies in mammals—in vivo						
Chromosomal aberrations	S-D rats, gavage, sacrifice at 6, 12, 24, and 48 hr	0, 1.5, 5, 15 mg/kg-bw	–	–	Not clastogenic at the tested concentrations. No significant increase in chromosome aberration frequency or mean mitotic indices.	Center for Human Development (1986)
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, 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)	Male and female (2/2 per dose) New Zealand white rabbits; percutaneous application of 6, 25, or 40 mg/kg; no control; LD_{50} values calculated as 1/2 $\log_{10}$ (LD_{84}/LD_{16})	Slight or moderate redness, slight swelling, slight necrosis, lethargy, labored breathing, convulsions, death.	Acute percutaneous absorption LD_{50} was 16 mg/kg (8–28 mg/kg, 95% confidence interval)	Dow Chemical Company (1981)
	Male (9-10 per group) CD-1 mice; i.p. injection of 0–12 mg/kg	Dyspnea, gasping, ataxia, corneal opacity, hypothermia, convulsions, death	Acute i.p. LD_{50} was 8.7 mg/kg (8–9 mg/kg, 95% confidence interval)	Willhite and Smith (1981)
Metabolism/toxicokinetic	Male (5) CD-1 mice; i.p. injection of 9 mg/kg; sacrificed 5 min after injection	Detectable liver and brain cyanide levels	Acetone cyanohydrin distribution displayed the same characteristics as its molar equivalent of free cyanide	Willhite and Smith (1981)
Short-term studies	ND			
Mode of action/ mechanistic	ND			
Immunotoxicity	ND			
Neurotoxicity	ND			

ND = no data.

Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity

Acetone cyanohydrin has been evaluated in several in vitro and in vivo genotoxicity (e.g., clastogenicity, mutagenicity) tests (see Table 3A). Results indicated that acetone cyanohydrin was not mutagenic to *S. typhimurium* and did not induce mutations in CHO cells in vitro. Additionally, acetone cyanohydrin did not induce significant increases in chromosome aberration frequency compared to that of control in a rat in vivo bioassay.

Other Toxicity Studies (Exposures Other Than Oral or Inhalation)

An acute dermal toxicity test on New Zealand white rabbits indicated that acetone cyanohydrin induced slight swelling at the application site and also induced clinical signs including labored breathing and lethargy (see Table 3B). A dermal LD_{50} of 16 mg/kg was determined by the study authors (Dow Chemical Company, 1981). An acute i.p. injection study in CD-1 mice indicated that acetone cyanohydrin induced clinical signs including labored breathing, ataxia, corneal opacity, hypothermia, and convulsions. A i.p. LD_{50} of 8.7 mg/kg was determined by the study authors (Willhite and Smith, 1981).

Metabolism/Toxicokinetic Studies

Cyanide distribution in the liver and brain were reported by Willhite and Smith (1981) following i.p. injection of 9 mg/kg acetone cyanohydrin in CD-1 mice. Acetone cyanohydrin distribution displayed the same characteristics as its molar equivalent of free cyanide.

Short-Term Studies

No information is available.

Mode of Action/Mechanistic Studies

No information is available.

Immunotoxicity

No information is available.

Neurotoxicity

No information is available.

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present a summary of noncancer reference and cancer values, respectively. IRIS data are indicated in the table, if available.

Table 4. Summary of Noncancer Reference Values for Acetone Cyanohydrin (CASRN 75-86-5)

Toxicity Type (Units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	NA	NA	NDr	NA	NDr	NDr	NA
Chronic p-RfD(mg/kg-d)	NA	NA	NDr	NA	NDr	NDr	NA
Screening Subchronic p-RfC (mg/m^3)	Rat/M+F	Increased incidence of clinical signs of breathing difficulties (extrarespiratory effect)	2×10^{-2}	NOAEL	5.7	300	Monsanto (1986b)
Screening Chronic p-RfC (mg/m^3)	Rat/M+F	Increased incidence of clinical signs of breathing difficulties (extrarespiratory effect)	2×10^{-3}	NOAEL	5.7	3000	Monsanto (1986b)

NA = Not applicable, NDr = Not determinable, M = male, F = female.

