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ACETONE CYANOHYDRIN

(CAS Reg. No. 75-86-5)

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

August 2005

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive or susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

EXECUTIVE SUMMARY

Acetone cyanohydrin is a colorless to yellowish liquid with a characteristic bitter almond odor due to the presence of free HCN. The major use of acetone cyanohydrin is in the production of α-methacrylic acid and its esters; the latter are used for the production of plexiglass. Further uses of acetone cyanohydrin are in the production of acrylic esters, polyacrylic plastics and synthetic resins as well as in the manufacture of insecticides, pharmaceuticals, fragrances and perfumes. Acetone cyanohydrin decomposes spontaneously in the presence of water to acetone and hydrogen cyanide.

Fatalities and life-threatening occupational intoxication have been described after accidental inhalation, skin contact and ingestion. Initial symptoms following mild exposure to acetone cyanohydrin range from cardiac palpitation, headache, weakness, dizziness, nausea, vomiting to nose, eye, throat and skin irritation. Acetone cyanohydrin behaves as its molar equivalent in cyanide both in vitro and in vivo. All of the pharmacological actions of cyanide result from cyanide's reversible complex with the ferric (+3) state of mitochondrial cytochrome c oxidase also known as ferrocytochrome c-oxygen oxidoreductase. Cessation of electron transport across the inner mitochondrial membrane results in inhibition of oxygen utilization and causes hypoxia and cellular destruction.

Four studies exposed rats repeatedly to acetone cyanohydrin at about 10, 30 and 60 ppm for 6 hours/day, 5 days/week for a total of 4 weeks (Monsanto, 1986a; using groups of 10 male and 10 female rats), 10 weeks (Monsanto, 1982b; using groups of 15 male rats) and 14 weeks (Monsanto, 1986b; using groups of 15 male and 15 female rats) or for 6 hours/day for 21 days (Monsanto, 1982c; using groups of 15 female rats). Death was observed at 60 ppm after the first exposure in 3 animals of the Monsanto (1986a) study, but not in subsequent exposures or in the other studies conducted under similar protocols. Preceding death, respiratory distress, prostration, convulsions and tremors were obvious. In all studies, exposure to 60 and 30 ppm caused signs of irritation (red nasal discharge, clear nasal discharge, perioral wetness, encrustations) during the first and subsequent weeks of exposure. At 10 ppm, red nasal discharge was not observed in one study (Monsanto, 1986a); its incidence was not increased compared to the concurrent control group in two studies (Monsanto, 1982b; 1982c), but it was increased compared to the control group in the fourth study (Monsanto, 1986b). No other signs of intoxication were reported in these four studies.

The derivation of AEGL-1 values was based upon the facts that acetone cyanohydrin decomposes spontaneously to hydrogen cyanide and acetone and that both local and systemic toxic effects of acetone cyanohydrin are due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-1 values (on a ppm basis) derived for hydrogen cyanide (NRC, 2002) to acetone cyanohydrin. This procedure is supported by the fact that similar values would be derived on the basis of available acetone cyanohydrin studies in rats (derivation basis would be exposure to 9.2 ppm for 6 hours/day, 5 days/week for 4 weeks, which did not result in red nasal discharge; Monsanto, 1986a) using a total uncertainty factor of 10.

The odor threshold of acetone cyanohydrin has not been firmly established. Shkodich (1966) published the odor threshold for acetone cyanohydrin in water (0.06 mg/l). However, the odor would necessarily be the consequence of a mixed presentation of the HCN and acetone cyanohydrin levels in air.

Since no definitive reports on the odor threshold of acetone cyanohydrin were located in the literature, no level of distinct odor awareness (LOA) was derived.

The derivation of AEGL-2 values was based upon the facts that acetone cyanohydrin decomposes spontaneously to hydrogen cyanide and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-2 values (on a ppm basis) derived for hydrogen cyanide (NRC, 2002) to acetone cyanohydrin. This procedure is supported by the fact that similar values would be derived on the basis of available acetone cyanohydrin studies in rats (derivation basis would be exposure to 29.9 ppm for 6 hours/day, 5 days/week for 4 weeks, which caused signs of irritation, while the next higher concentration produced respiratory distress, prostration, convulsions and tremors; Monsanto, 1986a) using a total uncertainty factor of 10.

The derivation of AEGL-3 values was based upon the facts that acetone cyanohydrin decomposes spontaneously to hydrogen cyanide and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-3 values (on a ppm basis) derived for hydrogen cyanide (NRC, 2002) to acetone cyanohydrin. This procedure is supported by the close similarity of acetone cyanohydrin and hydrogen cyanide regarding death in rats: Blank (1983) reported that 3 of 10 rats died after the first exposure to 68 ppm hydrogen cyanide, while the subsequent two exposures on the following days caused no additional deaths. This finding closely resembles that of Monsanto (1986a) reporting death of 3 of 20 animals after the first exposure to 60 ppm acetone cyanohydrin (the actual exposure concentration on the first day might have been slightly higher than the average 59.6 ppm), while no additional deaths were found in the 19 subsequent exposures.

The derived values are listed in the table below.

SUMMARY TABLE OF AEGL VALUES FOR ACETONE CYANOHYDRIN [a b]

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	2.5 ppm (8.8 mg/m³)	2.5 ppm (8.8 mg/m³)	2.0 ppm (7.0 mg/m³)	1.3 ppm (4.6 mg/m³)	1.0 ppm (3.5 mg/m³)	application of AEGL-1 values for hydrogen cyanide
AEGL-2 (Disabling)	17 ppm (60 mg/m³)	10 ppm (35 mg/m³)	7.1 ppm (25 mg/m³)	3.5 ppm (12 mg/m³)	2.5 ppm (8.8 mg/m³)	application of AEGL-2 values for hydrogen cyanide
AEGL-3 (Lethal)	27 ppm (95 mg/m³)	21 ppm (74 mg/m³)	15 ppm (53 mg/m³)	8.6 ppm (30 mg/m³)	6.6 ppm (23 mg/m³)	application of AEGL-3 values for hydrogen cyanide

[a] Acetone cyanohydrin decomposes spontaneously in the presence of water to yield hydrogen cyanide and acetone. Therefore, both acetone cyanohydrin and hydrogen cyanide concentrations should be considered.

[b] Cutaneous absorption may occur; direct skin contact with the liquid should be avoided.

References

Blank, T.L. 1983. Inhalation Pilot Study of Hydrogen Cyanide Exposure in Sprague-Dawley Rats. Report No. MSL-2985, Monsanto Company. U.S. EPA OTS Submission 88-920007543.

Monsanto, 1982b. Male fertility study of Sprague-Dawley rats exposed by inhalation route to acetone cyanohydrin. Monsanto Co. Report No. ML-82-144, Monsanto Co., St. Louis, MO, USA.

Monsanto, 1982c. Female fertility study of Sprague-Dawley rats exposed by inhalation route to acetone cyanohydrin. Monsanto Co. Report No. ML-82-125, Monsanto Co., St. Louis, MO, USA.

Monsanto, 1986a. One-month inhalation toxicity of acetone cyanohydrin in male and female Sprague-Dawley rats with cover letter dated 04-25-86. Report No. BN-81-178, Monsanto Co., St. Louis, MO, USA.

Monsanto, 1986b. Three-month inhalation toxicity of acetone cyanohydrin in male and female Sprague-Dawley rats with cover letter dated 04-25-86. Report No. ML-82-143, Monsanto Co., St. Louis, MO, USA.

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Shkodich P.E., 1966. Experimental determination of the maximum permissible concentration of acetone cyanohydrin in water basins. *Hygiene and Sanitation* 31, 335-341.

1. INTRODUCTION

Acetone cyanohydrin is a colorless to yellowish liquid with a characteristic bitter almond odor due to the presence of free hydrogen cyanide (HCN) (ACGIH, 1996). The major use of acetone cyanohydrin is in the preparation of α-methacrylic acid and its esters; the latter are used for the production of plexiglass. Further uses of acetone cyanohydrin are in the production of acrylic esters, polyacrylic plastics and synthetic resins as well as an intermediate in the manufacture of insecticides, pharmaceuticals, fragrances and perfumes (UN, 1997). About 0.5-1 million metric tons of acetone cyanohydrin are produced worldwide annually (IUCLID, 1996), principally by reaction of hydrogen cyanide with acetone. Chemical and physical properties of acetone cyanohydrin are listed in Table 1.

Since the elimination reaction of HCN from acetone cyanohydrin is an endothermic reaction, the decomposition of acetone cyanohydrin is accelerated by heat. At temperatures of 120 °C or higher, acetone cyanohydrin decomposes with the evolution of HCN (IUCLID, 1996). Water and ethanol (esp. in the presence of amines) exert specific dissociative effects on acetone cyanohydrin, rather than acting as mere diluents (Stewart and Fontana, 1940). The very rapid breakdown of acetone cyanohydrin with moisture would present some challenges in any accidental spill or release. Because acetone cyanohydrin breaks down so readily to HCN, and the toxicity is due to HCN, both materials are present in a mixture and the ratio of the two could be rapidly changing. Therefore, both materials would need to be tracked to give an indication of the risk.

