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HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR SELECTED NITRILES

Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

Prepared by

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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval, for example, one that does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs are not estimated. A carcinogenic potency factor, or q_1^* (U.S. EPA, 1980), is provided instead. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer-based RQs are defined in U.S. EPA, 1984 and 1986, respectively.

EXECUTIVE SUMMARY

Nicotinonitrile is a solid; succinonitrile is a colorless, waxy solid; and methacrylonitrile is a clear, colorless liquid at room temperature (Hawley, 1981). These compounds are expected to undergo reactions typical of nitriles. They are soluble in many common organic solvents and are slightly soluble in water (Dean, 1985; Hawley, 1981; Windholz, 1983). The 1985 Directory of Chemical Producers (SRI, 1985) reports that Nepera Inc. in Harriman, NY, and Reilly Tar and Chemical Corp. in Indianapolis, IN, are the only current domestic manufacturers of nicotinonitrile and that R.S.A. Corp. in Ardsley, NY, is the only current domestic manufacturer of succinonitrile. Nicotinonitrile is used as a chemical intermediate and succinonitrile is used in organic synthesis (Kuney, 1985; Hawley, 1981; Windholz, 1983). Methacrylonitrile is used as a vinyl nitrile monomer and as a copolymer with chemicals such as styrene and butadiene (Hawley, 1981).

If released to the atmosphere, these compounds are expected to exist almost entirely in the vapor phase (Eisenreich et al., 1981). The half-lives for nicotinonitrile, succinonitrile and methacrylonitrile vapor reacting with photochemically generated hydroxyl radicals have been estimated to be 2 days, 1 hour and 5 hours, respectively (U.S. EPA, 1987b). Small amounts of methacrylonitrile may react with ozone (estimated half-life, 1 day) (U.S. EPA, 1987b). Small amounts of these compounds may be removed from the atmosphere by wet deposition. If released to water, nicotinonitrile, succinonitrile and methacrylonitrile may be susceptible to chemical hydrolysis (Lyman et al., 1982). Volatilization of methacrylonitrile from water appears to be an important removal process (half-life in a typical river, 2 days) although volatilization of nicotinonitrile or succinonitrile

is not expected to be significant. Adsorption to sediments or suspended solids in water and bioaccumulation in aquatic organisms are not expected to be significant. Results of two biodegradation screening studies indicate that succinonitrile is resistant to biodegradation under aerobic conditions. If released to soil, the selected nitriles are expected to be very highly mobile and readily leach through most soil. These compounds may be susceptible to hydrolysis in moist soil. Evaporation of methacrylonitrile from moist or dry soil surfaces is expected to be significant.

Monitoring data pertaining to human exposure by inhalation (succinonitrile and methacrylonitrile), ingestion or dermal contact could not be located in the available literature as cited in Appendix A. Nicotinonitrile has been identified as a component of tobacco smoke (Schmeltz et al., 1979), which suggests that a significant number of people would be exposed to this compound by inhalation.

There is potential that these selected nitriles could be released to the environment in the effluent or in fugitive emissions from production and use facilities.

Pertinent data regarding toxicity of the selected nitriles to aquatic organisms could not be located in the available literature as cited in Appendix A.

Pertinent data regarding the rate and extent of absorption of the nitriles were not located, but the demonstrated toxicity of these chemicals (Chapter 6) indicates that methacrylonitrile is absorbed after inhalation exposure in dogs and rats, and after oral exposure in rats and mice, and that succinonitrile and nicotinonitrile are absorbed following oral exposure in rats and mice. Methacrylonitrile was lipophilic and distributed rapidly to various organs of the rat (Haguenoer et al., 1976). The metabolism of succinonitrile has been studied _in vivo_ and _in vitro_ in experimental animals

(mice, rats and rabbits), and the primary metabolic pathway appears to be liberation of free HCN from the parent compound (Willhite and Smith, 1981; Contessa and Santi, 1973; Floreani et al., 1980, 1981; Tanii and Hashimoto, 1985). Liberation of free cyanide also appears to be the primary pathway of methacrylonitrile metabolism *in vivo* and *in vitro* in experimental animals (Tanii and Hashimoto, 1984a,b, 1986; Peter and Bolt, 1985; Pozzani et al., 1968; Haguenoer et al., 1976). Succinonitrile administered intravenously to humans (Lodi et al., 1973) or intraperitoneally or intravenously to experimental animals (Cavanna and Pocchiari, 1972; Curry, 1974, 1975; Contessa et al., 1978; Contessa and Santi, 1973) is excreted in the urine primarily as the parent compound and thiocyanate ion. Methacrylonitrile administered intraperitoneally to rats was excreted in the urine as the parent compound, free cyanide and bound cyanide in the form of thiocyanate ion (Haguenoer et al., 1976).

One study was located regarding the toxicity of methacrylonitrile by subchronic inhalation exposure (Pozzani et al., 1968). In this study, exposure of rats to concentrations $\geq$52.6 ppm ($\geq$144 mg/m^3), but not 19.3 ppm (53 mg/m^3) for 7 hours/day, 5 days/week for 91 days resulted in increased liver weight and death. Exposure of dogs for 7 hours/day, 5 days/week for 90 days resulted in transiently elevated SGOT and SGPT levels at 8.8 ppm (24 mg/m^3) and loss of motor control of hind limbs and histopathological brain lesions at 13.5 ppm (37 mg/m^3). No effects were observed in dogs at 3.2 ppm (9 mg/m^3).

The acute toxicity of the nitriles appears to be due to release of cyanide during metabolism of the parent compound (Marigo and Pappalardo, 1966; Haguenoer et al., 1976; Pozzani et al., 1968).

Information regarding the carcinogenicity of succinonitrile, nicotinonitrile and methacrylonitrile, and the mutagenicity of methacrylonitrile and succinonitrile were not located. One study indicated that nicotinonitrile was not mutagenic in S. typhimurium (Florin et al., 1980).

A study by Doherty et al. (1983) indicated that succinonitrile was teratogenic in hamsters treated intraperitoneally at ≥4.56 mmol/kg. No information was located regarding the teratogenicity of either nicotinonitrile or methacrylonitrile.

