Acrylonitrile; CASRN 107-13-1

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Acrylonitrile

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	11/01/1991
Carcinogenicity Assessment (II.)	yes	09/30/1987

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Acrylonitrile
CASRN — 107-13-1

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Acrylonitrile
CASRN — 107-13-1
Last Revised — 11/01/1991

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Expposures*	UF	MF	RfC
Degeneration and inflammation of nasal respiratory epithelium; hyperplasia of mucous secreting cells **Rat 2-Year Inhalation Study** **Quast et al., 1980**	NOAEL: none LOAEL: 43 mg/cu.m (20 ppm) LOAEL (ADJ): 7.7 mg/cu.m LOAEL (HEC): 1.9 mg/cu.m	1000	1	2E-3 mg/cu.m

* Conversion Factors: MW = 53.06. Assuming 25C and 760 mmHg, LOAEL (mg/cu.m) = 20 ppm x 53.06/24.45 = 43. LOAEL(ADJ) = 43 mg/cu.m x 6 hours/24 hours x 5 days/7 days = 7.7 mg/cu.m. The LOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.33 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq. cm., Sh(ET) = 177 sq. cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.252. LOAEL(HEC) = LOAEL(ADJ) x RGDR = 7.7 mg/cu.m x 0.252 = 1.9 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Quast J.F., D.J. Schwetz, M.F. Balmer, T.S. Gushow, C.N. Park and M.J. McKenna. 1980. A two-year toxicity and oncogenicity study with acrylonitrile following inhalation exposure of rats. Dow Chemical Co., Toxicology Research Laboratory, Midland, MI.

Sprague-Dawley rats (100/sex/concentration) were exposed 6 hours/day, 5 days/week for 2 years to concentrations of 0, 20 or 80 ppm acrylonitrile (duration-adjusted concentrations of 7.7 and 31 mg/cu.m). The control group was exposed only to air. Additional animals were included for interim sacrifices at 6 months (n=7/sex/dose) and 12 months (n=13/sex/dose). A significant decrease in mean body weight was observed in the rats exposed to 80 ppm acrylonitrile. Less significant, but similar weight changes were noted in the 20-ppm females after approximately 1 month. A treatment-related effect on mean body weight was not observed in the 20-ppm males.

A statistically significant increase in mortality ($p<0.05$) was observed within the first year in both male and female rats administered 80 ppm and in the 20-ppm females during the last 10 weeks of the study. The apparent increase in reported mortality for the 20-ppm females was principally due to early sacrifice of rats with large, benign, mammary gland tumors (Quast, 1991). In Sprague-Dawley rats, these tumors occur spontaneously at a high rate, but in this experiment the tumors were observed earlier and more frequently, and became larger in exposed animals.

Exposure to acrylonitrile during the first 6-8 months resulted in a concentration-related increase in water consumption by both males and females. Urine specific gravity, which was repeatedly evaluated during this time interval, was usually decreased among rats exposed to 80 ppm. The authors noted increased pathologic changes to the heart and lungs of male rats of both groups, but indicated that they were identical to effects in the control rats that are usually associated with chronic renal disease. Microscopic analysis of the kidneys indicated a slight, nonstatistically significant increase in the incidence of spontaneously occurring advanced chronic renal disease. However, this slight increase could have been due to increased demand on the kidneys resulting from the increased water consumption seen earlier in the study.

Occasional significant deviation of the packed cell volume (PCV), and in the RBC, hemoglobin, and WBC counts were noted. However, the authors interpreted them as secondary changes associated with decreased growth, tumor formation, and hemorrhaging resulting from exposure to acrylonitrile. Urinalysis, hematology, and clinical chemistry were monitored. No other microscopic findings attributable to acrylonitrile exposure were observed. No adverse effects were observed on the bone marrow or liver function in rats in either sex exposed to 80 ppm.

Based on gross and histopathologic evaluation of tissues from over 40 different organs (including the respiratory tract and nasal turbinates), the two tissues which exhibited a treatment-related adverse effect due to acrylonitrile exposure were the nasal respiratory epithelium (4 transverse sections of the nasal turbinates were cut and examined) and the brain (9 sections through the CNS were cut and examined). Gross pathologic observations revealed significantly increased lung changes suggestive of pneumonia in 20-ppm male rats. Acute suppurative pneumonia was observed in the lungs of 10 male rats in the 80-ppm group between 7 and 12 months; it was occasionally observed in a single rat from the 20-ppm group. There were no indications of pneumonia in female rats of either exposure group. These changes are presumed to have been secondary effects related to the stress associated with the exposure.