Table 5. Summary of Cancer Values for Acetone Cyanohydrin (CASRN 75-86-5)

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

NDr = Not determined

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

No available studies investigating the effects of oral exposure to acetone cyanohydrin in humans are considered appropriate for derivation of a subchronic p-RfD. The available studies on oral exposure to acetone cyanohydrin in animals include one unpublished subchronic-duration study (i.e., Ogrowsky, 1988), one chronic-duration study (i.e., Motoc et al., 1971), and one unpublished developmental study (i.e., International Research and Development Corporation, 1986). The only published study on the oral exposure of acetone cyanohydrin to animals is a chronic-duration oral study by Motoc et al. (1971) that also included evaluation of toxicity following subchronic-duration (3 months). This study was originally written in French and translated to English. The information on experimental design and methods of dosing were not clearly documented. It is unclear what type of oral exposure method was used to treat the animals (e.g., gavage, drinking water). Additionally, it is not clear whether the biochemical results section refers to the oral exposure portion of the study or the inhalation exposure, and at what timepoint these changes occurred. Due to lack of clarity in reporting methods and results, this study is not selected as the principal study.

The remaining two studies are nonpeer-reviewed and, therefore, are candidates only for possible development of a screening subchronic p-RfD. In an unpublished study, Ogrowsky (1988) administered acetone cyanohydrin in 0.01 N sulfuric acid vehicle via daily gavage to Sprague-Dawley rats (20/sex/dose) at dose levels of 0 (vehicle), 2.5, 8.75, or 15 mg/kg-day for 13 weeks. The study authors evaluated mortality, clinical signs, body weights, food consumption, ophthalmologic examinations, hematology, clinical chemistry, organ weights, organ-to-body-weight ratios, gross pathology, and histopathology. In this study, frank effects (≥10% mortality) were reported at all doses tested in both male and female rats. The study authors determined a probable cause of death/moribundity for only 2 of 15 animals in the treatment groups that were found dead or were prematurely sacrificed. One male in the high-dose group likely died due to gavage error, and one male in the low-dose group died of a rare liver neoplasm. No animals in either the male or female control group died. Although the histopathology report states that "there were no histopathologic changes in the tissues examined that could be attributed to the test material" (p. 26), the study authors do not list an alternate cause of death. The pathology report also states that "most of the animals that died during study had gross observations of failure of the lung to collapse, red mottling of lung lobes, and/or frothy, clear fluid in the trachea" (p. 27). Because the study authors do not give an alternate cause of death for animals in the treatment groups, it is possible that the deaths may be related to compound administration and, thus, cannot be discounted. Additionally, the first deaths occurred during Week 4 of treatment, thus indicating that an acute effect of cyanide was not likely to be the cause of death. Because the LOAEL identified in Ogrowsky (1988) is also a FEL (2.5 mg/kg-day), this study is not appropriate for deriving a screening subchronic p-RfD. However, it is notable that the previous PPRTV document prepared in 2004 derived subchronic and chronic p-RfDs based on this study. In the previous PPRTV assessment, only male mortality in the high-dose group was considered to be treatment related. There was no explanation as to why mortality in the low-dose group (2/20 females, 2/20 males) was not considered related to treatment even though 10% mortality was observed.