TABLE 1: CHEMICAL AND PHYSICAL DATA

Parameter	Value	Reference
Molecular formula	$(CH_3)_2C(OH)CN$	IUCLID, 1996
Molecular weight	85,1	E.I. du Pont de Nemours and Co., 1998
CAS Registry Number	75-86-5	IUCLID, 1996
Physical state	liquid	E.I. du Pont de Nemours and Co., 1998
Color	colorless colorless to yellowish	E.I. du Pont de Nemours and Co., 1998 ACGIH, 1996
Synonyms	2-propanone cyanohydrin; 2-cyano-2-propanol; 2-cyano-2-hydroxypropane; α-hydroxyisobutyronitrile; 2-methyl-lactonitrile; 2-hydroxy-2-methyl-propionitrile; Acetoncyanhydrin	IUCLID, 1996
Vapor pressure	1.07 hPa at 20 °C 0.8 mm Hg at 20 °C 1 mm Hg at 25 °C 1.6 hPa at 40 °C 12.5 hPa at 72 °C	IUCLID, 1996 E.I. du Pont de Nemours and Co., 1998 E.I. du Pont de Nemours and Co., 1998 Grybat et al., 2003 Grybat et al., 2003
Density	0.932 g/cm^3 at 19 °C 0.9267 g/cm^3 at 25 °C	IUCLID, 1996 IUCLID, 1996
Melting point	-19 °C to -20 °C	IUCLID, 1996

Parameter	Value	Reference
Boiling point	81 °C at 30.7 hPa 82 °C at 23 mm Hg 95 °C at 1013 hPa (decomposition to acetone and HCN)	IUCLID, 1996 E.I. du Pont de Nemours and Co., 1998 IUCLID, 1996
Solubility	very soluble in water, alcohol and ether	E.I. du Pont de Nemours and Co., 1998
Odor	characteristic bitter almond odor of free HCN	ACGIH, 1996
Explosive limits in air	2.2 % (LEL) to 12 % (UEL)	IUCLID, 1996
Conversion factors	1 ppm = 3.5 mg/m³ 1 mg/m³ = 0.28 ppm	E.I. du Pont de Nemours and Co., 1998

Acetone cyanohydrin in air can be specifically determined using solid sorbent sampling (samples should be stored water-free and frozen to avoid decomposition), elution with a water-free solvent (ethylacetate) and gas chromatographic analysis (Glaser and Fey O'Connor, 1985; NIOSH, 1985). Also available are methods for total cyanide determination involving sampling in alkaline solutions or infrared spectroscopy (Singh et al., 1986). Electrochemical detectors for hydrogen cyanide and Draeger tubes for hydrogen cyanide will not detect acetone cyanohydrin. However, these devices can be used to detect hydrogen cyanide that will form rapidly in a case of acetone cyanohydrin release due to its decomposition to acetone and hydrogen cyanide.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Although deaths have occurred from exposures to acetone cyanohydrin, specific exposure concentrations and exposure periods have not been reported (Sunderman and Kincaid, 1953; NIOSH, 1978; DECOS, 1995; ACGIH, 1996). Fatalities and life-threatening poisonings with clonic-tonic convulsions in workers have been described after inhalation (Krefft, 1955) and skin contact (Sunderman and Kincaid, 1953; Thiess and Hey, 1969) as well as after accidental ingestion (Sunderman and Kincaid, 1953). Following mild exposure to acetone cyanohydrin patients presented with cardiac palpitation, headache, weakness, dizziness, nausea, vomiting and nose, eye, throat and skin irritation (Ballantyne and Marrs, 1987; DECOS, 1995).

2.2. Nonlethal Toxicity

No relevant studies documenting nonlethal effects in humans after a single inhalation exposure to acetone cyanohydrin were located in the available literature. Cases of intoxication in workers after dermal contact with acetone cyanohydrin have been reported (Lang and Stintzy, 1960; Zeller et al., 1969).

Sunderman and Kincaid, (1953) described at least 3 pumpers lost consciousness during the packing operation of acetone cyanohydrin. The men recovered after they had been revived on exposure to fresh air and cleaning their hands. No permanent injury apparently occurred following these exposures. It had been noted that the pumpers usually had their hands covered with grease. When the employees had covered their hands so, the effects of acetone cyanohydrin were minimal, suggesting dermal penetration of acetone cyanohydrin as the principal route of exposure in these cases. The symptoms following mild exposure to acetone cyanohydrin were predominantly cardiac palpitation, headache, nausea and vomiting. No details about the exposure conditions were reported.

Oral exposure to acetone cyanohydrin may occur as a consequence of its liberation from linamarin, a cyanogenic glycoside found in cassava and other plant foodstuffs (Conn 1979). Linamarin is the common name given to a molecule composed of glucose and acetone cyanohydrin. Since toxic effects of linamarin usually become evident only after long term, low dose exposure toxicity data for linamarin are not considered relevant to AEGL development and thus are not presented here.

Shkodich (1966) reported that according to a majority of people smelling and tasting acetone cyanohydrin-containing water, the sensory threshold of smell for this substance is at a level of 0.06 mg/l and that of the after taste is 0.48 mg/l. No experimental details were reported.

2.3. Developmental/Reproductive Toxicity

No studies documenting potential developmental or reproductive toxicity of acetone cyanohydrin exposure in humans were located in the available literature.

2.4. Genotoxicity

No studies documenting the genotoxic potential of acetone cyanohydrin exposure in humans were located in the available literature.

2.5. Carcinogenicity

No studies documenting the carcinogenic potential of acetone cyanohydrin exposure in humans were located in the available literature.

2.6. Summary

Deaths associated with inhaled acetone cyanohydrin have occurred, but exposure concentrations are unknown. Likewise, airborne exposure levels for those who survived the initial acute intoxication were not provided, but in each instance there was ample opportunity for skin absorption. No information on developmental/reproductive effects, genotoxicity or carcinogenicity was located.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Lethality data are available for the rat; only one study reporting lethality in mice was located. The lethality data are summarized in Table 2.

3.1.1. Rats

Smyth et al. (1962) exposed groups of 6 albino rats to acetone cyanohydrin vapors that were produced by passing a 2.5-l/min-air stream through a fritted glass disc immersed in 50 ml acetone cyanohydrin. Doses were logarithmically distributed, differing by a factor of two (doses were not stated explicitly). The observation period was 14 days. After exposure for 4 hours, 2/6 rats were killed at 62.5 ppm and 6/6 rats were killed at 125 ppm. The maximum time rats could be exposed to saturated vapor (about 1300 ppm) without producing any deaths was 5 minutes. No other signs of toxicity were reported.

Izmerov et al. (1982) reported an LC_{40} of 185 mg/m³ (51.8 ppm) for 2 hours in rats (no details were reported).

Sunderman and Kincaid (1953) using saturated vapors of commercially available acetone cyanohydrin reported that 6/6 rats died after 1.5 minutes. When the free HCN contained in the acetone cyanohydrin was removed by precipitation with silver nitrate prior to exposure, the authors found that collapse occurred after an average time of 4 minutes and 50 % mortality after 10 minutes (number of animals was not stated exactly).

Studies with repeated inhalation exposure

Monsanto (1986a) exposed groups of 10 female and 10 male Sprague-Dawley rats to acetone cyanohydrin at 0, 10, 30 or 60 ppm for 6 hours/day, 5 days/week for 20 exposure days (28 days in total). Concentrations in the exposure chamber were calculated by dividing the net amount of acetone cyanohydrin delivered to the chamber per unit time by the airflow per unit time and, in addition, measured by a Miran® infrared analyzer (using the C-N triple bond frequency, which detects both acetone cyanohydrin and hydrogen cyanide) four times daily. For the total exposure period, mean analytical concentrations (±SD) were determined as 9.2±0.9, 29.9±1.2 and 59.6±1.4 ppm, respectively. In the highest exposure group respiratory distress and tremors or convulsions or both, foaming at the mouth, and prostration were observed in 4 males following the first exposure. Of these 4 animals, 3 died. No deaths occurred in the 29.9-ppm group (see Section 3.2.4 for nonlethal effects). In three other studies conducted under similar protocols no deaths were observed at 60 ppm for 6 hours/day (Monsanto, 1982b; 1982c; 1986b) (see Sections 3.2.1 and 3.3.1 and Table 2). The authors suggested that the differences between the 28-day study and the 14-week study (Monsanto, 1986b) were possibly due to the very steep dose-response for acetone cyanohydrin or to the normal variation in experimental animals of the same strain. Evaluation of the nominal and analytical concentrations revealed that the animals in the 60-ppm group may, indeed, have been exposed to a slightly higher concentration during the second half of the first day: the nominal concentration of 64.8 ppm for the first day was the highest of all days (mean for the other 19 exposure days was 60.4±1.8 ppm), likewise, the last two analytical concentrations measured during the first day (55.5, 60.5, 63.5 and 63.5 ppm; mean 60.8±3.8) were greater than those measured on all

subsequent exposure days (the highest individual value for exposure days 2-20 was 61.5 ppm; mean for exposure days 2-20 was 59.5±1.4 ppm).

3.1.2. Mice

Gabor et al. (1962) exposed albino mice to different acetone cyanohydrin concentrations (0.5-3 mg/l (140-840 ppm)) for 2 hours. Deaths were reported as 0/10 at 140 ppm, 0/10 at 280 ppm, 8/10 at 420 ppm, 18/44 at 560 ppm, 4/10 at 700 ppm, and 10/10 at 840 ppm. The authors found a 50 % narcosis level at 1.65 mg/l (462 ppm) and calculated a LC_{50} of 2.05 mg/l (574 ppm). The mouse strain, analytical methods and postexposure observation period were not reported.

Izmerov et al. (1982) reported an LC_{30} of 70 mg/m³ (19.6 ppm) for 2 hours in mice (no details were reported).