Based on the NOEL in dogs of 3.2 ppm (9 mg/m^3), 7 hours/day, 5 days/week for 90 days, a subchronic inhalation RfD of 0.02 mg/m^3 or 0.4 mg/day, a chronic inhalation RfD of 0.002 mg/m^3 or 0.04 mg/day, a subchronic oral RfD of 0.003 mg/kg/day or 0.2 mg/day and a chronic oral RfD of 0.0003 mg/kg/day or 0.02 mg/day were derived for methacrylonitrile. Uncertainty factors of 100 (10 for interspecies extrapolation and 10 to protect the most sensitive individuals) for the subchronic RfDs and 1000 (an additional factor of 10 for the use of a subchronic study) for the chronic RfDs were used. Because the critical study was well-conducted, medium confidence was placed in the inhalation RfDs. Low confidence was placed in the oral RfDs, however, because the study used inhalation exposure. An RQ of 100 was derived for methacrylonitrile based on the dose-response data for loss of motor control and brain lesions in dogs exposed by inhalation in the study by Pozzani et al. (1968). Data were insufficient to derive risk assessment values for succinonitrile and nicotinonitrile.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BUN	Blood urea nitrogen
CNS	Central nervous system
CS	Composite score
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamic oxaloactic transaminase
SGPT	Serum glutamic pyruvic transaminase
TLV	Threshold limit value
TOD	Theoretical oxygen demand
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS REGISTRY NUMBER

The synonyms, structure, CAS Registry number, empirical formula and molecular weight of nicotinonitrile, succinonitrile and methacrylonitrile are provided in Table 1-1.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Nitriles are extremely versatile reactants and can be used to prepare amines, amides, carboxylic acids and esters, aldehydes, ketones, imines, heterocycles and other compounds (Smiley, 1981). Nicotinonitrile, succinonitrile and methacrylonitrile are expected to undergo reactions typical of nitriles. Nicotinonitrile is a solid; succinonitrile is a colorless, waxy solid; and methacrylonitrile is a clear, colorless liquid at room temperature (Hawley, 1981). These compounds are soluble in many common organic solvents (Dean, 1985; Hawley, 1981; Windholz, 1983). Relevant physical properties are listed in Table 1-2.

1.3. PRODUCTION DATA

The 1985 Directory of Chemical Producers (SRI, 1985) reports that Nepera Inc. in Harriman, NY, and Reilly Tar and Chemical Corp. in Indianapolis, IN, are the only current domestic manufacturers of nicotinonitrile and that R.S.A. Corp. in Ardsley, NY, is the only current domestic manufacturer of succinonitrile. The 1987 OPD Chemical Buyers Directory (CMR, 1986) lists three suppliers for nicotinonitrile, five suppliers for succinonitrile and four suppliers for methacrylonitrile. Nicotinonitrile can be prepared by the ammoxidation or ammonodehydrogenation of an alkylpyridine, primarily 3-methylpyridine or 2-methyl-5-ethylpyridine (Offermanns et al., 1984); succinonitrile can be prepared from ethylene dibromide and potassium cyanide in alcohol (Windholz, 1983); and methacrylonitrile can be prepared by the ammoxidation of isobutylene (Nemec and Kirch, 1981).

TABLE 1-1

CAS Registry Number, Synonyms and Structure of Selected Nitriles

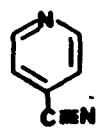
Compound	CAS Registry Number	Synonyms	Empirical Formula	Molecular Weight	Structure
Nicotinonitrile	100-54-9	3-cyanopyridine, 3-pyridinenitrile, 3-pyridinecarbonitrile, nicotinic acid nitrile	$C_6H_4N_2$	104.12	
Succinonitrile	110-61-2	butanedinitrile, 1,2-dicyanoethane, ethylene cyanide, ethylene dicyanide	$C_4H_4N_2$	80.09	$N\equiv C-CH_2-CH_2-C\equiv N$
Methacrylonitrile	126-98-7	2-cyanopropene, 2-methyl-2-propenitrile, α-methacrylonitrile, isopropene cyanide, 2-methyl acrylonitrile	C_4H_5N	67.09	$CH_2=\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}-C\equiv N$

TABLE 1-2

Relevant Physical Properties of Selected Nitriles

Property	Nicotinonitrile	Succinonitrile	Methacrylonitrile	Reference
Melting point (°C)	52	57.88	-35.8	Dean, 1985; Riddick et al., 1986
Boiling point (°C)	240-245	267	90.3	
Vapor pressure (mm Hg)	0.0016 mm Hg (25°C)*	0.0078 mm Hg (25°C)	60 mm Hg (21.5°C)	Riddick et al,. 1986; Perry and Green, 1984
Log K_{ow}	0.36	-0.82	0.54	Hansch and Leo, 1985; U.S. EPA, 1987a
Water solubility	109,000 mg/L (25.2°C)	115,000 mg/L (20°C)	25,700 mg/L (20°C)	Riddick et al., 1986; Offermanns et al., 1984
pKa	1.45 (25)	NA	NA	Jaffe and Doak, 1955
Refractive index	NA	1.41734^{60}	1.4007^{20}	Dean, 1985; Riddick et al., 1986
Density, g/cm³	0.870	0.98669^{60}	0.8001^{20}_{4}	Dean, 1985; Riddick et al., 1986; Offermanns et al., 1984
Flashpoint	84°C	132°C	12°C	Dean, 1985; Aldrich, 1984-1985; Hawley, 1981

*Estimated using the method of Neely and Blau (1985)

NA = Not available

1.4. USE DATA

Nicotinonitrile is used as an intermediate in the preparation of niacin and niacinamide (Kuney, 1985); succinonitrile is used in organic synthesis (Hawley, 1981); and methacrylonitrile is used as a vinyl nitrile monomer, as a copolymer with chemicals such as styrene and butadiene, and as an intermediate in the manufacture of elastomers, coatings, plastics, acids, amides, amines, esters and nitriles (Hawley, 1981; Windholz, 1983).

1.5. SUMMARY

Nicotinonitrile is a solid; succinonitrile is a colorless, waxy solid; and methacrylonitrile is a clear, colorless liquid at room temperature (Hawley, 1981). These compounds are expected to undergo reactions typical of nitriles. They are soluble in many common organic solvents and are slightly soluble in water (Dean, 1985; Hawley, 1981; Windholz, 1983). The 1985 Directory of Chemical Producers (SRI, 1985) reports that Nepera Inc. in Harriman, NY, and Reilly Tar and Chemical Corp. in Indianapolis, IN, are the only current domestic manufacturers of nicotinonitrile and that R.S.A. Corp. in Ardsley, NY, is the only current domestic manufacturer of succinonitrile. Nicotinonitrile is used as a chemical intermediate and succinonitrile is used in organic synthesis (Kuney, 1985; Hawley, 1981; Windholz, 1983). Methacrylonitrile is used as a vinyl nitrile monomer and as a copolymer with chemicals such as styrene and butadiene (Hawley, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT

Very limited data pertaining to the environmental fate and transport of nicotinonitrile, succinonitrile or methacrylonitrile were located in the available literature as cited in Appendix A. When possible, information concerning fate and transport of these chemicals was derived from physical property data or molecular structure.