The remaining unpublished developmental study, conducted by International Research and Development Corporation (1986), identified a NOAEL of 10 mg/kg-day, the highest dose tested in this experiment. Because the NOAEL from this study is not protective of the frank

effects observed at the lowest dose (2.5 mg/kg-day) in Ogrowsky (1988), a screening subchronic p-RfD is not derived from this study. Thus, due to lack of appropriate studies, derivation of a subchronic p-RfD or screening subchronic p-RfD is precluded.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

For reasons stated above, no appropriate studies are available to derive a chronic p-RfD or screening chronic p-RfD.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

No studies investigating the effects of inhalation exposure to acetone cyanohydrin in humans are considered appropriate for derivation of a subchronic provisional RfC. These studies are limited by poor exposure characterization, coexposures with other chemicals, or multiple routes of exposure. The database of inhalation studies on acetone cyanohydrin in animals includes two unpublished subchronic-duration studies (i.e., Monsanto 1986a,b), one published chronic-duration study (i.e., Motoc et al., 1971), and two unpublished reproductive studies (i.e., Monsanto 1986c,d). Although the chronic-duration study by Motoc et al. (1971) included subchronic-duration exposure regimens, the study report is not considered appropriate for deriving a subchronic p-RfC due to inadequate reporting of methods and results. No treatment-related effects were noted in the remaining subchronic-duration and reproductive studies (i.e., Monsanto 1986a,c,d). The most appropriate study for derivation of a subchronic p-RfC is an unpublished 28-day study in rats conducted by Monsanto (1986b) that identified increased incidence of clinical signs of breathing difficulties in male and female rats. Because the data are unpublished, the value is relegated to a screening subchronic p-RfC and is discussed further in Appendix A.

It is important to note that the laboratory that conducted the 28-day study in rats (Monsanto, 1986b) also performed three additional studies utilizing similar experimental conditions (e.g., same strain and species of rat, exposure regimen, exposure chamber, and test substance purities [ranging from 97.79% to 99.21%]) in which the study authors stated that no signs of toxicity was observed in exposed rats. These studies included a 14-week exposure of males and females (Monsanto, 1986a), a female reproductive toxicity study (21-day duration; Monsanto, 1986c), and a male reproductive toxicity study (10-week duration; Monsanto, 1986d). NOAELs identified from these studies ranged from 35.6 to 51.0 mg/m^3 compared to 5.7 mg/m^3 from the Monsanto (1986b) study based on increased incidence of clinical signs of breathing difficulties in male and female rats. The study authors do not state any potential reasons for the observed discrepancies in toxicity between the four studies (e.g., errors in quantifying acetone cyanohydrin concentrations, compromised animal health, etc.). Therefore, in the absence of any cogent evidence to discount the 28-day Monsanto (1986b) study, the screening subchronic p-RfC is derived based on effects observed in this study (see Appendix A).

Derivation of Chronic Provisional RfC (Chronic p-RfC)

Similar to the discussion above, the available published inhalation studies are considered insufficient for deriving a chronic provisional RfC. The most appropriate study for derivation of a chronic p-RfC is an unpublished subchronic-duration inhalation study in rats conducted by Monsanto (1986b). Therefore, the value is relegated to screening, and further discussion of the screening chronic p-RfC is provided in Appendix A.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 6 identifies the cancer weight-of-evidence (WOE) descriptor for acetone cyanohydrin.

Table 6. Cancer WOE Descriptor for Acetone Cyanohydrin

Possible WOE Descriptor	Designation	Route of entry (Oral, Inhalation, or Both)	Comments
"Carcinogenic to Humans"	NS	NA	NA
"Likely to Be Carcinogenic to Humans"	NS	NA	NA
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	NA
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No studies on the carcinogenic potential of acetone cyanohydrin in animals or humans via the oral or inhalation route are available.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	NA

NS = Not selected; NA = Not applicable.

MODE OF ACTION (MOA) DISCUSSION

In the case of acetone cyanohydrin, there are insufficient data to determine the mode of action.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

No studies on the carcinogenic potential of acetone cyanohydrin to animals or humans via the oral route are available in the literature; therefore, derivation of a provisional oral slope factor is precluded.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

No studies on the carcinogenic potential of acetone cyanohydrin to animals or humans via the inhalation route are available in the literature; therefore, derivation of a provisional inhalation unit risk is precluded.

