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HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR ADIPONITRILE

Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

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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, 1983 and 1986a, respectively.

EXECUTIVE SUMMARY

Adiponitrile is a colorless liquid at room temperature with no distinctive odor (Smiley, 1981). It is soluble in many organic solvents and is highly soluble in water (Smiley, 1981). It undergoes reactions typical of nitriles, e.g., hydrolysis to adipamide and adipic acid and alcoholysis to substituted amides and esters (Smiley, 1981). Adiponitrile can be produced commercially either by ammoniation of adipic acid, dimerization of acrylonitrile or hydrocyanation of butadiene (Smiley, 1981). Current domestic manufacturers are E.I. Dupont in Orange, TX and Victoria, TX and Monsanto Co. in Decatur, AL (SRI, 1986). As of January 1, 1986, the total adiponitrile production capacity of these plants was estimated to be 929 million pounds per year (SRI, 1986). The most important use for this compound is as an intermediate in the manufacturer of hexamethylenediamine, a precursor of Nylon 66 (Smiley, 1981). Adiponitrile may also be used in organic synthesis and as a solvent (Kuney, 1985; Hawley, 1981; Smiley, 1981).

In the atmosphere, adiponitrile is expected to exist almost entirely in the vapor phase. Reaction with photochemically generated hydroxyl radical (estimated $t_{1/2}$ ~10 days) and physical removal by wet deposition are predicted to be important fate processes. Adiponitrile is not susceptible to reaction with ozone (U.S. EPA, 1987b). In water, aerobic biodegradation is the important removal mechanism. Based on results of a biodegradation study, it appears that the biodegradation half-life of adiponitrile in unacclimated waters at 20°C is ~1 week (Ludzack et al., 1959a). Acclimation of microorganisms should increase the rate of biodegradation and lower temperatures should decrease the rate of biodegradation (Ludzack et al., 1959a). Adsorption to suspended solids and sediments, bioaccumulation in

aquatic organism and volatilization are not expected to be important fate processes in water. In soil, aerobic biodegradation is expected to be the important degradation mechanism. Adiponitrile has the potential to undergo extensive leaching; however, biodegradation of the compound would limit the movement of this compound through soil. Volatilization is not expected to be significant in soil.

Pertinent data regarding exposure to adiponitrile by inhalation, dermal contact or ingestion of food could not be located in the available literature as cited in Appendix A. Adiponitrile was tentatively identified in the drinking water obtained from New Orleans, LA, in January 1976 (Lucas, 1984). Adiponitrile was also detected in the effluent from a nylon manufacturing plant (Shackelford and Keith, 1980).

There was little information concerning toxicity of adiponitrile to aquatic organisms. The lowest reported acutely toxic concentration for freshwater fishes was 384 mg/ℓ, an LC_{50} for golden orfe (Knie et al., 1983). The lowest reported acutely toxic concentration for freshwater invertebrates was 445 mg/ℓ, an EC_{50} for immobilization of Daphnia magna (Bringmann and Kuehn, 1982). Data for saltwater species could not be located in the available literature as cited in Appendix A.

Studies of the metabolism of adiponitrile indicate that it is absorbed by the gastrointestinal tract, metabolized to cyanide and excreted in the urine as thiocyanate (Svirbely and Floyd, 1964; Ghiringhelli, 1955a; Tanii and Hashimoto, 1985). Tanii and Hashimoto (1985) found that the metabolism of adiponitrile to cyanide in mice was greatly inhibited by CCl_4 pretreatment, which inhibits certain drug metabolizing enzymes in the liver.

Nylon workers exposed to adiponitrile and hexamethylenediamine for 2-3 years showed a tendency for hyperchromic anemia of the hemolytic type and slight leukopenia (Ceresa, 1948a). Ceresa (1948b) attributed these effects to exposure to adiponitrile and hexamethylenediamine.

Dogs fed adiponitrile in the diet at levels $\leq$500 ppm had normal blood and urine values and tests for liver and kidney function (Svirbely and Floyd, 1964). During the first week of the study, dogs fed 1000 ppm were not able to consume the entire dose. In a rat study (Svirbely and Floyd, 1964), females treated with adiponitrile in the drinking water at 0.5, 5.0 and 50 ppm and males at 50 ppm were found to have advanced adrenal degeneration.

Vomiting, tightness in the chest, headache, profound weakness with difficulty standing, vertigo, respiratory difficulty, tachycardia and low blood pressure were experienced by a human who consumed a few mℓ of adiponitrile (Ghiringhelli, 1955b). Zeller et al. (1969) reported seven cases of skin irritation in workers dermally exposed to adiponitrile.

Adiponitrile rubbed on the backs of guinea pigs for 1 month resulted in weight loss, decreased calcium content of the blood, marked hyperchromic hemolytic anemia with leukopenia and lymphomonocytosis. Histological examinations revealed swelling and congestion of nearly all internal organs (Ceresa, 1948b).

Rats exposed to adiponitrile at 0.3 mg/ℓ for ten 6-hour exposures (5 days/week) showed increases in blood glucose, urea nitrogen, creatinine and urine glucose, and decreases in erythrocyte count, hemoglobin, leukocyte count and urine osmolality. At 0.1 mg/ℓ, increases in urea nitrogen and lymphocytes and decreases in the number of eosinophils and neutrophils were noted. No changes in clinical parameters were observed at 0.03 mg/ℓ (Smith and Kennedy, 1982).