2.1. AIR

Based on the vapor pressures listed in Table 1-1, these compounds are expected to exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al., 1981).

2.1.1. Reaction with Hydroxyl Radicals. The half-lives for nicotinonitrile, succinonitrile and methacrylonitrile vapor reacting with photochemically generated hydroxyl radicals in the atmosphere have been estimated to be 2 days, 1 hour and 5 hours, respectively, using an ambient hydroxyl radical concentration of 8.0×10^5 molecules/cm^3 and reaction rate constants of 5.0×10^{-12}, 2.4×10^{-10} and 5.0×10^{-11} cm^3/molecule-sec at 25°C (U.S. EPA, 1987b). The hydroxyl radical-initiated photooxidation of methacrylonitrile in the presence of nitrogen monoxide resulted in the formation of formaldehyde and acetyl cyanide as primary products (Hashimoto et al., 1984).

2.1.2. Reaction with Ozone. Nicotinonitrile and succinonitrile are not susceptible to oxidation by ozone (U.S. EPA, 1987b). The half-life for methacrylonitrile vapor reacting with ozone in the atmosphere has been estimated to be ~1 day, using an ambient ozone concentration of 6×10^{11} molecules/cm^3 and an estimated reaction rate constant of 1.3×10^{-17} cm^3/molecule-sec at 25°C (U.S. EPA, 1987b).

2.1.3. Photolysis. Nicotinonitrile in methanol absorbs very little UV light of wavelengths in the environmentally significant range >290 nm (Sadtler, 1961). Therefore, direct photolysis of this compound in the atmosphere may not be significant.

2.1.4. Physical Removal. Based on the water solubilities listed in Table 1-2, potentially significant amounts of these compounds could be removed from the atmosphere by wet deposition; however, rapid reaction with hydroxyl radicals would limit the importance of wet deposition as a removal process.

2.2. WATER

2.2.1. Hydrolysis. Because organic compounds containing the nitrile group are potentially susceptible to hydrolysis in water under environmental conditions (Lyman et al., 1982), nicotinonitrile, succinonitrile and methacrylonitrile may be susceptible to hydrolysis; however, no quantitative rate data for these reactions that would permit estimation of half-lives were available in the literature.

2.2.2. Photolysis. Nicotinonitrile in methanol does not significantly absorb UV light in the environmentally significant range (wavelengths >290 nm) (Sadtler, 1961), which indicates that potential for photolysis of this compound in water may not be significant.

2.2.3. Microbial Degradation. Based on TOD, 500 mg/ℓ succinonitrile incubated in activated sludge under aerobic conditions for 24 hours underwent 3.8% degradation (Malaney and Gerhold, 1969). When incubated for 72 hours in activated sludge samples obtained from three different wastewater treatment facilities in Tennessee, an initial concentration of 500 mg/ℓ succinonitrile was found to be resistant to biological oxidation (Lutin, 1970), which indicates that these compounds may be resistant to biodegradation in natural waters.

2.2.4. **Bioaccumulation.** Using the water solubilities listed in Table 1-2 and the following linear regression equation (Lyman et al., 1982): log BCF = 2.791 - 0.564 log S, BCF values of ≤ 2 have been estimated for the selected nitriles. Based on these BCF values, bioaccumulation of these compounds in aquatic organisms is not expected to be significant.

2.2.5. **Adsorption.** Based on estimated K_{OC} values of 7-16 (Section 2.3.3.), the selected nitriles are not expected to adsorb significantly to suspended solids or sediments in water.

2.2.6. **Volatilization.** Henry's Law constant for nicotinonitrile has been estimated to be 2×10^{-9} atm-m³/mol at 25°C using an estimated vapor pressure of 0.0016 mm Hg (Neely and Blau, 1985) and a water solubility of 109,000 mg/ℓ (Offermanns et al., 1984). Based on a method of group contributions to intrinsic hydrophilic character (Hine and Mookerjee, 1975), Henry's Law constant for succinonitrile has been estimated to be 3.3×10^{-9} atm-m³/mol at 25°C. Volatilization of nicotinonitrile and succinonitrile from water can be considered insignificant based on these values of Henry's Law constant (Lyman et al., 1982). Based on a method of bond contributions to intrinsic hydrophilic character (Hine and Mookerjee, 1975), Henry's Law constant for methacrylonitrile has been estimated to be 1.5×10^{-5} atm-m³/mol at 25°C. Based on this value of Henry's Law constant and following the method of Lyman et al. (1982), the volatilization half-life from water 1 m deep, flowing at a speed of 1 m/sec, with a wind speed of 3 m/sec has been estimated to be 2 days.

2.3. SOIL

2.3.1. **Chemical Degradation.** Since nitriles are potentially susceptible to hydrolysis in water under environmental conditions (Lyman et al., 1982), they may also be susceptible to hydrolysis in moist soils.

2.3.2. Microbial Degradation. Nocardia rhodochrous strain LL100-21 isolated from soil was found to use succinonitrile as its sole nitrogen and carbon source (DiGeronimo and Antoine, 1976). It is difficult to predict the biotic fate of these nitriles in natural soils from this experiment. Based on the conclusions regarding their biodegradability in water (see Section 2.2.3.), biodegradation of these compounds in soils may be a slow process.

2.3.3. Adsorption. Using the water solubilities listed in Table 1-2 and the following linear regression equation (Lyman et al., 1982): $\log K_{OC} = -0.55 \log S + 3.64$, soil adsorption coefficients of 7, 7 and 16 have been estimated for nicotinonitrile, succinonitrile and methacrylonitrile, respectively. These K_{OC} values suggest that these compounds would be highly mobile and would leach readily through most soil (Swann et al., 1983).

2.3.4. Volatilization. The relatively high vapor pressure of methacrylonitrile (60 mm Hg at 21.5°C (Perry and Green, 1984)) suggests that volatilization of this compound from dry soil surfaces may be significant. Evaporation from moist soil surfaces may also be significant since this compound does not have a tendency to adsorb to soil and apparently evaporates rapidly from water (see Section 2.3.3. and 2.2.6.).

