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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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HEALTH EFFECTS ASSESSMENT FOR ACRYLONITRILE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with tin and compounds. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Acrylonitrile. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-017. NTIS PB81-117285.

U.S. EPA. 1983a. Health Assessment Document for Acrylonitrile. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-82-007F. NTIS PB84-149152.

U.S. EPA. 1983b. Reportable Quantity Document for Acrylonitrile. Prepared by tdhe Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985. Health and Environmental Effects Profile for Acrylonitrile. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk - cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval 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 been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Acrylonitrile has been demonstrated to be carcinogenic in rats exposed in drinking water (Quast et al., 1980a; Bio/dynamics, Inc., 1980a,b,c) or by inhalation (Quast et al., 1980b). An epidemiological study (O'Berg, 1980) associated increased incidences of cancer, particularly lung cancer, with occupational exposure to acrylonitrile. U.S. EPA (1983a) derived a potency slope q_1^* of 5.4×10^{-1} $(mg/kg/day)^{-1}$ [corresponding to an upper limit unit risk of 1.5×10^{-5} $(\mu g/\ell)^{-1}$] for oral exposure to acrylonitrile based on the incidence of tumors at various sites in rats from the Quast et al. (1980a) and Bio/dynamics, Inc. (1980a,b) studies. A potency slope of 0.24 $(mg/kg/day)^{-1}$, corresponding to a unit risk of 6.8×10^{-5} $(\mu g/m^3)^{-1}$, was calculated for inhalation exposure from the incidence of total cancers in occupationally exposed humans (O'Berg, 1980). Acrylonitrile is classified by EPA as Group B1: a probable human carcinogen.

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LIST OF ABBREVIATIONS

CAS	Chemical Abstract Service
CNS	Central nervous system
DNA	Deoxyribonucleic acid
NOAEL	No-observed-adverse-effect level
ppb	Parts per billion
ppm	Parts per million
RfD	Reference Dose
RfD_S	Subchronic Reference Dose
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL FATE AND TRANSPORT

Selected physical and chemical properties of acrylonitrile (CAS No. 107-13-1) are reported in Table 1-1. Synonyms for acrylonitrile are 2-propenenitrile, vinyl cyanide, cyanoethylene, Acritet, Fumigrain and Ventox. In air, acrylonitrile is predicted to be removed predominantly by oxidation reactions with photochemically generated hydroxyl radicals. The half-lives reported in Table 1-1 are based on experimental data and an assumed hydroxyl radical concentration of $1x10^6$ molecules/cm^3. The aquatic half-lives reported in Table 1-1 are for volatilization only; thus, the half-life of acrylonitrile may vary greatly depending upon the characteristics of the aquatic system (U.S. EPA, 1979, 1983a). The half-life of acrylonitrile in soil could not be located in the available literature. Based on its relatively high water solubility, however, acrylonitrile is expected to be highly mobile in moist soils. The high vapor pressure indicates that evaporation from dry soil surfaces is expected to occur rapidly.

TABLE 1-1

Selected Physical and Chemical Properties and Half-Lives for Acrylonitrile

Property	Value	Reference
Chemical class:	cyanogenated olefinic hydrocarbon	
Formula:	CH_2=CHCN	
Molecular weight:	53.06	
Specific gravity:	0.8	ACGIH, 1986
Melting point:	-83.5°C	ACGIH, 1986
Boiling point:	77.3°C at 760 mm Hg	ACGIH, 1986
Vapor pressure:	85.5 mm Hg at 20°C	Weber et al.. 1981
Water solubility:	73.5 mg/ℓ at 20°C	U.S. EPA, 1979
Log octanol/water partition coefficient:	0.25	Hansch and Leo, 1985
Bioconcentration factor:	48 in bluegill sunfish	U.S. EPA. 1985
Half-lives in:		
Air:	2-9 days	U.S. EPA. 1985; Edney et al., 1983
Water:	0.6-0.8 hours (relatively rapid flowing shallow streams); ~13 hours (1 m deep, estimated)	Cadena et al., 1984; U.S. EPA, 1983a

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Young et al. (1977) administered single oral doses of 0.1 or 10 mg/kg ^{14}C-acrylonitrile to male rats. Excreta were collected for 72 hours. At the lower dose, the total recovery of radioactivity was 82.4% with 5.4% appearing in the feces, while at the higher dose the total recovery of radioactivity was 104.0% with 5.2% appearing in the feces. These data indicate that $\geq$95% of orally administered acrylonitrile is absorbed from the gastrointestinal tract.

2.2. INHALATION

Male rats exposed to 5 or 100 ppm (11 or 217 mg/m^3) ^{14}C-acrylonitrile for 6 hours excreted most of the absorbed radioactivity in the urine (Young et al., 1977). The investigators estimated total absorbed doses of 0.7 and 10.2 mg/kg for 5 and 100 ppm group rats, respectively. These data suggest that absorption following inhalation exposure is rapid and substantial, and indicate that ~41% and ~30% of inhaled radioactivity is absorbed at 5 and 100 ppm exposure levels, respectively.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. In the only available subchronic oral toxicity study of acrylonitrile (Quast et al., 1975), four dogs/sex were exposed to 0, 100, 200 or 300 ppm (mg/ℓ) acrylonitrile in drinking water for 6 months, which corresponded to 10, 16 and 18 mg/kg/day for male dogs, and 8, 17 and 18 mg/kg/day for females, respectively. Administration of either the 200 or 300 ppm (mg/ℓ) concentrations caused morbidity and death. Deaths were due to food aspirationrelated bronchopneumonia, and the esophageal walls of affected dogs were ulcerated. At 100 ppm, female dogs had sporadically lower water consumption and consistently lower food consumption; these findings were not observed in a supplemental part of the study using the same experimental design. Relative kidney weights were also increased in the 100 ppm males, although there were no remarkable renal lesions, and no other adverse effects were noted. The equivalent dose of 8-10 mg/kg/day can be considered a NOAEL for oral exposure.