The oral LD_{50} in the rat was reported to be 960 mg/kg (Plokhova and Rubakina, 1965) and 300 mg/kg (NIOSH, 1978). Mice, with an oral LD_{50} of 172 mg/kg, may be somewhat more sensitive to the acute oral toxicity of adiponitrile (Tanii and Hashimoto, 1985).

The carcinogenicity of adiponitrile following inhalation, oral or other routes of exposure has not been studied. Adiponitrile tested negative for reverse mutation in S. typhimurium at concentrations ≤10,000 µg/plate, both with and without metabolic activation.

Johannsen et al. (1986) orally dosed pregnant rats with adiponitrile at 0, 30, 50 or 80 mg/kg/day on gestation days 6-19. Two rats at 80 mg/kg/day and one rat at 50 mg/kg/day died. Fetal body weights were significantly reduced at 80 mg/kg/day, but this observation was not attributed to treatment. No other changes were noted. No changes in fertility, gestation or viability were noted in two litters from rats exposed to adiponitrile in their drinking water at 10, 100 or 500 ppm for 2 years (Svirbely and Floyd, 1964).

Chronic oral exposure to adiponitrile resulted in a LOAEL of 0.5 ppm (0.07 mg/kg/day) that was associated with adrenal degeneration in the 2-year rat study (Svirbely and Floyd, 1964). This study was unavailable for review and in addition appears to be an unpublished abstract. Data were considered inadequate for estimation of either an RfD or an RQ. It is recommended that comprehensive subchronic oral testing be initiated in the rat to determine a NOAEL. Data were insufficient for derivation of cancer-based risk assessment values. Adiponitrile was assigned to EPA Group D, not classifiable as to human carcinogenicity.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
BOD	Biological oxygen demand
CAS	Chemical Abstract Service
CS	Composite score
EC_{50}	Concentration effective to 50% of recipients (and all other subscripted concentration levels)
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Adiponitrile is also known as hexanedinitrile, adipic acid nitrile, tetramethyl cyanide and 1,4-dicyanobutane (SANSS, 1987). The structure, empirical formula, molecular weight and CAS Registry number are as follows:

$$N\equiv C\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}C\equiv N$$

Empirical formula: $C_6H_8N_2$

Molecular weight: 108.14

CAS Registry number: 111-69-3

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Pure adiponitrile is a colorless liquid at room temperature with no distinctive odor (Smiley, 1981). It undergoes reactions typical of nitriles, e.g., hydrolysis to adipamide and adipic acid and alcoholysis to substituted amides and esters (Smiley, 1981). Adiponitrile is soluble in methanol, ethanol, chloroalkane and aromatic solvents and has low solubility in carbon disulfide, ethyl ether and aliphatic hydrocarbons (Smiley, 1981). Selected physical properties are given below:

Melting point, °C:	2.49	Smiley, 1981
Boiling point, °C:	295	Smiley, 1981
Vapor pressure at 20°C:	3.0×10^{-3} mm Hg	Neely and Blau, 1985
Water solubility, 20°C:	8×10^{4} mg/ℓ	Smiley, 1981
Log K_{ow}:	-0.32 -0.42	Tanii and Hashimoto, 1985 U.S. EPA, 1987a
Density, 20°C:	0.965 g/cm³	Smiley, 1981
Refractive Index, n_D^{20}:	1.4343	Smiley, 1981
Flashpoint, °C:	159 (closed cup)	Smiley, 1981

1.3. PRODUCTION DATA

Adiponitrile can be prepared commercially using either adipic acid, acrylonitrile or butadiene as feedstock (Smiley, 1981). In the adipic acid process, the feedstock is allowed to react with ammonia over a catalyst to produce adiponitrile. In one butadiene-based production process, butadiene is directly hydrocyanated in two successive steps to produce adiponitrile. Another process involves dimerization of acrylonitrile in an electrolyte cell to produce adiponitrile (Smiley, 1981). Table 1-1 lists production information concerning current domestic manufacturers of adiponitrile. Although closed since 1980, the Monsanto plant in Pensacola, FL, has a yearly production capacity of 185 million pounds; this plant continues to hydrogenate adiponitrile produced at other Monsanto locations to make hexamethylenediamine (SRI, 1986).

1.4. USE DATA

The most important commercial use for adiponitrile is as an intermediate in the manufacture of hexamethylenediamine, a precursor of Nylon 66 (Smiley, 1981). Adiponitrile may also be used in organic synthesis and as a solvent (Kuney, 1985; Hawley, 1981; Smiley, 1981).