2.4. SUMMARY

If released to the atmosphere, these compounds are expected to exist almost entirely in the vapor phase (Eisenreich et al., 1981). The half-lives for nicotinonitrile, succinonitrile and methacrylonitrile vapor reacting with photochemically generated hydroxyl radicals have been estimated to be 2 days, 1 hour and 5 hours, respectively (U.S. EPA, 1987b). Small amounts of methacrylonitrile may react with ozone (estimated half-life, 1 day) (U.S. EPA, 1987b). Small amounts of these compounds may

be removed from the atmosphere by wet deposition. If released to water, nicotinonitrile, succinonitrile and methacrylonitrile may be susceptible to chemical hydrolysis (Lyman et al., 1982). Volatilization of methacrylonitrile from water appears to be an important removal process (half-life in a typical river, 2 days) although volatilization of nicotinonitrile or succinonitrile is not expected to be significant. Adsorption to sediments or suspended solids in water and bioaccumulation in aquatic organisms are not expected to be significant. Results of two biodegradation screening studies indicate that succinonitrile is resistant to biodegradation under aerobic conditions. If released to soil, the selected nitriles are expected to be highly mobile and leach readily through most soil. These compounds may be susceptible to hydrolysis in moist soil. Evaporation of methacrylonitrile from moist or dry soil surfaces is expected to be significant.

3. EXPOSURE

Monitoring data pertaining to human exposure by inhalation (succinonitrile and methacrylonitrile), ingestion or dermal contact could not be located in the available literature as cited in Appendix A. Nicotinonitrile has been identified as a component of tobacco smoke (Schmeltz et al, 1979), which suggests that a significant number of people would be exposed to this compound by inhalation.

The selected nitriles could potentially be released to the environment in the effluent or in fugitive emissions from production and use facilities.

4. AQUATIC TOXICITY

Pertinent data regarding toxicity of the selected nitriles to aquatic organisms could not be located in the available literature as cited in Appendix A.

5. PHARMACOKINETICS

5.1. ABSORPTION

Methacrylonitrile is absorbed after inhalation exposure, as indicated by the finding of cyanide liberated from methacrylonitrile in the blood of dogs exposed by inhalation to methocrylonitrile (Pozzani et al., 1968) and by symptoms of cyanide poisoning in rats exposed by inhalation to methacrylonitrile (Peter and Bolt, 1985) (Chapter 6). The only data that indicate absorption of methacrylonitrile after oral exposure in rats and mice is information regarding oral LD_{50} values (Anonymous, 1986; Hartung, 1982; Pozzani et al., 1968) (Section 6.1.3.).

Pertinent data regarding the absorption of succinonitrile and nicotinonitrile following an inhalation exposure could not be located in the available literature as cited in Appendix A. The only data that indicate absorption of succinonitrile and nicotinonitrile following oral exposure are LD_{50} studies using rats and mice (Hartung, 1982; NIOSH, 1987) (Section 6.1.3.).

5.2. DISTRIBUTION

The distribution of methacrylonitrile in the organs of rats following intraperitoneal injection has been studied by Haguenoer et al. (1976). At high doses of methacrylonitrile (1440, 600 and 300 mg/kg), rats died within 5-30 minutes following injection. Methacrylonitrile, free hydrogen cyanide and relatively low levels of bound hydrogen cyanide were found in the heart, lungs, liver, spleen, kidneys, stomach, intestines, skin, muscle, brain and testicles. Haguenoer et al. (1976) concluded that methacrylonitrile was lipophilic and was distributed rapidly to the various organs before death. At lower doses of methacrylonitrile (150 and 100 mg/kg), death was delayed between 2 and 24 hours following injection. Methacrylonitrile was found to be distributed to the same organs as when higher doses were administered,

although tissue concentrations of methacrylonitrile were predictably lower. Tissue concentrations of bound HCN were higher at the lower methacrylonitrile doses, which indicates that the rats had more time before death to bind the liberated HCN in the form of thiosulfate.

Pertinent data regarding the distribution of succinonitrile or nicotinonitrile could not be located in the available literature as cited in Appendix A.

5.3. METABOLISM

In vitro studies have demonstrated that rabbit, rat and mouse liver slices and microsomes are capable of liberating cyanide when incubated with succinonitrile (Willhite and Smith, 1981; Contessa and Santi, 1973; Floreani et al., 1980, 1981; Tanii and Hashimoto, 1985). Liver slices or microsomes taken from mice or rats pretreated with CCl_4 had a markedly diminished capacity to liberate cyanide from succinonitrile (Tanii and Hashimoto, 1985; Willhite and Smith, 1981; Contessa and Santi, 1973; Contessa et al., 1978). In contrast to CCl_4 pretreatment, liver slices taken from rats pretreated with ethanol showed a markedly elevated capacity for liberating cyanide from succinonitrile (Contessa et al., 1978).

Cyanide was found in the brain, liver and other organs of experimental animals (mice and rabbits) injected intravenously or intraperitoneally, or dosed orally with succinonitrile (Willhite and Smith, 1981; Contessa and Santi, 1973; Tanii and Hashimoto, 1985). In agreement with in vitro studies, pretreatment of these animals with CCl_4 inhibited the liberation of cyanide in vivo.

A series of in vitro experiments by Tanii and Hashimoto (1984a,b, 1986) demonstrated that mouse hepatic microsomes are capable of liberating cyanide from methacrylonitrile. As with succinonitrile, microsomes from mice pretreated with CCl_4 were unable to liberate cyanide from methacrylonitrile

(Tanii and Hashimoto, 1984a,b) and microsomes prepared from mice pretreated with ethanol had an enhanced ability to liberate cyanide from methacrylonitrile (Tanii and Hashimoto, 1986).

Rats exposed by inhalation to doses between 3180 and 5700 ppm (8726-15,641 mg/m^3) methacrylonitrile demonstrated signs that were similar to cyanide poisoning, indicating that cyanide had been liberated from the parent compound (Peter and Bolt, 1985). Further evidence indicating the in vivo liberation of cyanide from methacrylonitrile was the effectiveness of cyanide antidotes in the treatment of acute methacrylonitrile toxicity in rats and rabbits (Pozzani et al., 1968).

Haguenoer et al. (1976) found dose-related differences in the metabolism of methacrylonitrile in rats. Rats were injected intraperitoneally with methacrylonitrile at doses of 1440, 600, 300, 150 or 100 mg/kg. Death at each of the dose levels was from cyanide liberated from the parent compound, but the time until death increased with decreasing methacrylonitrile dose. Cyanide was found to be liberated very rapidly from methacrylonitrile in vivo, and at the three higher doses (1440, 600 and 300 mg/kg), death occurred ~5, 15 and 30 minutes, respectively, following injection. At the lower doses, death was delayed until ~2-24 hours following injection and more bound HCN in the form of thiocyanate was found in the organs of the rats. Haguenoer et al. (1976) hypothesized that at the lower doses, the rats had more time to detoxify the cyanide liberated from methacrylonitrile by binding the cyanide in the form of thiocyanate.

Pertinent data regarding the metabolism of nicotinonitrile could not be located in the available literature as cited in Appendix A.