3.1.2. Inhalation. In rats and rabbits exposed to 50 mg/m³ acrylonitrile for 6 months, for an unspecified number of hours per day, Knobloch et al. (1972) noted peripheral blood pattern changes and respiratory, cardiac, renal and neuronal dysfunction. CNS disorders and a variety of biochemical and hematological changes were observed by Babanov et al. (1972), who exposed rats to 0.495 mg/m³ acrylonitrile vapor, 5 hours/day, 6 days/week, for 6 months. Hematological changes included increased erythrocyte and decreased leukocyte counts, increased total protein and peroxidase content, and decreased blood ascorbic acid content. Further details were not available.

3.2. CHRONIC

3.2.1. Oral. The carcinogenicity studies discussed in Section 4.2.1. provide some data on nonneoplastic effects of chronic exposure to acrylonitrile. In the studies by Bio/dynamics, Inc. (1980a,b,c), groups of 100 male and 100 female Spartan or Fischer 344 rats were treated with acrylonitrile in drinking water at concentrations of 1-300 ppm or by gavage at 0.1 or 10.0 mg/kg/day, 5 days/week for 19-26 months. The equivalent doses in the drinking water studies and the treatment-related gross and clinical observations of all three studies are given in Table 3-1.

The consistently observed increased mortality in rats ingesting acrylonitrile at 8-10 mg/kg/day resulted from the debilitating effects of tumors. The only other effects observed, decreased body weight and changes in hematological and urine values, were not severe and in many cases could be attributed to the decreased food and water consumption. Relative organ weights of the liver and kidney (organ-to-body weight ratio) were increased in the high-dose males and females; however, the absolute organ weights were either the same as control values or only slightly increased. Similar increases in relative and absolute organ weights were noted for the heart in the high-dose groups in two of the studies (Bio/dynamics, Inc., 1980b,c). The lack of pair-fed controls makes interpretation of these observations difficult.

Quast et al. (1980a) exposed rats to acrylonitrile in the drinking water for 2 years. The concentrations used were 35, 85 and 210 ppm for 21 days, followed by 35, 100 and 300 ppm, for the duration of the study. The U.S. EPA (1985) stated that the amounts of acrylonitrile ingested were equivalent to 3.42, 8.53 and 21.18 mg/kg/day or 4.36, 10.76 and 24.97 mg/kg/day, for male or female rats, respectively. Early mortality was noted for males and

TABLE 3-1

Toxicological Findings in Rats Orally Exposed to Acrylonitrile*

Dose (mg/kg/day)	Sex	Mortality	Body Weight (% change)	Consumption	
				Food	Water
7.98	M	Increase	Decrease (10%)	Decrease	Decrease
0.093	M	ND	ND	ND	ND
10.69	F	Increase	Decrease (8%)	Decrease	Decrease
0.146	F	ND	ND	ND	ND
8.37	M	Increase	Decrease (12%)	Decrease	Decrease
2.49	M	ND	Decrease (<5%)	ND	ND
0.84	M	Increase	ND	ND	ND
0.25	M	ND	ND	ND	ND
0.08	M	ND	ND	ND	ND
10.89	F	Increase	Decrease (12%)	Decrease	Decrease
3.65	F	Increase	ND	ND	ND
1.25	F	ND	ND	ND	ND
0.36	F	Increase	ND	ND	ND
0.12	F	ND	ND	ND	ND
10.0	M	Increase	Decrease (<6%)	Decrease	ND
0.1	M	ND	ND	ND	ND
10.0	F	Increase	ND	ND	Increase
0.1	F	ND	ND	ND	ND

*Source: Bio/dynamics, Inc., 1980a,b,c

ND = No difference from control values

females at the highest concentration. Although the U.S. EPA (1985) stated that treatment of females with the two lowest concentrations also resulted in early mortality, this finding may have been due to an abnormally low mortality rate in control females. The only nonneoplastic histopathological lesions observed were hyperplasia of the stomach and mammary gland and glial proliferation in the brain.

3.2.2. Inhalation. In a 10-year study of a population of 576 workers exposed to 5-20 ppm acrylonitrile, headache, fatigue, nausea and weakness were frequently reported (Sakarai and Kusimoto, 1972). Clinically, the workers had anemia, jaundice and abnormal serum enzyme and urinalysis values, the extent of which was directly related to duration of exposure.

Quast et al. (1980b) exposed rats to 0, 20 or 80 ppm acrylonitrile vapor, 6 hours/day, 5 days/week, for 2 years. These concentrations correspond to 0, 43 and 174 mg/m^3, respectively. The low concentration was associated with the early onset of chronic renal disease, possibly because of increased water consumption. Early mortality apparently masked the appearance of renal disease at the high concentration.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Murray et al. (1978) exposed gravid rats to 0, 10, 25 or 65 mg/kg/day by gavage in water, on days 6-15 of gestation. Dams exposed to 25 mg/kg/day had slight maternal toxicity, whereas those given 65 mg/kg/day had decreased body weight, thickening of the nonglandular stomach and increased liver weight. There were no treatment-related effects on the number of litters, implants or live fetuses/litter. Administration of the high dose led to decreased fetal body weight and increased crown-rump length. There were dose-related effects on the incidence of litters with fetuses having

short tails or trunks, imperforate anus and missing vertebrae. The investigators concluded that the adverse effects were directly on the fetus rather than secondary to maternal toxicity.