TABLE 2: SUMMARY OF ACUTE LETHAL INHALATION DATA IN LABORATORY ANIMALS

Species	Concentration (ppm)	Exposure time	Effect	Reference
Rat	saturated vapor (about 1300 ppm)	1.5 min (time to death)	6/6 animals died during exposure period; using commercially available acetone cyanohydrin	Sunderman and Kincaid, 1953
Rat	saturated vapor (about 1300 ppm)	10 min (time to death)	6/6 animals died during exposure period; using commercial acetone cyanohydrin with free HCN removed	Sunderman and Kincaid, 1953
Rat	125	4 h	6/6 animals died	Smyth et al., 1962
Rat	62.5	4 h	2/6 animals died	Smyth et al., 1962
Rat	59.6	6 h/d, 5 d/w, 4 w	3/20 animals died (deaths occurred after first exposure during which exposure to an elevated concentration may have occurred)	Monsanto, 1986a
Rat	58.6	6 h/d, 7 d/w, 21 d	no deaths in 24 animals	Monsanto, 1982c
Rat	57.7	6 h/d, 5 d/w, 14 w	no deaths in 30 animals	Monsanto, 1986b
Rat	57.2	6 h/d, 5 d/w, 48 d	no deaths in 15 animals	Monsanto, 1982b
Rat	51.8	2 h	LC_{40}	Izmerov et al., 1982
Mouse	574	2 h	LC_{50}	Gabor et al., 1962
Mouse	19.6	2 h	LC_{30}	Izmerov et al., 1982

3.2. Nonlethal Toxicity

No studies evaluating nonlethal consequences of acetone cyanohydrin after a single inhalation exposure were located. Studies using repeated inhalation exposure report signs of irritation, such as red nasal discharge and perioral wetness. These data are summarized in Table 3.

3.2.1 Rats

Studies with repeated inhalation exposure

Monsanto (1986a) exposed groups of 10 female and 10 male Sprague-Dawley rats to mean acetone cyanohydrin concentrations of 9.2±0.9, 29.9±1.2 and 59.6±1.4 ppm, respectively for 6 hours/day, 5 days/week for 20 exposure days (28 days in total) (see Section 3.1.4). Three of 20 animals that inhaled 59.6 ppm died after the first exposure. The three animals that died and another animal that survived showed respiratory distress, prostration, tremors and/or convulsions (observed in 3 of the 4 animals) and foaming of the mouth (observed in 2 of the 4 animals). During the first week of exposure, red nasal discharge was reported in 0/20 control animals, 0/20 animals in the 10-ppm group, 4/20 animals in the 30-ppm group and 2/20 animals in the 60-ppm group (the authors reported incidences of irritation only for whole weeks, but not for single days). Reduced ($p>0.05$) body weight was found in the high exposure group. No gross or microscopic lesions attributable to acetone cyanohydrin exposure were observed. Total serum protein was reduced in male rats at all exposure levels, but only statistically significant in the mid- and high exposure groups.

Monsanto (1986b) conducted exposures of 15 female and 15 male Sprague-Dawley rats to acetone cyanohydrin at 0, 10, 30 or 60 ppm for 6 hours/day, 5 days/week for 14 weeks. Concentrations in the exposure chamber were calculated by dividing the net amount of acetone cyanohydrin delivered to the chamber per unit time by the airflow per unit time and, in addition, measured by a Miran® infrared analyzer (using the C-N triple bond frequency, which detects both acetone cyanohydrin and hydrogen cyanide). For the total exposure period, mean concentrations (±SD) were determined as 10.1±0.9, 28.6±1.8 and 57.7±2.9 ppm, respectively. No deaths were observed. During the first week of treatment, blood-like discharge about the nose was observed in 6/30 control animals, 17/30 animals in the 10-ppm group, 18/30 animals in the 30-ppm group and 20/30 animals in the 60-ppm group; clear nasal discharge was reported in 0/30, 3/30, 3/30 and 2/30 animals, respectively (the authors reported incidences of irritation only for whole weeks, but not for single days). No exposure related signs of toxicity or changes in hematological or clinical chemistry parameters were observed. No effect on body weight was found. No gross or microscopic lesions attributable to acetone cyanohydrin were observed.

Monsanto (1982b) exposed male Sprague-Dawley rats (15/dose group) by inhalation to acetone cyanohydrin at 0, 10, 30 or 60 ppm for 6 hours/day, 5 days/week for 48 exposure days (69 days in total). Concentrations in the exposure chamber were calculated by dividing the net amount of acetone cyanohydrin delivered to the chamber per unit time by the airflow per unit time and, in addition, measured by a Miran® infrared analyzer (using the C-N triple bond frequency, which detects both acetone cyanohydrin and hydrogen cyanide). For the total exposure period, mean concentrations (±SD) were determined as 10.0±1.0, 28.5±1.9 and 57.2±3.0 ppm, respectively. For the period of exposure days 1-10, red nasal discharge was observed in 10/15 concurrent control animals and in 10/15, 12/15 and 14/15 animals that inhaled 10, 30 or 60 ppm, respectively; perioral wetness/red stain was observed in 2/15, 2/15,

4/15 and 8/15 animals, respectively (the authors did not report the incidence of signs of irritation for single days).

Monsanto (1982c) exposed female Sprague-Dawley rats (24/dose group) by inhalation to acetone cyanohydrin at 0, 10, 30 or 60 ppm for 6 hours/day, 7 days/week for 21 days. Concentrations in the exposure chamber were calculated by dividing the net amount of acetone cyanohydrin delivered to the chamber per unit time by the airflow per unit time and, in addition, measured by a Miran® infrared analyzer (using the C-N triple bond frequency, which detects both acetone cyanohydrin and hydrogen cyanide). For the total exposure period, mean concentrations (±SD) were determined as 10.7±0.4, 30.4±2.1 and 58.6±2.3 ppm, respectively. During the first week of exposure, red nasal discharge or encrustations were observed in 6/24 animals of the control group and in 9/24, 10/24 and 12/24 animals exposed to 10, 30 and 60 ppm, respectively (the authors reported incidences of irritation only for whole weeks, but not for single days).

TABLE 3: SUMMARY OF NON-LETHAL SIGNS OF ACETONE CYANOHYDRIN EXPOSURE IN LABORATORY ANIMALS

Species	Target [analytical] concentration (ppm)	Exposure Time	Effect	Reference
Rat	60 [57.2]	6 h/d, 5 d/w, 48 d	red nasal discharge in 14/15 animals vs. 10/15 in controls and perioral wetness/red stain in 8/15 animals vs. 2/15 in controls during first 10-day period; 15 males tested	Monsanto, 1982b
Rat	60 [58.6]	6 h/d, 7 d/w, 21 d	red nasal discharge and encrustations during week 1 in 12/24 animals vs. 6/24 controls; 24 females tested	Monsanto, 1982c
Rat	60 [59.6]	6 h/d, 5 d/w, 4 w	respiratory distress, prostration, tremors/convulsions in 4/20, red nasal discharge in 2/20 animals vs. 0/20 in controls during week 1; 3/20 males died after first day; 10 females and 10 males tested	Monsanto, 1986a
Rat	60 [57.7]	6 h/d, 5 d/w, 14 w	blood-like discharge about the nose in 20/30 animals vs. 6/30 in controls and clear nasal discharge in 2/30 animals vs. 0/30 in controls during week 1; no deaths occurred; 15 females and 15 males tested	Monsanto, 1986b
Rat	30 [28.5]	6 h/d, 5 d/w, 48 d	red nasal discharge in 12/15 animals vs. 10/15 in controls and perioral wetness/red stain in 4/15 animals vs. 2/15 in controls during first 10-day period;15 males tested	Monsanto, 1982b
Rat	30 [30.4]	6 h/d, 7 d/w, 21 d	red nasal discharge and encrustations during week 1 in 10/24 animals vs. 6/24 controls; 24 females tested	Monsanto, 1982c

Species	Target [analytical] concentration (ppm)	Exposure Time	Effect	Reference
Rat	30 [29.9]	6 h/d, 5 d/w, 4 w	red nasal discharge in 4/20 animals vs. 0/20 in controls during week 1; 10 females and 10 males tested	Monsanto, 1986a
Rat	30 [28.6]	6 h/d, 5 d/w, 14 w	blood-like discharge about the nose in 18/30 animals vs. 6/30 in controls and clear nasal discharge in 3/30 animals vs. 0/30 in controls during week 1; 15 females and 15 males tested	Monsanto, 1986b
Rat	10 [10.0]	6 h/d, 5 d/w, 48 d	red nasal discharge during week 1 in 10/15 animals vs. 10/15 in controls; 15 males tested	Monsanto, 1982b
Rat	10 [10.7]	6 h/d, 7 d/w, 21 d	red nasal discharge and encrustations during week 1 in 9/24 animals vs. 6/24 in controls; 24 females tested	Monsanto, 1982c
Rat	10 [9.2]	6 h/d, 5 d/w, 4 w	no signs of irritation; 10 females and 10 males tested	Monsanto, 1986a
Rat	10 [10.1]	6 h/d, 5 d/w, 14 w	blood-like discharge about the nose in 17/30 animals vs. 6/30 in controls and clear nasal discharge in 3/30 animals vs. 0/30 in controls during week 1; 15 females and 15 males tested	Monsanto, 1986b

3.3. Developmental/Reproductive Toxicity

3.3.1 Rats

No studies documenting potential developmental or reproductive toxicity of acetone cyanohydrin after a single inhalation exposure were located in the available literature.

Studies with repeated inhalation exposure

In fertility studies, Monsanto (1982b) exposed male Sprague-Dawley rats (15/dose group) by inhalation to acetone cyanohydrin concentrations (±SD) of 0, 10.0±1.0, 28.5±1.9 or 57.2±3.0 ppm for 6 hours/day, 5 days/week for 48 exposure days (69 days in total) (see Section 3.2.1 for details and signs of irritation). After the treatment period, each male was mated consecutively with three untreated females. There were no adverse effects of inhaled acetone cyanohydrin on males as indicated by mortality, mean body weights (the high-exposure group showed a lower mean body weight which was not significantly different from that of the concurrent control group), clinical observations and necropsy (males were killed about 3 weeks after the end of the exposure period). The number of live implants and pre- and post-implantation losses were comparable for females mated with untreated or treated males. The authors concluded that exposure to 60 ppm acetone cyanohydrin failed to demonstrate any potential for reproductive toxicity in male rats.