5.4. EXCRETION

Succinonitrile injected intravenously into dogs at doses of 3 and 10 mg/kg had a half-life in the blood of 21 and 19 hours, respectively (Lodi et al., 1973). The half-life of succinonitrile in the blood of humans injected with 250 mg intravenously was ~24 hours. In humans, 95% of an intravenously administered dose of succinonitrile was eliminated as thiocyanate ion in the urine, while 2-3% was eliminated unchanged in the urine (Lodi et al., 1973).

Several investigators (Cavanna and Pocchiari, 1972; Curry, 1974, 1975; Contessa et al., 1978; Contessa and Santi, 1973) reported that experimental animals (mice, rats and rabbits) injected intraperitoneally or intravenously with succinonitrile excreted the unmetabolized parent compound or thiocyanate in the urine. CCl_4 pretreatment was found to inhibit the urinary excretion of thiocyanate in the rat (Contessa et al., 1978). Also, urinary excretion of cyanoacetic acid was observed in mice injected with succinonitrile (Merkow et al., 1959).

Methacrylonitrile and free and bound HCN were eliminated in the urine of rats injected intraperitoneally with methacrylonitrile (Haguenoer et al., 1976). Methacrylonitrile was eliminated in very small quantities in the urine, and 4-5 days following injection was not detected in the urine. Free HCN was not present in the urine in significant amounts after the first day. The levels of combined HCN in the urine were high the first 2 days and then declined rapidly to normal. Of the injected dose, 10-16% of methacrylonitrile was eliminated in the form of free and combined HCN in the urine.

Pertinent data regarding the excretion of nicotinonitrile could not be located in the available literature as cited in Appendix A.

5.5. SUMMARY

Pertinent data regarding the rate and extent of absorption of the nitriles were not located, but the demonstrated toxicity of these chemicals (Chapter 6) indicates that methacrylonitrile is absorbed after inhalation exposure in dogs and rats and after oral exposure in rats and mice, and that succinonitrile and nicotinonitrile are absorbed following oral exposure in rats and mice. Methacrylonitrile was lipophilic and distributed rapidly to various organs of the rat (Haguenoer et al., 1976). The metabolism of succinonitrile has been studied in vivo and in vitro using experimental animals (mice, rats and rabbits), and the primary metabolic pathway appears to be liberation of free HCN from the parent compound (Willhite and Smith, 1981; Contessa and Santi, 1973; Floreani et al., 1980, 1981; Tanii and Hashimoto, 1985). Liberation of free cyanide also appears to be the primary pathway of methacrylonitrile metabolism in vivo and in vitro in experimental animals (Tanii and Hashimoto, 1984a,b, 1986; Peter and Bolt, 1985; Pozzani et al., 1968; Haguenoer et al., 1976). Succinonitrile administered intravenously to humans (Lodi et al., 1973) or intraperitoneally or intravenously to experimental animals (Cavanna and Pocchiari, 1972; Curry, 1974, 1975; Contessa et al., 1978; Contessa and Santi, 1973) is excreted in the urine primarily as the parent compound and thiocyanate ion. Methacrylonitrile administered intraperitoneally to rats was found to be excreted in the urine as the parent compound, free cyanide and bound cyanide in the form of thiocyanate ion (Haguenoer et al., 1976).

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposures.

6.1.1.1. SUBCHRONIC -- Only one study was found on the systemic toxicity of methacrylonitrile following subchronic inhalation exposures in beagle dogs and Harlan-Wistar rats (Pozzani et al., 1968). Groups of 12 male and 12 female rats were exposed to 0, 19.3, 52.6 or 109.3 ppm (0, 53, 144 or 300 mg/m^3), 7 hours/day, 5 days/week for 91 days. Endpoints of toxicity examined were overt signs, body weight changes, liver and kidney weights and gross and histological examination of 19 tissues. The brain was not examined microscopically. The only treatment-related effects were deaths during the first or second day of one 52.6 ppm male and seven 109.3 ppm males, and significantly increased relative liver weights in males and females at 109.3 ppm and in males at 52.6 ppm.

Groups of three male dogs were exposed to methacrylonitrile at concentrations of 0, 3.2, 8.8 or 13.5 ppm (0, 9, 24 or 37 mg/m^3), 7 hours/day, 5 days/week for 90 days. Endpoints examined were body weight changes, overt signs, hematocrit, total and differential white cell counts, BUN, SGOT, SGPT, SAP, liver and kidney weights and gross and histological examination of 27 tissues, including the brain. At 13.5 ppm, CNS toxicity, as evidenced by convulsions and loss of motor control of the hindquarters, was observed in 2/3 dogs. One of these dogs had histopathological brain lesions, including some demyelination of the corpus callosum. SGOT and SGPT levels were markedly elevated in 1/3 dogs at 8.8 ppm, but the elevations were transient. No other treatment-related effects were observed.

Pertinent data regarding subchronic inhalation exposure to succinonitrile or nicotinonitrile could not be located in the available literature as cited in Appendix A.

6.1.1.2. CHRONIC -- Pertinent data regarding chronic inhalation exposure to succinonitrile, methacrylonitrile or nicotinonitrile could not be located in the available literature as cited in Appendix A.

6.1.2. Oral Exposures.

6.1.2.1. SUBCHRONIC -- Pertinent data regarding subchronic oral exposure to succinonitrile, methacrylonitrile or nicotinonitrile could not be located in the available literature as cited in Appendix A.

6.1.2.2. CHRONIC -- Pertinent data regarding chronic oral exposure to succinonitrile, methacrylonitrile or nicotinonitrile could not be located in the available literature as cited in Appendix A.

6.1.3. Other Relevant Information. The acute systemic toxicity of succinonitrile appears to be due to release of cyanide by metabolism of the parent compound. At autopsy, cyanide was found in the urine and various viscera of a man who had been receiving intramuscular injections of succinonitrile and died following convulsions. Cyanide derived from succinonitrile was thought to be the toxic agent (Marigo and Pappalardo, 1966). The blood of mice injected intraperitoneally with succinonitrile contained cyanide and thiocyanate (a major cyanide metabolite) (Doherty et al., 1982). Pretreatment with CCl_4 lowered the blood levels of cyanide and thiocyanate and prevented all signs of toxicity. Also, thiosulfate, a cyanide antagonist, protected mice treated with succinonitrile against death.

The toxicity of methacrylonitrile also appears to be due to cyanide liberation. Pozzani et al. (1968) found that a standard therapy for cyanide intoxication reduced the toxic effects of methacrylonitrile in rats and mice after an inhalation exposure. Haguenoer et al. (1976) found that the time to death of rats injected intraperitoneally correlated positively with dose and tissue level of cyanide (see Section 5.3.).

