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PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

Acrylonitrile

Canada

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Health Canada

May 2000

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List of Acronyms and Abbreviations

ABS	acrylonitrile-butadiene-styrene
ACN	acrylonitrile
BCF	bioconcentration factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CFC	chlorofluorocarbon
CTV	Critical Toxicity Value
EC_{50}	median effective concentration
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
GWP	Global Warming Potential
K_{oc}	organic carbon/water partition coefficient
K_{ow}	octanol/water partition coefficient
kg-bw	kilogram body weight
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEC	Lowest-Observed-Effect Concentration
LOEL	Lowest-Observed-Effect Level
MISA	Municipal/Industrial Strategy for Abatement
mRR	meta-relative risk
NOEC	No-Observed-Effect Concentration
NOEL	No-Observed-Effect Level
ODP	Ozone Depletion Potential
OECD	Organisation for Economic Co-operation and Development
POCP	Photochemical Ozone Creation Potential
PSL	Priority Substances List
SAN	styrene-acrylonitrile
TC	Tumorigenic Concentration
TD	Tumorigenic Dose

SYNOPSIS

Acrylonitrile is not produced in Canada but is imported and used to produce nitrile-butadiene rubber, acrylonitrile-butadiene-styrene (ABS) polymers and styrene-acrylonitrile (SAN) polymers. In 1994, 7600 tonnes of acrylonitrile were used in Canada, all of which was imported from the United States. It was projected that 8300 tonnes would be used in 1997. There are no known natural sources of acrylonitrile.

The atmosphere and the freshwater aquatic environment receive 97.3% and 2.7% of the releases of acrylonitrile, respectively. The releases are almost exclusively (97.4%) from the organic chemical manufacturing industry — namely, the chemicals and chemical products industry and the plastics industry — and occur in southern Ontario and southern Quebec. Municipal water treatment facilities may release small quantities of acrylonitrile to air via sludge incineration or to water via use of acrylonitrile polymers as conditioners.

Acrylonitrile is distributed largely to the environmental compartment to which it is released, where reaction and advection are the major removal mechanisms. Its movement from the atmosphere or water to soil, sediment or biota is limited.

In general, concentrations of acrylonitrile in air in Canada are below the detection limit. Predicted maximum levels (near a chemical industry processing plant in Sarnia, Ontario) are less than the Estimated No-Effects Value (ENEV) for the most sensitive terrestrial organism. Significant changes over the past 10 years to the treatment of industrial wastewaters have decreased the concentration in effluents discharged to the environment to below 4.2 µg/L. This is less than the ENEV for the most sensitive aquatic organism.

Because of its reactivity in the atmosphere, acrylonitrile's potential contribution to photochemical ozone (and also smog) creation is moderate; however, quantities and concentrations available for reaction (18.75 tonnes in Canada in 1996) make the contribution very low relative to those of other substances. The absence of chlorine and bromine atoms in the acrylonitrile molecule means that its potential contributions to stratospheric ozone depletion and climate change are both negligible.

Although limited, available data are consistent with air being the principal medium of exposure of the general population to acrylonitrile; intake from other media is likely to be negligible in comparison. The focus of the human health risk characterization is populations exposed through air in the vicinity of industrial sources.

Based on studies in animals, cancer is considered the critical endpoint for effects of acrylonitrile on human health. A range of tumours in rats — including those of the central nervous system (brain and/or spinal cord), ear canal, gastrointestinal tract and mammary glands — has been consistently observed following both ingestion and inhalation. While increases in cancer have not been observed in available epidemiological studies, their power is insufficient to rule out increases in particularly rare tumours. Available data are insufficient to support a consensus view on a plausible mode of action for induction of tumours by acrylonitrile by other than direct interaction with genetic material and as a result, there is considered to be a probability of harm at any level of exposure.

Based on the information available, it is concluded that acrylonitrile is not entering the environment in a quantity or concentration or under conditions that have or may have an

immediate or long term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends. It is concluded that acrylonitrile is entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Therefore, acrylonitrile is considered to be "toxic" as defined in Section 64 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999).

Based on comparison of worst-case estimates of exposure in air in the vicinity of industrial sources with the tumorigenic potency, it is recommended that options to reduce exposure in the vicinity of industrial point sources be investigated. It is also recommended that there be additional investigation of the magnitude of exposure of populations in the vicinity of industrial point sources as a basis for risk management.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of Environment and Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that should be given priority to determine whether they are harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" or are capable of becoming "toxic" as defined in Section 64 of the Act, which states:

> ...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
> (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
> (b) constitute or may constitute a danger to the environment on which life depends; or
> (c) constitute or may constitute a danger in Canada to human life or health.

Substances that are assessed as "toxic" as defined in Section 64 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on an initial screening of readily accessible information, the rationale for assessing acrylonitrile provided by the Ministers' Expert Advisory Panel on the Second Priority Substances List (Ministers' Expert Advisory Panel, 1995) was as follows:

> People living within a few kilometres of sites where acrylonitrile is used may have significant exposure. The compound can also be released from products made with polyacrylic fibre or from vehicle exhaust and cigarette smoke. Acrylonitrile is carcinogenic and genotoxic in animals, and there is some evidence that it is carcinogenic in humans. An assessment is needed to characterize the extent of exposure and associated risks for humans and the environment in Canada.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents. The document entitled "Environmental Assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance Manual Version 1.0 — March 1997" (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

> Environmental Protection Publications
> Environmental Technology
> Advancement Directorate
> Environment Canada
> Ottawa, Ontario
> K1A 0H3

It is also available on the Internet at www.ec.gc.ca/cceb1/eng/psap.htm under the heading "Technical Guidance Manual." It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The approach to assessment of effects on human health is outlined in the following publication of the Environmental Health Directorate of Health Canada: "*Canadian Environmental Protection Act* — Human Health Risk Assessment for Priority Substances" (Health Canada, 1994), copies of which are available from:

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

or on the Environmental Health Directorate publications web site (www.hc-sc.gc.ca/ehp/ehd/catalogue/bch.htm). The approach is also described in an article published in the *Journal of Environmental Science and Health — Environmental Carcinogenesis & Ecotoxicology Reviews* (Meek *et al*., 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Environmental Substances Division web site (www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The search strategies employed in the identification of data relevant to the assessment of potential effects on the environment (prior to May 1998) and on human health (prior to April 1998) are presented in Appendix A. Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether acrylonitrile is "toxic" under CEPA have been critically evaluated by staff of Environment Canada (entry and environmental exposure and effects) and Health Canada (human exposure and effects on human health).

An Environmental Resource Group was established by Environment Canada to assist in the preparation and review of the environmental sections of the Assessment Report and the supporting documentation (Environment Canada, 1998). Members were selected based on their expertise, notably in the areas of toxicology, process and automotive chemistry and engineering, environmental monitoring and environmental chemistry. Members included:

B. Benjey, U.S. Environmental Protection Agency
D. Brooke, United Kingdom Department of the Environment
L. Brownlee, Environment Canada
N. Bunce, University of Guelph
H. Campbell, Waste Water Technology Centre
P. Cureton, Environment Canada
M. Day, National Research Council of Canada
F. Edgecomb, Canadian Plastics Industry
J. Girard, Environment Canada
L. Graham, Environment Canada
P. Paine, Environment Canada
A. Pope, U.S. Environmental Protection Agency
I. Pratt, Health and Safety Authority, Ireland
J. Prinsen, Environment Canada
J. Sherry, Environment Canada
M. Wright, Bayer-Rubber Division

The environmental assessment was led by P. Cureton.

Environmental sections of the Assessment Report and the supporting documentation (Environment Canada, 1998) were also reviewed by internal reviewers at Environment Canada — namely, R. Hoff, K. Lloyd, J. Pasternak, E. Rezek and P. Thompson. External reviewers were W. Broadworth (G.E. Plastics Canada), N. Karellas (Ontario Ministry of the Environment), R. Keefe (Imperial Oil), A. Kerr (Bayer-Rubber Division), J. Murray (The Acrylonitrile Group), V. Nabholz (U.S. Environmental Protection Agency), J. Pellerin (*Université du Québec à Rimouski*), J. Soule (DuPont Canada) and A. Tomlin (Agriculture and Agri-Food Canada).

The health-related sections of this Assessment Report and supporting documentation were prepared by the following staff of Health Canada:

D. Blakey
D. Koniecki
G. Long
M.E. Meek

Sections of the Assessment Report and supporting documentation were reviewed by R. Beauchamp, R. Liteplo and L. Turner of the Environmental Substances Division of Health Canada. M. Walker of the Biostatistics and Computer Applications Division of Health Canada provided statistical support. The health-related sections of the Assessment Report and the supporting documentation were based in part upon a review of the epidemiological data, prepared under contract by J. Siemiatycki of the *Institut Armand-Frappier*.

In order to address primarily adequacy of coverage, sections of the supporting documentation pertaining to human health were reviewed externally by:

J.J. Collins, Solutia Inc., St. Louis, Missouri
B. Ghanayem, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina
G.L. Kedderis, Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina
N. Krivanek, E.I. du Pont de Nemours & Co., Newark, Delaware
D. Strother, BP Chemicals Inc., Cleveland, Ohio
J. Whysner, American Health Foundation, Valhalla, New York

Accuracy of reporting, adequacy of coverage and defensibility of conclusions with respect to hazard characterization and dose–response analyses were considered in written review by staff of the Information Department of BIBRA International and at a panel meeting of the following members, convened by Toxicology Excellence for Risk Assessment (TERA) on November 17, 1998, in Cincinnati, Ohio:

M.J. Aardema, The Procter & Gamble Co.
M.L. Dourson, TERA
S. Felter, The Procter & Gamble Co.
M.A. Friedman, private consultant
M.L. Gargas, ChemRisk Division, McLaren/Hart
R.G. Tardiff, The Sapphire Group, Inc.
V.T. Vu, U.S. Environmental Protection Agency
V. Walker, New York State Department of Health

The health-related sections of the Assessment Report were reviewed and approved by the Health Protection Branch Risk Management meeting of Health Canada.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

A draft of the Assessment Report was made available for a 60-day public comment period (June 26 to August 24, 1999) (Environment Canada and Health Canada, 1999). Following consideration of comments received, the Assessment Report was revised as appropriate. A summary of the comments and thier responses are available on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of "toxic" under Paragraphs 64(a) and (b)), followed by effects on human health (relevant to determination of "toxic" under Paragraph 64(c)).

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

Unpublished supporting documentation, which presents additional information, is available upon request from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or

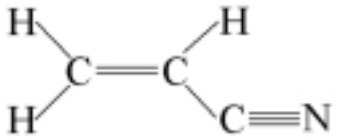
Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

2.0 Summary of Information Critical to Assessment of "Toxic" under CEPA 1999

2.1 Identity and physical/chemical properties

Acrylonitrile (ACN) is also known as acrylic acid nitrile, acrylon, carbacryl, cyanoethylene, fumigrain, propenenitrile, 2-propenenitrile, propenoic acid nitrile, propylene nitrile, VCN, ventox and vinyl cyanide. Its Chemical Abstracts Service (CAS) number is 107-13-1, its molecular formula is CH_2=CH–C≡N and its molecular weight is 53.06 g. Acrylonitrile's molecular structure is shown in Figure 1.

Figure 1 Chemical structure of acrylonitrile



The physical and chemical properties of acrylonitrile are shown in Table 1. At room temperature, acrylonitrile is a volatile, flammable, colourless liquid with a weakly pungent odour (WHO, 1983). Acrylonitrile has two chemically active sites, at the carbon–carbon double bond and at the nitrile group, where it undergoes a wide variety of reactions. It is a polar molecule because of the presence of the cyano (CN) group. It is soluble in water (75.1 g/L at 25°C) and miscible with most organic solvents. The vapours are explosive, with cyanide gas being produced.

Acrylonitrile may polymerize spontaneously and violently in the presence of concentrated caustic acid, on exposure to visible light or in the presence of concentrated alkali (WHO, 1983), and it is stored accordingly, often as an acrylonitrile–water formulation that acts as a polymerization inhibitor (Kirk *et al.*, 1983).

2.2 Entry characterization

2.2.1 Production, importation and uses

Acrylonitrile has not been produced in Canada since 1972, although it is imported and used. The amount of acrylonitrile imported into Canada has generally declined over the last two decades, falling from 21 000 tonnes in 1976 to 7600 tonnes — all from the United States — in 1994. Camford Information Services (1995) forecast the demand for acrylonitrile in 1997 to be 8300 tonnes (Table 2). The large majority of acrylonitrile is used as a feedstock or chemical aid in the production of nitrile-butadiene rubber (68% of 1994 imports) and in acrylonitrile-butadiene-styrene (ABS) and styrene-acrylonitrile (SAN) polymers (30% of 1994 imports).

2.2.2 Sources and releases

2.2.2.1 Natural sources

Acrylonitrile is not known to occur naturally, and there are no known reactions that could lead to *in situ* formation of this substance in the atmosphere (Grosjean, 1990a).

2.2.2.2 Anthropogenic sources

The total release of acrylonitrile in 1996 was 19.1 tonnes (97.3% to air and 2.7% to water) (Environment Canada, 1997b). The major source of releases was the organic chemicals industry (97.4%) (namely, the chemicals and chemical products industries and the plastic products

TABLE 1 Physical and chemical properties of acrylonitrile[1]

Property	Mean (range)	Reference
Density at 20°C	806 g/L	American Cyanamid Co., 1959
Melting point	–83.55°C	Riddick *et al.*, 1986; Budavari, 1989
Boiling point	77.3°C	Langvardt, 1985; Howard, 1989
Water solubility at 25°C	75.1 g/L	Martin, 1961; Spencer, 1981; Langvardt, 1985; Howard, 1989; DMER and AEL, 1996
Solubility	Miscible with most organic solvents	American Cyanamid Co., 1959
Vapour pressure at 25°C	11 (11–15.6) kPa	Groet *et al.*, 1974; Riddick *et al.*, 1986; Banerjee *et al.*, 1990; BG-Chemie, 1990; Mackay *et al.*, 1995
Henry's law constant[2] at 25°C	11 (8.92–11.14) $Pa \cdot m^3/mol$	Mabey *et al.*, 1982; Howard, 1989; Mackay *et al.*, 1995
Log organic carbon/water partition coefficient (log K_{oc})	1.06 (–0.09–1.1)	Koch and Nagel, 1988; Walton *et al.*, 1992
Log octanol/water partition coefficient (log K_{ow})	0.25 (–0.92–1.2)	Collander, 1951; Pratesi *et al.*, 1979; Veith *et al.*, 1980; Tonogai *et al.*, 1982; Tanii and Hashimoto, 1984; Sangster, 1989; DMER and AEL, 1996
Log bioconcentration factor (BCF) in fish	0.48–1.68	Barrows *et al.*, 1980; Lech *et al.*, 1995
Half-life ($t_{½}$)		
air	55 or 96 (4–189) hours	Callahan *et al.*, 1979; Cupitt, 1980; Atkinson, 1985; DMER and AEL, 1996
	96 (13–198) hours	Atkinson *et al.*, 1992
water	170 (30–552) hours	Going *et al.*, 1979; Howard *et al.*, 1991
soil	170 (30–552) hours	Howard *et al.*, 1991
sediment	550 hours	DMER and AEL, 1996[3]

[1] Conversion factors between concentration by weight and concentration by volume: 1 mg/m^3 = 0.4535 ppmv (20°C, 101.3 kPa); 1 ppm in air = 2.205 mg/m^3.

[2] Vapour pressure (at given temperature) × molar mass/water solubility (at same temperature).

[3] No specific sediment value was found in the literature; this is based on the assumption of slower reactivity compared with soils (DMER and AEL, 1996).

TABLE 2 Demand for acrylonitrile in Canada, 1990–1997[1]

Use	Acrylonitrile demand (tonnes)					
	1990	1991	1992	1993	1994	1997[2]
Nitrile-butadiene rubber	3 800	3 300	3 600	4 400	5 200	5 700
ABS terpolymers, SAN	10 000	9 200	5 200	2 500	2 300	2 500
Miscellaneous	100	100	100	100	100	100
Total	**13 900**	**12 600**	**8 900**	**7 000**	**7 600**	**8 300**

[1] Camford Information Services (1995).

[2] Forecast.

industries), while municipal wastewater treatment facilities accounted for 2.6% of releases. All releases occurred in Ontario and Quebec.