Beliles et al. (1980) performed an extensive 3-generation reproductive study on rats with 0, 100 or 500 ppm acrylonitrile in drinking water. The parents of the first generation showed some adverse effects of treatment in the 500 ppm group, with food and water consumption and body weights significantly lower than those of control rats (other generations were not monitored for these parameters). Reproductive toxicity was observed in the two matings of the first generation, manifested as an increased number of deaths during the lactation period among pups of rats that had been treated at the 500 ppm level. These deaths may have been a result of acrylonitrile's effect on the dams, since pups fostered by untreated dams had normal survival. In the other generations, reproductive capacity and pup survival were within the normal range. The only adverse effect observed in pups that survived treatment was a decrease in body weight in the 500 ppm group. Poor weight gain in the pups may have been caused by poor lactation in the dams, which was due to the decreased water consumption. Ten weanlings of each sex from the control and high-dose groups of the F_{3b} litter were sacrificed for comprehensive histopathological evaluation. No adverse findings were noted in tissues taken routinely for histological evaluation. Acrylonitrile appeared to have little direct effect on the development of the embryo and pup up to the time of weaning.

3.3.2. Inhalation. Murray et al. (1978) exposed groups of gravid rats to 40 or 80 ppm (87 or 174 mg/m^3) acrylonitrile, 6 hours/day on gestation days 6-15. Treatment did not increase the number of specific individual

fetal malformations; however, when considering total malformations, exposure to 80 ppm increased the number of litters containing abnormal fetuses, although not significantly (p=0.06).

3.4. TOXICANT INTERACTIONS

Hydrogen cyanide and carbon monoxide have been found to enhance the toxicity of acrylonitrile (Yamamoto, 1976; Ostirovskaya et al., 1976). A number of researchers (Dudley and Neal, 1942; Ghiringhelli, 1954; Graham, 1965; McLaughlin et al., 1976) have found that the traditional antidotes for cyanide poisoning, including sodium thiosulfate, methylene blue, sodium nitrite and hydroxycobalamine, were only minimally effective or ineffective in cases of experimental acrylonitrile poisoning.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity in humans of oral exposure to acrylonitrile were not located in the available literature.

4.1.2. Inhalation. Although a number of occupational studies regarding the carcinogenic risks of acrylonitrile exposure were available, only one study (O'Berg, 1980) estimated actual exposure levels. A cohort of 1345 male employees in a textile plant was studied over a 16-year exposure period (1950-1966), with a minimum 10-year follow-up. Levels of exposure to acrylonitrile, as documented by U.S. EPA (1983a), were designated as "high" (20 ppm, ~41 mg/m^3), "medium" (10 ppm, ~20 mg/m^3) or "low" (5 ppm, ~10 mg/m^3) with a mean of 15 ppm (~30 mg/m^3). Considering all employees, 25 cases of cancer were found, compared with 20.5 expected cases (based upon company records). Eight of these cancers were of the respiratory system, vs. 4.4 expected cases. Table 4-1 shows the significantly elevated cancer incidences in workers exposed for >6 months, who were subjected to the highest exposure concentrations. After adjustment for smoking patterns, the U.S. EPA (1983a) concluded that the excess risk for lung cancer in long-term workers was probably related to acrylonitrile. Smoking was not completely ruled out as a contributing factor, however.

Although several other epidemiological studies (Delzell and Monson, 1982; Thiess et al., 1980; Werner and Carter, 1981) reported positive evidence for lung, lymphatic or stomach cancer associated with acrylonitrile exposure, these studies contained a number of methodological flaws, including poor follow-up procedures and exposure to multiple compounds, and will not be considered further in this document.

TABLE 4-1

Observed and Expected Cancer Incidences, Based on Incidence Rates for Male Employees at DuPont Company Exposed for >6 Months[a]

Observation Years	Person-Years[b] (morbidity)	Person-Years[b] (mortality)	Total Cancers		Respiratory Cancers		Total Cancer Deaths		Respiratory-Related Cancer Deaths	
			Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
1956-1964	5,482	7,438	2	3.5	2	0.4	1	2.2	0	0.5
1965-1969	3,563	5,511	1	3.6	0	0.9	3	2.9	1	1.0
1970-1976	4,591	7,586	17	8.3[c]	6	2.1[d]	11	7.8	5	3.1
TOTAL	13,636	20,535	20	15.4	8	3.4[d]	15	12.9	6	4.6

[a]Sources: O'Berg, 1980; U.S. EPA, 1983a

[b]Person-year data based on all employees

[c]$p<0.05$

[d]$p<0.01$

4.2. BIOASSAYS

4.2.1. Oral. Quast et al. (1980a) found treatment-related increases in a variety of tumor types in rats exposed to acrylonitrile in the drinking water (Table 4-2). In males, these tumors included Zymbal gland carcinomas, squamous cell tumors of the tongue and forestomach, papillomas of the stomach, and glial cell proliferation and tumors of the CNS. Females had treatment-related increases in neoplasia at all these sites, in addition to tumors of the mammary gland and small intestine.

Bio/dynamics, Inc. (1980a) found increases in several tumor types (Table 4-3) in both male and female rats exposed in the drinking water to 1 or 100 ppm acrylonitrile for 19-22 months. Surviving females were sacrificed at 19 months and surviving males at 22 months.

In a more extensive study, Bio/dynamics, Inc. (1980b) found similar tumor types in rats exposed in drinking water to 1, 3, 10, 30 or 100 ppm acrylonitrile, for 23-26 months (Table 4-4). Interim sacrifices were performed at 6, 12 and 18 months. In another study (Bio/dynamics, Inc., 1980c), Spartan rats (100 males and 100 females/group) were given acrylonitrile in deionized water by gavage at 0.1 and 10.0 mg/kg/day, 5 days/week; however, the study was terminated at 19 and 20 months because of excessive mortality in the high-dose groups. Histopathological evaluation revealed increased incidences of tumors of the brain and ear canal (Zymbal gland) in high-dose males and females. Stomach tumors were observed only in high-dose males, and mammary gland tumors were observed in high-dose females.

In the 3-generation rat study described in Section 3.3.1. (Beliles et al., 1980), second-generation high-dose (500 ppm) offspring had higher incidences of astrocytomas and Zymbal gland tumors than did either control or F_0 rats, providing further evidence for acrylonitrile-induced carcinogenicity.