A significant increase ($p<0.05$) in focal gliosis and perivascular cuffing was observed in the brains of high-concentration males (1/100 controls; 7/100 exposed) and females (0/100 controls; 8/100 exposed), but not in low- concentration rats. The incidence of glial cell tumors (astocytomas) was significantly increased in the 80-ppm group over controls for both males (15/99 vs. 0/100 in controls) and females (16/100 vs. 0/100 in controls). The incidence of proliferative glial cell lesions suggestive of early tumors was significantly increased in the 80-ppm males (7/100 vs. 0/100 in controls), but not in the females at any level (4/100 at 80 ppm; 4/100 at 20 ppm; 0/100 in controls). Collectively, proliferative changes in the glial cells (i.e., tumors and early proliferation suggestive of tumors), were significantly increased in the 20-ppm (8/100) and 80-ppm (20/100) females over female controls (0/100), and in the 80-ppm males (22/99), but not in the 20-ppm males (4/99) when compared with male controls (0/100). NOAEL(HEC) and LOAEL(HEC) for noncarcinogenic, extrarespiratory effects are 20 ppm (7.7 mg/cu.m) and 80 ppm (31 mg/cu.m), respectively.

There were significant degenerative and inflammatory changes ($p<0.05$; one- sided Fisher's Exact test) in the respiratory epithelium of the nasal turbinates at both exposure concentrations (20 and 80 ppm) which are interpreted to be treatment-related irritation of the nasal mucosa. In the male 20-ppm group, there was a slight but not statistically significant increase in the incidence of respiratory epithelium hyperplasia in the nasal turbinates (0/11 in controls; 4/12 at 20 ppm; 10/10 at 80 ppm) and a statistically significant increase in hyperplasia of the mucous secreting cells (0/11; 7/12; 8/10). In the 20-ppm females there was a slight but not statistically significant increase in focal inflammation in the nasal turbinates (2/11; 6/10; 7/10) and a

statistically significant increase in flattening of the respiratory epithelium of the nasal turbinates (1/11; 7/10; 8/10). In the 80-ppm group, effects were more severe and were characterized by suppurative rhinitis, hyperplasia, focal erosions, and squamous metaplasia of the respiratory epithelium. No treatment-related effects in the olfactory epithelium, trachea, or lower respiratory system were observed in either males or females at either concentration. In this study, 20 ppm (HEC = 1.9 mg/cu.m) is considered a LOAEL for pathological alterations in the respiratory epithelium of the extrathoracic region of the respiratory system.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — The uncertainty factor of 1000 reflects a factor of 10 to protect unusually sensitive individuals and 3 to adjust from a minimally adverse LOAEL to a NOAEL. An uncertainty factor of 3 for interspecies variability is used because the use of the dosimetric adjustments account for part of this area of uncertainty. An additional factor of 10 is applied due to an incomplete database, or more specifically, the lack of an inhalation bioassay in a second species, and the lack of reproductive data by the inhalation route with the existence of an oral study showing reproductive effects.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

Several epidemiology studies have examined the morbidity and mortality of workers exposed to acrylonitrile. Mortality due to noncancer endpoints, including respiratory disease, have been investigated (O'Berg, 1980; Ott et al., 1980; Werner and Carter, 1981; O'Berg et al., 1985; Chen et al., 1987). No significant excess mortality has been noted for any noncarcinogenic endpoint. For further discussion of these cancer assessment studies see Section II.

Workers in a synthetic rubber manufacturing plant exposed to concentrations of 16 to 100 ppm acrylonitrile for 20 to 45 minutes experienced mucous membrane irritation, headaches, nausea, feelings of apprehension and nervous irritability. Low grade anemia, leukocytosis, kidney irritation and mild jaundice were also apparent; these effects subsided with exposure cessation (Wilson et al., 1948). Human volunteers exposed acutely (8 hours) to acrylonitrile at concentrations of 5.4-10.9 mg/cu.m (2.4-5.0 ppm) exhibited no deleterious effects (Jakubowski et al., 1987).