2.2.2.2.1 Organic chemicals industry

Data from the National Pollutant Release Inventory are in close agreement with Environment Canada (1997b), although the inventory does not capture releases from municipal facilities. Total on-site releases from industrial sources have decreased recently, with releases of 19.6, 16.8 and 10.7 tonnes in 1994, 1995 and 1996, respectively (Environment Canada, 1994, 1995, 1996). In 1996, the plastics products industry transferred 17 tonnes of acrylonitrile off-site in waste. This was a one-time cleaning procedure required to close a polymerization facility (Environment Canada, 1996, 1997b).

A small amount (0.21 tonnes) of acrylonitrile was released by industry to municipal wastewater treatment facilities in 1996, but it is expected that this is effectively biodegraded by the acclimated microbes present in wastewater treatment facilities (see Section 2.3.1.2).

Since acrylonitrile is explosive, flammable and able to spontaneously and violently polymerize, wherever possible it must be transported and stored in closed containers in cool, dry, well-ventilated areas away from sources of heat and ignition; alternatively, polymerization inhibitors can be added to the system (Kirk *et al.*, 1983; CCOHS, 1995).

Spills of acrylonitrile during transport are rare in Canada. One litre of acrylonitrile leaked from rail transport in 1992 (Charlebois, 1996). In 1991, a rail accident during transport of 76 tonnes of acrylonitrile did not result in any release of the substance (Charlebois, 1996).

2.2.2.2.2 Vehicles

The release of acrylonitrile from vehicle exhaust is not considered significant. Mizuno *et al*. (1980) reported acrylonitrile in vehicle exhaust; however, improved catalysts in motor vehicles contain a large amount of cerium oxide, which acts as an "oxygen reservoir." This, coupled with the engine control system, ensures more complete combustion to carbon dioxide, resulting in exhaust gas with low concentrations of hydrocarbons (Graham, 1997). The large majority of the vehicle fleet on the road today in Canada has stoichiometric control of engine operation coupled with cerium catalysts, which means that acrylonitrile is unlikely to be released in significant quantities, if at all.

2.2.2.2.3 Municipal wastewater treatment

Three (Toronto Main, Toronto Highland Creek and Québec) of seven Canadian municipalities that used sewage sludge incineration in 1997 have facilities that can potentially produce acrylonitrile, although relevant monitoring data are not available (Campbell, 1997). If it is assumed that these facilities operate in a manner similar to U.S. facilities that emit acrylonitrile, an estimated 64.8 kg per year may be emitted from each of the three Canadian facilities, for a total of 194 kg (0.19 tonnes) per year. This represents approximately 1% of the releases of acrylonitrile to air from chemical industries. Given the small number of wastewater sludge incineration facilities, the small amount of acrylonitrile produced and the reactivity of acrylonitrile in air (see Section 2.3.1.1), possible releases of acrylonitrile to air in the Canadian environment during incineration of wastewater sludge are not considered significant.

Only one community (Montréal) using acrylonitrile polymers as conditioners for wastewater treatment was identified based on a Canada-wide survey of municipalities conducted in late 1997. Based on manufacturers' specifications for the polymer and the amount of

polymer used annually at the site, 0.29 tonne of acrylonitrile is estimated to be released per year.

If sludge containing acrylonitrile were spread on soil for agricultural use, it is possible that the substance might react in soil and volatilize to air. However, no data on potential losses from this exposure pathway were identified.

2.2.2.2.4 Transboundary sources

Acrylonitrile is produced in Texas, Louisiana and Ohio. Going *et al.* (1979) reported levels of acrylonitrile in air in the vicinity of acrylonitrile production or processing facilities in 11 industrial areas of the United States ranging from <0.1 to 325 µg/m^3 (detection limit 0.3 µg/m^3). It should be noted, however, that since this study, increasingly stringent controls on emissions have reduced reported atmospheric levels in the vicinity of such facilities. Wiersema *et al.* (1989) did not detect acrylonitrile over a six-month monitoring period of urbanized and industrialized air in the Gulf Coast of Texas (detection limit 0.122 µg/m^3). The U.S. EPA (1986) reported levels of acrylonitrile in urban air in the United States; mean levels of 0.35–0.46 µg/m^3 were found in three cities in New Jersey in July–August 1981, and a mean level of 0.46 µg/m^3 was reported for Texas cities sampled between October 1985 and February 1986.

Based on its half-life in air of between 55 and 96 hours (Section 2.3.1.1), acrylonitrile could travel as far as 2000 km from its source (Hoff, 1998). However, concentrations of acrylonitrile were not detected (detection limit 0.5 µg/m^3) in a 1991 study of transboundary air quality in Windsor, Ontario (Karellas, 1996) or elsewhere (Section 2.3.2.1). Therefore, under current conditions, it is believed that long-range transport is not a significant source of acrylonitrile input to the Canadian environment.

2.2.2.2.5 Pesticide use

Acrylonitrile was used in Canada in the past as a pesticide fumigant for stored grain. However, it is no longer present in registered pesticides and was last registered in Canada as a grain fumigant in 1976 (Ballantine, 1997). Therefore, releases of acrylonitrile from pesticidal uses are considered to be zero.

2.3 Exposure characterization

2.3.1 Environmental fate

2.3.1.1 Air

Acrylonitrile emitted to air reacts primarily with photochemically generated hydroxyl radicals (·OH) in the troposphere (Atkinson *et al.*, 1982; Edney *et al.*, 1982; Munshi *et al.*, 1989; U.S. DHHS, 1990; Bunce, 1996). The atmospheric half-life, based on hydroxyl radical reaction rate constants, is calculated to be between four and 189 hours (Callahan *et al.*, 1979; Cupitt, 1980; Edney *et al.*, 1982; Howard, 1989; Grosjean, 1990b; Kelly *et al*., 1994). DMER and AEL (1996) and Bunce (1996) selected mean half-lives of acrylonitrile in air of 55 and 96 hours, respectively, in order to calculate environmental partitioning (Section 2.3.1.5) and abiotic atmospheric effects (Section 2.4.2).

The reaction of acrylonitrile with ozone and nitrate is slow, because of the absence of chlorine and bromine atoms in the molecule, and is not likely to constitute a major route of degradation (Bunce, 1996).

The reaction of hydroxyl radicals with acrylonitrile yields formaldehyde and, to a lesser extent, formic acid, formyl cyanide, carbon monoxide and hydrogen cyanide (Edney *et al*., 1982; Spicer *et al*., 1985; Munshi *et al*., 1989; Grosjean, 1990a).

2.3.1.2 Water

The significant fate processes of acrylonitrile in water are biodegradation by acclimatized microorganisms and volatilization (Going *et al*., 1979). In water, half-lives of 30–552 hours are estimated based on aqueous aerobic biodegradation (Ludzack *et al*., 1961; Going *et al*., 1979; Howard *et al*., 1991). DMER and AEL (1996) selected a mean half-life of 170 hours (seven days) for use in environmental partitioning (Section 2.3.1.5). The half-life based on volatilization is 1–6 days (Howard *et al*., 1991). The hydrolysis of acrylonitrile is slow, with half-lives under acidic and basic conditions of 13 and 188 years, respectively (Ellington *et al*., 1987).

Acrylonitrile has an initial inhibitory effect on activated sludge systems and other microbial populations and does not meet the Organisation for Economic Co-operation and Development (OECD) Test Method 301C for ready biodegradability (Chemicals Inspection and Testing Institute of Japan, 1992; AN Group, 1996; BASF AG, 1996). However, acrylonitrile will be extensively degraded (95–100%) following a short acclimation period if emitted to wastewater treatment plants (Tabak *et al*., 1980; Kincannon *et al*., 1983; Stover and Kincannon, 1983; Freeman and Schroy, 1984; Watson, 1993).

2.3.1.3 Soil and sediment

Acrylonitrile is biodegraded in a variety of surface soils (Donberg *et al*., 1992) and by isolated strains of soil bacteria and fungi (Wenzhong *et al*., 1991). Concentrations of acrylonitrile up to 100 mg/kg were degraded in under two days (Donberg, 1992). Similar breakdown by microbial populations present in sediment is likely (DMER and AEL, 1996; EC, 1998). Experimental adsorption studies (Zhang *et al*., 1990), together with calculation of soil sorption coefficients using either quantitative structure–activity relationships (Koch and Nagel, 1988; Walton *et al*., 1992) or water solubility (Kenaga, 1980), indicate that acrylonitrile shows little potential for adsorption to soil or sediments.

Half-lives of acrylonitrile in soil of 1–30 days have been calculated based on ready biodegradability data (EC, 1998) and the work performed by Donberg *et al*. (1992) and reported by Howard *et al*. (1991). DMER and AEL (1996) selected a mean half-life in soil of 170 hours (seven days). The half-life in the oxic zone of sediment can be assumed to be similar.

2.3.1.4 Biota

Bioaccumulation of acrylonitrile is not anticipated, given experimentally derived values of log K_{ow} ranging from –0.92 to 1.2 (mean 0.25) (Collander, 1951; Pratesi *et al*., 1979; Veith *et al*., 1980; Tonogai *et al*., 1982; Tanii and Hashimoto, 1984; Sangster, 1989) and a log bioconcentration factor (log BCF) of 0 calculated from the water solubility of acrylonitrile (EC, 1998).

Log BCF values of 0.48–1.68 have been derived from experiments with bluegill (*Lepomis macrochirus*) (Barrows *et al*., 1980) and rainbow trout (*Oncorhynchus mykiss*) (Lech *et al*., 1995). The experimentally derived log BCF of 1.68 reported by Barrows *et al*. (1980) in whole-body tissue of bluegill may overestimate the BCF, since the ^{14}C uptake method may include degradation products in the BCF value (EC, 1998).

2.3.1.5 Environmental partitioning

Fugacity modelling was conducted to characterize key reaction, intercompartment and advection (movement out of a compartment) pathways for acrylonitrile and its overall distribution in the environment. A steady-state, non-equilibrium model (Level III fugacity model) was run using the methods developed by Mackay (1991) and DMER and Paterson (1991). Assumptions, input parameters and results are presented in Mackay and AEL (1996) and summarized here. Values for input parameters were as follows: molecular weight, 53.06 g/mol; water solubility, 75.5 g/L; vapour pressure, 11.0 kPa; log K_{ow}, 0.25; Henry's law constant, 11 $Pa \cdot m^3/mol$; half-life in air, 55 hours; half-life in water, 170 hours;

half-life in soil, 170 hours; half-life in sediments, 550 hours. Modelling was based on an assumed default emission rate of 1000 kg/hour into a region of 100 000 km^2, which includes a surface water area (20 m deep) of 10 000 km^2. The height of the atmosphere was set at 1000 m. Sediments and soils were assumed to have an organic carbon content of 4% and 2% and a depth of 1 cm and 10 cm, respectively. The estimated percent distribution predicted by this model is not affected by the assumed emission rate.

As a result of acrylonitrile's physical and chemical properties, modelling indicates that when acrylonitrile is continuously discharged into a specific medium, most of it (84–97%) can be expected to be found in that medium (DMER and AEL, 1996). More specifically, Level III fugacity modelling by DMER and AEL (1996) predicts that:

- when acrylonitrile is released into air, the distribution of mass is 92.8% in air, 6.4% in water, 0.8% in soil and 0.0% in sediment;
- when acrylonitrile is released into water, the distribution of mass is 2.5% in air, 97.3% in water, 0.0% in soil and 0.1% in sediment;
- when acrylonitrile is released into soil, the distribution of mass is 4.4% in air, 11.9% in water, 83.7% in soil and 0.0% in sediment.

The major removal mechanisms in air, water and soil are reaction within the medium and, to a lesser degree, advection and volatilization. Abiotic and biotic degradation in the various compartments result in low persistence overall and little, if any, bioaccumulation.

Fugacity modelling with the ChemCAN3 model (version 4) was also conducted with the conservative assumption that all known 1996 releases (Environment Canada, 1997b) in Canada occurred in southern Ontario. Since the half-life of acrylonitrile in air is the major determinant of its fate in the environment, the model was run using the minimum, median and maximum half-life values (four, 55 and 189 hours) under summer, winter and year-round conditions. The results of the ChemCAN3 model indicate that long-term continuous release of acrylonitrile may result in very low levels in air, water, soil and sediment across the southern Ontario region (Table 3). Modelling predictions do not purport to reflect actual expected measurements in the environment, but rather indicate the broad characteristics of the fate of the substance in the environment over a large region and its general distribution between the media. The model does not address the likely impact of point source releases on a local level. Information on measured concentrations in air and water and dispersion modelling carried out at the local level are presented in Section 2.3.2.

2.3.2 Environmental concentrations

Since the use of acrylonitrile and resulting emissions are highly localized, concentrations of acrylonitrile are not measured on a routine basis in Canadian air monitoring programs. There are, however, some data on both measured concentrations and those predicted from dispersion modelling for ambient air and air close to industrial sites.

2.3.2.1 Ambient air

Maximum predicted rates of emission of acrylonitrile during any half-hour period were 0.003, 0.018 and 0.028 g/s for stacks 14, 17 and 11 m high, respectively, near the site of the largest user in Canada (a Sarnia, Ontario, plant), based on dispersion modelling conducted in 1998 as part of the requirements for the Ontario Ministry of the Environment emissions inventory (Michelin, 1999). The two most common atmospheric stability classes in dispersion modelling are class C (where inversion occurs just above stack height, and the plume is therefore forced to the ground) and class D (close to stable or neutral conditions). Predicted concentrations at 11, 25, 41 and 1432 m from the stacks under atmospheric stability class C were 6.6, 2.2, 0.4 and 0.1 µg/m^3. Predicted concentrations at 11, 35, 41 and 3508 m under atmospheric stability

TABLE 3 Predicted concentrations of acrylonitrile in southern Ontario from ChemCAN3 modelling with various half-lives in air given (reported releases under Section 16 of CEPA for 1996)[1]

Season	Air		Water		Soil[4]		Sediment		Residence time (h)		
	Dist.[2] (%)	Conc.[3] (µg/m^3)	Dist. (%)	Conc. (mg/L)	Dist. (%)	Conc. (µg/g)	Dist. (%)	Conc. (µg/g)	Overall	Reaction	Burial
Year-round average											
Short half-life	41.9	3.3×10^{-5}	57.9	1.1×10^{-8}	0.17	3.2×10^{-9}	0.02	5.1×10^{-9}	12.2	13.3	3.6×10^{5}
Long half-life	78.1	3.0×10^{-4}	21.6	1.9×10^{-8}	0.31	2.9×10^{-9}	0.007	9.2×10^{-9}	59	266	1.9×10^{5}
Average half-life	74.7	2.1×10^{-4}	25.0	1.6×10^{-8}	0.3	2.0×10^{-8}	0.009	7.8×10^{-9}	43.3	95.8	2.1×10^{5}
Winter											
Short half-life	40.9	3.3×10^{-5}	58.7	1.1×10^{-9}	0.39	7.5×10^{-9}	0.006	5.3×10^{-9}	12.5	13.7	2.8×10^{5}
Long half-life	76.2	3.0×10^{-4}	23.1	2.1×10^{-8}	0.72	6.7×10^{-8}	0.008	1.0×10^{-8}	60	266	1.5×10^{5}
Average half-life	72.8	2.1×10^{-4}	26.4	1.7×10^{-8}	0.7	4.7×10^{-8}	0.009	8.5×10^{-9}	44.3	97.2	1.6×10^{5}
Summer											
Short half-life	43.3	3.3×10^{-5}	56.6	9.9×10^{-9}	0.08	1.5×10^{-9}	0.02	4.8×10^{-4}	11.8	12.9	4.0×10^{5}
Long half-life	80.2	3.0×10^{-4}	19.7	1.7×10^{-8}	0.15	1.4×10^{-8}	0.007	8.2×10^{-9}	57.8	267	2.1×10^{5}
Average half-life	76.8	2.1×10^{-8}	23.1	1.4×10^{-8}	0.2	9.6×10^{-9}	0.008	7.1×10^{-9}	42.2	94.2	2.2×10^{5}

[1] Mackay *et al*. (1995). ChemCAN3 modelling (model available from Trent University web site). Model assumed release to air was 18.75 tonnes per year and to water 0.529 tonnes per year simultaneously.
[2] dist. = distribution.
[3] conc. = concentration.
[4] Soil solids runoff rate was corrected to 5.71×10^{-9} m per hour as in version 4 of the model.