TABLE 4-2

Tumor Incidence in Sprague-Dawley Rats Treated for 24 Months with Acrylonitrile of High Purity in Drinking Water[a,b]

Sex/Number	Dose or Exposure (mg/kg/day)[c]	Target Organ	Tumor Type	Tumor Incidence (p value)[d]
M/80	0 ppm (0.0)	brain/spinal cord	astrocytoma	1/80
		Zymbal gland	carcinoma	3/80
		stomach	all tumors	0/80
		tongue	squamous cell tumors	1/75[e]
M/48	35 ppm (3.42)	brain/spinal cord	astrocytoma	12/47 (p<0.05)
		Zymbal gland	carcinoma	4/47
		stomach	all tumors	3/46 (p<0.05)
		tongue	squamous cell tumors	2/7[e]
M/48	100 ppm (8.53)	brain/spinal cord	astrocytoma	22/48 (p<0.05)
		Zymbal gland	carcinoma	3/48
		stomach	all tumors	23/48 (p<0.05)
		tongue	squamous cell tumors	4/9[e] (p<0.05)
M/48	300 ppm (21.18)	brain/spinal cord	astrocytoma	30/48 (p<0.05)
		Zymbal gland	carcinoma	15/48
		stomach	all tumors	39/47 (p<0.05)
		tongue	squamous cell tumors	5/40[e] (p<0.05)
F/80	0 ppm (0.0)	brain/spinal cord	astrocytoma	0/80
		Zymbal gland	carcinoma	1/80
		stomach	all tumors	1/80
		tongue	squamous cell tumors	0/78
		mammary gland	malignant/benign	57/80

TABLE 4-2 (cont.)

Sex/Number	Dose or Exposure (mg/kg/day)[c]	Target Organ	Tumor Type	Tumor Incidence (p value)[d]
F/48	35 ppm (4.36)	brain/spinal cord	astrocytoma	17/48 (p<0.05)
		Zymbal gland	carcinoma	4/48
		stomach	all tumors	1/47
		tongue	squamous cell tumors	1/48
		mammary gland	malignant/benign	42/48 (p<0.05)
F/48	100 ppm (10.76)	brain/spinal cord	astrocytoma	22/48 (p<0.05)
		Zymbal gland	carcinoma	6/48
		stomach	all tumors	12/48 (p<0.05)
		tongue	squamous cell tumors	1/5[e]
		mammary gland	malignant/benign	42/48 (p<0.05)
F/48	300 ppm (24.97)	brain/spinal cord	astrocytoma	24/48 (p<0.05)
		Zymbal gland	carcinoma	14/48 (p<0.05)
		stomach	all tumors	30/48 (p<0.05)
		tongue	all tumors	2/3[e] (p<0.05)
		mammary gland	malignant	35/48

[a]Sources: Quast et al., 1980a; U.S. EPA, 1983a

[b]The acrylonitrile was stablized with hydroquinone monoethyl ether (39 ppm).

[c]The dose in mg/kg/day was calculated from measured water consumption and body weight.

[d]Tumor incidence expressed as number of rats with tumors/the number of rats examined microscopically for that particular organ.

[e]All samples were not taken from all rats.

TABLE 4-3

Tumor Incidence in Spartan Rats Treated with 100% Pure Acrylonitrile in Drinking Water[a,b]

Sex/Number	Dose or Exposure (mg/kg/day)[c]	Duration of Treatment (months)	Duration of Study (months)	Target Organ	Tumor Type	Tumor Incidence (p value)
M/100	0 ppm (0.0)	NA	22	brain	astrocytoma	2/98
				Zymbal gland	carcinoma	1/100
				stomach	papilloma/carcinoma	3/98
M/100	1 ppm (0.093)	22	22	brain	astrocytoma	3/95
				Zymbal gland	carcinoma	0/91
				stomach	papilloma/carcinoma	3/98
M/100	100 ppm (7.98)	22	22	brain	astrocytoma	23/97 (p<0.05)
				Zymbal gland	carcinoma	14/93 (p<0.05)
				stomach	papilloma/carcinoma	12/97 (p<0.05)
F/100	0 ppm (0.0)	NA	19	spinal cord	astrocytoma	0/96
				brain	astrocytoma	0/99
				Zymbal gland	carcinoma	0/99
				stomach	papilloma/carcinoma	1/100
F/100	1 ppm (0.146)	19	19	spinal cord	astrocytoma	0/99
				brain	astrocytoma	1/100
				Zymbal gland	carcinoma	0/95
				stomach	papilloma/carcinoma	4/99
F/100	100 ppm (10.69)	19	19	spinal cord	astrocytoma	7/98 (p<0.05)
				brain	astrocytoma	32/97 (p<0.05)
				Zymbal gland	carcinoma	7/98 (p<0.05)
				stomach	papilloma/carcinoma	7/99 (p<0.05)

[a]Sources: Bio/dynamics, Inc., 1980a; U.S. EPA, 1983a

[b]The authors reported that the acrylonitrile was "100% active ingredient."

[c]The dose in mg/kg/day was calculated from measured water consumption and body weight.