1.5. SUMMARY

Adiponitrile is a colorless liquid at room temperature with no distinctive odor (Smiley, 1981). It is soluble in many organic solvents and is highly soluble in water (Smiley, 1981). It undergoes reactions typical of nitriles, e.g., hydrolysis to adipamide and adipic acid, and alcoholysis to substituted amides and esters (Smiley, 1981). Adiponitrile can be produced commercially either by ammoniation of adipic acid, dimerization of acrylonitrile or hydrocyanation of butadiene (Smiley, 1981). Current domestic manufacturers are E.I. Dupont in Orange, TX and Victoria, TX and Monsanto

TABLE 1-1

Current Domestic Manufacturers of Adiponitrile[a]

Company	Location	Annual Capacity[b] (millions of pounds)
E.I. Dupont	Orange, TX	441
E.I. Dupont	Victoria, TX	293
Monsanto Co.	Decatur, AL	195
	Total	929

[a]Source: SRI, 1986

[b]Estimates as of January 1, 1986

Co. in Decatur, AL (SRI, 1986). As of January 1, 1986 the total adiponitrile production capacity of these plants was estimated to be 929 million pounds per year (SRI, 1986). The most important use for this compound is as an intermediate in the manufacturer of hexamethylenediamine, a precursor of Nylon 66 (Smiley, 1981). Adiponitrile may also be used in organic synthesis and as a solvent (Kuney, 1985; Hawley, 1981; Smiley, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT

Limited experimental data pertaining to the environmental fate and transport of adiponitrile could be located in the available literature as cited in Appendix A. When possible, therefore, information concerning the fate and transport of this compound was derived from physical property data or molecular structure.

2.1. AIR

Based on the estimated vapor pressure of 3.0×10^{-3} mm Hg at 20°C, adiponitrile is expected to be present almost entirely in the vapor phase in the atmosphere (Eisenreich et al., 1981).

2.1.1. Reaction with Hydroxyl Radicals. The estimated rate constant for the reaction of adiponitrile with photochemically generated hydroxyl radicals is ~10^{-10} cm^3/molecule-sec at 25°C using the method of Atkinson (1985). Given the average hydroxyl radical concentration in air of 8×10^5 molecules/cm^3 (U.S. EPA, 1987b), the estimated half-life for this reaction is ~10 days (Atkinson, 1985).

2.1.2. Reaction with Ozone. Adiponitrile is not susceptible to oxidation by ozone in the atmosphere (U.S. EPA, 1987b).

2.1.3. Physical Removal Processes. Based on a water solubility of 8×10^4 mg/ℓ at 20°C (Smiley, 1981), it appears that significant amounts of adiponitrile may be removed from the atmosphere by wet deposition.

2.2. WATER

2.2.1. Hydrolysis. In an abstract of a Russian study (Linetskii and Serebryakov, 1965), the first-order hydrolysis rate constant for adiponitrile in 2-5% NaOH solution at 100°C was reported as 1.18 min^{-1}. Under environmental conditions, however, adiponitrile is not likely to hydrolyze significantly (U.S. EPA, 1986b).

2.2.2. Microbial Degradation. Results of a biodegradation screening study, which used a natural water sample as seed, indicate that biodegradation is likely to be the most significant route of decomposition for adiponitrile under aerobic conditions in water (Ludzack et al., 1959a). Incubation of 0.5-10 mg/ℓ adiponitrile in unacclimated Ohio River water resulted in BOD values equivalent to theoretical oxygen demands of 0, 40 and >100% after 2, 5 and 12 days, respectively. Acclimation of microorganisms was examined by redosing, and degradation occurred twice as fast after acclimation was achieved. The effect of temperature on biodegradation was also studied; biodegradation at 5°C required ~3.5 times longer than at 20°C. Ludzack et al. (1959b) studied the biodegradation of adiponitrile by activated sludge in a continuous feed test at 22-25°C; 93-98% BOD removal was measured with a mean aerator detention time of 7-13 hours at an influent adiponitrile concentration equivalent to a BOD of 275-350 mg/ℓ. Adiponitrile at 500 mg/ℓ incubated for 72 hours in three different activated sludge inocula, was found to be resistant to biological oxidation (Lutin, 1970). Ludzack et al. (1959a) found that nitrile oxidation proceeds by enzymatic hydrolysis leading to the formation of ammonia, followed by nitrification.

2.2.3. Bioconcentration. A BCF of 1 was estimated for adiponitrile using a water solubility of 8.0×10^4 mg/ℓ at 20°C (Smiley, 1981) and the following linear regression equation (Lyman et al., 1982): log BCF = 2.791 - 0.564 log S. This BCF value suggests that adiponitrile will not bioaccumulate significantly in aquatic organisms.

2.2.4. Adsorption. An estimated K_{oc} value of 9 for adiponitrile (Section 2.3.3.) suggests that adsorption to sediments or suspended solids in water would not be significant.

2.2.5. Volatilization. Henry's Law constant for adiponitrile was estimated to be ~7×10^{-9} atm-m^3/mol at 25°C using a method of group contributions to intrinsic hydrophilic character (Hine and Mookerjee, 1975). This value of Henry's Law constant suggests that volatilization from water would not be an important removal mechanism (Lyman et al., 1982).

2.3. SOIL

2.3.1. Hydrolysis. Because of the lack of experimental data the significance of this reaction cannot be determined.

2.3.2. Microbial Degradation. In the only study available regarding the biodegradation of adiponitrile by soil microorganisms, Kuwahara et al. (1980) found that Aeromonas sp. BN 7013 isolated from soil is capable of using adiponitrile as its sole source of nitrogen. Relatively rapid biodegradation of adiponitrile in natural water samples and activated sludge inocula suggests that biodegradation may also be the most important removal mechanism in soil.