TABLE 4 Maximum predicted ground-level concentrations of acrylonitrile at an Ontario industrial site[1]

Stack[2]	Atmospheric stability class[3]	Emission rate (g/s)	Wind speed (m/s)	Distance from stack (m)	Maximum predicted concentration[4] (µg/m^3)
N2	C	0.003	5.0	41	0.4
N2	D	0.003	5.0	41	0.6
N4	C	0.018	5.0	11	6.6
N4	D	0.018	5.0	11	9.3
N5	C	0.028	5.0	25	2.2
N5	D	0.028	5.0	35	2.9
H5	C	0.050	2.2	1432	0.1
H5	D	0.050	2.7	3508	0.1

[1] Source: Michelin (1999).
[2] Stacks:
N2: NBR Reactor Opening and Vent Gas Unit (stack height = 14 m)
N4: Latex Stripping Column (stack height = 17 m)
N5: NBR Finishing Building (stack height = 11 m)
H5: East Flare (stack height = 66 m)
[3] Atmospheric stability classes:
C: Inversion occurs just above stack height; plume is therefore forced to the ground.
D: Close to stable or neutral conditions.
[4] For all stacks tested, the maximum off-property ground-level concentration was found to be 3.6 µg/m^3 within 10 m of the property fence line (atmospheric stability class: D, wind speed 5.0 m/s).

class D were 9.3, 2.9, 0.6 and 0.1 µg/m^3 (Table 4). This recent determination of 9.3 µg/m^3 at 11 m from the stack of the largest user of acrylonitrile is considered to be the highest reliable (predicted or measured) concentration in ambient air in Canada. It is noted that, in reality, discharges from each of the stacks are not continuous over time. For example, the reactor opening occurred six times in 1998 and gave a combined loss of 0.3 g of acrylonitrile. The latex stripping column was opened five times in 1998, and the combined loss of acrylonitrile was estimated at 31 g. The maximum predicted concentration of 9.3 µg/m^3 was only for five 30-minute periods during the year (Wright, 1999). In addition, testing by the Ontario ministry of the Environment on the accuracy of the model indicated that the model overpredicts the actual value by about two orders of magnitude.

The most recent sampling of air for acrylonitrile at an industrial site was at the site of nitrile-butadiene rubber production in Sarnia, Ontario. Sampling took place on January 8, 1997 (four samples) and on January 13, 1997 (two samples), 5 m outside the company fence line, 2 m above ground and directly downwind of the stacks. Acrylonitrile was not detected in any of the six samples. The concentration in the ambiant air downwind of the plant was therefore less than the detection limit of 52.9 µg/m^3 (Sparks, 1997; Wright, 1998).

Acrylonitrile levels ranged from 0.12 to 0.28 µg/m^3 in ambient air sampled for six days near a chemical manufacturing plant in Cobourg, Ontario, that uses acrylonitrile. Measurements from stacks of the facility in 1993 ranged from <251 to 100 763 µg/m^3 (Ortech Corporation, 1994). These measurements were used in dispersion modelling to estimate the point of impingement concentration (the concentration of acrylonitrile in air at the point where the plume contacts the ground). The estimated point of impingement value was 1.62 µg/m^3, or 0.5% of the Ontario Ministry of the Environment half-

hour allowable point of impingement concentration of 300 µg/m^3.

At six urban stations in Ontario in 1990, concentrations of acrylonitrile in 10 of 11 samples were below the detection limit of 0.0003 µg/m^3. In this study, the maximum and only detectable concentration of acrylonitrile was 1.9 µg/m^3 in one sample (OMOE, 1992a).

Levels of acrylonitrile were <0.64 µg/m^3 in all seven samples of ambient air taken in the industrialized area of Windsor, Ontario, in August 1991 (Ng and Karellas, 1994).

Ambient air samples were collected from downtown (n = 16) and residential (n = 7) areas of Metropolitan Toronto, Ontario, during a personal exposure pilot survey. The air samples were obtained at 1.5 m above ground for 12 consecutive hours. Acrylonitrile was not detected (detection limit 0.9 µg/m^3) in any sample analysed (Bell *et al*., 1991).

Air samples were collected within the inhalation zone by a personal unit for 1–2 hours while commuting to and from work (n = 19) and while spending the noon-hour period (n = 8) in downtown Toronto, Ontario, from June to August 1990. Acrylonitrile was not detected (detection limit 0.9 µg/m^3) in any sample analysed. Acrylonitrile was also not detected (detection limit 0.9 µg/m^3) in four special composite samples collected during the same study; the first two samples were collected while the participants were attending meetings, the third was collected at a barbecue, and the fourth was an overall composite sample of the afternoon and morning commutes and the overnight residential indoor air quality (Bell *et al*., 1991).

2.3.2.2 Indoor air

Acrylonitrile was not detected in samples collected overnight (duration up to 16 hours) from June to August 1990 in four different residences near Toronto, Ontario (detection limit 0.9 µg/m^3) (Bell *et al*., 1991).

Environmental tobacco smoke appears to be a source of acrylonitrile in indoor air (CARB, 1994). Data on acrylonitrile levels in indoor air in a survey conducted in the United States indicate that there may also be unidentified non-smoking sources (CARB, 1996).

2.3.2.3 Surface water and groundwater

Acrylonitrile has been detected only in water associated with industrial effluent; it has not been detected in ambient surface water in Canada (detection limit 4.2 µg/L).

The most comprehensive sampling of acrylonitrile in effluents in Canada was that conducted in 1989–90 under Ontario's Municipal/Industrial Strategy for Abatement (MISA) Program. Acrylonitrile occurred at six of the 26 industrial sites sampled, but only five of these companies had waste streams that were discharged to the environment. Of the effluents sampled from these five companies, acrylonitrile was detected in 12 of 256 samples (OMOE, 1993). Daily concentrations ranged from 0.7 to 3941 µg/L; annual site averages ranged from 2.7 to 320 µg/L.

In the intervening decade since the widespread MISA sampling took place, there have been important changes in the organic chemical manufacturing industry. Three of the five companies did not report commercial activity involving acrylonitrile in 1997, and the two remaining companies have both added biological treatment reactors (e.g., Biox reactors) to process their waste streams before discharge to the environment. Currently, levels from both sites are below the recommended method detection limit of 4.2 µg/L (Hamdy, 1998).

In 1989–90, acrylonitrile was detected in 12 of 382 effluent samples from five of the 26 organic chemical manufacturing plants in Ontario mentioned above (OMOE, 1992b). The maximum daily concentrations ranged from 0.7 to 120 µg/L. The means at different sites ranged from 0.4 to 20 µg/L. The maximum concentration occurred in

one sample of clarifier effluent discharged to Lake Ontario at Cobourg. At this site, acrylonitrile was detected in two of 50 samples (mean 4 µg/L). In the same study, intake water (i.e., ambient water) at the 26 Ontario organic chemical manufacturing plants did not contain detectable amounts of acrylonitrile in 207 samples (detection limit 4.2 µg/L) sampled over 12 months in 1989–90 under the MISA Program (OMOE, 1992b).

In a large study of Canadian municipal water supplies in 1982–83, acrylonitrile was not detected in any of the 42 raw (and 42 treated) water samples from nine municipalities on the Great Lakes (detection limit 5 µg/L) (Otson, 1987). Acrylonitrile was not detected (detection limit 2.1 µg/L) in groundwater samples downgradient of a wastewater treatment pond at an Ontario chemical industry site (Environment Canada, 1997b).

2.3.2.4 Drinking water

Acrylonitrile was monitored in municipal water supplies at 150 locations in Newfoundland, Nova Scotia, New Brunswick and Prince Edward Island over the period 1985–1988. It was detected at a trace concentration (0.7 µg/L) in only one sample of treated water in Nova Scotia in June 1988 (detection limit 0.5–1.0 µg/L) (Environment Canada, 1989a,b,c,d).

Acrylonitrile was not identified in treated (or raw) water at facilities near the Great Lakes in 1982–83 (n = 42; detection limit 5 µg/L during the initial sampling and <1 µg/L during later sampling after the technique was modified) over three sampling periods (Otson, 1987). Analyses were by gas chromatography/mass spectrometry.

No other Canadian data were identified.

2.3.2.5 Soil and sediment

Significant concentrations of acrylonitrile are not expected in Canadian soil or sediment based on the release patterns and the environmental partitioning, behaviour and fate of the substance (see Section 2.3.1).

Significant levels of acrylonitrile have not been detected in Canadian soils. Levels in 18 soil samples at an Alberta chemical blending plant were below the detection limit of 0.4 ng/g (Dinwoodie, 1993). Significant quantities of acrylonitrile in soil at a LaSalle, Quebec, chemical industrial site have not been identified since regular monitoring began at the site in 1992 (Environment Canada, 1997b).

Data on levels of acrylonitrile in Canadian sediment have not been identified.

2.3.2.6 Biota

Information on the levels of acrylonitrile in biota in Canada was not identified.

2.3.2.7 Food

Acrylonitrile-based polymers are not used in Canada to any great extent in direct food contact application. If used, they would be primarily applied as the outside layer of laminated structures (Salminen, 1993, 1996). Past analysis of food products indicates that residual acrylonitrile from acrylonitrile-based polymers, if used in this manner, could conceivably migrate into foods, although at low concentrations (Page and Charbonneau, 1983; Page, 1995).

Regulations of the *Food and Drugs Act* prohibit the sale of food containing acrylonitrile as determined by official method FO-41 (Determination of Acrylonitrile in Food). The detection limit of that method is approximately 15 ng/g (Salminen, 1999).

Page and Charbonneau (1983) measured concentrations of acrylonitrile in five types of food packaged in acrylonitrile-based plastic containers, purchased from several stores in Ottawa, Ontario. Average concentrations of acrylonitrile (measured in three duplicate samples of each food type by gas chromatography with a nitrogen-phosphorus selective detector) ranged from 8.4 to 38.1 ng/g (see footnote 12 in Table 9, Section 3.3.1).

A survey of food packed in acrylonitrile-based plastics, containing up to 2.6 mg acrylonitrile/kg, was conducted in Ottawa, Ontario. The samples represented five food companies and a variety of luncheon meats, including mock chicken, ham, salami, pizza loaf and several types of bologna. Acrylonitrile was not identified (detection limit 2 ng/g). Analyses were by gas chromatography, with nitrogen-phosphorus selective detection (Page and Charbonneau, 1985).

No other Canadian data were identified, and limited data from other countries are inadequate to serve as the basis for characterization of exposure through foodstuffs.

2.3.2.8 Multimedia study

In a multimedia study carried out for Health Canada (Conor Pacific Environmental and Maxxam Ltd., 1998), exposure to several volatile organic chemicals, including acrylonitrile, was measured for 50 participants across Canada. Thirty-five participants were randomly selected from the Greater Toronto Area in Ontario, six participants from Liverpool, Nova Scotia, and nine from Edmonton, Alberta. For each participant, samples of drinking water, beverages and indoor, outdoor and personal air were collected over a 24-hour period. Acrylonitrile was not detected in air (detection limit 1.36 $\mu g/m^3$), water (detection limit 0.7 ng/mL), beverages (detection limit 1.8 ng/mL) or food (detection limit 0.5 ng/g).

2.4 Effects characterization

2.4.1 Ecotoxicology

The toxicity of acrylonitrile to aquatic organisms has been studied in a wide range of organisms, while a smaller data set exists on the toxicity of acrylonitrile to terrestrial organisms. A brief summary of effects is presented below, with an emphasis on the most sensitive endpoints for aquatic and terrestrial organisms. More extensive descriptions of environmental effects are provided in several reviews (U.S. EPA, 1980, 1985; WHO, 1983; EC, 1998) and in the environmental supporting documentation (Environment Canada, 1998).

2.4.1.1 Terrestrial organisms

While no data on the toxicity of acrylonitrile to terrestrial vertebrate wildlife were found in the literature, data are available from mammalian toxicology studies (Section 2.4.3). No data were found on avian toxicity. The focus of this section is on studies of insect species exposed to acrylonitrile in air.

In nine studies conducted on 13 insect species — including pulse beetle, rice weevil, lesser grain borer, granary weevil, saw-toothed grain beetle, red flour beetle, confused flour beetle, Mediterranean fruit fly, Oriental fruit fly and honey bee — acute and chronic exposure via fumigation with acrylonitrile affected survival, reproduction and enzyme activity. These studies are presented in the environmental supporting documentation (Environment Canada, 1998). LC_{50}s in insects ranged from 0.107 to 36.7 mg/L air (1.07×10^5 –3.67×10^7 $\mu g/m^3$). In 14 of 17 studies on 11 species, the 24-hour LC_{50} was ≤5 mg/L air (≤5×10^6 $\mu g/m^3$).

The most sensitive effect on growth, survival or reproduction in insects exposed to acrylonitrile via the atmosphere was the effect of fumigation on the one-day-old eggs of the pulse beetle (*Callosobruchus chinensis*) (Adu and Muthu, 1985). The LC_{50} for eggs exposed to a

constant concentration of the fumigant for 24 hours and examined for survival up to 30 days post-fumigation was 0.107 mg/L air (1.07×10^5 µg/m^3) (95% confidence limits 0.094–0.122 mg/L air) (Adu and Muthu, 1985).

Rajendran and Muthu (1981a) reported that for adults and pupae of rice weevil (*Sitophilus oryzae* L.) exposed to the LC_{50} of 0.40 mg/L air (4.0×10^5 µg/m^3) for eight hours, there was a 50% decrease in the number of progeny.

Of the knockdown times reported for insects, the most sensitive organisms were *Sitophilus oryzae* L. adults, for which exposure to 1–1.5 mg/L air ($1–1.5 \times 10^6$ µg/m^3) for four hours resulted in 100% mortality (Rajendran and Muthu, 1977).

Of phosphorylase, trehalase and acetylcholinesterase enzymes involved in carbohydrate and energy metabolism, phosphorylase was the most susceptible and diminished to below detectable activity (100% decrease) at a concentration of 1.05 mg/L air (1.05×10^6 µg/m^3) in adult red flour beetle (*Tribolium castaneum*), which survived exposure to the LC_{50} of 0.79 mg/L (7.9×10^5 µg/m^3) (Rajendran and Muthu, 1981b).

2.4.1.2 Aquatic organisms

The data set for acrylonitrile includes a wide range of information on short- and long-term toxicity in 34 species of fish, amphibians, aquatic invertebrates and algae, although none complies totally with the requirements of OECD or similar test guideline protocols.

The majority of studies did not take into account the volatility of acrylonitrile. Those tests in which concentrations were not measured or could not be adequately adjusted, as explained below, are not considered valid for risk assessment purposes. Below, a brief summary is presented of the key studies carried out in general compliance with current OECD testing protocols and appropriate for risk assessment purposes.

Due to potential loss from water via volatilization and biodegradation, concentrations of acrylonitrile should be measured in static or static-renewal tests. Alternatively, for flow-through tests with nominal concentrations, there should be roughly five turnovers per day (Henderson *et al*., 1961; Bailey *et al*., 1985; Nabholz, 1998). Tests with measured concentrations or flow-through tests with this rate of turnover are considered primary evidence for the assessment.

Sabourin (1987) determined the ratio of flow-through to static concentrations at the 96-hour period to be 0.23. Therefore, studies with 96-hour endpoints can be adjusted by multiplying the reported concentration by 0.23, although the data provided by these studies are considered secondary evidence. Tests done under static conditions or those with nominal concentrations only at a time period different from 96 hours are considered as supporting evidence only.

Of the freshwater studies, there are five studies on five fish species and one study with an amphibian that are considered to provide primary data (Henderson *et al*., 1961; Sloof, 1979; ABCL, 1980a; Bailey *et al*., 1985; Zhang *et al*., 1996). In addition to these, there is secondary evidence (adjusted concentrations) from studies with six fish, seven invertebrate and one plant species. In these studies, a variety of endpoints was examined, including survival, growth, respiration and mobility at exposure durations ranging from 24 to 840 hours (1–35 days). The remainder of the studies were considered as providing supporting evidence.

Based on the primary and secondary studies, acrylonitrile is moderately toxic to fish and amphibians, with the 96-hour LC_{50}s for freshwater fish generally lying in the range of 10–20 mg/L (nominal) (Henderson *et al*., 1961; ABCL, 1980b; Zhang *et al*., 1996). Toxicity to

acrylonitrile increases with increasing exposure duration. Reported 48-hour LC_{50} values lie between 14.3 and 33.5 mg/L. At 840 hours, the LC_{50} for fathead minnow (*Pimephales promelas*) was 0.89 mg/L (ABCL, 1980a).

Based on the primary evidence, the most sensitive aquatic endpoint was that following chronic exposure of the frog, *Bufo bufo gargarizans*, in its early life stage (Zhang *et al*., 1996). Three-day-old tadpoles were exposed for 28 days in a flow-through system with four turnovers per day. The most sensitive endpoint was foreleg growth, where the lower and upper chronic limits around the 28-day EC_{50} were 0.4 mg/L and 0.8 mg/L, respectively. The 96-hour and 48-hour EC_{50} for immobility were 11.59 mg/L and 14.22 mg/L, respectively.