APPENDIX A. PROVISIONAL SCREENING VALUES

For reasons noted in the main document, it is inappropriate to derive provisional subchronic or chronic p-RfCs for acetone cyanohydrin. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center 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 PPRTV documents 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 is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

DERIVATION OF SCREENING PROVISIONAL INHALATION REFERENCE CONCENTRATIONS

Derivation of Screening Subchronic Provisional RfC (Subchronic p-RfC)

The study by Monsanto (1986b) is selected as the principal study for derivation of a screening subchronic p-RfC. The critical endpoint is increased incidence of clinical signs of breathing difficulties in both male and female Sprague-Dawley rats (see Table B.3). The critical effect is considered extrarespiratory because breathing difficulties may result from the effect of cyanide inhibition of cellular respiration and histotoxic anoxia (HSDB, 2011). Acetone cyanohydrin is thought to release free cyanide during metabolism (HSDB, 2011). Additionally, the study authors did not observe any gross pathology or histopathological lesions in the airway or lungs of the animals. Although the study by Monsanto (1986b) is unpublished and not stated to be conducted under GLP guidelines, it meets the standards of study design and performance, with numbers of animals, examination of potential toxicity endpoints, and presentation of information. Details are provided in the "Review of Potentially Relevant Data" section. Among the available, acceptable studies, this study represents the lowest point of departure (POD) for developing a screening subchronic p-RfC.

A POD of 5.7 mg/m^3 is determined by the NOAEL/LOAEL approach and is adjusted for continuous exposure as follows. The high and intermediate doses showed 100% response; the data are not amenable to BMD analysis.

$NOAEL_{ADJ}$ = $NOAEL_{Monsanto,1986b}$ × (Molecular Weight ÷ 24.45) × (Hours per Day ÷ 24) × (Days Dosed ÷ Total Days)
= 9.2 ppm × (85.1 g/mole ÷ 24.45) × (6 ÷ 24) × (5 ÷ 7)
= 5.7 mg/m^3

Dosimetric adjustment to a Human Equivalent Concentration (HEC) is calculated for extrarespiratory effects. In the absence of blood gas partition coefficient information [$H_{(B/G)A} \div H_{(B/G)H}$] for acetone cyanohydrin (a Class 3 gas), a value of 1 is used. Therefore, the $NOAEL_{HEC,EXRESP}$ is calculated as follows:

$NOAEL_{HEC,EXRESP} = NOAEL_{ADJ} \times [H_{(B/G)A} \div H_{(B/G)H}]$
$= 5.7\ mg/m^3 \times 1$
$= 5.7\ mg/m^3$

The screening subchronic p-RfC is calculated as follows:

Screening Subchronic p-RfC $= NOAEL_{HEC,EXRESP} \div UF_C$
$= 5.7\ mg/m^3 \div 300$
$= \mathbf{2 \times 10^{-2}\ mg/m^3}$

The UF_C for the screening subchronic p-RfC for acetone cyanohydrin is 300, as explained in Table A.1.

Table A.1. Uncertainty Factors for Screening Subchronic p-RfC of Acetone Cyanohydrin

UF	Value	Justification
UF_A	3	A UF_A of 3 is applied for animal-to-human extrapolation to account for the toxicodynamic portion of the UF_A because the toxicokinetic portion ($10^{0.5}$) is addressed in dosimetric conversions.
UF_D	10	A UF_D of 10 is applied because there are no acceptable two-generation reproductive toxicity studies or developmental toxicity studies via the inhalation route.
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 to humans.
UF_L	1	A UF_L of 1 is applied because the POD is developed using a NOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study is used to derive the screening subchronic provisional value.
$UF_C \leq 3000$	300	Composite uncertainty factor

Derivation of Screening Chronic Provisional RfC (Chronic p-RfC)

The only available chronic-duration inhalation study by Motoc et al. (1971) is considered inappropriate for derivation of a screening chronic p-RfC due to inadequate reporting of methods and results. Therefore, the subchronic-duration inhalation study by Monsanto (1986b) is selected as the principal study for derivation of a screening chronic p-RfC. The critical endpoints and POD are the same as the screening subchronic p-RfC. Among the available, acceptable studies, this study represents the lowest POD for developing a screening chronic p-RfC.