2.3.3. Adsorption. A K_{oc} of 9 was estimated using a water solubility of 8.0×10^4 mg/ℓ at 20°C (Smiley, 1981) and the following linear regression equation (Lyman et al., 1982): $\log K_{oc} = -0.55 \log S + 3.64$. This K_{oc} value indicates that adiponitrile should be highly mobile in soil and susceptible to significant leaching (Swann et al., 1983).

2.3.4. Volatilization. Based on a vapor pressure of 3.0×10^{-9} mm Hg at 20°C and a Henry's Law constant of 7×10^{-9} atm-m^3/mol at 25°C, volatilization of adiponitrile from moist and dry soil surfaces is not expected to be a significant fate process.

2.4. SUMMARY

In the atmosphere, adiponitrile is expected to exist almost entirely in the vapor phase. Reaction with photochemically generated hydroxyl radical (estimated $t_{1/2}$ ~10 days) and physical removal by wet deposition are predicted to be important fate processes. Adiponitrile is not susceptible to reaction with ozone (U.S. EPA, 1987b). In water, aerobic biodegradation is the important removal mechanism. Based on results of a biodegradation study, it appears that the biodegradation half-life of adiponitrile in unacclimated waters at 20°C is ~1 week (Ludzack et al., 1959a). Acclimation of microorganisms should increase the rate of biodegradation and lower temperatures should decrease the rate of biodegradation (Ludzack et al., 1959a). Adsorption to suspended solids and sediments, bioaccumulation in aquatic organism and volatilization are not expected to be important fate processes in water. In soil, aerobic biodegradation is expected to be the important degradation mechanism. Adiponitrile has the potential to undergo extensive leaching; however, biodegradation of the compound would limit the movement of this compound through soil. Volatilization is not expected to be significant in soil.

3. EXPOSURE

Pertinent data regarding exposure to adiponitrile by inhalation, dermal contact or ingestion of food could not be located in the available literature as cited in Appendix A. Adiponitrile was tentatively identified in the drinking water obtained from New Orleans, LA, in January 1976 (Lucas, 1984). Adiponitrile was also detected in the effluent from a nylon manufacturing plant (Shackelford and Keith, 1976).

4. AQUATIC TOXICITY

4.1. ACUTE TOXICITY

Two available studies reported acute toxicity data for fish or aquatic invertebrates exposed to adiponitrile. Henderson et al. (1961) reported 96-hour LC_{50} values of 820 and 1250 mg/ℓ for fathead minnows, Pimephales promelas, in hard and soft water, respectively. These authors also reported 96-hour LC_{50} values of 720 mg/ℓ for bluegills, Lepomis macrochirus, and 775 mg/ℓ for guppies, Lebistes reticulatus, both in soft water. Hardness in these studies was 20 mg/ℓ for soft water and 380 mg/ℓ for hard water. An LC_{50} of 384 mg/ℓ was reported for the golden orfe, Leuciscus idus (Knie et al., 1983).

The only invertebrate species for which there was information about adiponitrile toxicity was the cladoceran, Daphnia magna. Bringmann and Kuehn (1982) reported a 24-hour EC_{50} for immobilization of 445 mg/ℓ, while Knie et al. (1983) reported an EC_{50} of 1250 mg/ℓ.

4.2. CHRONIC EFFECTS

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

4.3. PLANT EFFECTS

Knie et al. (1983) reported that 408 mg/ℓ was a 30-minute EC_{10} for inhibition of culture growth of the bacterium Pseudomonas putida. Other data for aquatic plants or bacteria could not be located in the available literature as cited in Appendix A.

4.4. SUMMARY

There was little information concerning toxicity of adiponitrile to aquatic organisms. The lowest reported acutely toxic concentration for freshwater fishes was 384 mg/ℓ, an LC_{50} for the golden orfe (Knie et al., 1983). The lowest reported acutely toxic concentration for freshwater invertebrates was 445 mg/ℓ, an EC_{50} for immobilization of Daphnia magna (Bringmann and Kuehn, 1982). Data for saltwater species could not be located in the available literature as cited in Appendix A.

5. PHARMACOKINETICS

5.1. ABSORPTION

Approximately 50% of the adiponitrile consumed in the diet by mongrel female dogs was recovered in the urine as thiocyanate (Svirbely and Floyd, 1964). Dietary concentrations ranged from 10-1000 ppm.

5.2. DISTRIBUTION

Cyanide, an important metabolite of adiponitrile, has been shown to cross the blood-brain barrier and locate in the brain. Tanii and Hashimoto (1985) measured cyanide at ~0.71 μg/g of wet tissue in the brains of male ddY mice given an oral 4.8 mmol/kg (519 mg/kg) dose of adiponitrile. The brains were harvested at the time of death, ~83 minutes after treatment. In mice pretreated with CCl_4 to inhibit the hepatic mixed function oxidase system (and presumably prevent degradation of adiponitrile to cyanide), a 519 mg/kg dose of adiponitrile did not cause death and cyanide was not found in the brain 83 minutes after treatment.