The effect of acrylonitrile on the growth (length and wet weight) and mortality of the early life stage (<18-hour-old eggs) of the fathead minnow (ABCL, 1980a) in a flow-through system with more than 5.5 turnovers per day has been examined. Mean measured concentrations were 98% of nominal. The most sensitive endpoint in the study was the 840-hour (35-day) Lowest-Observed-Effect Concentration (LOEC) for weight (20% reduction in wet weight) at 0.44 mg/L; the corresponding No-Observed-Effect Concentration (NOEC) was 0.34 mg/L. For mortality, the 840-hour NOEC (LC_{15}) was 0.44 mg/L and the LOEC (LC_{46}) was 0.86 mg/L.

Henderson *et al*. (1961) reported mortality of fathead minnow exposed to acrylonitrile in a flow-through system in which solutions were renewed every 100 minutes. Test durations were 24, 48, 72 and 96 hours and five, 10, 15, 20, 25 and 30 days (720 hours). Effects ranged from the 24-hour LC_{50} of 33.5 mg/L through decreasing concentrations to the most sensitive endpoint in the study, the 720-hour LC_{50} at 2.6 mg/L.

Sloof (1979) reported the impact of acrylonitrile as increased respiration in rainbow trout within 24 hours of exposure to 5 mg/L in a flow-through system with continuous injection.

Bailey *et al*. (1985) examined the effect of acrylonitrile on the mortality of bluegill in a flow-through system with measured concentrations. The most sensitive endpoint in the study was the 96-hour LC_{50} at 9.3 mg/L.

In addition to primary studies with adequate flow-through or measured concentrations, 96-hour LC_{50}s in six species of fish in studies conducted with static/static-renewal nominal concentrations can be adjusted by the factor 0.23 (Sabourin, 1987; Nabholz, 1998). Using this method, the adjusted 96-hour LC_{50}s ranged from 1.18 to 5.4 mg/L. The lowest 96-hour LC_{50} of 1.18 mg/L was that for grass carp (*Ctenopharyngodon idella*) (Zhang *et al*., 1996).

It is noted that for vertebrate species, the most sensitive endpoints were observed in primary studies. That is, overall, the most sensitive endpoint for aquatic vertebrates was the lower chronic limit around the EC_{50} of 0.4 mg/L in the frog, *Bufo bufo gargarizans*, determined by Zhang *et al*. (1996) in a flow-through system with measured concentrations.

Of the studies on 14 invertebrate and one freshwater plant species, 96-hour tests in seven invertebrate and one plant species can be adjusted and considered to provide secondary evidence. Based on the secondary information, which must be interpreted with caution, it appears that, overall, invertebrates are more sensitive to acrylonitrile than vertebrates, although this was not discussed further by the authors. Effects in invertebrates range from the most sensitive, the 96-hour LC_{80} at 0.16 mg/L (adjusted concentration 0.04 mg/L) in the pond snail (*Lymnaea stagnalis*) (Erben and Beader, 1983), to the 96-hour immobility EC_{50} at 17.94 mg/L (adjusted concentration 4.1 mg/L) in the common stream snail, *Lymnaea plicatula* (Zhang *et al*., 1996).

More sensitive endpoints have been reported for invertebrates but are considered supporting information only, not primary or secondary data, since the tests were based on nominal concentrations under static conditions for exposure durations other than 96 hours. The remainder are considered to provide supporting information only, since there was no replication of doses or there were other confounding factors (e.g., lack of aeration).

In the one study on freshwater aquatic plants, the effect of a 96-hour exposure to acrylonitrile on plant growth was examined in duckweed (*Lemna minor*) (Zhang *et al*., 1996). Solutions were renewed every 24 hours, with five test concentrations, 10 fronds per concentration and four replicates. The 96-hour growth inhibition EC_{50} was 6.25 mg/L (adjusted EC_{50} is 1.44 mg/L).

2.4.1.3 Mode of action

The toxicity of acrylonitrile to environmental organisms is believed to result largely from direct effects of the acrylonitrile itself or other organic metabolites, such as hydrogen peroxide or an epoxide (Heald, 1980). The blocking of important enzymes containing sulphydryl groups by cyanoethylation has been suggested as a possible mechanism for acrylonitrile toxicity (Kayser *et al*., 1982). The liberation of free cyanide was originally thought to be responsible for the toxicity of acrylonitrile, since cyanide easily diffuses to all body tissues and rapidly inhibits specific enzymes responsible for respiration on the cellular level, stopping the utilization of molecular oxygen by cells. The signs of acrylonitrile poisoning are typical of hydrogen cyanide poisoning, but with a slight delay of the onset of symptoms (Patterson *et al*., 1976).

2.4.1.4 Microbial populations

There is considerable evidence of the effectiveness of acclimated soil or sludge microorganisms in degrading acrylonitrile in industrial wastewater treatment systems (e.g., Biox reactors). Wyatt and Knowles (1995a,b) demonstrated that complex mixtures of microorganisms in combination with different dilution rates and a combination of batch and continuous culture can be used to mineralize (degrade) acrylonitrile, acrylamide, acetic acid, cyanopyridine and succinonitrile, as well as more recalcitrant compounds (e.g., maleimide, fumaronitrile and acrolein), to carbon dioxide, ammonia and biomass.

Generally, concentrations of acrylonitrile up to 5000 mg/L do not appear to be toxic to bacteria, since they are readily degraded by *Corynebacterium boffmanii* and *Arthrobacter flavescens* (Wenzhong *et al*., 1991), *Arthrobacter* sp. (Narayanasamy *et al*., 1990), *Acinobacter* sp. (Finnegan *et al*., 1991) and an assemblage of acclimated anaerobic microorganisms (Mills and Stack, 1955). *Nocardia rhodochrous* can degrade acrylonitrile in a more limited manner, based on its use as a nitrogen rather than carbon source (DiGeronimo and Antoine, 1976).

Kincannon *et al*. (1983) reported almost complete biodegradation with 99.9% and 99.1% removal of acrylonitrile after eight hours in batch reactors and two days in complete mixture activated sludge, respectively. Initial concentrations of acrylonitrile were 110 and 152 mg/L, respectively; effluent concentrations post-treatment were 1.0 mg/L after eight hours and <0.05 mg/L after two days, respectively. In the batch reactor, biodegradation accounted for 75% and stripping accounted for 25% of acrylonitrile removal. In the activated sludge system, biodegradation was responsible for 100% of the removal.

Tabak *et al*. (1980) reported 100% biodegradation within seven days in a static screening flask test method when microbial inoculum from a sewage treatment plant was mixed with 5 and 10 mg acrylonitrile/L.

2.4.2 Abiotic atmospheric effects

Worst-case calculations were made to determine whether acrylonitrile has the potential to

contribute to depletion of stratospheric ozone, ground-level ozone formation or climate change (Bunce, 1996).

The Ozone Depletion Potential (ODP) was calculated to be 0, since acrylonitrile does not contain chlorine or bromine atoms.

The Photochemical Ozone Creation Potential (POCP) was estimated to be 25 (relative to the value of an equal mass of the reference compound ethene, which has a POCP of 100), based on the following formula:

$$POCP = (k_{ACN}/k_{ethene}) \times (M_{ethene}/M_{ACN}) \times 100$$

where:

- k_{ACN} is the rate constant for the reaction of acrylonitrile with OH radicals (4×10^{-12} cm^3/mol per second),
- k_{ethene} is the rate constant for the reaction of ethene with OH radicals (8.5×10^{-12} cm^3/mol per second),
- M_{ethene} is the molecular weight of ethene (28.1 g/mol), and
- M_{ACN} is the molecular weight of acrylonitrile (53.1 g/mol).

The Global Warming Potential (GWP) was calculated to be 4.3×10^{-4} (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula:

$$GWP = (t_{ACN}/t_{CFC\text{-}11}) \times (M_{CFC\text{-}11}/M_{ACN}) \times (S_{ACN}/S_{CFC\text{-}11})$$

where:

- t_{ACN} is the lifetime of acrylonitrile (0.0099 years),
- $t_{CFC\text{-}11}$ is the lifetime of CFC-11 (60 years),
- $M_{CFC\text{-}11}$ is the molecular weight of CFC-11 (137.5 g/mol),
- M_{ACN} is the molecular weight of acrylonitrile (53.1 g/mol),
- S_{ACN} is the infrared absorption strength of acrylonitrile (2389/cm^2 per atmosphere, default), and
- $S_{CFC\text{-}11}$ is the infrared absorption strength of CFC-11 (2389/cm^2 per atmosphere).

Actual contribution to formation of photochemical ozone depends on both reactivity and concentration in an area or region. The POCP value indicates a moderate potential for photochemical ozone formation. However, acrylonitrile is released from only a few point sources in Canada, and, importantly, levels of acrylonitrile in ambient urban air have generally been below detection levels of 0.9 µg/m^3 (Bell *et al*., 1991; OMOE, 1992a; Ng and Karellas, 1994), which indicates that acrylonitrile is likely to be only a very minor contributor to photochemical ozone formation. The absence of chlorine and bromine atoms in the molecule means that the potential contributions of acrylonitrile to stratospheric ozone depletion and climate change are both negligible.

2.4.3 Experimental animals and in vitro

2.4.3.1 Acute toxicity

The acute toxicity of acrylonitrile is relatively high, with four-hour LC_{50}s ranging from 300 to 900 mg/m^3 (Knobloch *et al*., 1971, 1972) and LD_{50}s ranging from 25 to 186 mg/kg-bw (Maltoni *et al*., 1987). Signs of acute toxicity include respiratory tract irritation and central nervous system dysfunction, resembling cyanide poisoning. Superficial necrosis of the liver and hemorrhagic gastritis of the forestomach have also been observed following acute exposure.

Acrylonitrile-induced neurotoxicity following acute exposure has been described as a two-phase phenomenon. The first phase, which occurs shortly after exposure and is consistent with cholinergic overstimulation, has been likened to toxicity caused by acetylcholinesterase inhibition. Cholinomimetic signs in rats exposed to acrylonitrile have included vasodilation, salivation, lacrimation, diarrhea and gastric secretion. These effects are maximal within one hour of dosing. The second phase of toxicity is delayed by four or more hours and includes signs of central nervous system disturbance, such as trembling, ataxia, convulsions and respiratory failure (TERA, 1997). The acetylcholine-like

toxicity is thought to be caused by acrylonitrile, while the central nervous system depression is caused by cyanide (the latter does not cause acetylcholine-like effects).

2.4.3.2 Short-term toxicity

Available short-term inhalation studies are restricted to a few investigations involving administration of single dose levels and, for one, examination of clinical signs only. Exposure response has not, therefore, been well characterized. There were effects on biochemical parameters, clinical signs and body weight, although no histopathological effects on principal organs, following exposure of rats to 280 mg/m^3 (Gut *et al*., 1984, 1985).

In short-term studies by the oral route, effects on the liver, adrenal and gastric mucosa have been observed, with effects on the gastric mucosa occurring at lowest doses in all studies in which they were examined. Effects on the adrenal cortex observed in short-term repeated-dose toxicity studies from one laboratory have not been noted in longer-term investigations in animals exposed to higher concentrations. In investigations by Szabo *et al*. (1984), effects on the non-protein sulphydryl in gastric mucosa and hyperplasia in the adrenal cortex have been reported at levels as low as 2 mg/kg-bw per day administered by drinking water and gavage, respectively, for 60 days. Effects on hepatic glutathione were also observed by these authors at similar doses administered by gavage but not in drinking water (2.8 mg/kg-bw per day for 21 days), although Silver *et al*. (1982) noted only slight biochemical effects but no histopathological effects in the liver at doses up to 70 mg/kg-bw per day (drinking water, 21 days). Significant increases in proliferation in the forestomach but no changes in the liver or glandular stomach have been observed at 11.7 mg/kg-bw (Ghanayem *et al*., 1995, 1997).

Effects of pretreatment with inducers of the mixed-function oxidase system or antioxidants on toxicity in short-term studies have been consistent with metabolism to the epoxide 2-cyanoethylene oxide being the putatively toxic metabolic pathway.

2.4.3.3 Subchronic toxicity

Results of identified subchronic toxicity studies are limited to an early 13-week inhalation study in rats and dogs that has not been validated (IBT, 1976) and a preliminary brief report of the results of a 13-week gavage study in mice (NTP, 1996). Lack of validation and inadequate detail limit the utility of these studies for hazard evaluation or characterization of dose–response.

2.4.3.4 Chronic toxicity and carcinogenicity

In the descriptions of the following studies, tumour types are reported as described by the authors. However, it should be noted that the histopathology of the tumours may be unclear (see footnote 2 on page 28).

2.4.3.4.1 Inhalation

Quast *et al*. (1980b) conducted a bioassay in which Sprague-Dawley (Spartan substrain) rats (100 per sex per group) were exposed by inhalation to average concentrations of 0, 20 or 80 ppm (0, 44 or 176 mg/m^3) of acrylonitrile six hours per day, five days per week, for two years. Non-neoplastic histopathological changes related to the treatment were found in the nasal turbinates and the central nervous system of both males and females. In the brain, the changes were characterized by focal gliosis and perivascular cuffing at the highest concentration. The inflammatory changes in the nasal turbinates were considered to be due to acrylonitrile irritation. These effects were not observed at 20 ppm, and this dose is considered as a No-Observed-Effect Level (NOEL). An early onset of chronic renal disease in the 20 ppm group was observed upon histopathological examination. The renal effect was not apparent at the high dose because of early mortality. The chronic renal disease was considered a secondary effect caused by increased water intake and is commonly observed in older

rats of this strain. A pair-fed control study was not performed, and further clinical analyses are required to understand the chronic renal effect.

In both sexes, there was an increase in the combined incidence of malignant and benign tumours of the brain and spinal cord (Table 5) and benign and malignant tumours of the Zymbal gland at the high dose. In males, the combined incidence of benign and malignant tumours of the small intestine and the tongue was increased at the high dose. The incidence of adenocarcinoma of the mammary gland was increased at the high dose in females (Quast *et al*., 1980b).

In an earlier study, Maltoni *et al*. (1977) exposed Sprague-Dawley rats to 0, 5, 10, 20 or 40 ppm (0, 11, 22, 44 and 88 mg/m^3) acrylonitrile for four hours per day, five days per week, for 52 weeks. Increases in the incidence of tumours were observed in the mammary gland in males and females, in the forestomach in males and in the skin in females. The authors concluded that because of the lack of a dose-related response in tumour incidence, the results could be evaluated as "borderline carcinogenic effects." Low concentrations of acrylonitrile, short exposure time and small group size (n = 30) limit the sensitivity of the study.

In a follow-up study by Maltoni *et al*. (1987, 1988), 54 female Sprague-Dawley rat breeders and male and female offspring were administered 60 ppm (132 mg/m^3) by inhalation for 4–7 hours per day, five days per week. The breeders and some of the offspring were exposed for 104 weeks; the remaining offspring were exposed for 15 weeks only. The non-neoplastic treatment-related changes included slight, but significant, increases in the incidence of encephalic glial cell hyperplasia and dysplasia in offspring exposed for 104 weeks. A significantly increased incidence of various tumours was observed in the exposed offspring, both males and females. Tumours with increased incidence included mammary gland tumours in females, Zymbal gland tumours in males, extrahepatic angiosarcoma in both males and females, hepatomas in males and encephalic gliomas in both males and females. The most pronounced acrylonitrile-related tumour was encephalic glioma (in control and exposure groups, respectively: 2/158 and 11/67 in males; 2/149 and 10/54 in females) in the offspring treated with acrylonitrile for 104 weeks.

2.4.3.4.2 Drinking water

Quast *et al*. (1980a) administered acrylonitrile in drinking water to groups of 48 Sprague-Dawley rats of each sex (n = 80 for controls) for two years at dose levels of 0, 35, 100 or 300 ppm (based upon data for water consumption and body weight, the authors reported intakes of 0, 3.4, 8.5 or 21.2 mg/kg-bw per day for males and 0, 4.4, 10.8 or 25.0 mg/kg-bw per day for females). There was treatment-related hyperplasia and hyperkeratosis of the squamous epithelium of the forestomach in females at all dose levels and in males at 100 and 300 ppm. In the brain of females, there was a significantly increased incidence of focal gliosis and perivascular cuffing in the 35 and 100 ppm groups. Other changes were not considered to be directly treatment related, but, rather, secondary to decreased food and water consumption, although supporting information from pair-fed controls was not available.