Screening Chronic p-RfC $= NOAEL_{HEC,EXRESP} \div UF_C$
$= 5.7\ mg/m^3 \div 3000$
$= \mathbf{2 \times 10^{-3}\ mg/m^3}$

The UF_C for the screening chronic p-RfC for acetone cyanohydrin is 3000, as explained in Table A.2.

Table A.2. Uncertainty Factors for Screening Chronic p-RfC of Acetone Cyanohydrin

UF	Value	Justification
UF_A	3	A UF_A of 3 is applied for animal-to-human extrapolation to account for the toxicodynamic portion of the UF_A because the toxicokinetic portion ($10^{0.5}$) is addressed in dosimetric conversions.
UF_D	10	A UF_D of 10 is applied because there are no acceptable two-generation reproductive toxicity studies or developmental toxicity studies via the inhalation route.
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 to humans.
UF_L	1	A UF_L of 1 is applied because the POD is developed using a NOAEL.
UF_S	10	A UF_S of 10 is applied for using data from a subchronic-duration study to assess potential effects from chronic exposure because data for evaluating response from chronic exposure are insufficient.
UF_C $\leq$3000	3000	Composite uncertainty factor

APPENDIX B. DATA TABLES

Table B.1. Summary of Liver Weights of Male and Female Sprague-Dawley Rats After Daily Oral Gavage with Acetone Cyanohydrin for 13 Weeks[a]

Parameter	Dose Group, mg/kg-d			
Male	**0**	**2.5**	**8.75**	**15**
Original sample size	20	20	20	20
Terminal sample size	20	18	18	15
Necropsy body weight (g)[b]	554.9 ± 55.2	ID	ID	547.4 ± 59.8 (99)
Absolute liver weight (g)[b]	14.03 ± 1.38	13.56 ± 2.12 (97)	15.38 ± 2.50 (110)	16.64 ± 3.55[c] (119)
Relative liver weight (%)[b]	ID	ID	ID[c]	ID[c]
Female	**0**	**2.5**	**8.75**	**15**
Original sample size	20	20	20	20
Terminal sample size	20	18	18	18
Necropsy body weight (g)[b]	283.7 ± 21.8	277.4 ± 25.3 (98)	287.7 ± 28.9 (101)	ID
Absolute liver weight (g)[b]	7.36 ± 0.83	7.25 ± 0.73 (99)	7.50 ± 1.26 (102)	7.87 ± 1.12 (107)
Relative liver weight (%)[b]	2.596 ± 0.243	2.620 ± 0.217 (101)	ID	2.704 ± 0.205 (104)

[a]Ogrowsky (1988).
[b]Values expressed as mean ± SD (% of control); % is calculated.
[c]Significantly different from control ($p < 0.05$); Dunnett's test.

ID – Illegible data.

Table B.2. Summary of Group Mean Maternal and Fetal Observations at Cesarean Section of COBS CD Rats after Oral Administration of Acetone Cyanohydrin on GDs 6–15[a]