Other toxic effects have been observed in animals treated with methacrylonitrile and succinonitrile. Szabo and Reynolds (1975) and Szabo et al. (1982) reported that methacrylonitrile and succinonitrile were weakly to moderately ulcerogenic and adrenocorticolytic in Sprague-Dawley rats dosed either orally or subcutaneously (route not clearly specified), 3 times/day for 4 days. Total doses were 34 mmol/kg for methacrylonitrile and 5.3 mmol/kg for succinonitrile.

Information regarding the toxicity of nicotinonitrile is limited. Majka et al. (1979) found that nicotinonitrile caused irreversible opacity of the cornea when introduced into the eyes of rats and rabbits. LD_{50} and LC_{50} values for methacrylonitrile are presented in Table 6-1. The oral LD_{50} for succinonitrile in rats is 450 mg/kg and 129 mg/kg for mice (Hartung, 1982); the intraperitoneal LD_{50} is 63.1 mg/kg (NIOSH, 1987). The oral LD_{50} for mice in rats for nicotinonitrile is 1185 mg/kg (NIOSH, 1987).

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the carcinogenicity of succinonitrile, nicotinonitrile or methacrylonitrile by inhalation exposure could not be located in the available literature as cited in Appendix A.

6.2.2. Oral. Pertinent data regarding the carcinogenicity of succinonitrile, nicotinonitrile or methacrylonitrile by oral exposure could not be located in the available literature as cited in Appendix A.

6.2.3. Other Relevant Information. Bolt et al. (1986) predicted that methacrylonitrile would prove more carcinogenic than the known carcinogen, acrylonitrile. Carcinogenicity studies with methacrylonitrile were not located and this chemical is not scheduled for testing by NTP (1987).

TABLE 6-1

LD_{50} or LC_{50} Values for Methacrylonitrile

Species	Route of Administration	LD_{50} or LC_{50}	Reference
Rat	oral	250 mg/kg	Anonymous, 1986
Rat	oral	25-50 mg/kg	Hartung, 1982
Rat	oral	240 mg/kg	Pozzani et al., 1968
Rat	oral	120 mg/kg	Kurzaliev, 1985
Mouse	oral	20-25 mg/kg	Hartung, 1982
Mouse	oral	11.6 mg/kg	Kurzaliev, 1985
Rabbit	oral	16 mg/kg	Kurzaliev, 1985
Rat	inhalation	328 ppm (900 mg/m^3) for 4 hours	Anonymous, 1986
Mouse	inhalation	36 ppm (99 mg/m^3) for 4 hours	Anonymous, 1986
Mouse	inhalation	400 ppm (1098 mg/m^3) for 4 hours	Hartung, 1982
Rabbit	inhalation	37 ppm (102 mg/m^3) for 4 hours	Anonymous, 1986
Guinea pig	inhalation	88 ppm (241 mg/m^3) for 4 hours	Anonymous, 1986
Rabbit	dermal	320 mg/kg	Pozzani et al., 1968

6.3. MUTAGENICITY

Nicotinonitrile was not mutagenic in Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 with or without rat liver S-9 when tested in the spot test at 3 μmol/plate (Florin et al., 1980). Pertinent data regarding the mutagenicity of succinonitrile or methacrylonitrile could not be located in the available literature as cited in Appendix A.

6.4. TERATOGENICITY

Succinonitrile appears to be a teratogen in the hamster. Pregnant Syrian golden hamsters were dosed intraperitoneally with succinonitrile dissolved in distilled water (Doherty et al., 1983) on day 8 of gestation. The single doses of succinonitrile given and the number of dams at each dose level were 0.78-3.02 mmol/kg (18), 4.56 mmol/kg (9) and 6.24 mmol/kg (10). Six dams received water intraperitoneally and served as controls. The hamsters were sacrificed on day 11 of gestation and the number of resorptions and malformed fetuses were noted; there were no malformed fetuses in the controls. Doses of succinonitrile ranging from 0.78-3.02 mmol/kg did not produce significant teratogenic effects, although 2 fetuses had exencephaly and one fetus had a crooked tail. At 4.56 or 6.24 mmol/kg, a high incidence of malformations (60-80% of the litters) was noted in the offspring. The most frequent abnormalities were neural tube defects (exencephaly and encephalocoele). A dose-related significantly decreased crown-rump length was also observed at 4.56 and 6.24 mmol/kg. Succinonitrile treatment did not affect the incidence of resorptions. Maternal toxicity (dyspnea, hypothermia and ataxia) was evident in 20% of the animals treated at the higher doses.

The teratogenic effects of succinonitrile appear to be due to cyanide released during metabolism of the parent molecule (Doherty et al., 1983).

Treatment of succinonitrile-dosed dams with sodium thiosulfate, a cyanide antagonist, provided significant protection against fetal anomalies.

Pertinent data regarding the teratogenicity of nicotinonitrile and methacrylonitrile could not be located in the available literature as cited in Appendix A.

6.5. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of succinonitrile, methacrylonitrile or nicotinonitrile could not be located in the available literature as cited in Appendix A.

6.6. SUMMARY

One study was located regarding the toxicity of methacrylonitrile by subchronic inhalation exposure (Pozzani et al., 1968). In this study, exposure of rats to concentrations $\geq$52.6 ppm ($\geq$144 mg/m^3), but not 19.3 ppm (53 mg/m^3) for 7 hours/day, 5 days/week for 91 days resulted in increased liver weight and death. Exposure of dogs for 7 hours/day, 5 days/week for 90 days resulted in transiently elevated SGOT and SGPT levels at 8.8 ppm (24 mg/m^3) and loss of motor control of hind limbs and histopathological brain lesions at 13.5 ppm (37 mg/m^3). No effects were observed in dogs at 3.2 ppm (9 mg/m^3).

The acute toxicity of the nitriles appears to be due to release of cyanide during metabolism of the parent compound (Marigo and Pappalardo, 1966; Haguenoer et al., 1976; Pozzani et al., 1968).

Information regarding the carcinogenicity of succinonitrile, nicotinonitrile and methacrylonitrile, and the mutagenicity of methacrylonitrile and succinonitrile was not located. One study indicated that nicotinonitrile was not mutagenic in S. typhimurium (Florin et al., 1980).

A study by Doherty et al. (1983) indicated that succinonitrile was teratogenic in hamsters treated intraperitoneally at $\geq$4.56 mmol/kg. No information was located regarding the teratogenicity of either nicotinonitrile or methacrylonitrile.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

ACGIH (1986-1987) adopted a TWA-TLV for methacrylonitrile of 1 ppm or 3 mg/m^3. The TLV was based on the subchronic inhalation study using beagle dogs by Pozzani et al. (1968) and by analogy to acrylonitrile (ACGIH, 1986). The TWA workplace environmental limit for a 10-hour workshift for succinonitrile is 6 ppm (20 mg/m^3) NIOSH (1978).