NA = Not applicable

TABLE 4-4

Tumor Incidence in Fisher Rats Treated with 100% Pure Acrylonitrile in Drinking Water[a,b]

Sex/Number	Dose or Exposure (mg/kg/day)[c]	Duration of Treatment (months)	Duration of Study (months)	Target Organ	Tumor Type	Tumor Incidence (p value)
M/200	0 ppm (0.0)	NA	26	brain	astrocytoma	2/200
				ear canal	carcinoma/adenoma	2/89
				stomach	all tumors	0/199
				spinal cord	astrocytoma	1/196
M/100	1 ppm (0.08)	26	26	brain	astrocytoma	2/100
				ear canal	carcinoma/adenoma	1/97
				stomach	all tumors	1/100
				spinal cord	astrocytoma	0/99
M/100	3 ppm (0.25)	26	26	brain	astrocytoma	1/100
				ear canal	carcinoma/adenoma	0/93
				stomach	all tumors	4/97 ($p<0.05$)
				spinal cord	astrocytoma	0/92
M/100	10 ppm (0.84)	26	26	brain	astrocytoma	2/100
				ear canal	carcinoma/adenoma	2/88
				stomach	all tumors	4/100 ($p<0.05$)
				spinal cord	astrocytoma	0/98
M/100	30 ppm (2.49)	26	26	brain	astrocytoma	10/99 ($p<0.05$)
				ear canal	carcinoma/adenoma	7/94 ($p<0.05$)
				stomach	all tumors	4/100 ($p<0.05$)
				spinal cord	astrocytoma	0/99
M/100	100 ppm (8.37)	26	26	brain	astrocytoma	21/99
				ear canal	carcinoma/adenoma	16/93
				stomach	all tumors	1/100
				spinal cord	astrocytoma	4/93
F/200	0 ppm (0.0)	NA	23	brain	astrocytoma	1/199
				ear canal	carcinoma/adenoma	0/193
				stomach	all tumors	1/99
				spinal cord	astrocytoma	1/197
F/100	1 ppm (0.12)	23	23	brain	astrocytoma	1/100
				ear canal	carcinoma/adenoma	0/94
				stomach	all tumors	1/100
				spinal cord	astrocytoma	0/97

TABLE 4-4 (cont.)

Sex/Number	Dose or Exposure (mg/kg/day)[c]	Duration of Treatment (months)	Duration of Study (months)	Target Organ	Tumor Type	Tumor Incidence (p value)
F/100	3 ppm (0.36)	23	23	brain	astrocytoma	2/101
				ear canal	carcinoma/adenoma	2/92
				stomach	all tumors	2/100
				spinal cord	astrocytoma	0/99
F/100	10 ppm (1.25)	23	23	brain	astrocytoma	4/95 (p<0.05)
				ear canal	carcinoma/adenoma	4/90
				stomach	all tumors	2/97
				spinal cord	astrocytoma	1/92 (p<0.05)
F/100	30 ppm (3.65)	23	23	brain	astrocytoma	6/100 (p<0.05)
				ear canal	carcinoma/adenoma	5/94 (p<0.05)
				stomach	all tumors	4/100 (p<0.05)
				spinal cord	astrocytoma	0/96
F/100	100 ppm (10.89)	23	23	brain	astrocytoma	23/98 (p<0.05)
				ear canal	carcinoma/adenoma	10/86 (p<0.05)
				stomach	all tumors	2/97
				spinal cord	astrocytoma	1/91

[a]Sources: Bio/dynamics, Inc., 1980b; U.S. EPA, 1983a

[b]The authors reported that the acrylonitrile was "100% active ingredient."

[c]The dose in mg/kg/day was calculated from measured water consumption and body weight.

4.2.2. Inhalation. Quast et al. (1980b) has shown that chronic exposure to acrylonitrile vapors is tumorigenic in rats (Table 4-5).

4.3. OTHER RELEVANT DATA

Information regarding the mutagenicity of acrylonitrile has been summarized by U.S. EPA (1985). Variable responses for reverse mutations have been observed in plate incorporation assays using Salmonella typhimurium (DeMeester et al., 1978). In vitro, acrylonitrile was shown to be transformed to a reactive epoxide, which binds irreversibly to nucleic acids and proteins (Guengerich et al., 1981), and is directly mutagenic toward S. typhimurium (Cerna et al., 1981). Positive results have been obtained with Escherichia coli (Venitt et al., 1977). Acrylonitrile was ineffective in inducing clastogenic events in mouse bone marrow cells (Leonard et al., 1981) and in lymphocytes of exposed human workers (Thiess and Fleig, 1978); however, the compound did increase the frequency of sister chromatid exchange (Perocco et al., 1982), unscheduled DNA synthesis in cultured human lymphocytes (Perocco et al., 1982) and DNA single strand breaks in cultured Syrian golden hamster cells (Parent and Casto, 1979).

4.4. WEIGHT OF EVIDENCE

IARC (1979) did not have sufficient data to allow classification of the carcinogenic potential of acrylonitrile. The U.S. EPA (1980a) indicated that, based on then newly available preliminary evidence, acrylonitrile was "likely" to be a human carcinogen. In 1983, on the basis of subsequent epidemiological and animal experimentation, U.S. EPA stated that using IARC criteria the level of animal evidence should be considered "sufficient," and that the level of human data is between "sufficient" and "limited."

TABLE 4-5

Tumor Incidences in Male and Female Sprague-Dawley Rats Exposed by Inhalation for 24 Months to Acrylonitrile of High Purity[a,b]

Sex/Number	Dose or Exposure	Target Organ	Tumor Type	Tumor Incidence[c] (p value)
M/100	0.0 ppm	brain/spinal cord	glial cell tumors	0/100
		tongue	all tumors	1/96
		small intestine	benign and malignant	2/99
		Zymbal gland	benign and malignant	2/100
M/100	20 ppm (43 mg/m³), 6 hours/day, 5 days/week	brain/spinal cord	glial cell tumors	4/99
		tongue	all tumors	0/14
		small intestine	benign and malignant	2/20
		Zymbal gland	benign and malignant	4/100
M/100	80 ppm (174 mg/m³), 6 hours/day, 5 days/week	brain/spinal cord	glial cell tumors	22/99 (p<0.05)
		tongue	all tumors	7/89 (p<0.05)
		small intestine	benign and malignant	15/98 (p<0.05)
		Zymbal gland	benign and malignant	11/100 (p<0.05)
F/100	0.0 ppm	brain/spinal cord	glial cell tumors	0/100
		Zymbal gland	benign and malignant	0/100
		mammary gland	adenocarcinoma	9/100
F/100	20 ppm (43 mg/m³), 6 hours/day, 5 days/week	brain/spinal cord	glial cell tumors	8/100 (p<0.05)
		Zymbal gland	benign and malignant	1/100
		mammary gland	adenocarcinoma	8/100

TABLE 4-5 (cont.)