Parameter		Dose Group, mg/kg-d			
		0	**1**	**3**	**10**
Maternal sample size		25	25	25	25
No. of gravid animals		25	25	25	25
No. of dams with viable fetuses		25	25	25	25
Viable fetuses per dam[b]		14.1 ± 2.24	14.2 ± 2.64	13.4 ± 2.08	13.6 ± 1.47
Postimplantation loss per dam[b]		1.4 ± 1.41	1 ± 1.17	1.0 ± 0.93	0.9 ± 1.01
Total implantations per dam[b]		15.5 ± 1.42	15.1 ± 2.07	14.4 ± 2.33	14.4 ± 1.33[e]
Corpora lutea per dam[b]		16.9 ± 1.62	16.8 ± 2.18	16.3 ± 2.82	15.9 ± 1.54[f]
Group mean preimplantation loss (%)[c]		8.3	9.8	11.5	9.1
Group mean postimplantation loss (%)[d]		8.8	6.3	7.2	6.1
Mean fetal body weight[b] (g)		3.2 ± 0.36	3.3 ± 0.24	3.2 ± 0.20	3.2 ± 0.24
Fetal sex distribution (%)	Male	52.4	49.2	46.9	52.2
	Female	47.6	50.8	53.1	43.8

[a]International Research and Development Corporation (1986).
[b]Values expressed as mean ± SD.
[c]Preimplantation loss = [(Total No. Corpora Lutea - Total No. Implantations) ÷ Total No. Corpora Lutea] × 100.
[d]Postimplantation loss = [(Total No. Implantations - Total No. Viable Fetuses) ÷ Total No. Implantations] × 100.
[e]Significantly different from control group ($p < 0.01$); test was not reported.
[f]Significantly different from control group ($p < 0.05$); test was not reported.

Table B.3. Serum Chemistry, Urinalysis, and Respiratory Clinical Signs of Male and Female Sprague-Dawley Rats After Inhalation Exposure to Acetone Cyanohydrin for 28 Days[a]

Parameter		Exposure Concentration, ppm (Human Equivalent Concentration, mg/m^3)[b]			
Male		**0**	**9.2 (5.7)**	**29.9 (18.6)**	**59.6 (37.0)**
Sample size		10	10	10	7
Hematology (units not reported)[c]	RBC	6.43 ± 0.24	6.22 ± 0.57 (97)	6.40 ± 0.55 (100)	6.21 ± 0.32 (97)
	HGB	14.4 ± 0.5	13.9 ± 1.6 (97)	14.3 ± 1.3 (99)	13.7 ± 0.9 (95)
	MCHC	39.8 ± 0.5	40.0 ± 0.6 (101)	40.3 ± 0.5 (101)	39.9 ± 0.4 (100)
Thiocyanate[c]	Serum (mg/dL)	9.6 ± 1.1	13.5 ± 1.4[e] (141)	13.1 ± 1.8[e] (136)	11.3 ± 2.8 (118)
	Urine (mg/dL)	31.9 ± 12.2	127.3 ± 38.8 (399)	273.2 ± 70.1[e] (856)	571.6 ± 207.4[e] (1792)
Incidence of clinical signs of breathing difficulties		0/10	0/10	10/10	10/10
Female		**0**	**9.2 (5.7)**	**29.9 (18.6)**	**59.6 (37.0)**
Sample size		10	10	10	10
Hematology (units not reported)[c]	RBC	6.37 ± 0.5	6.21 ± 0.34 (97)	6.49 ± 0.5 (102)	5.78 ± 0.55[d] (91)
	HGB	13.9 ± 1.2	13.7 ± 0.8 (99)	14.2 ± 1.0 (102)	12.5 ± 1.1[d] (90)
	MCHC	39.6 ± 0.7	39.5 ± 0.4 (100)	39.9 ± 0.8 (101)	38.8 ± 0.4[d] (98)
Thiocyanate[c]	Serum (mg/dL)	12.6 ± 4.0	22.7 ± 11.3[e] (180)	21.1 ± 5.4[d] (167)	17.5 ± 4.4 (139)
	Urine (mg/dL)	42.4 ± 13.1	125.0 ± 27.2 (295)	396.6 ± 177.8[e] (935)	555.9 ± 180.4[e] (1311)
Incidence of clinical signs of breathing difficulties		0/10	0/10	10/10	10/10

[a]Monsanto (1986b).
[b]Doses are converted from ppm to HEC assuming 25ºC and 1 atmosphere using conversion factor MW = 85.1 and the following equation: HEC_{EXRESP} = (Dose × MW ÷ 24.45) × (Hours Exposed per Day ÷ 24) × (Days Exposed per Week ÷ 7) × Blood:Gas Partition Coefficient.
[c]Values expressed as mean ± SD (% of control); % is calculated.
[d]Significantly different from control ($p \leq 0.05$); two tailed Dunnett's Test.
[e]Significantly different from control ($p \leq 0.01$); two tailed Dunnett's Test.