Pertinent guidelines and standards for nicotinonitrile, including EPA ambient water and air quality criteria drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits could not be located in the available literature as cited in Appendix A.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the effects of the selected nitriles could not be located in the available literature as cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of succinonitrile, nicotinonitrile and methacrylonitrile following inhalation, oral or other routes could not be located in the available literature as cited in Appendix A. Therefore, an EPA classification of D is assigned to these compounds.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure.

8.2.1.1. LESS THAN LIFETIME EXPOSURES (SUBCHRONIC) -- The only study that examined the toxicity of methacrylonitrile after subchronic inhalation exposure is that of Pozzani et al. (1968). Exposure of rats to concentrations $\geq$52.6 ppm ($\geq$144 mg/m^3), but not 19.3 ppm (53 mg/m^3), for 7 hours/day, 5 days/week for 91 days resulted in increased liver weight and death. Exposure of dogs for 7 hours/day, 5 days/week for 90 days resulted in transiently elevated SGOT and SGPT levels at 8.8 ppm (24 mg/m^3) and loss of motor control of hind limbs and histopathological brain lesions at 13.5 ppm (37 mg/m^3). No effects were observed in dogs at 3.2 ppm (9 mg/m^3). Thus, the LOAEL is 24 mg/m^3. Expanding this exposure concentration over a 24-hour day and 7 day-week gives a calculated LOAEL of 5 mg/m^3. The NOEL is 9 mg/m^3. Expanding this exposure over a 24-hour day and a 7-day week, and multiplying by the reference dog inhalation rate of 4.3 m^3/day and dividing by the reference dog body weight of 12.7 kg (U.S. EPA, 1985) yields a NOEL of 0.63 mg/kg/day. Dividing by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to protect sensitive individuals), the subchronic RfD human exposure level is estimated as 0.006 mg/kg/day or 0.4

mg/day for a 70 kg human. Dividing the RfD exposure level by 20 m^3/day, the inhalation rate for a 70 kg human, yields a concentration in air of 0.02 mg/m^3.

Pertinent data regarding the effects of subchronic inhalation exposure to succinonitrile or nicotinonitrile could not be located in the available literature as cited in Appendix A.

8.2.1.2. CHRONIC EXPOSURES -- Pertinent data regarding the effects of chronic inhalation exposure of methacrylonitrile, succinonitrile or nicotinonitrile could not be located in the available literature as cited in Appendix A. A chronic inhalation RfD for methacrylonitrile can be estimated by dividing the subchronic inhalation RfD by an additional uncertainty factor of 10. Applying the additional uncertainty factor, the chronic inhalation RfD for methacrylonitrile is 0.002 mg/m^3, or 0.04 mg/day for a 70 kg human. The level of confidence in this RfD is medium because it is based on a well conducted subchronic study using two species; both a NOEL and a LOAEL can be distinguished from the observations and results.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME EXPOSURES (SUBCHRONIC) -- Pertinent data regarding the effects of subchronic oral exposure to methacrylonitrile, succinonitrile and nicotinonitrile could not be located in the available literature as cited in Apppendix A. A subchronic oral RfD for methacrylonitrile can be calculated using inhalation data from Pozzani et al. (1968). The NOEL from the study of Pozzani et al. (1968) occurred at a concentration of 9 mg/m^3, 7 hours/day, 5 days/week. Expanding for an equivalent human exposure and multiplying by the reference inhalation rate of 4.3 m^3/day for a dog and by an absorption factor of 0.5, and then dividing by the reference dog body weight of 12.7 kg, a transformed animal dose of 0.32 mg/kg/day can be calculated.

The RfD is calculated by dividing the NOEL by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for sensitive individuals). The calculated subchronic oral RfD is 0.003 mg/kg/day, or 0.2 mg/day for a 70 kg human.

The level of confidence in the subchronic oral RfD is low because it is based on only one study (Pozzani et al., 1968), and because this was an inhalation study of the toxicity of methacrylonitrile.

8.2.2.2. **CHRONIC EXPOSURES** -- Pertinent data regarding the effects of chronic oral exposure to methacrylonitrile, succinonitrile and methacrylonitrile could not be located in the available literature as cited in Appendix A. A chronic oral RfD can be derived by dividing the subchronic oral RfD by an additional uncertainty factor of 10 to extrapolate from subchronic to chronic exposure. Dividing the subchronic RfD derived from the study of Pozzani et al. (1968) by 10, a chronic oral RfD of 0.0003 mg/kg/day, or 0.02 mg/day for a 70 kg human is derived. The level of confidence in this RfD is low for reasons stated previously (see Section 8.2.2.1.) and because the study was subchronic.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The toxicity of methacrylonitrile was discussed in Chapter 6. Table 9-1 summarizes the only studies in which toxic effects of subchronic or chronic exposure were observed.

Reportable quantities were determined using data from the subchronic inhalation toxicity study of methacrylonitrile by Pozzani et al. (1968). The most severe effect, death in Harlan-Wistar rats, occurred at an equivalent human dose of 3.27 mg/kg/day. Dividing by an uncertainty factor of 10 to approximate chronic exposure and 70 kg gives an MED of 22.9 mg/day (Table 9-2). This MED corresponds to an RV_d of 3.5. The RV_e corresponding to death is 10, and multiplication of this RV_e by the RV_d yields a CS of 35. This CS corresponds to an RQ of 100 (see Table 9-2).

The second most severe effects were loss of motor control in the hind limbs of beagle dogs and histopathological brain lesions, which occurred at a human equivalent dose of 1.48 mg/kg/day. When this is divided by an uncertainty factor of 10 (to convert subchronic exposure to chronic exposure) and then multiplied by 70 kg, a MED of 10.4 mg/day is obtained. This MED corresponds to an RV_d of 4.0. The RV_e corresponding to loss of motor control is 9 and multiplication of this RV_e by the RV_d yields a CS of 36 (see Table 9-2). This CS corresponds to an RQ of 100.

The third most severe effect was a marked but transitory elevation of SGOT and SGPT values in beagle dogs. This occurred at a human equivalent dose of 0.96 mg/kg/day. Division of this dose by 10 (to convert subchronic to chronic exposure) and multiplication by 70 kg yields an MED of 6.7 mg/day. This MED corresponds to an RV_d of 4.3.