Sex/Number	Dose or Exposure	Target Organ	Tumor Type	Tumor Incidence[c] (p value)
F/100	80 ppm (174 mg/m³), 6 hours/day, 5 days/week	brain/spinal cord Zymbal gland mammary gland	glial cell tumors benign and malignant adenocarcinoma	21/100 ($p<0.05$) 11/100 ($p<0.05$) 20/100 ($p<0.05$)

[a]Sources: Quast et al., 1980b; U.S. EPA, 1983a

[b]The acrylonitrile contained the inhibitor hydroquinone monomethyl ether.

[c]The tumor incidence is expressed as tumors per number of animals examined.

Therefore, acrylonitrile was considered by the EPA to be an IARC Group 2A carcinogen (U.S. EPA, 1983a). For the same reasons, the EPA classification has been designated B1, a probable human carcinogen (U.S. EPA, 1985). An EPA classification of B1 signifies that the available animal evidence on carcinogenicity may be sufficient and human evidence is limited (U.S. EPA, 1986). The available animal evidence is sufficient and would also yield a weight of evidence classification of B (B2 specifically). Thus, by both human and animal data acrylonitrile is considered to be a probable human carcinogen. No additional information that would alter these classifications was available.

5. REGULATORY STANDARDS AND CRITERIA

U.S. EPA (1980a) derived a criterion of 0.58 µg/ℓ for acrylonitrile, based upon excess cancer risk associated with the increased incidence of astrocytomas in the CNS of female rats in the chronic drinking water bioassay by Quast et al. (1980a).

The ACGIH (1985) adopted a TLV-TWA of 2 ppm (~4.5 mg/m³) for acrylonitrile, accompanied by a "skin" notation. The compound is classified by EPA as "Probable Human Carcinogen," Group B1 based upon limited epidemiological evidence and demonstration of carcinogenesis in several animal species. The ACGIH (1986) based the TLV-TWA upon the "consistent production of tumors in rats and the suspicion of cancer in humans raised by the [O'Berg (1980)] study."

The current OSHA (1985) standards for acrylonitrile are an 8-hour TWA of 2 ppm (~4 mg/m³) and a 15-minute ceiling limit of 10 ppm (~22 mg/m³).

The U.S. EPA (1983a) classifies acrylonitrile in Group B1, a probable human carcinogen, based on sufficient animal evidence and limited human evidence of carcinogenicity.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

Sufficient evidence exists to indicate that acrylonitrile is carcinogenic by the oral and inhalation routes. It is, therefore, inappropriate to derive RfD_S values for oral or inhalation exposure.

6.2. REFERENCE DOSE (RfD)

Sufficient evidence exists to indicate that acrylonitrile is carcinogenic by the oral and inhalation routes. It is, therefore, inappropriate to derive RfD values for oral or inhalation exposure.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The U.S. EPA (1983a, 1985) calculated q_1^* values from three drinking water studies in rats (Bio/dynamics, Inc., 1980a,b; Quast et al., 1980a), using the multistage linearized model adopted by the U.S. EPA (1980b). In the Bio/dynamics, Inc. (1980a,b) studies, U.S. EPA (1983a, 1985) combined incidences of CNS astrocytomas, Zymbal gland carcinomas and forestomach tumors. In the Quast et al. (1980a) study, U.S. EPA (1983a, 1985) considered the total number of tumors described in Section 4.2.1., except for female mammary gland tumors. The geometric mean of the q_1^*s from these three studies was calculated to be 5.4×10^{-1} $(mg/kg/day)^{-1}$ from data in males and 4.6×10^{-1} $(mg/kg/day)^{-1}$ from data in females (U.S. EPA, 1983a). Since the value derived from the data in males was higher and would result in a more protective estimate for humans, the U.S. EPA (1983a, 1985) adopted it as the estimate of lifetime risk to humans from oral exposure. In the absence of more recent carcinogenicity data, it would be prudent to retain the q_1^* value of 5.4×10^{-1} $(mg/kg/day)^{-1}$, corresponding to an upper limit unit risk of 1.5×10^{-5} $(\mu g/\ell)^{-1}$, which was calculated by U.S. EPA (1983a) and subjected to extensive peer review, as the estimate of oral carcinogenic potency for the purposes of this document.

6.3.2. Inhalation. The U.S. EPA (1983a) calculated a unit risk, representing the increased probability of cancer associated with a unit increase in the concentration of chemical of 1.5×10^{-4} $(ppb)^{-1}$ or 6.8×10^{-5} $(\mu g/m^3)^{-1}$ for acrylonitrile in air, based upon the epidemiological data of O'Berg (1980). Time weighted average exposure level of 15 ppm (~31 mg/m^3) was estimated for occupational exposure. Assuming a reference human body weight of 70 kg and an inhalation rate of 20 m^3 of air daily (U.S. EPA, 1980b), the increased probability of lung cancer with each unit increase of acrylonitrile may be expressed as 0.24 $(mg/kg/day)^{-1}$.

The U.S. EPA (1983a) also derived an inhalation unit risk of 3.35×10^{-2} $(ppm)^{-1}$, equivalent to a unit risk of 1.5×10^{-2} $(mg/m^3)^{-1}$, from the incidence data of tumors of the Zymbal gland, brain and spinal cord in female rats from the Quast et al. (1980b) inhalation study, using the linearized multistage model outlined by U.S. EPA (1980b). The potency slope, q_1^*, which may be expressed as 5.3×10^{-2} $(mg/kg/day)^{-1}$, is lower than the q_1^* calculated from the human epidemiological data from the O'Berg (1980) study [0.24 $(mg/kg/day)^{-1}$]. Therefore, to avoid the uncertainties associated with interspecies extrapolation, the more conservative q_1^* value, equivalent to 0.24 $(mg/kg/day)^{-1}$, is chosen as the estimate of carcinogenic potency to humans of inhalation exposure to acrylonitrile.