No statistically significant increases ($p<0.05$) in adverse health effects attributable to acrylonitrile were detected by clinical examination in a cross-sectional investigation of Japanese workers (n=102) when compared with matched controls (n=62) employed in 6 different acrylic fiber factories for a minimum of 5 years (Sakurai et al., 1978). Arithmetic mean exposure levels

at the different factories (as determined by personal sampling) ranged from 0.1-4.2 ppm. Significantly higher exposure levels (arithmetic mean = 4.2 ppm, geometric mean = 3.7, geometric standard deviation = 1.7) and exposure durations (mean, 12.6 years; stand. dev., 2.1 years) were reported for workers from one factory (n=18). While a slight increase in reddening of conjunctiva and pharynx (3/10 controls; 9/18 exposed) was reported in these workers, it was not statistically significant (Z test with Yates' correction and Fisher's Exact test used). Palpable liver was also elevated in this high exposure group, but was not statistically significant, and blood chemistry evaluations did not indicate liver damage. These study results are inconclusive due to the small size of the cohort, examiner bias (i.e., the medical examiner was not blind to the exposure status of each subject), and shift bias (i.e., the study required shift workers; less fit workers may have transferred to day work). However, it is worth noting that the HEC value for the only exposure level that appears to show any effects (4.2 ppm), HEC = 4.2 x (53.06/24.45) x (10/20) x (5/7) = 3 mg/cu.m, is consistent with the LOAEL(HEC) calculated from Quast et al. (1980).

The death of a child (age 3) who was sleeping in a room fumigated with acrylonitrile has been described by Grunske (1949). Respiratory malfunction, lip cyanosis, and tachycardia were among the symptoms described prior to death. Five adults who spent the night and much of the day in the room complained only of eye irritation or showed no signs of acrylonitrile poisoning. The concentration of acrylonitrile in the air was not given. Several other instances of death in children with only mild irritation in adults were reported by Grunske (1949), but not described in detail.

In a subchronic inhalation experiment, repeated 4-hour exposures (5 days/week) at various concentrations and durations resulted in moderate toxicity to guinea pigs (265 ppm or 575 mg/cu.m, 8 weeks), rats (100 ppm or 217 mg/cu.m, 8 weeks) and rabbits (100 ppm or 217 mg/cu.m, 8 weeks), and more severe toxicity (including mortality) to cats (153 ppm or 332 mg/cu.m, 8 weeks), dogs (56 ppm or 122 mg/cu.m, 4 weeks) and monkeys (153 ppm or 332 mg/cu.m, 4 weeks) (Dudley et al., 1942). The moderately toxic effects included irritation of the eyes and nose, gastrointestinal disturbances, and weakness of the hind legs. The animals recovered from these effects following exposure cessation. This study is of limited value due to the small number of animals tested, the lack of statistical analyses, and the lack of concurrent controls.

Sprague-Dawley rats (30/sex/concentration) were exposed to 0, 5, 10, 20 and 40 ppm 4 hours/day, 5 days/week for 52 weeks (duration-adjusted concentrations of 0, 1.3, 2.6, 5.2, and 10.4 mg/cu.m, respectively) (Maltoni et al., 1977; Maltoni et al., 1988) and at 60 ppm, 4-7 hours/day, 5 days/week for 104 weeks (Maltoni et al., 1988). Although histopathologic examinations were performed on various organ systems including the lungs, brain, kidney, and

liver, no noncarcinogenic effects were reported. The exposures did not have affect on body weight gain. No mortality data were reported.

Beliles et al. (1980) evaluated reproductive capacity in three generations of male (15/generation) and female (30/generation) Charles River rats exposed to mean acrylonitrile concentrations of 0, 106 and 522 ppm in drinking water ad libitum. All three generations of parents were exposed for 100 days and throughout a 6 day mating period, gestation and lactation. Parents were examined daily for signs of neurotoxicity. Body weights were obtained every 2 weeks; food consumption was measured weekly; water consumption was measured twice a week. Offspring were examined on days 0, 4 and 21 of lactation. All litters were reduced to 10 pups on day 4 to achieve an equal sex ratio. Body weights were obtained on day 4 (litter) and day 21 (individual). Exposure to 522 ppm acrylonitrile in drinking water (70 mg/kg/day) resulted in reduced viability and lactation indices ($p<0.05$) in all generations. Dams of all generations were reported to have decreased water intake through the lactation period. Cross-fostering of pups on untreated dams lessened pup mortality. There were no changes in reproductive capacity at 106 ppm relative to controls.