TABLE 9-1

Inhalation Toxicity Summary for Methacrylonitrile (99% Pure)[a]

Species/Strain	Sex/No.	Exposure (7 hours/day, 5 days/week for 91 days)	Transformed Animal Dose[b] (mg/kg/day)	Equivalent Human Dose[c] (mg/kg/day)	Response
Dog/beagle[d]	M/3	13.5 ppm (37 mg/m³)	2.6	1.48	2/3 experienced CNS effects (loss of motor control in hind limbs) and histopathological brain lesions
		8.8 ppm (24 mg/m³)	1.69[c]	0.96	1/3 experienced a marked but transitory elevation of SGOT and SGPT values
Rat/Harlan-Wistar[e]	M/12	109.3 ppm (300 mg/m³)	39.8	6.81	7/12 dead; increased relative liver weight
		52.6 ppm (144 mg/m³)	19.2	3.27	1/12 dead; increased relative liver weight
	F/129	109.3 ppm (300 mg/m³)	39.8	6.81	increased relative liver weight

[a]Source: Pozzani et al., 1968

[b]Calculated by multiplying the concentration by 7 hours/day x 5 days/week and by the animal inhalation rate [4.3 m³/day for dogs (U.S. EPA, 1985) and 0.223 m³/day for rats (U.S. EPA, 1985)] and dividing by the body weight.

[c]Calculated by multiplying the animal transformed dose by the cube root of the ratio of the animal body weight to the human body weight (70 kg).

[d]Reference dog body weight is 12.7 kg (U.S. EPA, 1985)

[e]Reference rat body weight is 0.35 kg (U.S. EPA, 1985)

TABLE 9-2

Inhalation Composite Scores for Methacrylonitrile*

Species/Strain	Transformed Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ
Rat/ Harlan-Wistar	19.1	22.9	3.5	death	10	35	100
Dog/beagle	2.61	10.4	4.0	loss of motor control in hind limbs	9	36	100
Dog/beagle	1.69	6.7	4.3	marked but transitory elevation	6	26	100

*Source: Pozzani et al., 1968

The RV_e associated with elevation of SGOT and SGPT values is 6 and multiplication of this RV_e by the RV_d yields a CS of 26. The RQ associated with this CS is 100 (see Table 9-2).

The RQs determined from the three effects (death, loss of motor control in hind limbs and elevated SGOT and SGPT levels) are the same (100). The highest CS (36) corresponded to the effect of loss of motor control and brain lesions in dogs and this was chosen as the basis for the RQ (Table 9-3). Data were insufficient to derive RQs for succinonitrile and nicotinonitrile (Tables 9-4 and 9-5).

9.2. BASED ON CARCINOGENICITY

Pertinent data regarding the carcinogenicity of methacrylonitrile, succininonitrile or nicotinonitrile could not be located in the available literature as cited in Appendix A; therefore an RQ based on carcinogenicity cannot be derived.

TABLE 9-3

Methacrylonitrile

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	10.4 mg/day
Effect:	loss of motor control and brain lesions
Reference:	Pozzani et al., 1968
RV_d:	4.0
RV_e:	9
Composite Score:	36
RQ:	100

*Equivalent human dose

TABLE 9-4

Succinonitrile

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	
Dose:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data were insufficient to derive an RQ

TABLE 9-5

Nicotinonitrile

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	
Dose:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data were insufficient to derive an RQ

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U.S. EPA. 1987a. Graphical Exposure Modeling System (GEMS). CLOGP computer program. Office of Toxic Substances, Washington, DC.

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APPENDIX A

LITERATURE SEARCHED

This HEED is based on data identified by computerized literature searches of the following:

TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in January, 1987. In addition, hand searches were made of Chemical Abstracts (Collective Indices 5-9), and the following secondary sources should be reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1986 1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1986-1987. Cincinnati, OH. 111 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

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Grayson, M. and D. Eckroth, Ed. 1978 1984. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed Publishing Sciences Group, Inc., Littleton, MA. 575 p.

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Jaber, H.M., W.R. Mabey, A.T. Lieu, T.W. Chou and H.L. Johnson. 1984. Data acquisition for environmental transport and fate screening for compounds of interest to the Office of Solid Waste. SRI International, Menlo Park, CA. EPA 600/6-84-010. NTIS PB84 243906.

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Sax, I.N. 1984. Dangerous Properties of Industrial Materials, 6th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1986. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1986. Report on Status Report in the Special Review Program, Registration Standards Program and the Data Call in Programs. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1985. Synthetic Organic Chemicals. U.S. Production and Sales, 1984, USITC Publ. 1422, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9 79-003. NTIS PB 80-196876.

APPENDIX B

Summary Table for Methacrylonitrile†

	Species	Exposure	Effect	RfD or q_1*	Reference
Inhalation Exposure					
Subchronic	dog	3.2 ppm (9 mg/m³) 7 hours/day, 5 days/week for 90 days (2 mg/m³) (NOEL) (0.63 mg/kg/day) 8.8 ppm (24 mg/m³) same schedule (5 mg/m³) (LOAEL)	increased SGOT and SGPT	RfD: 0.02 mg/m³ or 0.4 mg/day	Pozzani et al., 1968
Chronic	dog	3.2 ppm (9 mg/m³) 7 hours/day, 5 days/week for 90 days (2 mg/m³) (NOEL) (0.63 mg/kg/day) 8.8 ppm (24 mg/m³) same schedule (5 mg/m³) (LOAEL)	increased SGOT and SGPT	RfD: 0.002 mg/m³ or 0.04 mg/day	Pozzani et al., 1968
Carcinogenicity	ID	ID	ID	ID	ID
Oral Exposure					
Subchronic	dog	3.2 ppm (9 mg/m³) 7 hours/day, 5 days/week for 90 days (0.32 mg/kg/day) (NOEL) 8.8 ppm (24 mg/m³) same schedule (0.85 mg/kg/day) (LOAEL)	increased SGOT and SGPT	RfD: 0.003 mg/kg/day or 0.2 mg/day	Pozzani et al., 1968
Chronic	dog	3.2 ppm (9 mg/m³) 7 hours/day, 5 days/week for 90 days (0.32 mg/kg/day) (NOEL) 8.8 ppm (24 mg/m³) same schedule (0.85 mg/kg/day) (LOAEL)	increased SGOT and SGPT	RfD: 0.0003 mg/kg/day or 0.02 mg/day	Pozzani et al., 1968
Carcinogenicity	ID	ID	ID	ID	ID
REPORTABLE QUANTITIES					
Based on chronic toxicity:		100			Pozzani et al., 1968
Based on carcinogenicity:		ID			ID

†Data were insufficient to derive values for succinonitrile and nicotinonitrile.

ID = Insufficient data