In fertility studies, Monsanto (1982c) exposed female Sprague-Dawley rats (24/dose group) by inhalation to acetone cyanohydrin at 0, 10.7±0.4, 30.4±2.1 and 58.6±2.3 ppm for 6 hours/day, 7 days/week for 21 days (see Section 3.2.1 for details and signs of irritation). There was no indication of a treatment-related adverse effect on body weight during exposure or during gestation. After cessation of exposure, the females were mated with untreated males. At examination on gestational day 13-15, fertility of mated females was comparable between treated groups and the control group for mating efficiency, pregnancy rates, number of live implants and pre- and post-implantation losses. The authors concluded that repeated inhalation of 60 ppm acetone cyanohydrin failed to demonstrate any adverse effects on fertility of female rats.

Studies with repeated non-inhalation exposure

Monsanto (1982a; 1983) treated groups of 25 pregnant Sprague-Dawley rats by gavage to 0, 1, 3 or 10 mg acetone cyanohydrin/kg/day on days 6-15 of gestation. No deaths were observed. Maternal toxicity was evident by slight reductions in body weight gain in the mid- and high dose groups. Statistically significant differences between the high dose group and controls were observed for the reduction of the number of corpora lutea per dam and the number of implantations per dam. Numbers of viable fetuses/dam, post-implantation losses/dam (non-viable fetuses, early and late resorptions), mean fetal body weight and fetal sex distribution for all dose groups were comparable with controls. The incidence of malformations and developmental variations for all fetuses of treated animals were comparable to the concurrent control group fetuses.

3.4. Genotoxicity

In tests using different *Salmonella* strains, acetone cyanohydrin failed to yield a reproducible positive response. No mutagenic activity was observed in vitro using the Chinese hamster ovary (CHO) gene mutation assay. No significant increases in the frequency of chromosome aberrations were observed in bone marrow cells of Sprague-Dawley rats (24 rats/sex/group) taken 6, 12, 24 or 48 hours after administration of 0, 1.5, 5 or 15 mg acetone cyanohydrin/kg by gavage (IUCLID, 1996; E.I. du Pont de Nemours and Co., 1998).

3.5. Carcinogenicity

No information regarding the carcinogenic potential of acetone cyanohydrin exposure was located in the available literature. Genotoxicity studies with cyanide salts were generally negative, and no cancers were induced in rats in a two-year feeding study with HCN (NRC, 2002).

3.6. Summary

Inhalation data were available mainly for the rat. During exposure of rats, death was observed at saturated concentration (about 1300 ppm) after 1.5 or 10 minutes (Sunderman and Kincaid, 1953) or 5 minutes (Smyth et al., 1962). Other studies [failing to provide experimental details] report death of 2/6 rats after 4 hours at 62.5 ppm (Smyth et al., 1962), an LC_{40} of 51.8 ppm for rats and an LC_{30} of 19.6 ppm for mice (Izmerov et al., 1982) and an LC_{50} of 574 ppm for 2 hours in mice (Gabor et al., 1962). In a series of studies exposing rats repeatedly at about 60 ppm for 6 hours/day, deaths in 3/20, 0/20, 0/24 and 0/15 animals were observed (Monsanto, 1986a; 1986b; 1982c; 1982b). Preceding death, respiratory distress, prostration, convulsions and tremors were observed after the first exposure to 60 ppm

(Monsanto, 1986a). In the other three studies exposure at 60 ppm and in all studies exposure at 30 ppm caused red nasal discharge and encrustations during the first week of exposure. At 10 ppm, the incidence of red nasal discharge was significantly increased in one of the four Monsanto studies.

4. SPECIAL CONSIDERATIONS

4.1. Stability, Metabolism and Disposition

Upon release into moist air, acetone cyanohydrin decomposes to yield hydrogen cyanide and acetone. This process is accelerated by heat and catalyzed by the presence of water. In dilute aqueous solutions acetone cyanohydrin will fully decompose. The half-life for decomposition is pH dependent and was calculated for a 0.1 % solution as 57 minutes at pH 4.9, 28 minutes at pH 6.3 and 8 minutes at pH 6.8 (ICI, 1993). From the rate constant for decomposition at pH 7 and 26 °C of 4.47 $hours^{-1}$, a half-life of 9 minutes was calculated (Ellington et al., 1986).

In the humid air and the moist mucosa of the respiratory tract, acetone cyanohydrin decomposes to yield its molar equivalent in hydrogen cyanide and acetone. This reaction is a result of the physical chemistry of acetone cyanohydrin (Stewart and Fontana, 1940) and it is not known to be enzyme-catalyzed in animals or humans (DECOS, 1995; Kaplita and Smith, 1986).

Acetone cyanohydrin is miscible with water and is taken up by the moist respiratory passages. The pulmonary retention of acetone cyanohydrin has not been reported, but it is probably in the range for hydrogen cyanide (about 58%; ATSDR, 1997), acrylonitrile (about 50 %; ATSDR, 1990) and acetone (70-80 %; ATSDR, 1992). Cyanide concentrations in liver and brain of CD-1 mice were similar after a single intraperitoneal injection of an equimolar dose of acetone cyanohydrin or sodium cyanide. After injection of 9 mg/kg acetone cyanohydrin, 108.0±27.5 and 30.0±4.6 mmol/kg were found in liver and brain, respectively. After a single injection of a single dose of 4.8 mg/kg sodium cyanide, cyanide concentrations in liver and brain were 87.8±31.2 mmol/kg and 24.9±4.8 mmol/kg, respectively (Willhite and Smith, 1981).

With regard to the metabolism of cyanide, it is important to distinguish between low-dose cyanide metabolism, which occurs under circumstances in which cyanide is present in physiological concentrations, and high-dose cyanide disposition, in which there are amounts of cyanide far in excess of those present under normal physiological conditions. Low-dose cyanide metabolism involves incorporation via vitamin B_{12}-dependent enzymes of cyanide into the C_1-metabolite pool from which it can be eliminated as carbon dioxide. Under physiological conditions, the normal capacity of rhodanese to handle cyanide is not overwhelmed and circulating cyanide remains in metabolic equilibrium with the C_1-metabolic pool (DECOS, 1995; ATSDR, 1997).

At high doses of cyanide, the metabolic pathway via the C_1-metabolite pool becomes quickly saturated and detoxification occurs involving enzymatic thiocyanate formation. The enzyme rhodanese (E.C. 2.8.1.1) catalyzes the transfer of a sulfane sulfur atom from sulfur donors, such as thiosulfate, to cyanide, which acts as an sulfur acceptor, thus forming thiocyanate (DECOS, 1995; ATSDR, 1997). The activity of rhodanese is variable between species and tissues, but is high in liver and kidney in most species (Ballantyne and Marrs, 1987). The quantitative contribution to thiocyanate formation of beta-mercaptopyruvate-cyanide sulfurtransferase (E.C. 2.8.1.2), which is found in blood, liver and kidney and catalyzes the transfer of a sulfur atom from 2-mercaptopyruvate to cyanide forming pyruvate and thiocyanate, is not known (DECOS, 1995). The half-life time for the conversion of cyanide to thiocyanate from a non-lethal dose in man is between 20 and 60 minutes (ATSDR, 1997).

A minor pathway for cyanide detoxification is the formation of 2-aminothiazoline-4-carboxylic acid from cyanide and cystine. This reaction occurs spontaneously both in vitro and in vivo and is not enzyme-dependent. The reaction product has been identified in urine of experimental animals and in humans exposed to high concentrations of cyanide (Wilson, 1987; Wood and Cooley, 1956).

Acetone is oxidized in the liver by cytochrome P450 2E1 to acetol. Acetol in turn can be used for gluconeogenesis, i.e. biosynthesis of glucose, either via further oxidation to methylglyoxal in the liver or extrahepatically via reduction to L-1,2-propanediol which can return to the liver where it is oxidized to L-lactaldehyde and further to L-lactate which is then incorporated into glucose. Alternatively, L-1,2-propanediol can be degraded to acetate and formate in the liver (Casazza et al., 1984; Kosugi et al., 1986).

Data regarding the excretion of acetone cyanohydrin per se are not available. The cyanide metabolic products thiocyanate, cyanocobalamin and 2-aminothiazole-4-carboxylic acid are excreted into urine. Hydrogen cyanide and carbon dioxide are expired (DECOS, 1995; ATSDR, 1997).

4.2. Mechanism of Toxicity

Acetone cyanohydrin behaves as its molar equivalent in cyanide both in vitro and in vivo. All of the pharmacological actions of cyanide result from cyanide's reversible complex with the ferric (+3) state of mitochondrial cytochrome c oxidase also known as ferrocytochrome c-oxygen oxidoreductase. This enzyme is also known as cytochrome aa3, and it is the terminal oxidase in aerobic metabolism of all animals, plants, yeasts, and some bacteria. This enzyme is a heme-copper lipoprotein and cytochromes a and a3 are combined in the same large oligomeric protein molecule. Mammalian cytochrome c oxidase contains two molecules of heme A and two copper atoms. This helical protein also contains 820 amino acids. The integrity of the disulfide groups to maintain the 30% helix structure is essential to the oxidase mechanism. Cessation of the mitochondrial electron transport results in inhibition of oxygen utilization and causes hypoxia and cellular destruction.

The interaction of cytochrome c oxidase with cytochrome c was reviewed by Lemberg (1969). The reaction proceeds by first-order kinetics with respect to the concentration of cytochrome c (Smith et al., 1979). Once absorbed, cyanide complexes with many metal ions and interferes with the activities of at least 39 heme-zinc, -copper, and -disulfide enzymes (e.g., catalase, peroxidase) whose activities depend on either metals as cofactors or prosthetic groups (Dixon and Webb, 1964). Cyanide also binds to non-hematin metal-containing enzymes, like tyrosinase, ascorbic acid oxidase, xanthine oxidase, amino acid oxidase, formic dehydrogenase, and various phosphates. The cyanide concentration required for cytochrome c oxidase inhibition is 2-6 orders of magnitude less than that required for inhibition of these other enzymes. Thus, it is the critical position of cytochrome c oxidase in aerobic metabolism that makes its inhibition felt earliest, such that the effects of HCN on other enzyme systems have scant chance to appear (Rieders, 1971). The oxidase-HCN (not CN-) (Stannard and Horecker, 1948; Gibson and Greenwood, 1963) complex is dissociable (Swinyard, 1975).