5.3. METABOLISM

A number of studies indicate that adiponitrile is metabolized to cyanide. Svirbely and Floyd (1964) found that dogs fed adiponitrile in the diet at 10-1000 ppm showed a dose-related increase in thiocyanate excreted in the urine, which is equivalent to ~50% of the dose of adiponitrile. The amount of thiocyanate in the bloodstream of guinea pigs injected subcutaneously with adiponitrile at 3-30 mg/kg was proportional to the administered dose (Ghiringhelli, 1955a). Tanii and Hashimoto (1985) identified cyanide in the brains of mice orally dosed with adiponitrile. The metabolism of adiponitrile to cyanide was greatly inhibited in mice pretreated with CCl_4, as evidenced by the fact that cyanide was not found in the brains of pretreated mice.

In an *in vitro* study using mouse liver microsomes, 6.23 ng cyanide/mg protein/minute were formed from an adiponitrile concentration of 3.1 mM (Tanii and Hashimoto, 1985). When mice were treated with CCl_4 before microsomes were harvested, cyanide was not detected after adiponitrile was added to the cultures. Tanii and Hashimoto (1985) stated that adiponitrile is probably hydroxylated at the α-carbon to form cyanohydrin, which degrades spontaneously in alkaline medium to form hydrogen cyanide.

5.4. EXCRETION

Approximately 79% of the adiponitrile (3-30 mg/kg) injected subcutaneously into guinea pigs was accounted for as thiocyanate excreted in the urine (Ghiringhelli, 1955a). Dogs excreted ~50% of an oral dose of adiponitrile as urinary thiocyanate; negligible amounts of thiocyanate were found in the feces (Svirbely and Floyd, 1964).

5.5. SUMMARY

Studies of the metabolism of adiponitrile indicate that it is absorbed by the gastrointestinal tract, metabolized to cyanide and excreted in the urine as thiocyanate (Svirbely and Floyd, 1964; Ghiringhelli, 1955a; Tanii and Hashimoto, 1985). Tanii and Hashimoto (1985) found that the metabolism of adiponitrile to cyanide in mice was greatly inhibited by CCl_4 pretreatment, which inhibits certain drug metabolizing enzymes in the liver.

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposures.

6.1.1.1. SUBCHRONIC -- Pertinent data regarding the toxicity of adiponitrile following subchronic inhalation exposure could not be located in the available literature as cited in Appendix A.

6.1.1.2. CHRONIC -- Ceresa (1948a) reported that 27 individuals who had worked in the nylon industry, handling adiponitrile and hexamethylenediamine for 2-3 years, showed a definite tendency for hyperchromic anemia of the hemolytic type and slight leukopenia or lymphomonocytosis.

6.1.2. Oral Exposures.

6.1.2.1. SUBCHRONIC -- Pertinent data regarding the toxicity of adiponitrile following subchronic oral exposure could not be located in the available literature as cited in Appendix A.

6.1.2.2. CHRONIC -- NIOSH (1978) reviewed chronic oral studies of adiponitrile in dogs and rats completed by Svirbely and Floyd (1964). The original study report could not be obtained. However, the original report from the fourth portion of this series (Svirbely, n.d.) was located. Apparently each of the segments were only reported in abstract form. In the dog study, an unspecified number of female mongrel dogs were fed adiponitrile in the diet at "the equivalent of" 10, 100, 500 and 1000 ppm for an unspecified period of time. Blood and urine values and tests for liver and kidney function were normal in dogs fed adiponitrile at $\leq$500 ppm. During the first week, dogs fed 1000 ppm were not able to consume the entire dose; the dogs vomited or failed to eat a portion of it.

In the rat study, an unspecified number of male and female Wistar rats were provided with 0.5, 5.0 or 50 ppm adiponitrile in their drinking water

for 2 years. Throughout the study, body weights remained normal and no hematologic abnormalities were observed. At the end of the study, advanced adrenal degeneration was found in female rats at all three adiponitrile concentrations and in male rats exposed to 50 ppm. Degeneration of other organs was also noted, but was not considered to be compound-related. Determination of organ (spleen, liver, kidney) to body weight ratios revealed no significant differences. No effect on survival was reported.

6.1.3. Other Relevant Information. NIOSH (1978) summarized a report by Ghiringhelli (1955b) concerning a case of acute poisoning in which an 18-year-old man consumed a few mℓ of adiponitrile. The man experienced vomiting, tightness in the chest, headache, profound weakness with difficulty standing, vertigo, respiratory difficulty, tachycardia and low blood pressure. The man recovered after being treated with sodium thiosulfate.

As reviewed by NIOSH (1978), Zeller et al. (1969) reported seven cases of dermal exposure to adiponitrile. Mild skin irritation and inflammation developed in six of the workers within 5-15 minutes of exposure. The seventh worker, whose shoe had been drenched with adiponitrile, had extensive destruction of the skin of the foot. The injury required surgical treatment and the worker was incapacitated for 117 days.