Table B.4. Mean Body Weight of Male and Female Sprague-Dawley Rats After Inhalation Exposure to Acetone Cyanohydrin for 28 Days[a]

Parameter		Exposure Concentration, ppm (Human Equivalent Concentration, mg/m^3)[b]			
Male		**0**	**9.2 (5.7)**	**29.9 (18.6)**	**59.6 (37.0)**
Initial sample size		10	10	10	10
Mean initial body weight[c] (g)		243.7 ± 7.8	243.0 ± 7.60 (100)	243.2 ± 7.96 (100)	244.7 ± 13.41 (100)
Final sample size		10	10	10	7
Mean final body weight[c] (g)		416.3 ± 29.92	420.1 ± 25.15 (101)	420.5 ± 25.37 (101)	396.6 ± 35.75 (95)
Mean liver weight relative to terminal body weight (%)[c]		3.045 ± 0.045	3.144 ± 0.115 (103)	3.249 ± 0.057[d] (107)	3.263 ± 0.159 (107)
Female		**0**	**9.2 (5.7)**	**29.9 (18.6)**	**59.6 (37.0)**
Sample size		10	10	10	10
Mean body weight[c] (g)	Initial	180.5 ± 4.55	179.8 ± 4.61 (100)	180.2 ± 4.21 (100)	179.0 ± 8.88 (99)
	Final	236.9 ± 14.87	243.5 ± 16.76 (103)	234.6 ± 12.25 (99)	234.9 ± 14.57 (99)
Mean liver weight relative to terminal body weight (%)[c]		2.944 ± 0.071	3.092 ± 0.065 (105)	3.065 ± 0.126 (104)	3.060 ± 0.087 (104)

[a]Monsanto (1986b).
[b]Doses are converted from ppm to HEC assuming 25ºC and 1 atmosphere using conversion factor MW = 85.1 and the following equation: HEC_{EXRESP} = (Dose × MW ÷ 24.45) × (Hours Exposed per Day ÷ 24) × (Days Exposed per Week ÷ 7) × Blood:Gas Partition Coefficient.
[c]Values expressed as mean ± SD (% of control); % is calculated.
[d]Significantly different from control ($p \leq 0.05$); Mann-Whitney U-test with Bonferroni inequality.

Table B.5. Serum Chemistry and Urinalysis of Male and Female Sprague-Dawley Rats After Inhalation Exposure to Acetone Cyanohydrin for 14 Weeks[a]