Willhite and Smith (1981) measured the inhibition of the oxidation of purified bovine cardiac cytochrome c in vitro by a number of nitriles. In the presence of KCN or acetone cyanohydrin the reaction was inhibited in a concentration-dependent fashion. The addition of acetone cyanohydrin inhibited the reaction in a manner kinetically similar to the addition of KCN. Since the inhibitory effects of KCN and acetone cyanohydrin were observed at pH 6.0 and the pKa of HCN is 9.2, the data indicate that the

inhibitory species is the undissociated acid HCN as suggested previously (Stannard and Horecker, 1948; Gibson and Greenwood, 1963).

4.3. Structure-Activity Relationships

Willhite and Smith (1981) demonstrated that the behavior of acetone cyanohydrin parallels that of its molar equivalent of cyanide in vivo. For example, the intraperitoneal LD_{50} in mice for acetone cyanohydrin (equivalent to 2.65 mg cyanide ion/kg) is similar to that of sodium cyanide at 2.54 mg cyanide ion/kg; mean time-to-death was 5 minutes for both compounds. Pretreatment with sodium nitrite or thiosulfate [standard cyanide antidotes] protected mice against lethal doses of acetone cyanohydrin and hydrogen cyanide. The authors also studied the acute toxicity in mice for a series of seven aliphatic nitriles (acetonitrile, propionitrile, acrylonitrile, n-butyronitrile, malononitrile, succinonitrile, acetone cyanohydrin) and sodium cyanide. Only the latter two compounds produced death within 5 minutes. All other nitriles produced death at widely varying intervals from a few minutes to many hours. Pretreatment with the liver toxicant carbon tetrachloride protected mice against death from all nitriles, except acetone cyanohydrin, suggesting that all nitriles examined (except for acetone cyanohydrin) possess little if any acute toxicity in the absence of normal hepatic function and that these nitriles (except acetone cyanohydrin) underwent hepatic metabolism to release cyanide which accounts for their acute toxicity. In contrast, acetone cyanohydrin did not require metabolic activation and released its cyanide moiety spontaneously in vivo.

Johannsen and Levinskas (1986) undertook a structure-activity comparison of acetone cyanohydrin, lactonitrile, four mononitriles (aceto-, propio-, butyro- and acrylonitrile) and two dinitriles (succino- and adiponitrile). The authors observed that with regard to oral and dermal LD_{50} as well as repeated administration, acetone cyanohydrin was the most potent compound tested. While for other nitriles the time to onset of signs of toxicity in rats was between 50 and 300 minutes after exposure, a rapid onset of signs (within 5 minutes) before death was found for acetone cyanohydrin. The authors concluded that the signs of acetone cyanohydrin toxicity resembled those seen after exposure to sodium cyanide.

4.4. Other Relevant Information

4.4.1. Effects of Cyanides and Acetone in Humans

Since acetone cyanohydrin exerts toxicity through rapid release of cyanide, it is appropriate to take relevant studies describing effects in humans after exposure to cyanide into consideration (summarized in NRC, 2002). Several studies reporting effects after repeated occupational exposure to cyanides are available, however, accurate empirical exposure data usually were not reported.

Bonsall (1984) described the case of a worker who was exposed to hydrogen cyanide during inspecting a tank containing a thin layer of hydrazodiisobutyronitrile. The tank had been washed with water, which resulted in hydrolysis of the nitrile into hydrogen cyanide and acetone. The man collapsed after 3 minutes, was fitted with a breathing apparatus after another 3 minutes and removed from the tank after 13 minutes. At this time the worker was unconscious with imperceptible breathing and dilated pupils and was covered with chemical residue. Immediately after the accident, a concentration of hydrogen

cyanide of about 500 mg/m³ (450 ppm) was measured. The victim was administered sodium thiosulfate and was discharged from hospital two weeks later without apparent sequelae.

El Ghawabi et al. (1975), compared the symptoms of 36 workers exposed to HCN in three electropating factories in Egypt with a control group; employment ranged between 5 and 17 years. None of the workers in either the exposed or control groups were smokers. Cyanide exposure resulted from a plating bath that contained copper cyanide, sodium cyanide, and sodium carbonate. Concentrations of cyanide in the breathing zone of the workers ranged from 4.2 to 12.4 ppm (means in the three factories: 6, 8, and 10 ppm). Fifteen-minute air samples were collected in NaOH and analyzed colorimetrically. Symptoms reported most frequently by exposed workers compared with the referent control group were, in descending order of frequency: headache, weakness, and changes in taste and smell. Lacrimation, vomiting, abdominal colic, precordial pain, salivation, and nervous instability were less common. The authors made no attempt to correlate the incidences of these symptoms with concentrations. Although there were no clinical manifestations of hypo- or hyperthyroidism, 20 of the workers had thyroid enlargement to a mild or moderate degree; this condition was accompanied by higher ^{131}I uptake compared with the referent controls. Exposed workers also had significantly higher blood hemoglobin, lymphocyte cell counts, cyanmethemoglobin, and urinary thiocyanate levels than controls. Urinary thiocyanate levels were correlated with cyanide concentration in workplace air. Two workers in the factory with a mean exposure of 10 ppm suffered psychotic episodes; recovery occurred within 36 to 48 hours. Although the sample size was small, the study used well-matched controls and included a biological index of exposure (urinary thiocyanate). The NRC Subcommittee on Spacecraft Maximum Allowable Concentrations, in evaluating the El Ghawabi et al. (1975) data, concluded that “8 ppm would likely produce no more than mild CNS effects (e.g., mild headache) which would be acceptable for 1-hours exposures” of healthy adults (NRC, 2000).

Blanc et al. (1985) surveyed and examined 36 former employees of a silver reclaiming facility in order to determine acute and potential residual adverse health effects resulting from occupational HCN exposure. The study was prompted by a worker fatality from acute cyanide poisoning. The workers had been chronically exposed to airborne cyanide at time-weighted average (TWA) concentrations (taken 24 hours after the plant had closed down) of at least 15 ppm. The most frequent symptoms included headache, dizziness, nausea or vomiting, and a bitter or almond taste, eye irritation, loss of appetite, epistaxis, fatigue, and rash. The most prevalent symptoms (headache, dizziness, nausea or vomiting, and a bitter or almond taste) were consistent with cyanide poisoning. A concentration-response relationship corresponding to high- and low-exposure jobs was demonstrated, but exact breathing zone concentrations were not quantified. Some symptoms exhibiting a dose-response trend occurring seven or more months after exposure had ceased. Mild abnormalities of vitamin B_{12}, folate, and thyroid function were detected and those results suggested cyanide and/or thiocyanide involvement. The NRC (2000), pointed out that the 24-hour TWA of 15 ppm was measured one day after the plant had ceased operation, suggesting that these workers may have been exposed to cyanide at more than 15 ppm.

Leeser et al. (1990) reported a cross-sectional study of the health of cyanide-salt production workers. Sixty-three cyanide production workers employed for 1 to 40 years were compared with 100 referent workers from a diphenyl oxide plant. Workers were examined before and after a block of six 8-hour shifts. All workers had full medical examinations, routine clinical chemistry tests, and blood samples taken for measurement of blood cyanide and carboxyhemoglobin. In addition, circulating levels of vitamin B_{12} and thyroxin (T4) were measured. Atmospheric cyanide was monitored with static monitors,

Draeger pump tests, and personal monitoring. For the personal monitoring, air was drawn through bubblers which contained sodium hydroxide. Cyanide collected in the sodium hydroxide solution was measured using an anion-selective ion electrode. All results (a total of 34 samples) were between 0.01 and 3.6 mg/m³ (0.01 and 3.3 ppm). Geometric mean values for eight job categories ranged between 0.03 and 1.05 mg/m³ (0.03 and 0.96 ppm). Values for only one job category (eight personal samples) averaged 0.96 ppm. Results of routine Draeger pump tests (area samples) were between 1 and 3 ppm (measurement method not stated). This increased exposure was reflected in an increase in mean blood cyanide level in the workers following a block of six 8-hour shifts, and there was an increase of 5.83 µmol during the 6 ppm exposure compared with a decrease of 0.46 µmol across the shift block in the spring. Static monitors on all floors, set to trigger alarms at 10 ppm, failed to sound during the study. Circulating cyanide concentrations in exposed workers, though low, were generally higher than in control workers, and the highest levels were measured in cyanide-exposed nonsmokers compared with the nonsmoking control group (cyanide-exposed nonsmokers, 3.32 µmol; controls 1.14 µmol; $p<0.001$). For ex-smokers, the difference was smaller (cyanide exposed, 2.16 µmol; controls, 1.46 µmol), and for current smokers, the blood cyanide level was actually higher in the control group (2.94 µmol for cyanide workers who smoked; 3.14 µmol for controls who smoked). The percentage of workers reporting shortness of breath and lack of energy was higher in cyanide workers than in the diphenyl oxide plant workers. These differences were partially explained by the greater number of cyanide workers who were shift workers. Slightly higher hemoglobin values and lymphocyte counts in the cyanide workers were not dose-related. Results of clinical and physical examinations and evaluation of medical histories failed to reveal any exposure-related health problems.