Sacrifice and necropsy were carried out on moribund animals. Tumours (including astrocytomas) were observed as early as 7–12 months in females in the high-dose group; in other dose groups, they appeared initially in the 13- to 18-month period. In both males and females, the combined incidence of benign and malignant tumours of the brain and spinal cord was significantly increased in a dose-related manner at all levels of exposure (Table 6). The incidence of carcinoma of the Zymbal gland was significantly increased at the highest dose in males and at the two highest doses in females (Quast *et al*., 1980a).

In a study conducted by Bio/Dynamics Inc. (1980a), groups of 100 male and 100 female

TABLE 5 Quantitative estimates of carcinogenic potency, derived for tumour incidences reported in an inhalation bioassay with Sprague-Dawley rats[1]

	Animal data		Parameter estimates	Human equivalent values
	Dose	**Incidence**		
Males: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 6 months	control 44 mg/m^3 (20 ppm) 176 mg/m^3 (80 ppm)	0/98 4/97 (4 astrocytoma) 22/98 (15 astrocytoma, 7 benign)	TC_{05}[2] = 52 mg/m^3 95% LCL[3] = 29 mg/m^3 Chi-square = 0.73 degrees of freedom = 1 p-value = 1.00	TC_{05}[4] = 8.9 mg/m^3 95% LCL = 5 mg/m^3
Males: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 10 months (TERA, 1997)	control 44 mg/m^3 (20 ppm) 176 mg/m^3 (80 ppm)	0/97[5] 4/93[5] 15/83[5]	TC_{05}[2] = 51 mg/m^3 95% LCL = 33 mg/m^3 Chi-square = 0.00 degrees of freedom = 1 p-value = 1.00	TC_{05}[4] = 8.7 mg/m^3 95% LCL = 5.6 mg/m^3
Females: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 6 months	control 44 mg/m^3 (20 ppm) 176 mg/m^3 (80 ppm)	0/99 8/100 (4 astrocytoma, 4 benign) 21/99 (17 astrocytoma, 4 benign)	TC_{05}[2] = 35 mg/m^3 95% LCL = 26 mg/m^3 Chi-square = 0.65 degrees of freedom = 2 p-value = 0.72	TC_{05}[4] = 6 mg/m^3 95% LCL = 4.5 mg/m^3
Females: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 6 months (TERA, 1997)	control 44 mg/m^3 (20 ppm) 176 mg/m^3 (80 ppm)	0/99[5] 8/99[5] 21/99[5]	TC_{05}[2] = 35 mg/m^3 95% LCL = 26 mg/m^3 Chi-square = 0.69 degrees of freedom = 2 p-value = 0.71	TC_{05}[4] = 5.9 mg/m^3 95% LCL = 4.4 mg/m^3

[1] Quast *et al*. (1980b).
[2] For this study, the resulting TC_{05}s were multiplied by (6 hours per day/24 hours per day) × (5 days per week/7 days per week) to adjust for intermittent to continuous exposure.
[3] 95% LCL = lower 95% confidence limit.
[4] To scale from rats to humans, the TC_{05}s were multiplied by (0.11 m^3 per day/0.35 kg-bw) × (70 kg-bw/23 m^3 per day), where 0.11 m^3 per day is the breathing rate of a rat, 0.35 kg-bw is the body weight of a rat, 23 m^3 per day is the breathing rate of a human and 70 kg-bw is the body weight of a human.
[5] These incidence data could not be verified in an examination of mortality data in Quast *et al*. (1980b).

TABLE 6 Quantitative estimates of carcinogenic potency, derived for tumour incidences reported in a drinking water bioassay with Sprague-Dawley rats[1]

	Animal data		Parameter estimates	Human equivalent values
	Dose	**Incidence**		
Males: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 6 months	control 3.4 mg/kg-bw per day (35 ppm) 8.5 mg/kg-bw per day (100 ppm) 21.2 mg/kg-bw per day (300 ppm)	1/79 (1 astrocytoma) 12/47 (8 astrocytoma, 4 benign) 23/47 (19 astrocytoma, 4 benign) 31/48 (23 astrocytoma, 8 benign)	TD_{05} = 0.84 mg/kg-bw per day 95% LCL^2 = 0.68 mg/kg-bw per day Chi-square = 3.68 degrees of freedom = 2 p-value = 0.16	TD_{05} = 0.84 mg/kg-bw per day 95% LCL = 0.68 mg/kg-bw per day
Females: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 6 months	control 4.4 mg/kg-bw per day (35 ppm) 10.8 mg/kg-bw per day (100 ppm) [25.0 mg/kg-bw per day (300 ppm)]	1/80 (1 astrocytoma) 22/48 (17 astrocytoma, 5 benign) 26/48 (22 astrocytoma, 4 benign) [31/47 (24 astrocytoma, 7 benign)]	Parameter estimates excluding high-dose group: TD_{05}[3] = 0.56 mg/kg-bw per day 95% LCL = 0.44 mg/kg-bw per day Chi-square = 4.77 degrees of freedom = 1 p-value = 0.08	TD_{05}^2 = 0.56 mg/kg-bw per day 95% LCL = 0.44 mg/kg-bw per day

[1] Quast *et al*. (1980a).
[2] 95% LCL = lower 95% confidence limit.
[3] Excludes high-dose group. A dose-related increase in mortality was observed for females, resulting in a plateau in the dose–response function and lack of fit of the model to brain/spinal tumours. However, when the model was refit excluding the highest dose group, this lack of fit was no longer apparent.

Sprague-Dawley rats were administered acrylonitrile at dose levels of 0, 1 or 100 ppm in drinking water (0, 0.09 and 8.0 mg/kg-bw per day for males and 0, 0.15 and 10.7 mg/kg-bw per day for females, based upon body weight and water consumption[1]) for 19 and 22 months. The mean absolute and relative weights of the kidneys in the high-dose females were increased (not always significantly) at all sacrifice intervals. There was an increase in testicular weight to body weight ratio in the high-dose males at the 12- and 18-month sacrifices and at the end of the experiment. No such changes were evident at 1 ppm. This concentration can be considered as a NOEL and 100 ppm as a Lowest-Observed-Adverse-Effect Level (LOAEL) for non-neoplastic effects.

In high-dose males, increased incidences of squamous cell carcinoma of the stomach and carcinoma of the Zymbal gland were observed at the 12-month sacrifice. In high-dose females, astrocytoma of the brain and carcinoma of the Zymbal gland were increased at 12 months. At the high dose, there was an increased cumulative incidence of astrocytoma of the brain, carcinoma of the Zymbal gland and papilloma/carcinoma of the stomach in both males and females. In females, the incidence of astrocytoma of the spinal cord was significantly increased at the high dose. The spinal cord tissue of the males was not examined, although overall histological examination was rather extensive (Bio/Dynamics Inc., 1980a).

A bioassay in Fischer 344 rats exposed to acrylonitrile in drinking water was also conducted by Bio/Dynamics Inc. (1980b). Rats (200 per sex, control group; 100 per sex per dose group) were administered acrylonitrile in drinking water for approximately two years. The dose levels were 0, 1, 3, 10, 30 and 100 ppm acrylonitrile (0, 0.1, 0.3, 0.8, 2.5 and 8.4 mg/kg-bw per day for males and 0, 0.1, 0.4, 1.3, 3.7 and 10.9 mg/kg-bw per day for females, as reported by U.S. EPA, 1985). Serial sacrifices were conducted at 6, 12 and 18 months (20 per sex per control group and 10 per sex per treated group). To ensure at least 10 rats per sex per group for histopathological evaluation, all females were sacrificed at 23 months, owing to low survival. The males were continued on test until the 26th month.

The consistently elevated mortality in the highest dose groups was a consequence of tumours. Other changes observed primarily in the highest exposure group included consistently lower body weights in females and males and consistent reduction in hemoglobin, hematocrit and erythrocyte counts in females throughout the study. A decrease in water intake was also observed, while food consumption was comparable for all groups (Bio/Dynamics Inc., 1980b).

An increase in the relative organ weights of the liver and kidney was noted at the highest dose levels; however, the mean absolute weights for these organs were either comparable to those in the controls or only slightly increased. At terminal sacrifice, the absolute liver and heart weights were elevated in females exposed to 30 ppm, but body weight was comparable to that in controls. A LOAEL of 100 ppm and a Lowest-Observed-Effect Level (LOEL) of 30 ppm for non-neoplastic effects can be designated. In both males and females, the incidence of astrocytoma of the brain (Table 7) and the incidence of carcinoma of the Zymbal gland were significantly increased at the two highest dose levels (Bio/Dynamics Inc., 1980b).

In a multigeneration reproductive study, 0, 100 or 500 ppm acrylonitrile (0, 14 or 70 mg/kg-bw per day; Health Canada, 1994) was administered in drinking water to breeders (F_0) and the offspring of Charles River Sprague-Dawley rats (Litton Bionetics Inc., 1980). Rats of the F_{1b} generation in the high-exposure

[1] Values presented here are the means of 23 (males) and 20 (females) intakes presented by Bio/Dynamics Inc. (1980a).

TABLE 7 Quantitative estimates of carcinogenic potency, derived for tumour incidences reported in a drinking water bioassay with F344 rats[1]

Animal data			Parameter estimates	Human equivalent values
	Dose	**Incidence**		
Males: Nervous system, combined incidence, astrocytoma and focal gliosis, excluding animals dying or sacrificed before 6 months	control 0.08 mg/kg-bw per day (1 ppm) 0.25 mg/kg-bw per day (3 ppm) 0.84 mg/kg-bw per day (10 ppm) 2.49 mg/kg-bw per day (30 ppm) 8.37 mg/kg-bw per day (100 ppm)	5/182 (3 astrocytoma, 2 benign) 2/90 (2 astrocytoma) 1/89 (1 astrocytoma) 2/90 (2 astrocytoma) 10/89 (10 astrocytoma) 22/90 (21 astrocytoma, 1 benign)	TD_{05}[2] = 1.8 mg/kg-bw per day 95% LCL[3] = 1.2 mg/kg-bw per day Chi-square = 3.0 degrees of freedom = 3 p-value = 0.39	TD_{05} = 2.3 mg/kg-bw per day 95% LCL = 1.6 mg/kg-bw per day
Females: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 6 months	control 0.10 mg/kg-bw per day (1 ppm) 0.40 mg/kg-bw per day (3 ppm) 1.30 mg/kg-bw per day (10 ppm) 3.70 mg/kg-bw per day (30 ppm) 10.90 mg/kg-bw per day (100 ppm)	1/178 (1 astrocytoma) 1/90 (1 astrocytoma) 2/90 (2 astrocytoma) 5/88 (4 astrocytoma, 1 benign) 6/90 (6 astrocytoma) 26/90 (24 astrocytoma, 2 benign)	TD_{05} = 2.3 mg/kg-bw per day 95% LCL = 1.4 mg/kg-bw per day Chi-square = 1.8 degrees of freedom = 3 p-value = 0.62	TD_{05} = 2.3 mg/kg-bw per day 95% LCL = 1.4 mg/kg-bw per day

[1] Bio/Dynamics Inc. (1980b).

[2] The experimental length for this study was 24 months for females and 26 months for males, so the resulting TD_{05}s for males were multiplied by (26 months/24 months) × (26 months/24 months)^2, where the first term amortizes the dose to be constant over the standard lifetime of a rat (24 months) and the second factor, suggested by Peto *et al.* (1984), corrects for an experimental length that is unequal to the standard lifetime.

[3] 95% LCL = lower 95% confidence limit.

group had a significantly increased incidence of astrocytomas and Zymbal gland tumours. For control, low-exposure and high-exposure groups, the incidence of astrocytomas was 0/20, 1/19 and 4/17 ($p < 0.05$), respectively, and the incidence of Zymbal gland tumours was 0/20, 2/19 and 4/17 ($p < 0.05$), respectively. The tumour incidence was low, but the exposure and observation period (approximately 45 weeks) was also relatively short. Not all tissues were examined histopathologically.

More recently, Bigner *et al*. (1986) observed neuro-oncogenic effects in Fischer 344 rats administered 0, 100 or 500 ppm acrylonitrile in drinking water (0, 14 and 70 mg/kg-bw per day; Health Canada, 1994). Each exposure group consisted of 50 male and 50 female rats. A fourth group of 300 rats (147 males, 153 females) was exposed to 500 ppm acrylonitrile. Although the protocol of the study indicated that rats were exposed for their lifetime, results were presented for an 18-month observation period. There was a dose-related significant reduction in body weight in both males and females at 500 ppm. In rats exposed for 12–18 months, neurological signs such as decreased activity, paralysis, head tilt, circling and seizures were observed in the 100 and 500 ppm groups. In control, low-exposure and two high-exposure groups, the incidence of neurological signs was 0/100, 4/100, 16/100 and 29/300, respectively. Histopathological examination of 215 animals in the 500 ppm group revealed 49 primary brain tumours, which were difficult to classify.[2] Other tumours frequently observed included Zymbal gland tumours, forestomach papillomas and subcutaneous papillomas. No further details, however, were presented. The authors reported that the increase in incidence of the primary brain tumour in the highest exposure group was significant (p-values were not reported, data poorly presented). Other endpoints were not examined. The results are inadequate, therefore, for establishing effect levels for non-neoplastic effects or for characterizing exposure–response for tumours.

Gallagher *et al*. (1988) investigated the carcinogenicity of acrylonitrile administered via drinking water at 0, 20, 100 or 500 ppm (approximately 0, 2.8, 14 and 70 mg/kg-bw per day; Health Canada, 1994) to male Sprague-Dawley rats (20 per group) for two years. There was no survival in the 500 ppm exposure group at two years. Ingestion of acrylonitrile at concentrations up to and including 100 ppm did not increase mortality. The necropsy results revealed a significant increase in Zymbal gland tumours at 500 ppm (0/18, 0/20, 1/19 and 9/18 [$p < 0.005$] in control, low-, mid- and high-dose groups, respectively). No increase in tumours of other organs including brain was observed, although four rats developed papillomatous proliferation of the epithelium of the forestomach in the high-exposure group.

It is of interest to note that whereas Gallagher *et al*. (1988) reported increased incidence of tumours of the Zymbal gland only at a dose level of 70 mg/kg-bw per day in Sprague-Dawley rats, Bio/Dynamics Inc. (1980a) reported increased incidence of astrocytoma of the brain, carcinoma of the Zymbal gland and papilloma/carcinoma of the stomach in the same strain of rats at 8 mg/kg-bw per day.

2.4.3.4.3 Gavage

Groups of 100 male and 100 female Sprague-Dawley (Spartan substrain) rats were exposed in another Bio/Dynamics Inc. (1980c) study to

[2] "The brain tumours were remarkably similar from animal to animal, regardless of their size or anatomical location within the brain. They were also similar to, and probably indistinguishable from, a subset of spontaneously occurring rat-brain tumours that have been generally classified as astrocytomas or anaplastic astrocytomas by light-microscopic evaluation of H&E-stained slides. Despite this superficial similarity to astrocytomas, we have found no hard evidence on which to identify any of the neoplastic cells as astrocytic in lineage or relatedness" (Bigner *et al*., 1986).

acrylonitrile in deionized water by intubation at 0, 0.1 or 10 mg/kg-bw per day for five days per week for 20 months. The non-neoplastic effects in the high-dose group included consistently higher mortality in both males and females and decreased body weights in males. Relative liver weight was increased in males at the high dose. The dose of 10 mg/kg-bw per day is proposed as a LOAEL, based upon decreased body weight and increased liver to body weight ratio in male rats. In both males and females at the high dose, there was an increased incidence of astrocytoma of the brain, squamous cell carcinoma of the Zymbal gland and papilloma/carcinoma of the stomach. In both sexes, squamous cell papilloma of the stomach was reported at the high dose as early as 12 months. At the 18-month sacrifice, squamous cell carcinoma of the stomach was reported in males at the high dose. Astrocytoma of the brain and carcinoma of the Zymbal gland were reported in high-dose females at the 18-month sacrifice.

Maltoni *et al*. (1977) exposed 40 Sprague-Dawley rats of each sex by gavage to acrylonitrile in olive oil at 0 or 5 mg/kg-bw per day, three days per week, for 52 weeks. In females, there was some evidence of increases in mammary gland carcinomas (7/75 and 4/40 in control and exposed groups, respectively) and forestomach epithelial tumours (0/75 and 4/40 in control and exposed groups, respectively) in females. However, a high spontaneous incidence of mammary gland tumours in this strain of rats, the single dose level and the short duration of exposure limit the adequacy of the study.

2.4.3.5 Genotoxicity

2.4.3.5.1 In vitro *studies*

In the *Salmonella* mammalian microsome assay, acrylonitrile has induced reverse mutations in strains TA1535 (Lijinsky and Andrews, 1980), TA1535 and TA100 (Zeiger and Haworth, 1985), but only when hamster or rat S9 was present. Weak positive results were also reported in several *Escherichia coli* strains in the absence of metabolic activation (Venitt *et al*., 1977).