One developmental study conducted in rats examined both oral and inhalation exposure routes. Rats (30/concentration) were exposed to 0, 40 or 80 ppm acrylonitrile vapors 6 hours/day during gestational days 6 to 15. In accordance with current EPA policy, these values are not duration adjusted. The group exposed to 80 ppm exhibited a significant increase ($p=0.06$) in fetal malformations which include short tail, missing vertebrae, short trunk, omphalocele and hemivertebra. Mean number of implantations, live fetuses and resorptions were not significantly altered by exposure to 40 or 80 ppm. Maternal toxicity was reported at both concentration levels tested, as evidenced by decreased weight gain, but no effects on fetal body size were evident (Murray et al., 1978). No evidence of embryotoxicity or teratogenicity was discerned in rats administered 40 ppm via inhalation. This study identifies a NOAEL(HEC) = 15.5 mg/cu.m and a LOAEL(HEC) = 31 mg/cu.m (with maternal toxicity).

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

The critical study is given medium confidence, because although it was a well-conducted chronic study in an appropriate number of animals (100/sex/concentration), it was performed on only one species, did not identify a NOAEL, was confounded by the early sacrifice of rats with large mammary gland tumors and the target organ (nasal turbinates) was only examined at the end of the study in relatively few animals (10-12/sex/concentration). Confidence in the database can be

considered medium to low due to a lack of chronic or subchronic inhalation data in a second species, the lack of reproductive data by the inhalation route and the existence of an oral study showing reproductive effects. Confidence in the RfC can also be considered medium to low.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1983

Agency Work Group Review — 12/19/1990, 08/15/1991

Verification Date — 08/15/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Acrylonitrile conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Acrylonitrile
CASRN — 107-13-1
Last Revised — 09/30/1987

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk

per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B1; probable human carcinogen

Basis — The observation of a statistically significant increase in incidence of lung cancer in exposed workers and observation of tumors, generally astrocytomas in the brain, in studies in two rat strains exposed by various routes (drinking water, gavage, and inhalation) forms the basis for this classification.

II.A.2. Human Carcinogenicity Data

O'Berg (1980) observed 25 cases of cancer, including eight cases of respiratory cancer, in 1345 male textile workers exposed to acrylonitrile and followed for 10 or more years. Estimated levels of exposure were 5-20 ppm acrylonitrile. All of the cancer cases, except for one nonrespiratory cancer, occurred among 1128 workers with 6 or more months exposure (SIR=126, SMR=113). A trend of increased cancer incidence was seen with increased duration of exposure and increased length of follow-up time. The excess of respiratory cancer was statistically significant and remained so upon evaluation of the contribution of smoking (five observed vs. 1.6 expected).

Three other studies reported a statistically significant increased incidence of lung cancer from exposure to acrylonitrile. All suffer from problems with methodology (e.g., exposure to other carcinogens, no smoking history, exposure not quantified). Delzel and Monson (1982) studied 327 male workers at a rubber manufacturing plant and reported a statistically significant increase in lung cancer among workers employed 5 or more years. Thiess et al. (1980) studied 1469 workers employed 6 months or more in acrylonitrile processing. A statistically significant increase in lung cancer and cancer of the lymph system was seen. Werner and Carter (1981) studied 934 men employed at least 1 year in polymerization of acrylonitrile and spinning of acrylic fiber. A statistically significant increase was seen for stomach cancer in all age groups and for pulmonary cancer in the 15-44 year age group. One other study reported a statistically

nonsignificant increase in deaths from cancer from exposure to acrylonitrile (Monson, 1978), but workers were also exposed to other carcinogens. Five additional studies reported no evidence of increased risk, but all suffer from deficiencies in design or methodology.

II.A.3. Animal Carcinogenicity Data

Quast et al. (1980a) administered acrylonitrile in drinking water at dose levels of 35, 100, and 300 ppm to 48 Sprague-Dawley rats/sex for 2 years. A statistically significant increase in tumors was observed in the CNS (astrocytomas), Zymbal gland, stomach, tongue, and small intestine for both sexes and in the mammary gland of female rats. In general, the increase was dose-dependent.

Biodynamics (1980a) administered acrylonitrile in drinking water at doses of 0, 1, and 100 ppm to 100 Sprague-Dawley rats/sex/group. Interim necropsies were performed at 6, 12, and 18 months (10/sex/group). The study was terminated early because of low survival rates. There was increased incidence of astrocytomas of the brain and spinal cord, carcinomas and adenomas of the Zymbal gland or ear canal, and squamous cell carcinomas and papillomas of the forestomach in high-dose animals.