The Appendix contains the appropriate summary information for oral and inhalation exposure.

7. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold limit values for chemical substances and physical agents in the work environment adopted by ACGIH with intended changes for 1985-1986. Cincinnati, OH. p. 9.

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH. p. 15-16.

Babanov, G.P., A.L. Isakhanov, Y.A. Burov, N.A. Skobei, A.G. Babanov and L.I. Savrasova. 1972. Adaptation of an organism to acrylonitrile as a low concentration factor in an industrial environment. Toksikol. Gig. Prod. Neftekhim. 45: 58. (Cited in U.S. EPA, 1980a)

Belles, R.P., H.J. Paulin, N.G. Makris and R.J. Weir. 1980. Three-generation reproductive study of rats receiving acrylonitrile in drinking water. Prepared by Litton Bionetics, Inc., Kensington, MD, under LBI Project No. 2660 for the Chemical Manufacturers Association, Washington, DC. (Cited in U.S. EPA, 1983a)

Bio/dynamics, Inc. 1980a. A 24-month oral toxicity/carcinogenicity study of acrylonitrile administered to Spartan rats in the drinking water. Final Report. Vol. 1 and 2. Prepared by Bio/dynamics, Inc., Division of Biology and Safety Evaluation, East Millstone, NJ, under Project No. 77-1745 for Monsanto Company, St. Louis, MO. (Cited in U.S. EPA, 1983a)

Bio/dynamics, Inc. 1980b. A 24-month oral toxicity/carcinogenicity study of acrylonitrile administered in drinking water to Fischer 344 rats. Final Report. Vol. 1-4. Prepared by Bio/dynamics, Inc., Division of Biology and Safety Evaluation, East Millstone, NJ, under Project No. 77-1744 (BDN-77-27) for Monsanto Company, St. Louis, MO. (Cited in U.S. EPA, 1983a)

Bio/dynamics, Inc. 1980c. A 24-month oral toxicity/carcinogenicity study of acrylonitrile administered by intubation to Spartan rats. Final Report. Vol. 1 and 2. Prepared by Bio/dynamics, Inc., Division of Biology and Safety Evaluation, East Millstone, NJ, under Project No. 77-1746 for Monsanto Company, St. Louis, MO. (Cited in U.S. EPA, 1983a)

Cadena, F., G.A. Eiceman and V.J. Vandiver. 1984. Removal of volatile organic pollutants from rapid streams. J. Water Pollut. Control. Fed. 56: 460-463.

Cerna, M., J. Kocisova, I. Kodytkova, J. Kopecky and R.J. Sram. 1981. Mutagenic activity of oxiranecarbonitrile (glycidonitrile). In: Ind. Environ. Xenobiotics, Proc. Int. Corf. p. 251-254. (Cited in U.S. EPA, 1985)

Delzell, E. and R.R. Monson. 1982. Mortality among rubber workers. VI. Men with exposure to acrylonitrile. J. Occup. Med. 24(10): 767-769. (Cited in U.S. EPA, 1983a)

DeMeester, C., F. Poncelet, M. Roberfroid and M. Mercier. 1978. Mutagenicity of acrylonitrile. Toxicology. 11: 19-27.

Dudley, H.C. and P.A. Neal. 1942. Toxicology of acrylonitrile. I. A study of the acute toxicity. J. Ind. Hyg. Toxicol. 24: 27. (Cited in U.S. EPA, 1980a)

Edney, E., S. Mitchell and J. Bufalini. 1983. Atmospheric chemistry of several toxic compounds. U.S. EPA, Research Triangle Park, NC. EPA 600/53-82-092.

Ghiringhelli, L. 1954. Acrylonitrile toxicity and mechanism of action. Med. Lavoro. 45: 305. (Ital.) (Cited in U.S. EPA, 1980a)

Graham, J.D.P. 1965. Hydroxycobalamine as an antidote to acrylonitrile. Toxicol. Appl. Pharmacol. 1: 367. (Cited in U.S. EPA, 1980a)

Guengerich, F.P., L.E. Geiger, L.L. Hogy and P.L. Wright. 1981. In vitro metabolism of acrylonitrile to 2-cyanoethylene oxide, reaction with glutathione and irreversible binding to proteins and nucleic acids. Cancer Res. 41: 4925-4933.

Hansch, C. and A.J. Leo. 1985. MedChem Project. Issue No. 26. Pomona College, Claremont, CA.

IARC (International Agency for Research on Cancer). 1979. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Acrylonitrile, acrylic and modacrylic fibers, and acrylonitrile-butadiene-styrene and styrene-acrylonitrile copolymers. Some Monomers, Plastics and Synthetic Elastomers and Acrolein. WHO, IARC, Lyon, France. Vol. 19, p. 73-113.

Knobloch, K., S. Szendzikowski and T. Czajkowski. 1972. Chronic toxicity of acrylonitrile. Med. Pr. 23(3): 243-257. (CA 78:12332h) (Cited in U.S. EPA, 1985a)

Leonard, A., F. Garny, F. Poncelet and M. Mercier. 1981. Mutagenicity of acrylonitrile in the mouse. Toxicol. Lett. 7: 329-334. (Cited in U.S. EPA, 1983a, 1985)

McLaughlin, M., et al. 1976. Evaluation of antidotes for acrylonitrile poisoning. Toxicol. Appl. Pharmacol. 37: 133. (Abstract) (Cited in U.S. EPA, 1980a)

Murray, F.J., B.A. Schwetz, K.D. Nitschke, J.A. John, J.M. Norris and P.J. Gehring. 1978. Teratogenicity of acrylonitrile given to rats by gavage or by inhalation. Food Cosmet. Toxicol. 16(6): 547-552.