Compared to cyanide, the acute toxicity of acetone is low (ATSDR, 1992). This fact is reflected in comparatively high values for the TLV (ACGIH, 1996) of 500 ppm for 8 hours with a 750 ppm STEL, the IDLH (Immediately Dangerous to Life and Health Concentrations) of 2500 ppm (NIOSH, 1996) and the EEGL (Emergency Exposure Guidance Levels) of 1000 ppm for 24 hours and 8500 ppm for 1 hour (NRC, 1985). Acetone and its metabolic products (Casazza et al., 1984; Gentry et al., 2003; Kosugi et al., 1986) contribute only insignificantly to the toxicity of acetone cyanohydrin.

4.4.2. Lethality of hydrogen cyanide in animals

Only one study was located that evaluated lethality of hydrogen cyanide in rats for an exposure time comparable to that of the 6-hour studies of Monsanto (1982b; 1982c; 1986a; 1986b) using acetone cyanohydrin.

Five male and five female Sprague-Dawley Crl:CD rats were exposed at 68 ppm hydrogen cyanide in a stainless steel chamber for 6 hours/day for 3 days (Blank, 1983). Hydrogen cyanide was generated by passing nitrogen over the liquid contained in a 500-mL flask. The concentration in the cage was measured with an infrared analyzer. During the exposures, hypoactivity and quick shallow breathing were observed in all animals. During the first day, three males exhibited anoxia/hypoxia followed by convulsions (one male). One male rat died during the exposure, a second male died during the post-exposure observation period, and a third male was found dead prior to the second day of exposure. Two additional males and all five females exhibited breathing difficulties following the first exposure. No additional mortality was observed following the second and third days of exposure; body weights by the third day were below pre-exposure weights. Necropsy of the three dead males revealed cyanosis of the extremities, moderate-to-severe hemorrhage of the lung, lung edema, tracheal edema, blanched

appearance of the liver, singular occurrences of blood engorgement of the heart and surrounding vessels, chromorhinorrhea, urine-filled bladder, and gaseous distension of the gastrointestinal tract. Survivors were sacrificed following the last exposure. Of the seven survivors, three females developed slight-to-moderate pulmonary hemorrhage.

4.4.3. Species Variability

Due to the lack of sufficient data (see Table 2), the potential interspecies variability for acute inhalation toxicity of acetone cyanohydrin cannot be assessed directly. However, data on acute lethality after oral administration (see Table 4) indicate that lethal doses are similar for different species.

Likewise, nearly identical LD_{50} values have been found in rats and mice after parenteral application: LD_{50} values of 8.7 mg/kg (95% C.I. 8-9 mg/kg) (mean time to death 5±1 min) have been found after intraperitoneal injection in CD-1 male mice (Willhite and Smith, 1981) and 8.5 mg/kg after subcutaneous injection in male albino rats (Magos, 1962).

TABLE 4: SUMMARY OF ORAL LD_{50} DATA FOR ACETONE CYANOHYDRIN

Species	LD_{50} (mg/kg)	References
Rat	17	Smyth et al., 1962
Rat	13.3	Shkodich, 1966
Rat	17.8	Marhold, 1972
Mouse	14	Marhold, 1972
Mouse	15	Hamblin, 1953
Mouse	2.9	Shkodich, 1966
Guinea pig	9	Shkodich, 1966
Rabbit	13.5	Shkodich, 1966

For hydrogen cyanide, LC_{50} values for various species differ by a factor of 2-3 (ATSDR, 1997) and an interspecies extrapolation factor of 2 was used for derivation of AEGL-3 and -2 values for hydrogen cyanide (NRC, 2002).

4.4.4. Intraspecies Variability

People at potentially increased risk for toxic effects caused by exposure to acetone cyanohydrin include those with chronic exposure to cyanide (e.g. heavy smokers) or cyanogenic glycosides from edible plants (e.g., cassava or lima beans) and those with an inadequate detoxification of cyanide (reviewed in NRC, 2002). The latter condition can result from inadequate dietary intake of vitamin B_{12} and/or sulfur-containing amino acids as well as from inborn metabolic errors, such as the genetic component responsible for Leber‘s hereditary optic atrophy, which is possibly associated with a reduction in rhodanese activity, dominantly inherited optic atrophy and recessively inherited optic atrophy (DECOS, 1995). However, for a single acute exposure to high acetone cyanohydrin concentrations, the interindividual differences are probably not great because the decomposition of acetone cyanohydrin to

cyanide is not dependent on metabolism and the cyanide detoxification pathway becomes quickly saturated at higher exposure concentrations. Due to conservatism of the cytochrome c oxidase during evolution, interindividual differences in the affinity of cyanide binding to its target receptor are unlikely to occur.

For hydrogen cyanide, an intraspecies extrapolation factor of 3 has been used for derivation of AEGL-3 and -2 values for hydrogen cyanide (NRC, 2002).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

The odor threshold of acetone cyanohydrin has not been firmly established. Shkodich (1966) published the odor threshold for acetone cyanohydrin in water (0.06 mg/l). However, the odor would necessarily be the consequence of a mixed presentation of the HCN and cyanohydrin levels in air. Human data on irritation effects of acetone cyanohydrin are lacking.

Since the effects of acetone cyanohydrin are due to the release of cyanide after its rapid decomposition, data on exposure of humans to cyanide are relevant. In humans occupationally exposed to cyanide, no adverse effects have been found after exposure to a geometric mean cyanide concentration of 1 ppm (Leeser et al., 1990). At concentrations of 6-10 ppm, there were increased complaints of mild headache after repeated occupational exposure (El Ghawabi et al., 1975).

5.2. Animal Data Relevant to AEGL-1

During the first week of repeated 10 ppm 6-hour exposure studies in rats, there was no sign of red nasal discharge in one study (Monsanto, 1986a). The incidence of nasal discharge was not increased compared to concurrent control groups in two studies (Monsanto, 1982b; 1982c), but it was increased compared to the control group in a fourth study (Monsanto, 1986b). No other adverse effects were reported in these four studies.

5.3. Derivation of AEGL-1

Human data on acetone cyanohydrin relevant for the derivation of AEGL-1 are lacking. One study in rats (Monsanto, 1986a) reported red nasal discharge (which was interpreted as a sign of local irritation in the upper respiratory tract) in 4/20 animals at 29.9 ppm and in 2/20 animals at 59.6 ppm, but not in control animals and in animals exposed to 9.2 ppm, during the first week of repeated 6-hours/day exposures. However, red nasal discharge was not consistently seen in any of the other Monsanto studies and, when present, was not always dose-responsive. In addition, control animals varied widely in terms of whether that endpoint was present or not. In light of the variability of the red nasal discharge in repeat studies, it seemed a poor endpoint on which to base the AEGL-1. Also, the repeat exposures used in the Monsanto studies were not appropriate for the derivation of AEGL-1 values.

The pathogenesis of red nasal discharge in rats is not entirely clear. In the case of acetone cyanohydrin it may be related to local tissue hypoxia leading to vasodilatation and subsequent extravasation of red blood cells, which could explain the lack of histopathological findings. Red nasal discharge in rats occurs at the plexus antebrachii, which is very prominent in the rat. In the rat, extravasation of red blood cells visible as red nasal discharge is caused easily not only by locally acting chemicals, but also by stress, dry air or upper respiratory tract infections.

The derivation of AEGL-1 values was based upon the facts that acetone cyanohydrin decomposes spontaneously to hydrogen cyanide and acetone and that the local and systemic toxic effects of acetone cyanohydrin are due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner

identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-1 values (on a ppm basis) derived for hydrogen cyanide (NRC, 2002) to acetone cyanohydrin.

This procedure is supported by the fact that similar values would be derived on the basis of available acetone cyanohydrin studies in rats. The derivation basis would be an exposure at 9.2 ppm for 6 hours/day, 5 days/week for 4 weeks, which did not result in red nasal discharge (Monsanto, 1986a). Using the default time scaling procedure and a total uncertainty factor of 10 AEGL-1 values of 2.1, 2.1, 1.7, 1.1 and 0.69 ppm would be derived for the 10 and 30 minute and 1, 4 and 8 hour periods, respectively.

The AEGL-1 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-1 values for hydrogen cyanide (NRC, 2002). The values are listed in Table 5 below.

Since no definitive reports on the odor threshold of acetone cyanohydrin were located in the literature (see Section 5.1), no level of distinct odor awareness (LOA) was derived.

TABLE 5: AEGL-1 VALUES FOR ACETONE CYANOHYDRIN [a]

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	2.5 ppm (8.8 mg/m³)	2.5 ppm (8.8 mg/m³)	2.0 ppm (7.0 mg/m³)	1.3 ppm (4.6 mg/m³)	1.0 ppm (3.5 mg/m³)

[a] Acetone cyanohydrin decomposes spontaneously in the presence of water to yield hydrogen cyanide and acetone. Therefore, both acetone cyanohydrin and hydrogen cyanide concentrations should be considered.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Human exposure data relevant for the derivation of AEGL-2 values are lacking. Since the effects of acetone cyanohydrin are caused by the release of cyanide after rapid decomposition of acetone cyanohydrin, data on exposure of humans to cyanide are relevant. Chronic occupational exposure to cyanide concentrations of about 6-10 produced mild CNS effects (mild headache) (El Ghawabi et al., 1975) while more distinct symptoms were reported for occupational exposure to 15 ppm and higher (Blanc et al., 1985).

6.2. Animal Data Relevant to AEGL-2

Four studies using repeated 6-hour inhalation exposures of rats, performed according to good laboratory practice, report signs of irritation at an exposure concentration of about 30 ppm (Monsanto, 1982b; 1982c; 1986a; 1986b), such as red nasal discharge and encrustations and perioral wetness/red stain. Red nasal discharge was also observed also at about 10 ppm in two of the four studies. At higher concentrations of about 60 ppm, in one study (Monsanto, 1986a) respiratory distress, prostration, tremors/convulsions were observed after the first exposure in 4/20 animals and of these 3 animals died. No studies showing irreversible, nonlethal effects in animals were available in the literature.