In mammalian cells, acrylonitrile induced hprt mutations in human lymphoblasts without metabolic activation (Crespi *et al*., 1985), but not at the same locus in Chinese hamster V79 cells (Lee and Webner, 1985). In several studies, acrylonitrile was positive at the TK locus in mouse lymphoma L5178 TK+/– cells, either with or without rat S9 (Amacher and Turner, 1985; Lee and Webber, 1985; Myhr *et al*., 1985; Oberly *et al*., 1985), and in mouse lymphoma P388F cells with metabolic activation (Anderson and Cross, 1985). It was also mutagenic at the TK locus in human lymphoblasts with metabolic activation (Crespi *et al*., 1985; Recio and Skopek, 1988).

Acrylonitrile induced structural chromosomal aberrations either with or without metabolic activation in Chinese hamster ovary cells (Danford, 1985; Gulati *et al*., 1985; Natarajan *et al*., 1985) and without metabolic activation in Chinese hamster lung cells (Ishidate and Sofuni, 1985).

Acrylonitrile induced sister chromatid exchanges in Chinese hamster ovary cells with or without metabolic activation (Gulati *et al*., 1985) or only with metabolic activation (Brat and Williams, 1982; Natarajan *et al*., 1985). In human lymphocytes, results for sister chromatid exchanges were mixed, with one positive study with phenobarbital sodium-induced or 5,6-benzoflavone-induced rat liver (Perocco *et al*., 1982) and one negative study with Aroclor-induced rat liver (Obe *et al*., 1985). Sister chromatid exchanges were induced in human bronchial epithelial cells in the absence of S9 (Chang *et al*., 1990).

Results of *in vitro* assays for DNA single strand breaks and DNA repair (unscheduled DNA synthesis) were mixed but more commonly negative in a range of cell types from rats and humans, with and without activation. Cell transformation in mouse and hamster embryo cells has also been investigated, with mixed results.

Binding of 2-cyanoethylene oxide to nucleic acids has also been reported in *in vitro* studies at high concentrations (Hogy and Guengerich, 1986; Solomon and Segal, 1989; Solomon *et al*., 1993; Yates *et al*., 1993, 1994[3]). The formation of DNA adducts is increased substantially in the presence of metabolic activation. Under non-activating conditions involving incubation of calf thymus DNA with either acrylonitrile or 2-cyanoethylene oxide *in vitro*, 2-cyanoethylene oxide alkylates DNA much more readily than acrylonitrile (Guengerich *et al*., 1981; Solomon *et al*., 1984, 1993). Incubation of DNA with 2-cyanoethylene oxide yields 7-(2-oxoethyl)-guanine (Guengerich *et al*., 1981; Hogy and Guengerich, 1986; Solomon and Segal, 1989; Solomon *et al*., 1993; Yates *et al*., 1993, 1994) as well as other adducts. Compared with studies with rat liver microsomes, little or no DNA alkylation was observed with rat brain microsomes (Guengerich *et al*., 1981). DNA alkylation in human liver microsomes was much less than that observed with rat microsomes (Guengerich *et al*., 1981).

2.4.3.5.2 In vivo *studies*

Limitations of the few *in vivo* studies conducted in which the genotoxicity of acrylonitrile has been investigated preclude definitive conclusions.

Exposure to acrylonitrile in drinking water resulted in increased frequency of mutants at the hprt locus in splenic T-cells (Walker and Walker, 1997).[4] Female F344 rats were exposed to 0, 33, 100 or 500 ppm (0, 8, 21 or 76 mg/kg-bw per day; Health Canada, 1994) in drinking water for up to four weeks. Serial sacrifices were carried out throughout exposure and up to eight weeks post-exposure. At four weeks post-exposure, the average observed mutant frequency in splenic T-cells was increased in a dose-related manner (significant at the two highest doses).

Results of a range of assays for structural chromosomal aberrations, micronuclei in bone marrow and micronuclei in peripheral blood cells have been negative or inconclusive, although there was no indication in the published accounts of three of the four studies that the compound reached the target site. These include studies in Swiss (Rabello-Gay and Ahmed, 1980), NMRI (Leonard *et al*., 1981) and C57B1/6 (Sharief *et al*., 1986) mice and a collaborative study using multiple routes of exposure in mice and rats (Morita *et al*., 1997).

Results of dominant lethal assays were inconclusive in mice (Leonard *et al*., 1981) and negative in rats (Working *et al*., 1987).

In assays for unscheduled DNA synthesis in rats, results were positive only for the liver (Hogy and Guengerich, 1986), equivocal in lung, testes and gastric tissues (Ahmed *et al*., 1992a,b; Abdel-Rahman *et al*., 1994) and, notably, negative in the brain (Hogy and Guengerich, 1986). In these studies, however, unscheduled DNA synthesis was measured by liquid scintillation counting to determine ^{3}H-thymidine uptake in the cell population, which does not discriminate between cells undergoing repair and those that are replicating. Results for unscheduled DNA synthesis in rat liver and spermatocytes were negative when ^{3}H-thymidine uptake in individual cells was determined by autoradiography, which eliminates replicating cells from the analysis (Butterworth *et al*., 1992).

Urine from acrylonitrile-exposed rats and mice was also mutagenic in *Salmonella typhimurium* following intraperitoneal administration of acrylonitrile to rats and mice (Lambotte-Vandepaer *et al*., 1980, 1981). In both species, mutagenic activity occurred without activation. Mutagenic activity was also observed in urine of rats administered acrylonitrile by

[3] Yates *et al.* (1994) also reported single and double strand breaks in plasmid DNA incubated with 2-cyanoethylene oxide.

[4] Additional information was provided by the authors.

stomach intubation (Lambotte-Vandepaer *et al*., 1985). Thiocyanate, hydroxyethylmercapturic acid and cyanoethylmercapturic acid were not believed to be responsible for urinary mutagenicity.

In *in vivo* studies in F344 rats administered 50 mg acrylonitrile/kg-bw intraperitoneally, 7-(2-oxoethyl)-guanine adducts were detected in liver (Hogy and Guengerich, 1986). Incorporation of acrylonitrile into hepatic RNA was observed following intraperitoneal administration to rats (Peter *et al*., 1983). However, no DNA adducts were detected in the brain, which is the primary target for acrylonitrile-induced tumorigenesis, in this or a subsequent study in which F344 rats received 50 or 100 mg acrylonitrile/kg-bw by subcutaneous injection (Prokopczyk *et al*., 1988). In contrast, in three studies from one laboratory, exposure of SD rats to 46.5 mg [^{14}C]acrylonitrile/kg-bw (50 μCi/kg-bw) resulted in apparent binding of radioactivity to DNA from liver, stomach, brain (Farooqui and Ahmed, 1983), lung (Ahmed *et al*., 1992a) and testicles (Ahmed *et al*, 1992b). In each tissue, there was a rapid decrease in radioactivity of DNA samples collected up to 72 hours following treatment.

It is not clear why acrylonitrile–DNA binding was detected in the brain in these studies and not by Hogy and Guengerich (1986) or Prokopczyk *et al*. (1988). The DNA isolation protocols and method for correcting for contaminating protein in the DNA sample used by Hogy and Guengerich (1986) may have allowed a more stringent determination of DNA-bound material. Alternatively, the methods used to achieve greater DNA purity might have caused the loss of adducts or inhibited the recovery of adducted DNA; more likely, 7-(2-oxoethyl)-guanine and cyanoethyl adducts are of little consequence in the induction of acrylonitrile-induced brain tumours. Indeed, investigation of the role of cyanohydroxy-ethylguanine in the induction of these tumours seems warranted.

2.4.3.6 Reproductive and developmental toxicity

Consistent effects on the reproductive organs of male or female animals have not been observed in repeated-dose toxicity and carcinogenicity studies conducted to date. In a specialized investigation in CD-1 mice, however, degenerative changes in the seminiferous tubules and associated decreases in sperm counts were observed at 10 mg/kg-bw per day (NOEL, 1 mg/kg-bw per day) (Tandon *et al*., 1988). Although epididymal sperm motility was reduced in a 13-week study with B6C3F$_1$ mice, there was no dose–response and no effect upon sperm density at doses up to 12 mg/kg-bw per day by gavage, although histopathological results were not reported (Southern Research Institute, 1996). In a three-generation study in rats exposed via drinking water (14 or 70 mg/kg-bw per day), adverse effects on pup survival and viability and lactation indices were attributed to maternal toxicity (Litton Bionetics Inc., 1980).

In two studies by inhalation, developmental effects (fetotoxic and teratogenic) were not observed at concentrations that were not toxic to the mothers (Murray *et al*., 1978; Saillenfait *et al*., 1993a). In the investigation in which concentration–response was best characterized (four exposure concentrations and controls with two-fold spacing), the LOEL for maternal toxicity and for fetotoxicity was 55 mg/m^3; the NOEL was 26.4 mg/m^3 (Saillenfait *et al*., 1993a).

Similarly, in two studies by the oral route, developmental effects have not been observed at doses that were not also toxic to the mothers (lowest reported effect level in the mothers, 14 mg/kg-bw per day) (Murray *et al*., 1978; Litton Bionetics Inc., 1980). Reversible biochemical effects on the brain but not functional neurological effects were observed in offspring of rats exposed to 5 mg/kg-bw per day (a dose that did not impact on body weight of the dams); dose–response was not investigated in this study (Mehrotra *et al*., 1988).

Results of *in vitro* studies in rat embryos indicate that developmental effects may be due to monooxygenase-mediated liberation of cyanide (Saillenfait *et al*., 1992, 1993b).

2.4.3.7 Neurological effects and effects on the immune system

In recently published studies in rats exposed by inhalation to 25 ppm (55 mg/m^3) acrylonitrile and above for 24 weeks, there were partially reversible time- and concentration-dependent reductions in motor and sensory conduction (Gagnaire *et al*., 1998).

In the few identified investigations of the immunological effects of acrylonitrile, effects on the lung following inhalation (Bhooma *et al*., 1992) and on the gastrointestinal tract following ingestion (Hamada *et al*., 1998) have been observed at concentrations and doses at which histopathological effects have also been observed.

2.4.3.8 Toxicokinetics and mode of action

2.4.3.8.1 Toxicokinetics

Based on studies conducted primarily in laboratory animals, acrylonitrile is rapidly absorbed and distributed throughout examined tissues. However, there appears to be little potential for significant accumulation in any organ, with most of the compound being excreted primarily as metabolites in urine in the first 24–48 hours following administration.

Acrylonitrile is metabolized primarily by two pathways: conjugation with glutathione to form N-acetyl-S-(2-cyanoethyl)cysteine and oxidation by cytochrome P-450 to form remaining urinary metabolites. Oxidative metabolism of acrylonitrile leads to the formation of 2-cyanoethylene oxide, which is either conjugated with glutathione or directly hydrolysed by epoxide hydrolase.

Available data[5] are consistent with conjugation with glutathione being the major detoxification pathway of acrylonitrile, while the oxidation of acrylonitrile to 2-cyanoethylene oxide can be viewed as an activation pathway, producing a greater proportion of the total metabolites in mice than in rats. Available data also indicate that there are route-specific variations in metabolism. Based on studies in which 2-cyanoethylene oxide has been administered, there is no indication of preferential uptake or retention in specific organs, including the brain.

Liver microsomes from rats, mice and humans produced 2-cyanoethylene oxide at a greater rate than lung or brain microsomes, suggesting that the liver is the major site of 2-cyanoethylene oxide formation *in vivo* (Roberts *et al*., 1989; Kedderis and Batra, 1991). Studies in subcellular hepatic fractions indicate that there is an active epoxide hydrolase pathway for 2-cyanoethylene oxide in humans, which is inactive, although inducible, in rodents (Kedderis and Batra, 1993). Studies with inhibitory antibodies in human hepatic microsomes indicate that the 2E1 isoform of cytochrome P-450 is primarily involved in acrylonitrile epoxidation (Guengerich *et al*., 1991; Kedderis *et al*., 1993).

A physiologically based pharmacokinetic model has been developed and verified for the rat (Gargas *et al*., 1995; Kedderis *et al*., 1996), and work is under way to scale it to humans. In a recent, although incompletely reported, study, Kedderis (1997) estimated *in vivo* activity of epoxide hydrolase in humans based on the ratio of epoxide hydrolase to P-450 activity in subcellular hepatic fractions multiplied by the P-450 activity *in vivo*. Human blood to air coefficients for acrylonitrile and 2-cyanoethylene oxide have also been recently determined, although incompletely reported at present (Kedderis and Held, 1998). Research is in progress to determine partition coefficients for other human tissues.

[5] Including results of short-term toxicity studies in which the oxidative pathway has been induced prior to administration with acrylonitrile or antioxidants have been administered concomitantly with acrylonitrile.

2.4.3.8.2 Mode of action

Data on the genotoxicity of acrylonitrile are addressed in Section 2.4.3.5.

There are some suggestions from *in vitro* studies reported as abstracts that free radicals ($\cdot OH$, H_2O_2, $O_2\cdot$) may be directly implicated in the oxidation of acrylonitrile and DNA damage. Formation of free radicals may be partially related to the release of cyanide or other mechanisms responsible for cellular and DNA damage (Ahmed and Nouraldeen, 1996; Ahmed *et al*., 1996; El-zahaby *et al*., 1996; Mohamadin *et al*., 1996).

In more recent investigations, the results of which have been presented incompletely at this time, Prow *et al*. (1997) reported that acrylonitrile inhibited gap junctional intercellular communication in a rat astrocyte cell line in a dose-dependent manner, possibly through an oxidative stress mechanism. Similarly, Zhang *et al*. (1998) assayed acrylonitrile with Syrian hamster embryo cells, with and without an antioxidant, and concluded that oxidative stress contributed to morphological transformation in the cells. Jiang *et al*. (1998) assayed acrylonitrile with a rat astrocyte cell line and reported oxidative damage (indicated by the presence of 8-hydroxy-2'-deoxyguanosine) at all concentrations tested.

Jiang *et al*. (1997) exposed male Sprague-Dawley rats to 0 or 100 ppm acrylonitrile in drinking water for two weeks. Endpoints examined were levels of glutathione and reactive oxygen species in brain and liver, presence of 8-hydroxy-2'-deoxyguanosine (indicative of oxidative DNA damage) in several tissues and determination of activation of NF-$_\kappa$B (a transcription factor strongly associated with oxidative stress). Glutathione in brain was decreased. (Whysner *et al*. [1998a] reported no effects upon concentrations of glutathione in the brain of male Sprague-Dawley rats exposed to 3, 30 or 300 ppm acrylonitrile in drinking water for three weeks.) In addition, reactive oxygen species were increased four-fold, levels of 8-hydroxy-2'-deoxyguanosine were increased three-fold and activation of NF-$_\kappa$B was observed in the brain.

In recently published studies, levels of 8-oxodeoxyguanosine, cytochrome oxidase, glutathione and cyst(e)ine in the brain of rats exposed to acrylonitrile in drinking water in each of the three following protocols have been examined (Whysner *et al*., 1997, 1998a):

(a) In male Sprague-Dawley rats exposed for 21 days to 0, 3, 30 or 300 ppm (0, 0.42, 4.2 and 42 mg/kg-bw per day; Health Canada, 1994), there was a significant increase in 8-oxodeoxyguanosine in brain nuclear DNA at the two highest doses. Assays of brain for glutathione, cytochrome oxidase, catalase and glutathione peroxidase did not show differences between exposed and control groups. There was a higher concentration of cyst(e)ine at the highest dose. In the liver, nuclear DNA 8-oxodeoxyguanosine concentrations were significantly increased at the two highest doses. Although there was no significant change in hepatic glutathione or cyst(e)ine, there was a significant trend for increased hepatic cyst(e)ine. In the forestomach, glutathione and cyst(e)ine were significantly increased at the highest dose. In a bioassay with comparable dose levels, the incidence of brain and/or spinal cord tumours was significantly increased in male Sprague-Dawley rats exposed to 35 ppm (3.4 mg/kg-bw per day) acrylonitrile and higher for two years (Quast *et al*., 1980a).

(b) In male F344 rats exposed for 21 days to 0, 1, 3, 10, 30 or 100 ppm (0, 0.14, 0.42, 1.4, 4.2 or 14 mg/kg-bw per day; Health Canada, 1994), analyses were limited to the brain. There were no significant differences between groups for 8-oxodeoxyguanosine, cytochrome oxidase, glutathione or cyst(e)ine.