A second study was conducted by Biodynamics (1980b) wherein acrylonitrile was administered in drinking water to 100 Fischer 344 rats/sex/group at dose levels of 1, 3, 10, 30, and 100 ppm and to a control group of 200/sex. Interim necropsies were performed at 6, 12, and 18 months (10/sex/ exposed group and 20/sex/control group). The study was terminated early because of the low survival rate. Increased incidence of tumors (astrocytomas of the brain and spinal cord, and carcinomas of the Zymbal gland) was seen in dose groups of 3 ppm or higher, and the incidence was dose-dependent. An increased incidence of mammary gland tumors was seen in females at the 100 ppm dose level. In a three-generation reproductive study in rats [CRL:COBS CD (SD) BR] were exposed to acrylonitrile in drinking water. The second generation showed an increased incidence of cancer (astrocytoma and Zymbal gland) at the 500 ppm exposure level (Beliles, 1980).

Maltoni et al. (1977) administered acrylonitrile in olive oil 3 times/week for 52 weeks to Sprague-Dawley rats in doses of 0 ppm to 75 rats/sex and 5 ppm to 40 rats/sex. Increased incidence of tumors of the mammary gland and forestomach was observed in female rats. In another study (Biodynamics, 1980c), acrylonitrile was administered at doses of 0, 0.10, and 10.0 mg/kg/day for 5 days to 70 Sprague-Dawley rats/sex/group. The study was terminated at 20 months. Statistically significant increased incidences of brain (astrocytoma) and Zymbal gland tumors were observed in the high-dose group. A statistically significant increased incidence of stomach and intestinal tumors was observed in males and of the mammary gland in females.

In a second study by Quast et al. (1980b), acrylonitrile was administered by inhalation at 0, 20, and 80 ppm to 100 male and female Sprague-Dawley rats for 6 hours/day, 5 days/week for 2 years. A statistically significant increase was observed in tumors of the CNS and other sites.

Acrylonitrile was also administered by inhalation at lower doses of 0, 5, 10, 20, and 40 ppm, 4 hours/day, 5 days/week for 12 months to 30 Sprague- Dawley rats/sex/group by Maltoni et al. (1977). This resulted in a statistically significant increase of mammary tumors in males and skin carcinomas in females.

II.A.4. Supporting Data for Carcinogenicity

Acrylonitrile can cause mutations in both Salmonella typhimurium (Venitt et al., 1977) and Escherichia coli (De Meester et al., 1978). It did not cause chromosomal aberrations in bone marrow cells of rats and mice (Rabello- Gay and Ahmed, 1980; Leonard et al., 1981) or in peripheral blood lymphocytes of exposed workers (Thiess and Fleig, 1978). Acrylonitrile did induce an increase in sister-chromatid-exchange (SCE) in CHO cells (Ved Brat and Williams, 1982), and has also been shown to bind to DNA (Guengerich et al., 1981). A metabolite, 2,3-epoxy-propionitrile, is mutagenic in Salmonella (Kier, 1982). Acrylonitrile has been shown to transform Syrian hamster embryo cells and to enhance transformation of these cells infected with an oncogenic virus (Parent and Casto, 1979).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 5.4E-1 per (mg/kg)/day

Drinking Water Unit Risk — 1.5E-5 per (ug/L)

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	6E+0 ug/L
E-5 (1 in 100,000)	6E-1 ug/L
E-6 (1in 1,000,000)	6E-2 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: brain and spinal cord astrocytomas, Zymbal gland carcinomas and stomach papillomas/carcinomas
Test animals: rats (see table)
Route: drinking water
Reference: biodynamics, 1980a,b; Quast et al., 1980a

Administered Dose		Human Equivalent Dose (mg/kg)/day	Tumor Incidence	Reference
(ppm)	**(mg/kg)/day**			
Rats/Spartan Sprague-Dawley, males				
0	0.00	0.00	6/100	Biodynamics,
1	0.09	0.02	6/98	1980a
100	7.98	1.36	36/98	
Rats/Fischer 344, males				