6.3. Derivation of AEGL-2

The derivation of AEGL-2 values was based upon the facts that acetone cyanohydrin decomposes spontaneously to hydrogen cyanide and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-2 values (on a ppm basis) derived for hydrogen cyanide (NRC, 2002) to acetone cyanohydrin.

This conclusion is supported by the fact that very similar AEGL-2 levels would be derived on the basis of chemical-specific data: in the Monsanto (1986a) study repeated exposures to 29.9 ppm acetone cyanohydrin for 6 hours/day, 5 days/week for 4 weeks, resulted in irritation, but not in respiratory distress, which was observed in 4/20 animals during the first exposure to 60 ppm. Using the default time scaling procedure and a total uncertainty factor of 10 AEGL-2 values of 6.8, 6.8, 5.4, 3.4 and 2.5 ppm would be derived for the 10 and 30 minute and 1, 4 and 8 hour periods, respectively.

The AEGL-2 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-2 values for hydrogen cyanide (NRC, 2002). The values are listed in Table 6 below.

TABLE 6: AEGL-2 VALUES FOR ACETONE CYANOHYDRIN [a]

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-2	17 ppm (60 mg/m³)	10 ppm (35 mg/m³)	7.1 ppm (25 mg/m³)	3.5 ppm (12 mg/m³)	2.5 ppm (8.8 mg/m³)

[a] Acetone cyanohydrin decomposes spontaneously in the presence of water to yield hydrogen cyanide and acetone. Therefore, both acetone cyanohydrin and hydrogen cyanide concentrations should be considered.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Human exposure data relevant for the derivation of AEGL-3 values are not available.

7.2. Animal Data Relevant to AEGL-3

Reliable LC_{50} studies for acetone cyanohydrin performed according to good laboratory practice are not available. Single-exposures killed 2/6 rats that inhaled 62.5 ppm for 4 hours (Smyth et al., 1962). The LC_{40} was 51.8 ppm for 2 hours in rats and the LC_{30} was 19.6 ppm for 2 hours in mice (Izmerov et al., 1982); however due to the small number of animals in the study by Smyth et al. (1962), the lack of information on the rodent strain and number of animals used in the study by Izmerov et al. (1982) and the failure of both studies to report experimental details, a thorough evaluation of these data is not possible.

The study by Sunderman and Kincaid (1953) used saturated acetone cyanohydrin vapor that led to death within 1.5 or 10 minutes. Likewise, Smyth et al. (1962) reported death of rats after 5 minutes of exposure to saturated vapor concentrations.

Four studies, performed according to good laboratory practice, exposed rats repeatedly at about 60 ppm acetone cyanohydrin for 6 hours/day (Monsanto, 1982b; 1982c; 1986a; 1986b). Only in one of the studies (Monsanto, 1986a) lethal effects were reported: 3/10 males died after the first exposure, while none of 10 female rats died and no further deaths of males were observed in subsequent exposures. No deaths occurred in the other studies that used 15 males and 15 females (Monsanto, 1986b), 24 females (Monsanto, 1982c) or 15 males (Monsanto, 1982b).

In the hydrogen cyanide study by Blank (1983), 3 of 10 rats died after the first exposure to 68 ppm hydrogen cyanide for 6 hours.

7.3. Derivation of AEGL-3

The derivation of AEGL-3 values was based upon the facts that acetone cyanohydrin decomposes spontaneously to hydrogen cyanide and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-3 values (on a ppm basis) derived for hydrogen cyanide (NRC, 2002) to acetone cyanohydrin.

This conclusion is supported by very similar observations of lethal effects in rats: Blank (1983) reported that 3 of 10 rats died after the first exposure to 68 ppm hydrogen cyanide, while the subsequent two exposures on the following days caused no additional deaths. This finding closely resembles that of Monsanto (1986a) reporting death of 3 of 20 animals after the first exposure to 60 ppm acetone cyanohydrin (as discussed in Section 3.1.1., the actual exposure concentration on the first day might have been slightly higher than the average 59.6 ppm), while no additional deaths were found in the 19 subsequent exposures.

The AEGL-3 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-3 values for hydrogen cyanide (NRC, 2002). The values are listed in Table 7 below.

TABLE 7: AEGL-3 VALUES FOR ACETONE CYANOHYDRIN [a]

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-3	27 ppm (95 mg/m³)	21 ppm (74 mg/m³)	15 ppm (53 mg/m³)	8.6 ppm (30 mg/m³)	6.6 ppm (23 mg/m³)

[a] Acetone cyanohydrin decomposes spontaneously in the presence of water to yield hydrogen cyanide and acetone. Therefore, both acetone cyanohydrin and hydrogen cyanide concentrations should be considered.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL values for various levels of effects and various time periods are summarized in Table 8. They were derived using the following key studies and methods.

The derivation of AEGL values was based upon the facts that acetone cyanohydrin decomposes spontaneously to hydrogen cyanide and acetone and that the local and systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL values (on a ppm basis) derived for hydrogen cyanide (NRC, 2002) to acetone cyanohydrin.

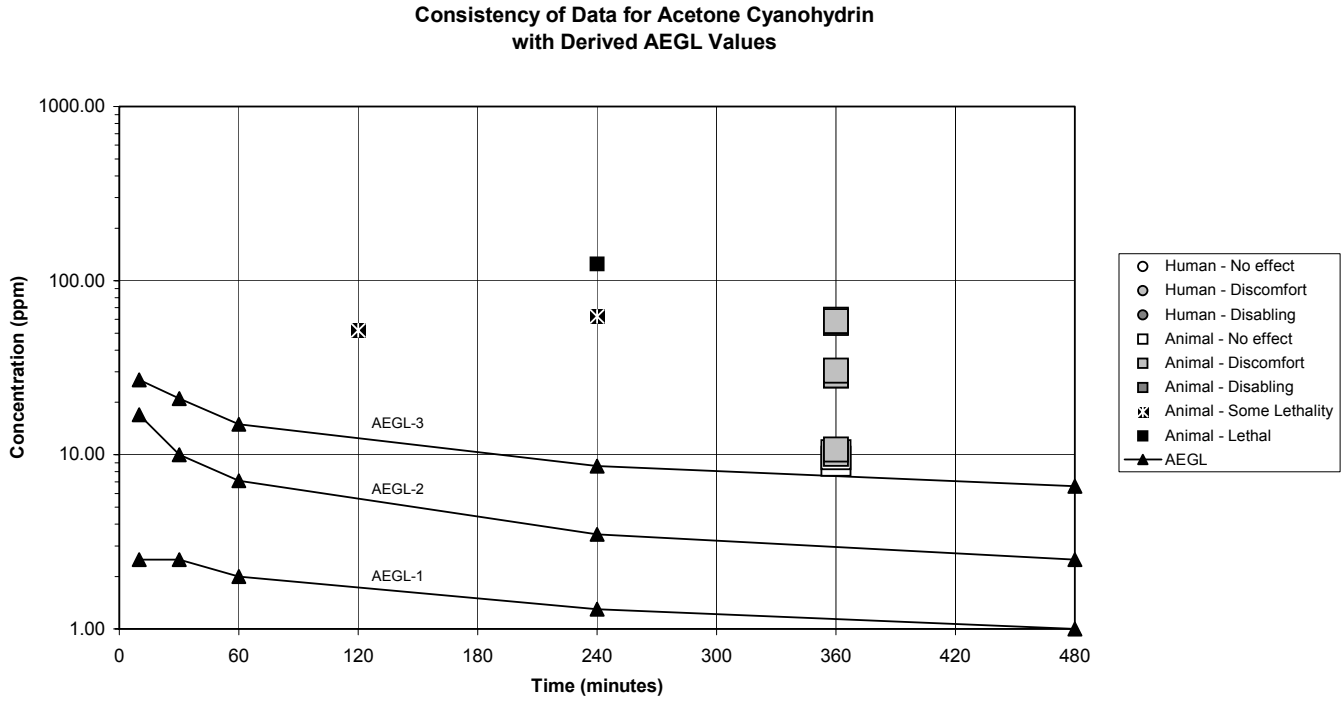
TABLE 8: SUMMARY/RELATIONSHIP OF AEGL VALUES FOR ACETONE CYANOHYDRIN [a] [b]

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	2.5 ppm (8.8 mg/m³)	2.5 ppm (8.8 mg/m³)	2.0 ppm (7.0 mg/m³)	1.3 ppm (4.6 mg/m³)	1.0 ppm (3.5 mg/m³)
AEGL-2 (Disabling)	17 ppm (60 mg/m³)	10 ppm (35 mg/m³)	7.1 ppm (25 mg/m³)	3.5 ppm (12 mg/m³)	2.5 ppm (8.8 mg/m³)
AEGL-3 (Lethal)	27 ppm (95 mg/m³)	21 ppm (74 mg/m³)	15 ppm (53 mg/m³)	8.6 ppm (30 mg/m³)	6.6 ppm (23 mg/m³)

[a] Acetone cyanohydrin decomposes spontaneously in the presence of water to yield hydrogen cyanide and acetone. Therefore, both acetone cyanohydrin and hydrogen cyanide concentrations should be considered.

[b] Cutaneous absorption may occur; direct skin contact with the liquid should be avoided.

All inhalation data are summarized in Figure 1 below. The data were classified into severity categories chosen to fit into definitions of the AEGL level health effects. The category severity definitions are "No effect"; "Discomfort"; "Disabling"; "Lethal"; "Some lethality" (at an experimental concentration in which some of the animals died and some did not, this label refers to the animals which did not die) and "AEGL". Note that the AEGL values are designated as triangles without an indication to their level. AEGL-3 values are higher than the AEGL-2 values and the AEGL-2 values are higher than the AEGL-1 values.



867 **FIGURE 1: CATEGORICAL REPRESENTATION OF ACETONE CYANOHYDRIN**
868 **INHALATION DATA**

8.2. Comparison with Other Standards and Criteria

Standards and guidance levels for workplace and community exposures are listed in Table 9.