To determine if the effects observed in humans occupationally exposed to adiponitrile and hexamethylenediamine (see Section 6.1.1.2.) could be attributed to adiponitrile, Ceresa (1948b) and Ceresa and De Blasiis (1950) examined the toxicity of adiponitrile and hexamethylenediamine in guinea pigs. An unspecified dose of adiponitrile was rubbed on the backs of guinea pigs daily for 1 month (Ceresa, 1948b). This treatment resulted in weight loss, decreased calcium content of the blood, marked hyperchromic hemolytic anemia with leukopenia and lymphomonocytosis. Histological examinations revealed swelling and congestion of nearly all internal organs. Because

hemolytic anemia with leukopenia and degenerative changes in the liver and kidney were also noted in guinea pigs treated with subcutaneous injections of hexamethylenediamine, Ceresa and De Blasiis (1950) concluded that both adiponitrile and hexamethylenediamine may contribute to the effects observed in humans.

Smith and Kennedy (1982) exposed groups of 10 male Charles River CD rats to adiponitrile vapor at 0, 0.03, 0.1 or 0.3 mg/ℓ (0, 30, 100 or 300 mg/m³) for ten 6-hour periods (5 days/week). After the ninth exposure, blood and urine analyses were completed. Following the tenth exposure, 5 rats/exposure group were sacrificed and comprehensive histological examinations were conducted. The remaining rats were allowed to recover for 14 days when they were sacrificed for histological examinations.

During the exposures, the signs of toxicity observed in all exposed groups included irregular breathing and mild salivation. Rats exposed at 0.3 mg/ℓ showed weight loss during the first 5 exposures, and after 10 exposures had changes in clinical pathology parameters including increases in blood glucose, urea nitrogen, creatinine and urine glucose, and decreases in erythrocyte count, hemoglobin, leukocyte count and urine osmolality. At 0.1 mg/ℓ, rats showed increased blood urea nitrogen and lymphocytes and decreased numbers of eosinophils and neutrophils. No changes in clinical chemistry parameters were observed at 0.03 mg/ℓ. No histological changes were noted at any exposure concentration. Fourteen days postexposure, clinical pathology parameters of all groups were normal and microscopic changes in the organs were not observed.

LD_{50} values for adiponitrile are presented in Table 6-1. Plokhova and Rubakina (1965) reported effects of acute lethal oral doses of adiponitrile as excitation, convulsions, dyspnea, coma with death in 2-6 hours. Histopathologic changes included hyperemia and dystrophic changes in brain,

TABLE 6-1

LD_{50} Values for Adiponitrile

Species	Route of Administration	LD_{50} Value	Reference
Rat	inhalation	1.71 mg/ℓ (1710 mg/m³) (4-hour LC_{50})	Smith and Kennedy, 1982
Rat	oral	960 mg/kg	Plokhova and Rubakina, 1965
Rat	oral	300 mg/kg	NIOSH, 1978
Mouse[a]	oral	1.59 mmol (~172 mg/kg)	Tanii and Hashimoto, 1985
Mouse[b]	oral	2.65 mmol (~287 mg/kg)	Tanii and Hashimoto, 1985
Guinea pig	subcutaneous	50 mg/kg	Ghiringhelli, 1955b
Rat	subcutaneous	200 mg/kg	NIOSH, 1978
Mouse	intraperitoneal	40 mg/kg	Plzak and Doull, 1969

[a]Mice pretreated with an intraperitoneal injection of olive oil served as controls in an experiment with mice pretreated with CCl_4 (see Section 5.2).

[b]Mice were pretreated with an intraperitoneal injection of CCl_4. Mice appear to be somewhat more sensitive than rats to the acute oral toxicity of adiponitrile.

liver, kidney and myocardium. Mice appear to be somewhat more sensitive than rats to the acute oral toxicity of adiponitrile.

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the carcinogenicity of adiponitrile following inhalation exposure could not be located in the available literature as cited in Appendix A.

6.2.2. Oral. A NIOSH (1978) summary of a 2-year drinking water study of adiponitrile in Wistar rats did not report carcinogenic effects. Additional information concerning the carcinogenicity of adiponitrile following oral exposure could not be located in the available literature as cited in Appendix A. The chemical is not currently scheduled for cancer testing by the NTP (1987).

6.2.3. Other Relevant Information. Pertinent data regarding the carcinogenicity of adiponitrile by other routes of exposure could not be located in the available literature as cited in Appendix A.

6.3. MUTAGENICITY

NIOSH (1978) reported that adiponitrile was negative for reverse mutation in Salmonella typhimurium strains TA1536, TA1537, TA1538 and TA98 at concentrations $\leq$10,000 µg/plate, both with and without metabolic activation.

6.4. TERATOGENICITY

Johannsen et al. (1986) dosed groups of 25 mated Charles River, COBD CD rats by gavage with adiponitrile at 0, 30, 50 or 80 mg/kg/day on gestation days 6-19. The dams were sacrificed on gestation day 20 and the number and location of viable and nonviable fetuses, early and late resorptions, and the total number of implants and corpora lutea were determined. The fetuses were examined for gross malformations and half were examined for visceral malformations while the remaining were examined for skeletal anomalies.

During the study, two 80 mg/kg/day rats and one 50 mg/kg/day rat died. No differences were found in uterine and fetal parameters measured at sacrifice. Fetal body weights were reduced significantly ($p<0.05$) at 80 mg/kg/day but not at 30 mg/kg/day, although the fetal body weights were essentially the same at these two dose levels. Because a dose-related change in fetal body weight was not observed, the investigators concluded that there was no treatment-related effect on fetal body weight. Fetal examinations revealed no treatment-related malformations.