(c) In male Sprague-Dawley rats exposed for up to 94 days to 0 or 100 ppm (0 or 14 mg/kg-bw per day; Health Canada, 1994),

concentrations of 8-oxodeoxyguanosine in the brain were significantly increased after three, 10 and 94 days of exposure. There were no effects upon glutathione or cytochrome oxidase. In liver, the concentration of 8-oxodeoxyguanosine was significantly increased at 10 days only. In the two-year drinking water bioassay with male Sprague-Dawley rats (Quast *et al*., 1980a), the incidence of brain and/or spinal cord tumours was significantly increased at 100 ppm (8.5 mg/kg-bw per day).

The endpoint for which changes were consistently observed in male Sprague-Dawley rats was the induction of oxidative DNA damage, including the accumulation of 8-oxodeoxy-guanosine in the brain. The authors drew correlations between these results and the incidence of brain/spinal cord tumours that had been reported in carcinogenicity bioassays in which male Sprague-Dawley rats were exposed to acrylonitrile via drinking water.

Increased levels of 8-oxodeoxyguanosine occur only in the anterior portion of the brain, which contains rapidly dividing glial cells (Whysner *et al*., 1998b).

2.4.4 Humans

In case reports of acute intoxication, effects on the central nervous system characteristic of cyanide poisoning and effects on the liver, manifested as increased enzyme levels in the blood, have been observed. There have also been reports that acrylonitrile is a skin irritant and sensitizer, the latter based on patch testing of workers.

In the few studies in which non-neoplastic effects of acrylonitrile have been investigated, only acute irritation has been reported consistently. In a cross-sectional investigation of workers exposed in acrylic fibre factories to approximately 1 ppm (2.2 mg/m^3), there was no consistent evidence of adverse effects based on examination of a wide range of clinical parameters, including liver function tests (Muto *et al*., 1992). However, there was an increase in subjective symptoms of acute irritation, consistent with observations in another cohort of acrylic fibre manufacturing workers (Kaneko and Omae, 1992).

In a cross-sectional investigation of a smaller group of workers producing acrylic textile fibres for which quantitative data on exposure were not reported, there was no evidence of induction of hepatic cytochrome P-450 or genotoxicity of urine (Borba *et al*., 1996).

Although there was some evidence in primarily early limited studies of excesses of lung cancer (Thiess *et al*., 1980), "all tumours" (Zhou and Wang, 1991) and colorectal cancer (Mastrangelo *et al*., 1993), such excesses have not been confirmed in well-conducted and well-reported recent investigations in four relatively large cohorts of workers (Benn and Osborne, 1998; Blair *et al*., 1998; Swaen *et al*., 1998; Wood *et al*., 1998). Indeed, there is no consistent, convincing evidence of an association between exposure to acrylonitrile and cancer of a particular site that fulfils, even in part, traditional criteria for causality in epidemiological studies.

The largest of the recent cohort studies was that conducted by Blair *et al*. (1998), which included 25 460 workers from eight plants producing and using acrylonitrile. Although an excess of lung cancer was observed in the highest quintile of cumulative exposure, analysis of exposure–response did not provide strong or consistent evidence of a causal relationship. The exposure categories were:

0.01–0.13 ppm-years:	121 430 person-years
0.14–0.57 ppm-years:	69 122 person-years
0.58–1.50 ppm-years:	49 800 person-years
1.51–8.00 ppm-years:	63 483 person-years
>8.00 ppm-years:	44 807 person-years

It should be noted that the power to detect moderate excesses was small for some sites (stomach, brain, breast, prostate, lymphatic/hematopoietic) because of small numbers of deaths.

3.0 ASSESSMENT OF "TOXIC" UNDER CEPA 1999

3.1 CEPA 1999 64(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Analysis of exposure pathways and subsequent identification of sensitive receptors are used to select environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community). For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor. A hyperconservative or conservative quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Assessment endpoints

Acrylonitrile enters the Canadian environment from anthropogenic sources, primarily from industrial on-site releases. Almost all releases in the environment are to air, with small amounts released to water.

Based on its physical-chemical properties, acrylonitrile undergoes various degradation processes in air, with very small amounts transferring to water. When released into water, it is expected to remain primarily in water, where it undergoes biodegradation after an acclimation period. Acrylonitrile does not bioaccumulate in organisms.

Based on the sources and fate of acrylonitrile in the environment, biota are expected to be exposed to acrylonitrile primarily in air and to a much lesser extent in water. Little exposure to soil or benthic organisms is expected. Therefore, the focus of the environmental risk characterization will be on terrestrial and aquatic organisms exposed directly to ambient acrylonitrile in air and water.

3.1.1.1 Terrestrial organisms

Terrestrial toxicity data are available for invertebrates (particularly grain insect pests) (Section 2.4.1.1) as well as from mammalian toxicology (Section 2.4.3). Identified sensitive endpoints via fumigation or inhalation routes of exposure include mortality of insect eggs (Adu and Muthu, 1985), decreased number of insect offspring (Rajendran and Muthu, 1981a), maternal and fetal toxicity in rats (Saillenfait *et al*., 1993a) and histopathological changes in the nasal turbinates in rats (Quast *et al*., 1980b). The single most sensitive response for these endpoints will be used as the CTV for the risk characterization for terrestrial effects.

3.1.1.2 Aquatic organisms

Aquatic toxicity data are available for a variety of plants, invertebrates, fish and amphibians (Section 2.4.1.2). Identified sensitive endpoints include growth inhibition in aquatic plants (Zhang *et al*., 1996), mortality in pond snails (Erben and Beader, 1983), mortality and reduced growth in fish (Henderson *et al*., 1961; ABCL, 1980a) and reduction in growth of frogs (Zhang *et al*., 1996).

The single most sensitive response for all these endpoints will be used as the CTV for the risk characterization for aquatic effects.

3.1.2 Environmental risk characterization

3.1.2.1 Terrestrial organisms

Environmental exposure to acrylonitrile in air is expected to be greatest near industrial point sources. Levels of acrylonitrile in ambient air in Canada are generally below detection. The highest concentration of acrylonitrile in outdoor air in a half-hour period in Canada is predicted to be 9.3 µg/m^3 (Michelin, 1999) at an 11-m distance from an industrial stack. The value 9.3 µg/m^3 will be used as the EEV in the hyperconservative analysis for terrestrial organisms.

For the exposure of terrestrial organisms to acrylonitrile in air, the CTV is the LOEL of 55 mg/m^3 causing decreased maternal weight and fetal toxicity in rats exposed for nine days during gestation (Saillenfait *et al*., 1993a). This LOEL was the most sensitive effect identified from a data set composed of acute and chronic toxicity studies conducted on 14 species of insects and mammals. Saillenfait *et al*. (1993a) reported that none of these effects were observed at 26.4 mg/m^3. For the hyperconservative analysis, the ENEV is derived by dividing the CTV by a factor of 100. This factor accounts for the extrapolation from laboratory to field conditions, conversion of the LOEL to a long-term no-effects value, interspecies and intraspecies variations in sensitivity and the moderate dataset. As a result, the ENEV is 0.55 mg/m^3 (550 µg/m^3).

The hyperconservative quotient is calculated by dividing the EEV of 9.3 µg/m^3 by the ENEV as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{9.3\ \mu g/m^3}{550\ \mu g/m^3}$$

$$= 0.02$$

Since the hyperconservative quotient is less than one, it is unlikely that acrylonitrile causes adverse effects on populations of terrestrial organisms in Canada.

Table 8 summarizes the risk quotients for the environmental media of concern.

3.1.2.2 Aquatic organisms

Environmental exposure to acrylonitrile is expected to be greatest near point sources. In general, releases to water are low (0.529 tonnes, or 2.7% of all releases). All known releases of acrylonitrile to water in Canada occur to freshwater environments.

TABLE 8 Risk characterization summary for environmental effects of acrylonitrile

Environmental compartment	EEV	CTV	Application factor (AF)	ENEV (CTV/AF)	Risk quotient (EEV/ENEV)
Air	9.3 µg/m^3 outside plant gate at Sarnia, Ontario, 1998 (estimated value)	55 mg/m^3 (25 ppm), decreased maternal rat body weight gain and decreased absolute body weight after nine-day inhalation exposure	100	0.55 mg/m^3 (550 µg/m^3)	0.02
Water — freshwater pelagic	<0.0042 mg/L (detection limit for ambient water)	0.40 mg/L retarded foreleg development in early life stage of frog, *Bufo bufo gargarizans*, after 28-day exposure	10	0.04 mg/L	<0.1

In general, levels of acrylonitrile in ambient surface water and groundwater are low. A large study of Canadian municipal water supplies conducted in 1987 detected no acrylonitrile in 84 samples at nine municipalities around the Great Lakes at the detection limit of 0.005 mg/L. Similarly, the level of acrylonitrile in 207 samples of intake water taken in 1989–90 at 26 Ontario organic chemical manufacturing plants was below the detection limit of 0.0042 mg/L.

Measurable levels of acrylonitrile were found in industrial effluents discharged to the environment in 1989–90. In 1997, however, only two companies in Ontario and one in Quebec used acrylonitrile in manufacturing. There have been significant changes to the effluent treatment process in these remaining facilities, such that levels in effluent are very low, below the recommended method detection limit of 0.0042 mg/L. Therefore, the value 0.0042 mg/L will be used as the EEV in the hyperconservative analysis for aquatic organisms.

For exposure of aquatic biota to acrylonitrile in water, the CTV is 0.4 mg/L, based on the lower chronic level around the EC_{50} of foreleg development after a 28-day exposure in the frog, *Bufo bufo gargarizans* (Zhange *et al*., 1996). This was the most sensitive value identified from the primary and secondary data composed of acute and chronic studies conducted on 16 species of aquatic invertebrates, plants, fish and amphibians.

For a hyperconservative analysis, the ENEV is derived by dividing this CTV by a factor of 10. This factor accounts for extrapolation from field to laboratory conditions and interspecies and intraspecies variations in sensitivity. The resulting ENEV is 0.04 mg/L.

The hyperconservative quotient is calculated by dividing the EEV of 0.0042 mg/L by the ENEV as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{0.0042 \text{ mg/L}}{0.04 \text{ mg/L}}$$

$$= 0.1$$

Since the hyperconservative quotient is less than one, it is unlikely that acrylonitrile causes adverse effects on populations of aquatic organisms in Canada.

3.1.2.3 Discussion of uncertainty

There are a number of potential sources of uncertainty in this environmental risk assessment. Regarding environmental exposure, there could be concentrations of acrylonitrile in Canada that are higher than those identified and used in this assessment. While no data or limited data were found for Canadian soils and sediments, significant concentrations of acrylonitrile are not expected because of the unlikely partitioning of acrylonitrile to these compartments from air. Levels of acrylonitrile in ambient air and water are not widely monitored in Canada. Concentrations of acrylonitrile in water have been measured in connection with point sources. Improvements to industrial effluent treatment systems over the last decade to take advantage of the biodegradability of acrylonitrile by acclimatized microorganisms appear to have resulted in acrylonitrile levels being below detection. Few data were available on acrylonitrile concentrations in air near industrial point sources, and these data indicate that in rare occasions, for small time periods, acrylonitrile is discharged from some stacks. The largest of these gave a “theoretical” point of impingement concentration of 9.3 µg/m^3 and was associated with a total annual discharge of 31 g of acrylonitrile. No acrylonitrile was detected off the industrial site property. However, the few measured data support the predicted concentrations in air, which are used to determine point of impingement concentrations for site registration permits.

Regarding effects of acrylonitrile on terrestrial and aquatic organisms, uncertainty inevitably surrounds the extrapolation from available toxicity data to potential ecosystem effects. Somewhat surprisingly, the data set lacks information on the toxicity of acrylonitrile in air to plant species. Studies of acrylonitrile in air have focussed on the effects via inhalation and fumigation on laboratory mammals (particularly rats) and pest insect species. There has been considerable examination of a wide range of effects in rats. It is not known to what extent the physiological effects observed in the rat are representative of long-term ecological effects. Regarding effects of acrylonitrile on aquatic organisms, the data set includes studies on organisms from a variety of ecological niches and taxa for both the short and long term. To counter these uncertainties, appropriate application factors were used in the environmental risk analysis to derive ENEVs.

Despite some data gaps regarding the environmental effects and exposure of acrylonitrile, the data available at this time are considered adequate for making a conclusion on the environmental risk of acrylonitrile in Canada.

3.2 CEPA 1999 64(b): Environment on which life depends

Once released into the atmosphere, reaction of acrylonitrile with hydroxyl radicals is the primary removal mechanism and yields formaldehyde, formic acid and formyl cyanide. Worst-case calculations were made to determine whether acrylonitrile has the potential to contribute to (ground-level) photochemical ozone formation, depletion of stratospheric ozone or climate change (Bunce, 1996).

Because of its reactivity in the atmosphere, acrylonitrile's potential contribution to photochemical ozone creation (and also smog) is moderate; however, quantities available for reaction (18.75 tonnes in Canada in 1996) make the contribution low relative to those of other smog-forming substances. Reaction with ozone and nitrate are negligible, and the absence of chlorine and bromine atoms in the molecule means that the potential contributions to stratospheric ozone depletion (ODP = 0) and climate change (GWP = 4.3×10^{-4}) are both negligible (Bunce, 1996).

It is therefore concluded that acrylonitrile is not "toxic" in the abiotic atmosphere as defined in Section 64(b) of CEPA 1999.

3.3 CEPA 1999 64(c): Human health

3.3.1 Estimated population exposure

Data on levels of acrylonitrile in environmental media in Canada to serve as a basis for development of estimates of population exposure are restricted to an almost complete lack of detection in limited surveys of outdoor and indoor air, similar lack of detection in a more extensive survey of drinking water and an early report of levels in a limited number of foodstuffs packaged in acrylonitrile-based plastic containers. Point estimates of average daily intake (per kilogram body weight), based on these few data (Section 2.3.2) and reference values for body weight, inhalation volume and amounts of food and drinking water consumed daily, are presented for six age groups in Table 9. These estimates, which should be considered to be bounding only, as a result of the limitations of the data on which they are based, range from 0.01 to 0.65 µg/kg-bw per day.

Although it is uncertain, based on this limited information, indoor air is likely the principal medium of exposure to acrylonitrile, followed by ambient air. Intakes from food and drinking water are likely to be negligible in comparison. This is consistent with the physical/chemical properties of acrylonitrile, which has moderate vapour pressure and a low log K_{ow}, and the results of fugacity modelling (Section 2.3.1.5). Indeed, that air is likely the principal medium of exposure has been confirmed

TABLE 9 Estimated daily intake of acrylonitrile by the population of Canada

Route of exposure	Estimated intake (µg/kg-bw per day) of acrylonitrile by various age groups						
	0–6 months[1]		6 months–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	formula fed[2]	not formula fed[3]					
Ambient air[9]	<0.01–0.07	<0.01–0.07	<0.01–0.14	<0.01–0.11	<0.01–0.06	<0.01–0.05	<0.01–0.05
Indoor air[10]	<0.01–0.22	<0.01–0.22	<0.01–0.47	<0.01–0.37	<0.01–0.21	<0.01–0.18	<0.01–0.16
Drinking water[11]	0.05–0.07	0.01–0.02	0.01	0.01	<0.01	<0.01	<0.01
Food[12]		<0.01	0.01–0.03	0.01–0.02	0.01–0.02	<0.01–0.01	<0.01–0.01
Soil[13]							
Total intake	**0.05–0.36**	**0.01–0.31**	**0.02–0.65**	**0.02–0.51**	**0.01–0.29**	**<0.01–0.24**	**<0.01–0.22**

[1] Assumed to weigh 7.6 kg and breathe 2.1 m^3/day (EHD, 1997).

[2] Assumed to ingest 0.8 L/day (reconstituted formula) (EHD, 1997). For formula-fed infants, intake from water is synonymous with intake from food.

[3] Assumed to ingest 0.2 L water per day and to consume on a daily basis 0.01 g natural cheese, 0.10 g margarine, 0.91 g butter, 0.073 g peanut butter and 0.24 g chocolate bar (EHD, 1997).

[4] Assumed to weigh 15.6 kg, breathe 9.3 m^3/day, ingest 0.2 L water per day and consume on a daily basis 2.59 g natural cheese, 5.69 g cold cuts, 0.94 g canned luncheon meat, 0.24 g ham luncheon meat, 2.66 g margarine, 7.32 g butter, 2.57 g peanut butter and 3.18 g chocolate bar (EHD, 1997).