TABLE 9. EXTANT STANDARDS AND GUIDELINES FOR ACETONE CYANOHYDRIN

Guideline	Exposure Duration				
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm
AEGL-2	17 ppm	10 ppm	7.1 ppm	3.5 ppm	2.5 ppm
AEGL-3	27 ppm	21 ppm	15 ppm	8.6 ppm	6.6 ppm
WEEL (AIHA)[a]	5 ppm for 15 minutes				2 ppm
TLV-Ceiling (ACGIH)[b]	4.7 ppm as cyanide				
REL-Ceiling (NIOSH)[c]	1 ppm				

[a] **AHIA WEEL (American Industrial Hygiene Association, Workplace Environmental Exposure Level Guide)** (AIHA, 1999) represent workplace exposure concentrations, to which, it is believed, nearly all employees could be repeatedly exposed without adverse effects. WEELs are expressed as time-weighted average values for different time periods.

[b] **ACGIH TLV-Ceiling (American Conference of Governmental Industrial Hygienists, Threshold Limit Value)** (ACGIH, 1996) is defined as a 15 minute TWA exposure concentration, which should not be exceeded at any time during the workday. Because acetone cyanohydrin behaves qualitatively and quantitatively both in vitro and in vivo exactly as does its molar equivalent in free cyanide, the TLV for acetone cyanohydrin is assigned so as to be identical to that for free hydrogen cyanide.

[c] **NIOSH REL-Ceiling (National Institute of Occupational Safety and Health, Recommended Exposure Limits)** (NIOSH, 1978)is defined analogous to the ACGIH-TLV-Ceiling. NIOSH based the value on the assumption that acetone cyanohydrin was approximately 18.3 times as toxic as acetonitrile by inhalation.

8.3. Data Adequacy and Research Needs

Definitive exposure-response data for acetone cyanohydrin in humans are not available. Data from earlier animal studies were often compromised by uncertain quantitation of exposure atmospheres, small numbers of animals and poor data presentation. Four more recent repeated inhalation exposure studies in rats sponsored by Monsanto Company utilized accurate and reliable methods for characterizing concentrations. However, repeat exposure studies were considered of limited relevance for the derivation of AEGL values.

With regard to toxic effects, the similarity between acetone cyanohydrin and hydrogen cyanide concerning both the mechanism of toxic effects and dose-response relationships was considered high enough to apply the AEGL-1, AEGL-2 and AEGL-3 values derived for hydrogen cyanide to acetone

cyanohydrin on a ppm basis. In contrast to hydrogen cyanide, for acetone cyanohydrin appropriate studies in exposed workers for the derivation of AEGL-1 or well-performed inhalation exposure studies evaluating neurotoxic or lethal effects for the derivation of AEGL-2 and AEGL-3 values are not available. However, the available results of studies in rats are in good agreement with hydrogen cyanide studies. LC_{50} studies for acetone cyanohydrin performed according to good laboratory practice would strengthen the derived AEGL-3 values.

It should be noted that due to the steep dose-response relationship, concentrations of AEGL-2 und AEGL-3 values differ only by a factor of 1.6 to 2.6, which could cause problems in regulatory applications of AEGL values especially when it is considered that uncertainties of measurements and dispersion (plume) calculations can be in the same order of magnitude or even higher.

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APPENDIX A

Derivation Summary for Acetone Cyanohydrin AEGLs

ACUTE EXPOSURE GUIDELINES FOR ACETONE CYANOHYDRIN (CAS NO. 75-86-5)

AEGL-1 VALUES [a]				
10 minutes	30 minutes	1 hour	4 hours	8 hours
2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm

Reference: The AEGL-1 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-1 values for hydrogen cyanide.
NRC, National Research Council, 2002. "Hydrogen Cyanide" in Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 2, pp. 211-276, National Academy Press, Washington, D.C.

[a] Acetone cyanohydrin decomposes spontaneously in the presence of water to yield hydrogen cyanide and acetone. Therefore, both acetone cyanohydrin and hydrogen cyanide concentrations should be considered.

Test Species/Strain/Number: not applicable

Exposure Route/Concentrations/Durations: not applicable

Effects: not applicable

Endpoint/Concentration/Rationale:
Human data on acetone cyanohydrin relevant for the derivation of AEGL-1 are lacking. One study in rats (Monsanto, 1986a) reported red nasal discharge (which was interpreted as a sign of local irritation in the upper respiratory tract) in 4/20 animals at 29.9 ppm and in 2/20 animals at 59.6 ppm, but not in control animals and in animals exposed to 9.2 ppm, during the first week of repeated 6-hours/day exposures. However, red nasal discharge was not consistently seen in any of the other Monsanto studies and, when present, was not always dose-responsive. In addition, control animals varied widely in terms of whether that endpoint was present or not. In light of the variability of the red nasal discharge in repeat studies, it seemed a poor endpoint on which to base the AEGL-1. Also, the repeat exposures used in the Monsanto studies were not appropriate for the derivation of AEGL-1 values.

The pathogenesis of red nasal discharge in rats is not entirely clear. In the case of acetone cyanohydrin it may be related to local tissue hypoxia leading to vasodilatation and subsequent extravasation of red blood cells, which could explain the lack of histopathological findings. Red nasal discharge in rats occurs at the plexus antebrachii, which is very prominent in the rat. In the rat, extravasation of red blood cells visible as red nasal discharge is caused easily not only by locally acting chemicals, but also by stress, dry air or upper respiratory tract infections.
The derivation of AEGL-1 values was based upon the facts that acetone cyanohydrin decomposes spontaneously to hydrogen cyanide and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-1 values (on a ppm basis) derived for hydrogen cyanide (NRC, 2002) to acetone cyanohydrin.

Uncertainty Factors/Rationale: not applicable

Modifying Factor: not applicable

Animal to Human Dosimetric Adjustment: not applicable
Time Scaling: not applicable
Data Quality and Support for AEGL Levels: Similar values would be derived on the basis of available acetone cyanohydrin studies in rats (derivation basis would be exposure to 9.2 ppm for 6 hours/day, 5 days/week for 4 weeks, which did not result in red nasal discharge; Monsanto, 1986a) using a total uncertainty factor of 10.

ACUTE EXPOSURE GUIDELINES FOR ACETONE CYANOHYDRIN (CAS NO. 75-86-5)

AEGL-2 VALUES [a]				
10 minutes	30 minutes	1 hour	4 hours	8 hours
17 ppm	10 ppm	7.1 ppm	3.5 ppm	2.5 ppm

Reference: The AEGL-2 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-2 values for hydrogen cyanide.
NRC, National Research Council, 2002. "Hydrogen Cyanide" in Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 2, pp. 211-276, National Academy Press, Washington, D.C.

[a] Acetone cyanohydrin decomposes spontaneously in the presence of water to yield hydrogen cyanide and acetone. Therefore, both acetone cyanohydrin and hydrogen cyanide concentrations should be considered.

Test Species/Strain/Sex/Number: not applicable

Exposure Route/Concentrations/Durations: not applicable

Effects: not applicable

Endpoint/Concentration/Rationale:
The derivation of AEGL-2 values was based upon the facts that acetone cyanohydrin decomposes spontaneously to hydrogen cyanide and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-2 values (on a ppm basis) derived for hydrogen cyanide (NRC, 2002) to acetone cyanohydrin.

Uncertainty Factors/Rationale: not applicable

Modifying Factor: not applicable

Animal to Human Dosimetric Adjustment: not applicable

Time Scaling: not applicable

Data Quality and Support for AEGL Levels:
Very similar values would be derived on the basis of available acetone cyanohydrin studies in rats (derivation basis would be exposure to 29.9 ppm for 6 hours/day, 5 days/week for 4 weeks, which caused red nasal discharge as a sign of irritation, while the next higher concentration produced respiratory distress, prostration, convulsions and tremors; Monsanto, 1986a) using a total uncertainty factor of 10.

ACUTE EXPOSURE GUIDELINES FOR ACETONE CYANOHYDRIN (CAS NO. 75-86-5)

AEGL-3 VALUES [a]				
10 minutes	30 minutes	1 hour	4 hours	8 hours
27 ppm	21 ppm	15 ppm	8.6 ppm	6.6 ppm

Reference: The AEGL-3 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-3 values for hydrogen cyanide.
NRC, National Research Council, 2002. "Hydrogen Cyanide" in Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 2, pp. 211-276, National Academy Press, Washington, D.C.

[a] Acetone cyanohydrin decomposes spontaneously in the presence of water to yield hydrogen cyanide and acetone. Therefore, both acetone cyanohydrin and hydrogen cyanide concentrations should be considered.

Test Species/Strain/Sex/Number: not applicable

Exposure Route/Concentrations/Durations: not applicable

Effects: not applicable

Endpoint/Concentration/Rationale:
The derivation of AEGL-3 values was based upon the facts that acetone cyanohydrin decomposes spontaneously to hydrogen cyanide and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-3 values (on a ppm basis) derived for hydrogen cyanide (NRC, 2002) to acetone cyanohydrin.

Uncertainty Factors/Rationale: not applicable

Modifying Factor: not applicable

Animal to Human Dosimetric Adjustment: not applicable

Time Scaling: not applicable

Data Quality and Support for the AEGL Levels:
Support comes from the close similarity of acetone cyanohydrin and hydrogen cyanide regarding death in rats: Blank (1983) reported that 3 of 10 rats died after the first exposure to 68 ppm hydrogen cyanide, while the subsequent two exposures on the following days caused no additional deaths. This finding closely resembles that of Monsanto (1986a) reporting death of 3 of 20 animals after the first exposure to 60 ppm acetone cyanohydrin (the actual exposure concentration on the first day might have been slightly higher than the average 59.6 ppm), while no additional deaths were found in the 19 subsequent exposures.