6.5. OTHER REPRODUCTIVE EFFECTS

Svirbely (n.d) reported in an unpublished abstract that exposure of Holtzman rats (number unspecified) to 10, 100 or 500 ppm adiponitrile for three generations (2 litters/generation) did not result in any adverse effects. Endpoints monitored included fertility, gestation (NOS) and viability.

6.6. SUMMARY

Nylon workers exposed to adiponitrile and hexamethylenediamine for 2-3 years showed a tendency for hyperchromic anemia of the hemolytic type and slight leukopenia (Ceresa, 1948a). Ceresa (1948b) attributed these effects to exposure to adiponitrile and hexamethylenediamine.

Dogs fed adiponitrile in the diet at levels $\leq$500 ppm had normal blood and urine values and tests for liver and kidney function (Svirbely and Floyd, 1964). During the first week of the study, dogs fed 1000 ppm were not able to consume the entire dose. In a rat study (Svirbely and Floyd, 1964), females treated with adiponitrile in the drinking water at 0.5, 5.0 and 50 ppm and males at 50 ppm were found to have advanced adrenal degeneration.

Vomiting, tightness in the chest, headache, profound weakness with difficulty standing, vertigo, respiratory difficulty, tachycardia and low

blood pressure were experienced by a human who consumed a few mℓ of adiponitrile (Ghiringhelli, 1955b). Zeller et al. (1969) reported seven cases of skin irritation in workers dermally exposed to adiponitrile.

Adiponitrile rubbed on the backs of guinea pigs for 1 month resulted in weight loss, decreased calcium content of the blood, marked hyperchromic hemolytic anemia with leukopenia and lymphomonocytosis. Histological examinations revealed swelling and congestion of nearly all internal organs (Ceresa, 1948b).

Rats exposed to adiponitrile at 0.3 mg/ℓ for ten 6-hour exposures (5 days/week) showed increases in blood glucose, urea nitrogen, creatinine and urine glucose, and decreases in erythrocyte count, hemoglobin, leukocyte count and urine osmolality. At 0.1 mg/ℓ, increases in urea nitrogen and lymphocytes and decreases in the number of eosinophils and neutrophils were noted. No changes in clinical parameters were observed at 0.03 mg/ℓ (Smith and Kennedy, 1982).

The oral LD_{50} in the rat was reported to be 960 mg/kg (Plokhova and Rubakina, 1965) and 300 mg/kg (NIOSH, 1978). Mice, with an oral LD_{50} of 172 mg/kg, may be somewhat more sensitive to the acute oral toxicity of adiponitrile (Tanii and Hashimoto, 1985).

The carcinogenicity of adiponitrile following inhalation, oral or other routes of exposure has not been studied. Adiponitrile tested negative for reverse mutation in S. typhimurium at concentrations ≤10,000 µg/plate, both with and without metabolic activation.

Johannsen et al. (1986) orally dosed pregnant rats with adiponitrile at 0, 30, 50 or 80 mg/kg/day on gestation days 6-19. Two rats at 80 mg/kg/day and one rat at 50 mg/kg/day died. Fetal body weights were significantly

reduced at 80 mg/kg/day, but this observation was not attributed to treatment. No other changes were noted. No changes in fertility, gestation or viability were noted in two litters from rats exposed to adiponitrile in their drinking water at 10, 100 or 500 ppm for 2 years (Svirbely and Floyd, 1964).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

NIOSH (1978) recommended that employee exposure to adiponitrile not exceed 4 ppm (18 mg/m^3) as a TWA for up to a 10-hour work shift in a 40-hour workweek. This recommendation is based on the comparative acute toxicity of isobutyronitrile and adiponitrile injected subcutaneously in female rats. Other guidelines or standards 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 adiponitrile 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 adiponitrile by any route of exposure could not be located in the available literature as cited in Appendix A.

8.1.1. Weight of Evidence. Data were not located regarding the carcinogenicity of adiponitrile in humans or experimental animals; therefore, adiponitrile is placed in EPA Group D (U.S. EPA, 1986c), not classifiable as to human carcinogenicity.

8.1.2. Quantitative Risk Estimates. The lack of data concerning the carcinogenicity of adiponitrile precludes the derivation of risk assessment values based on carcinogenicity.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure.

8.2.1.1. LESS THAN LIFETIME EXPOSURES (SUBCHRONIC) -- The lack of data concerning the toxicity of adiponitrile following subchronic inhalation exposure precludes the derivation of a subchronic inhalation RfD.

8.2.1.2. CHRONIC EXPOSURES -- Nylon workers exposed to adiponitrile and hexamethylenediamine for 2-3 years showed a definite tendency for hyperchromic anemia of the hemolytic type and slight leukopenia (Ceresa, 1948a). The study is inadequate for the derivation of an inhalation RfD because exposure was to a mixture of chemicals and because of the lack of quantitative exposure data. The recommended occupational standard of 4 ppm (18 mg/m^3) (NIOSH, 1978) based on acute subcutaneous toxicity of adiponitrile compared with isobutyronitrile in female rats is not adequate for determination of an RfD for inhalation exposure.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME EXPOSURES (SUBCHRONIC) -- The toxicity of adiponitrile following subchronic oral exposure has not been studied.