Administered Dose		Human Equivalent Dose (mg/kg)/day	Tumor Incidence	Reference
0	0.00	0.00	5/200	Biodynamics,
1	0.11	0.02	4/100	1980b
3	0.25	0.04	5/100	
10	0.81	0.14	7/100	
30	2.49	0.43	20/100	
100	8.15	1.39	36/100	
Rats/Sprague-Dawley, males				
0	0.00	0.00	4/80	Quast et al.,
35	3.42	0.58	18/47	1980a
100	8.53	1.46	36/48	
300	21.18	3.62	45/48	

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The quantitative estimate is a geometric mean of these three slope factors: 4.0E-1 (Biodynamics, 1980a), 4.0E-1 (Biodynamics, 1980b) and 9.9E-1 per (mg/kg)/day (Quast et al., 1980a). The overall risk of tumors was determined from the number of animals having tumors that were statistically significant at any site.

The unit risk should not be used if the water concentration exceeds 600 ug/L, since above this concentration the unit risk may not be appropriate.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Relatively large numbers of animals were treated and observed and a dose- response effect was observed in all studies. The slope factors derived from data on male rats (Quast et al., 1980a; Biodynamics, 1980a,b) were similar [9.9E-1, 4.0E-1, and 4.0E-1 per (mg/kg)/day] and within a factor of 3. The slope factors based on the three female rat studies [9.2E-1, 3.7E-1, and 2.9E- 1 per (mg/kg)/day] were similar to those of the respective male rat studies, as was their geometric mean (4.6E-1 per (mg/kg)/day. In two of the studies (Biodynamics, 1980a,b) the increases reported could vary considerably since interim necropsies were included with the final sacrifice.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 6.8E-5 per (ug/cu.m)

Extrapolation Method — Average relative risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+0 ug/cu.m
E-5 (1 in 100,000)	1E-1 ug/cu.m
E-6 (1 in 1,000,000)	1E-2 ug/cu.m

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type: respiratory cancer
Test animals: humans
Route: inhalation
Reference: O'Berg, 1980

The unit risk (BH) was calculated from a relative risk model adjusted for smoking and based on a continuous lifetime equivalent of occupational exposure

BH = PO(R-1)/X

= 1.5E-4/ppb x 0.45 ppb/ug/cu.m

= 6.8E-5 per (ug/cu.m)

where: PO = 0.036 = background lifetime probability of death from respiratory cancer

R = 5.0/1.6 = 3.1 = relative risk of respiratory cancer adjusted for smoking (O'Berg, 1980)

X 500 ppb = continuous equivalent lifetime exposure when 9 years = estimated average exposure duration, and 60 years = estimated maximum possible age at end of observation period.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

The excess incidence of respiratory cancer in the O'Berg (1980) study was adjusted for smoking. An exposure of 15 ppm was assumed to be the 8-hour TWA with an average exposure duration of 9 years. The maximum possible age at the end of the observation period was assumed to be 60 years.

The unit risk should not be used if the air concentration exceeds 1E+2 ug/cu.m, as above this concentration the unit risk may not be appropriate.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

The cohort was sufficiently large and was followed for an adequate time period. A dose-response relationship was seen for the increased cancer risk. The increased risk remained after adjustment for smoking. Exposure levels were estimated by company representatives. The unit risk based on the Quast et al. (1980b) rat inhalation study was 1.5E-5 per (ug/cu.m).

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1983

The values in the 1983 Health Assessment Document for Acrylonitrile have received both Agency and outside review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 02/11/1987

Verification Date — 02/11/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Acrylonitrile conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Acrylonitrile
CASRN — 107-13-1

VI.A. Oral RfD References

None

VI.B. Inhalation RfD References

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VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — Acrylonitrile
CASRN — 107-13-1

Date	Section	Description
11/01/1991	I.B.	Inhalation RfC summary on-line
12/03/2002	I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Acrylonitrile
CASRN — 107-13-1
Last Revised — 09/30/1987

- 107-13-1
- ACRITET
- ACRYLNITRIL
- ACRYLON
- Acrylonitrile
- ACRYLONITRILE MONOMER
- AKRYLONITRYL
- CARBACRYL
- CIANURO DI VINILE
- CYANOETHYLENE
- CYANURE DE VINYLE
- ENT 54
- FUMIGRAIN
- MILLER'S FUMIGRAIN
- NITRILE ACRILICO
- NITRILE ACRYLIQUE

- PROPENENITRILE
- 2-PROPENENITRILE
- RCRA WASTE NUMBER U009
- TL 314
- UN 1093
- VCN
- VENTOX
- VINYL CYANIDE