Parameter		Exposure Group, ppm (Human Equivalent Concentration, mg/m^3)[b]			
Male		**0**	**10.1 (6.3)**	**28.6 (17.8)**	**57.7 (35.9)**
Sample size		15	15	14	15
Serum chemistry[c]	Glucose (mg/dL)	174 ± 29.3	174 ± 25.8 (100)	178 ± 51.1 (102)	192 ± 26.9 (110)
	Total Protein (g/dL)	6.5 ± .031	6.4 ± 0.27 (98)	6.5 ± 0.26 (100)	6.7 ± .036 (103)
	Thiocyanate (mg/dL)	0.56 ± 0.26	0.83 ± 0.29 (148)[d]	0.70 ± 0.22 (125)	0.58 ± 0.34 (103)
	Globulin (g/dL)	3.0 ± 0.27	3.0 ± 0.18 (100)	3.1 ± 0.28 (103)	3.1 ± 0.27 (104)
Sample size		15	15	15	15
Urinalysis[c]	Thiocyanate (mg/dL)	0.29 ± 0.45	3.14 ± 2.10 (108)	9.40 ± 5.53 (3241)[e]	18.27 ± 7.94 (6300)[e]
Female		**0**	**10.1 (6.3)**	**28.6 (17.8)**	**57.7 (35.9)**
Sample size		15	15	15	15
Serum chemistry[c]	Glucose (mg/dL)	171 ± 27.8	162 ± 30.8 (95)	144 ± 27.3 (84)[d]	139± 27.1 (81)[e]
	Total protein (g/dL)	7.3 ± 0.46	6.9± 0.28 (95)[e]	6.8 ± 0.44 (93)[e]	7.1 ± 0.24 (97)
	Thiocyanate (mg/dL)	0.43 ± 0.21	0.86 ± 0.18 (200)[e]	0.84 ± 0.38 (195)[e]	0.48 ± 0.26 (112)
	Globulin (g/dL)	3.3 ± 0.20	3.0 ± 0.18 (91)[e]	2.9 ± 0.21(88)[e]	3.1 ± 0.16 (94)
Sample size		15	14	15	15
Urinalysis[c]	Thiocyanate (mg/dL)	0.01 ± 0.05	2.40 ± 1.98 (24,000)	5.60 ± 3.88 (56,000)[e]	11.49 ± 6.69 (114,900)[e]

[a]Monsanto (1986a).
[b]Doses are converted from ppm to HEC assuming 25ºC and 1 atmosphere using conversion factor MW = 85.1 and the following equation: HEC_{EXRESP} = (Dose × MW ÷ 24.45) × (Hours Exposed per Day ÷ 24) × (Days Exposed per Week ÷ 7) × Blood:Gas Partition Coefficient.
[c]Values expressed as mean ± SD (% control); % is calculated.
[d]Significantly different from control ($p \leq 0.05$); two tailed Dunnett's Test.
[e]Significantly different from control ($p \leq 0.01$); two tailed Dunnett's Test.

Table B.6. Incidence of Fertility Effects in Female Sprague-Dawley Rats After Inhalation Exposure to Acetone Cyanohydrin for 6 Hours/Day for 21 Days[a]

Parameter[c]	Exposure Concentration, ppm (Human Equivalent Concentration, mg/m^3)[b]			
	0.0 (0.0)	**10.7 (9.3)**	**30.4 (26.5)**	**58.6 (51.0)**
Sample Size	22	22	22	23
No. of live implants	14.0 ± 0.7	14.6 ± 0.5 (104)	14.0 ± 0.8 (100)	15.5 ± 0.4[d] (111)
No. of resorptions	0.5 ± 0.2	0.5 ± 0.2 (100)	1.0 ± 0.4 (200)	0.7 ± 0.2 (140)
No. of nidations	14.6 ± 0.7	15.1 ± 0.5 (103)	15.1± 0.7 (103)	16.2 ± 0.4[d] (111)
No. of corpora lutea	15.8 ± 0.5	16.1 ± 0.5 (102)	16.9 ± 0.4 (107)	16.8 ± 0.5 (106)

[a]Monsanto (1986c).
[b]Doses are converted from ppm to HEC assuming 25ºC and 1 atmosphere using conversion factor MW = 85.1 and the following equation: HEC_{EXRESP} = (Dose × MW ÷ 24.45) × (Hours Exposed per Day ÷ 24) × (Days Exposed per Week ÷ 7) × Blood:Gas Partition Coefficient.
[c]Values expressed as mean number observed in each group ± SE (% of control).
[d]Significantly different from pooled control (p = 0.05) using the Mann-Whitney U test; no significant difference from control (p = 0.05) using Bonferroni inequality.

APPENDIX C. BMD OUTPUTS

BMD analysis is not performed for this assessment.

APPENDIX D. REFERENCES

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