8.2.2.2. CHRONIC EXPOSURES -- In a study by Svirbely and Floyd (1964), blood and urine values and tests for liver and kidney function were normal in dogs fed adiponitrile at ≤500 ppm for an unspecified length of time. During the first week of the study, dogs fed 1000 ppm were not able to consume the entire dose.

Female rats provided with adiponitrile in their drinking water at 0.5, 5.0 or 50 ppm and males at 50 ppm for 2 years were found to have advanced adrenal degeneration (Svirbely and Floyd, 1964). No changes in body weight, organ weights or hematological values were noted and no increase in mortality was reported. Advanced adrenal degeneration was observed in all treated groups of females, but in males only at 50 ppm. These observations suggest that 0.5 ppm may be near the threshold for adrenal effects in females. Increased mortality was not reported in any treatment group which suggests that the effects on the adrenal were not life threatening. The drinking water concentration of 0.5 ppm, therefore, constitutes a NOAEL in male rats and may be considered a LOAEL in female rats. The fact that this study was not available for review and that it appears from the evaluation of other reports from this series that the report only existed as an unpublished abstract precludes use of these data for RfD development.

It is known that adiponitrile is metabolized to cyanide. Therefore, the possibility that an RfD for adiponitrile could be derived by analogy to cyanide was investigated. However, the effects on the adrenal gland reported by Svirbely and Floyd (1964) are inconsistent with the reported critical effects of cyanide which are predominately CNS lesions. In addition the dose of adiponitrile causing these adrenal lesions is much

lower than reported effect levels for cyanide (ATSDR, 1988). As a result of discrepancy in both critical effects and effective doses for adiponitrile compared with cyanide, an RfD based on analogy is not derived. Adiponitrile has not been examined for carcinogenicity, and the one teratogenicity study (Johannsen et al., 1986) located did not find fetal effects at doses below those that caused maternal toxicity.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The toxicity of adiponitrile was discussed in Chapter 6. The only data potentially suitable for the derivation of an RQ are summarized in Table 9-1. In the 2-year rat study (Svirbely and Floyd, 1964), advanced adrenal degeneration was observed in female rats provided with adiponitrile in the drinking water at 0.5 ppm. Due to reporting deficiencies as discussed in Sections 6.1.2. and 8.2.2., these data are not used to estimate an RQ (Table 9-2).

9.2. BASED ON CARCINOGENICITY

Data were not located regarding the carcinogenicity of adiponitrile in humans or animals and the compound was assigned to EPA Group D, not classifiable as to human carcinogenicity. Hazard ranking based on carcinogenicity, therefore, is not possible.

TABLE 9-1

Oral Toxicity Summary for Adiponitrile Using Female Wistar Rats[a,b]

Average Weight (kg)	Vehicle/ Physical State	Exposure	Transformed Animal Dose[c] (mg/kg/day)	Equivalent Human Dose[d] (mg/kg/day)	Response
0.35[e]	drinking water	0.5 ppm in the drinking water for 2 years	0.07	0.01	advanced adrenal degeneration

[a]Source: Svirbely and Floyd, 1964; NIOSH, 1978

[b]Number of animals at start of experiment and purity of compound were not reported.

[c]Calculated by multiplying the 0.5 ppm drinking water level by 0.049 ℓ/day, the reference water intake for a 0.35 kg rat (U.S. EPA, 1985) and by dividing by the rat body weight.

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

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

TABLE 9-2

Adiponitrile

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

Route:	
Dose*:	
Effect:	
Reference:	Data are insufficient to evaluate an RQ.
RV_d:	
RV_e:	
Composite Score:	
RQ:	

*Equivalent human dose

10. REFERENCES

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Swann, R.L., D.A. Laskowski, P.J. McCall, K. Vander Kuy and H.J. Dishburger. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio and water solubility. Res. Rev. 85: 17-28.

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U.S. EPA. 1985. Reference Values for Risk Assessment. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

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U.S. EPA. 1986b. OHMTADS (Oil and Hazardous Materials Technical Assistance Data Systems). On-line: February, 1987.

U.S. EPA. 1986c. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

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

U.S. EPA. 1987b. Graphical Exposure Modeling System (GEMS). Fate of Atmospheric Pollutants (FAP). Office of Toxic Substances, U.S. EPA, Washington, DC.

Zeller, H.V., H.T. Hofmann, A.M. Thiess and W. Hey. 1969. Toxicity of nitriles. Zentralbl. Arbeitsmed. Arbeitsschutz. 19: 225-238. (Cited in NIOSH, 1978)

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 February, 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.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

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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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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.

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APPENDIX B

Summary Table for Adiponitrile

	Species	Exposure	Effect	RfD or q_1^*	Reference
Inhalation Exposure					
Subchronic	ID				
Chronic	ID				
Carcinogenicity	ID				
Oral Exposure					
Subchronic	ID				
Chronic	ID				
Carcinogenicity	ID				
REPORTABLE QUANTITIES					
Based on Chronic Toxicity:		ID			
Based on Carcinogenicity:		ID			

ID = Insufficient Data