O'Berg, M. 1980. Epidemiologic study of workers exposed to acrylonitrile. J. Occup. Med. 22: 245-252.

OSHA (Occupational Safety and Health Association). 1985. Safety and Health Standards. 29 CFR 1910.1000.

Ostirovskaya, R.S., et al. 1976. Health status of workers currently engaged in production of acrylonitrile. Gig. T. Prof. Zabol. 6: 8. (Cited in U.S. EPA, 1980a)

Parent, R.A. and B.C. Casto. 1979. Effect of acrylonitrile on primary Syrian golden hamster embryo cells in culture. Transformation and DNA fragmentation. J. Natl. Cancer Inst. 62(4): 1025-1029.

Perocco, P., G. Pane, S. Bolognesi and M. Zannotti. 1982. Increase of sister chromatid exchange and unscheduled synthesis of deoxyribonucleic acid by acrylonitrile in human lymphocytes in vitro. Scand. J. Work Environ. Health. 8(4): 290-293.

Quast, J.F., C.G. Humiston, B.A. Schwetz, L.A. Frauson, C.E. Wade and J.M. Norris. 1975. A 6-month oral toxicity study incorporating acrylonitrile in the drinking water of purebred beagle dogs. Prepared by the Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical USA, Midland, MI, for the Chemical Manufacturers Association, Washington, DC. (Cited in U.S. EPA, 1985)

Quast, J.F., C.E. Wade, C.G. Humiston, et al. 1980a. A 2-year toxicity and oncogenicity study with acrylonitrile incorporated in the drinking water of rats. Prepared by the Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical USA, Midland, MI, for the Chemical Manufacturers Association, Washington, DC. (Cited in U.S. EPA, 1983a, 1985)

Quast, J.F., D.J. Schwetz, M.F. Balmer, T.S. Gushow, C.N. Park and M.J. McKenna. 1980b. A 2-year toxicity and oncogenicity study with acrylonitrile following inhalation exposure of rats. Prepared by the Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical USA, Midland, MI, for the Chemical Manufacturers Association, Washington, DC. (Cited in U.S. EPA, 1983a, 1985)

Sakarai, H. and M. Kusimoto. 1972. Epidemiologic study of health impairment among AN workers. Rodo Kagaku. 48: 273. (Cited in U.S. EPA, 1980a)

Thiess, A.M. and I. Fleig. 1978. Analysis of chromosomes of workers exposed to acrylonitrile. Arch. Toxicol. 41(2): 149-52. (Cited in U.S. EPA, 1983a, 1985)

Thiess, A.M., R. Frentzel-Beyme, R. Link and H. Wild. 1980. Mortalitatsstudie Bei Chemiefacharbeitern Verschiedener Produktionsbetriebe Mit Exposition Auch Gegenuber Acrylonitrile. Zentralbl. Arbeitsmed. 30: 267-359. (Ger.) (Cited in U.S. EPA, 1983a)

U.S. EPA. 1979. Water-related environmental fate of 129 priority pollutants. Vol. 2. Office of Water Planning and Standards, Office of Water and Management, Washington, DC. EPA 440/4-79-029B.

U.S. EPA. 1980a. Ambient Water Quality Criteria for Acrylonitrile. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-017. NTIS PB81-117285.

U.S. EPA. 1980b. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45(231): 79347-79357.

U.S. EPA. 1983a. Health Assessment Document for Acrylonitrile. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-82-007F. NTIS P884-149152.

U.S. EPA. 1983b. Reportable Quantity Document for Acrylonitrile. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1984. Methodology and Guidelines for Reportable Quantity Determination Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985. Health and Environmental Effects Profile for Acrylonitrile. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Remedial Response, Washington, DC.

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

Venitt, S., C.T. Bushell and M. Osborne. 1977. Mutagenicity of acrylonitrile (cyanoethylene) in Escherichia coli. Mutat. Res. 45(2): 283-288.

Weber, R.C., P.A. Parker and M. Bowser. 1981. Vapor pressure distribution of selected organic chemicals. U.S. EPA, Cincinnati, OH. EPA-600/2-81-021. 39 p.

Werner, J.B. and J.T. Carter. 1981. Mortality of United Kingdom acrylonitrile polymersation workers. Br. J. Ind. Med. 38: 247-253. (Cited in U.S. EPA, 1983a)

Yamamoto, K. 1976. Acute combined effects of HCN and CO, with the use of combustion products from PAN (polyacrylonitrile)--gauze mixtures. Z. Rechtsmed. 78: 303. (Cited in U.S. EPA, 1980a)

Young, J.D., R.W. Slauter and R.J. Karbowski. 1977. The pharmacokinetic and metabolic profile of ^{14}C-acrylonitrile given to rats by three routes. Prepared by the Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical USA, Midland, MI, for the Chemical Manufacturers Association, Washington, DC.

APPENDIX

Summary Table for Acrylonitrile

Route	Species	Experimental Exposure/Dose	Effect	q_1^* or Unit Risk	Reference
Oral	rat	1-295 ppm (1-295 mg/ℓ) in drinking water for 6-26 months (0.08-23.0 mg/kg/day)	multiple tumor sites	5.4×10^{-1} (mg/kg/day)$^{-1}$ (geometric mean)	Quast et al., 1980a; Bio/dynamics, Inc., 1980a,b; U.S. EPA, 1983a
Inhalation	human	15 ppm (~31 mg/m^3) occupational	total cancer	$B_H = 1.5 \times 10^{-4}$ (ppb)$^{-1}$, 0.24 (mg/kg/day)$^{-1}$	O'Berg, 1980; U.S. EPA, 1983a