[5] Assumed to weigh 31.2 kg, breathe 14.5 m^3/day, ingest 0.4 L water per day and consume on a daily basis 3.18 g natural cheese, 7.57 g cold cuts, 0.97 g canned luncheon meat, 0.24 g ham luncheon meat, 6.10 g margarine, 12.93 g butter, 4.99 g peanut butter and 5.45 g chocolate bar (EHD, 1997).

[6] Assumed to weigh 59.7 kg, breathe 15.8 m^3/day, ingest 0.4 L water per day and consume on a daily basis 5.68 g natural cheese, 9.61 g cold cuts, 2.22 g canned luncheon meat, 1.33 g ham luncheon meat, 8.25 g margarine, 16.35 g butter, 4.84 g peanut butter and 8.07 g chocolate bar (EHD, 1997).

[7] Assumed to weigh 70.7 kg, breathe 16.2 m^3/day, ingest 0.4 L water per day and consume on a daily basis 8.83 g natural cheese, 9.63 g cold cuts, 2.39 g canned luncheon meat, 0.38 g ham luncheon meat, 5.11 g margarine, 15.19 g butter, 1.55 g peanut butter and 4.31 g chocolate bar (EHD, 1997).

[8] Assumed to weigh 70.6 kg, breathe 14.3 m^3/day, ingest 0.4 L water per day and consume on a daily basis 7.17 g natural cheese, 6.26 g cold cuts, 1.70 g canned luncheon meat, 0.39 g ham luncheon meat, 8.10 g margarine, 10.18 g butter, 1.20 g peanut butter and 1.92 g chocolate bar (EHD, 1997).

[9] In monitoring of ambient air at six urban stations in Ontario in 1990, concentrations of acrylonitrile were below the limit of detection (0.0003 µg/m^3) in 10 of 11 samples. The maximum and only detectable concentration was 1.9 µg/m^3 in one sample (OMOE, 1992a,b). Canadians are assumed to spend three of 24 hours outdoors (EHD, 1997). The limit of detection (0.0003 µg/m^3) and the highest reported concentration (1.9 µg/m^3) were used to calculate the range of exposures in ambient air.

[10] Acrylonitrile was not detected (limit of detection 0.9 µg/m^3) in limited monitoring of indoor air in Toronto in 1990 (Bell *et al*., 1991). Canadians are assumed to spend 21 of 24 hours indoors (EHD, 1997). Concentrations of 0 and 0.9 µg/m^3 (limit of detection) were used to calculate the range of exposures from indoor air.

[11] The range of exposure from drinking water is calculated from the lowest limit of detection (0.5 µg/L, for minimum estimate) and the highest concentration reported, 0.7 µg/L (Environment Canada, 1989a).

[12] Page and Charbonneau (1983) measured concentrations of acrylonitrile in five types of food packaged in acrylonitrile-based plastic containers, purchased from several stores in Ottawa, Ontario. Average concentrations of acrylonitrile (measured in three duplicate samples of each food type) ranged from 8.4 to 38.1 ng/g:

8.4–31.0 ng/g in honey butter (natural or cinnamon)
23.8–31.5 ng/g in cold pack cheese
<10–38.1 ng/g in peanut butter
<2.5 ng/g in soft butter and creamed coconut

Concentrations in other foods were assumed to be zero.

[13] Concentrations of acrylonitrile in soil in Canada were not identified.

TABLE 10 Estimated relative daily intake of acrylonitrile by the population of Canada based upon the results of fugacity modelling

Route of exposure	Estimated relative intake of acrylonitrile (%)						
	0–6 months[1]		6 months–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	formula fed[2]	not formula fed[3]					
Ambient air[9]	12	12	12	12	12	12	12
Indoor air[9]	84	84	87	86	88	86	86
Drinking water[9]	3	0.01	0.2	0.2	0.2	0.2	0.2
Food[10]		4	2	1	1	1	1
Soil[9]							

[1] Assumed to weigh 7.6 kg, breathe 2.1 m^3/day and ingest 30 mg soil per day (EHD, 1997).
[2] For formula-fed infants, intake from water is synonymous with intake from food.
[3] Assumed to consume 1010 g food/day (EHD, 1997).
[4] Assumed to weigh 15.6 kg, breathe 9.3 m^3/day, ingest 0.2 L water per day, ingest 100 mg soil per day and consume 1413 g food/day (EHD, 1997).
[5] Assumed to weigh 31.2 kg, breathe 14.5 m^3/day, ingest 0.4 L water per day, ingest 65 mg soil per day and consume 1834 g food/day (EHD, 1997).
[6] Assumed to weigh 59.7 kg, breathe 15.8 m^3/day, ingest 0.4 L water per day, ingest 30 mg soil per day and consume 2074 g food/day (EHD, 1997).
[7] Assumed to weigh 70.7 kg, breathe 16.2 m^3/day, ingest 0.4 L water per day, ingest 30 mg soil per day and consume 2353 g food/day (EHD, 1997).
[8] Assumed to weigh 70.6 kg, breathe 14.3 m^3/day, ingest 0.4 L water per day, ingest 30 mg soil per day and consume 1969 g food/day (EHD, 1997).
[9] The results of the ChemCAN3 model (Section 2.3.1.5) indicate that when all Canadian releases are assumed to occur in southern Ontario, release over the long term may result in very low levels across the region. The predicted levels are:
air: 2.1×10^{-4} µg/m^3
water: 1.6×10^{-8} mg/L
soil: 2.0×10^{-8} µg/g; calculated intakes from soil were negligible.
[10] The concentration of acrylonitrile in foods was assumed to be the same as that in soil.

by point estimates of average daily intake based on concentrations of acrylonitrile predicted in various media by fugacity modelling and reference values for body weight, inhalation volume and amounts of food and drinking water consumed daily for six age groups (Table 10). On this basis, intake from ambient and indoor air ranges from 96% to 100% of total intake.

Exposures from ambient air may be substantially higher for populations in the vicinity of point sources. Based upon the limit of detection in sampling at the site of nitrile-butadiene rubber production in Sarnia, Ontario, the maximum concentration would be <52.9 µg/m^3. Assuming the same reference values and intake in other media as for the general population, worst-case upper-bound estimates of exposure in the vicinity of industrial sources range from 10.7 to 31.6 µg/kg-bw per day (Table 11). The only other (earlier) data on concentrations in the vicinity of point sources indicate that populations in the area might be exposed to levels considerably less than these (in the range of tenths of µg/m^3) (Ng and Karellas, 1994; Ortech Corporation, 1994). Additional data from the United States indicate that levels vary considerably in the vicinity of various point sources.[6]

[6] Table 6.3.3 in the supporting documentation (Health Canada, 1999).

TABLE 11 Estimated daily intake of acrylonitrile by the population of Canada: worst-case upper-bound estimates

Route of exposure	Estimated intake (µg/kg-bw per day) of acrylonitrile by various age groups						
	0–6 months[1]		6 months–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	formula fed[2]	not formula fed[3]					
Ambient air[9]	1.83	1.83	3.94	3.07	1.75	1.52	1.34
Indoor air[10]	12.79	12.79	27.59	21.51	12.25	10.61	9.38
Drinking water[11]	0.07	0.02	0.01	0.01	0	0	0
Food[12]		0	0.03	0.02	0.02	0.01	0.01
Soil[13]							
Total intake[14]	**14.69**	**14.64**	**31.57**	**24.61**	**14.02**	**12.14**	**10.73**

[1] Assumed to weigh 7.6 kg and breathe 2.1 m^3/day (EHD, 1997).

[2] For formula-fed infants, intake from water is synonymous with intake from food. Assumed to ingest 0.8 L/day (reconstituted formula) (EHD, 1997).

[3] Assumed to ingest 0.2 L water per day and to consume on a daily basis 0.01 g natural cheese, 0.10 g margarine, 0.91 g butter, 0.073 g peanut butter and 0.24 g chocolate bar (EHD, 1997).

[4] Assumed to weigh 15.6 kg, breathe 9.3 m^3/day, ingest 0.2 L water per day and consume on a daily basis 2.59 g natural cheese, 5.69 g cold cuts, 0.94 g canned luncheon meat, 0.24 g ham luncheon meat, 2.66 g margarine, 7.32 g butter, 2.57 g peanut butter and 3.18 g chocolate bar (EHD, 1997).

[5] Assumed to weigh 31.2 kg, breathe 14.5 m^3/day, ingest 0.4 L water per day and consume on a daily basis 3.18 g natural cheese, 7.57 g cold cuts, 0.97 g canned luncheon meat, 0.24 g ham luncheon meat, 6.10 g margarine, 12.93 g butter, 4.99 g peanut butter and 5.45 g chocolate bar (EHD, 1997).

[6] Assumed to weigh 59.7 kg, breathe 15.8 m^3/day, ingest 0.4 L water per day and consume on a daily basis 5.68 g natural cheese, 9.61 g cold cuts, 2.22 g canned luncheon meat, 1.33 g ham luncheon meat, 8.25 g margarine, 16.35 g butter, 4.84 g peanut butter and 8.07 g chocolate bar (EHD, 1997).

[7] Assumed to weigh 70.7 kg, breathe 16.2 m^3/day, ingest 0.4 L water per day and consume on a daily basis 8.83 g natural cheese, 9.63 g cold cuts, 2.39 g canned luncheon meat, 0.38 g ham luncheon meat, 5.11 g margarine, 15.19 g butter, 1.55 g peanut butter and 4.31 g chocolate bar (EHD, 1997).

[8] Assumed to weigh 70.6 kg, breathe 14.3 m^3/day, ingest 0.4 L water per day and consume on a daily basis 7.17 g natural cheese, 6.26 g cold cuts, 1.70 g canned luncheon meat, 0.39 g ham luncheon meat, 8.10 g margarine, 10.18 g butter, 1.20 g peanut butter and 1.92 g chocolate bar (EHD, 1997).

[9] The concentration of acrylonitrile in ambient air is assumed to be 52.9 µg/m^3, based upon sampling at the site of nitrile-butadiene rubber production in Sarnia, Ontario (Wright, 1998).

[10] The concentration in indoor air is predicted to be the same as in ambient air (above).

[11] The range of exposure in drinking water is calculated from the lowest limit of detection (0.5 µg/L, for minimum estimate) and the highest concentration reported, 0.7 µg/L (Environment Canada, 1989a).

[12] Page and Charbonneau (1983) measured concentrations of acrylonitrile in five types of food packaged in acrylonitrile-based plastic containers, purchased from several stores in Ottawa, Ontario. Average concentrations of acrylonitrile (measured in three duplicate samples of each food type) ranged from 8.4 to 38.1 ng/g:

8.4–31.0 ng/g in honey butter (natural or cinnamon)
23.8–31.5 ng/g in cold pack cheese
<10–38.1 ng/g in peanut butter
<2.5 ng/g in soft butter and creamed coconut

Concentrations in other foods were assumed to be zero.

[13] Concentrations of acrylonitrile in soil were not identified.

[14] Medium-specific and total intakes were calculated on Microsoft Excel spreadsheet.

Limitations of the data preclude development of meaningful probabilistic estimates of exposure to acrylonitrile in the general population.

3.3.2 Hazard characterization

3.3.2.1 Effects in humans

In case reports of acute intoxication, effects on the central nervous system characteristic of cyanide poisoning and effects on the liver, manifested as increased enzyme levels in the blood, have been observed. There have also been reports that acrylonitrile is a skin irritant and sensitizer, the latter based on patch testing of workers.

In the few studies in which non-neoplastic effects of acrylonitrile have been investigated, only acute irritation has been reported consistently.

Although the database is relatively extensive, there is no consistent, convincing evidence of an association between exposure to acrylonitrile and cancer of a particular site that fulfils traditional criteria for causality in epidemiological studies.

3.3.2.2 Effects in experimental animals

The acute toxicity of acrylonitrile is relatively high. Signs of acute toxicity include respiratory tract irritation and two phases of neurotoxicity, the first characterized by signs consistent with cholinergic overstimulation and the second being central nervous system dysfunction, resembling cyanide poisoning. Superficial necrosis of the liver and hemorrhagic gastritis of the forestomach have also been observed following acute exposure.

Data on the non-neoplastic effects of acrylonitrile following repeated exposure are restricted to primarily early, limited studies, most often unpublished carcinogenesis bioassays, a few more recent investigations of specialized endpoints or more recent studies for which full accounts are not yet available.

In available short-term inhalation studies with single dose levels and a limited range of examined endpoints, effects on biochemical parameters, clinical signs and body weight were observed following exposure of rats, although there were no histopathological effects on principal organs.

In short-term studies by the oral route, biochemical effects on the liver and hyperplasia of the gastric mucosa have been observed, with effects on the gastric mucosa occurring at lowest doses in all studies in which they were examined. Effects on the adrenal cortex observed in short-term repeated-dose toxicity studies from one laboratory have not generally been noted in longer-term investigations in animals exposed to higher concentrations. In a preliminary report of a recent subchronic study in mice, decreases in survival and body weight and hematological effects were noted, although data presented therein were inadequate for characterization of dose–response.

In early carcinogenesis bioassays in rats for which few published accounts are available, non-neoplastic effects included reductions in body weight gain, hematological effects, increases in liver and kidney weights and, at higher doses, increased mortality. Following inhalation, inflammatory changes in the nasal turbinates were also observed.

There is considerable evidence of the carcinogenicity of acrylonitrile, based on the results of primarily early unpublished investigations, which have been restricted to one species (rats).[7] In the most sensitive bioassays, a range of tumours (both benign and malignant) has

[7] A carcinogenesis study in mice exposed to acrylonitrile by gavage is under way (NTP, 1998).

been consistently observed following both ingestion and inhalation, including those of the central nervous system (brain and/or spinal cord), ear canal, gastrointestinal tract and mammary glands. In almost all adequate bioassays, there have been reported increases in astrocytomas of the brain and spinal cord, which are rarely observed spontaneously in experimental animals; these have occurred at highest incidence consistently across studies. Increases have been statistically significant, and there have been clear dose–response trends. Tumours have sometimes been reported at non-toxic doses or concentrations and at periods as early as 7–12 months following onset of exposure. Tumours have also been observed in exposed offspring of a multi-generation reproductive study at 45 weeks.

In numerous studies on the genotoxicity of acrylonitrile involving examination of a broad spectrum of endpoints both *in vitro*, with and without metabolic activation, and *in vivo* in mice and rats, the pattern of results has been quite mixed, including in *in vitro* assays where there were adequate precautions to control volatilization. Although the results of many of these studies were negative, there was also a substantial number of positive results for a variety of endpoints that cannot be discounted. While acrylonitrile was weakly positive in bacterial assays, the database on mutagenicity in mammalian cells *in vitro* is considered inadequate because of limitations of the studies. Limitations of the *in vivo* investigations also preclude definite conclusions concerning genotoxic potential.

Results of the few identified investigations in which the relative potency of acrylonitrile was compared with that of 2-cyanoethylene oxide are consistent with the oxidative pathway of metabolism being critical in genotoxicity. In an assay with two strains of *S. typhimurium*, 2-cyanoethylene oxide was mutagenic without activation, whereas acrylonitrile required activation (Cerna *et al*., 1981). In one study, 2-cyanoethylene oxide was approximately 15-fold more mutagenic than acrylonitrile at the TK locus in cultured human lymphoblastoid cells (Recio and Skopek, 1988). *In vitro*, the formation of DNA adducts at high unphysiological concentrations is increased substantially in the presence of metabolic activation. Under non-activating conditions, 2-cyanoethylene oxide alkylates DNA much more readily than acrylonitrile.

The role of mutagenesis and the primary mutagenic lesion induced by acrylonitrile in acrylonitrile-induced carcinogenesis are uncertain. Acrylonitrile–DNA adducts can be induced *in vitro* and in the liver *in vivo*, although at levels considerably less than those associated with, for example, ethylene oxide. However, when measures were taken to eliminate contamination of samples by adducted protein and unbound acrylonitrile, acrylonitrile–DNA adducts were not detected in the brain, the primary target for acrylonitrile-induced carcinogenesis. This is in contrast to observations for ethylene oxide, which is also associated with gliomas of the brain. If the methods used to achieve greater DNA purity did not cause the loss of adducts or inhibit the recovery of adducted DNA, this suggests that acrylonitrile-induced DNA damage and mutagenicity may occur by a mechanism other than the formation of acrylonitrile–DNA adducts. Alternatively, they may be associated with an uninvestigated adduct (e.g., cyanohydroxyethyl adducts).

Investigations of the potential role of free radicals and oxidative stress in the carcinogenesis of acrylonitrile are under way, with results of most being presented incompletely at this time. Exposure to acrylonitrile has been associated with the accumulation of 8-oxodeoxyguanine in the DNA isolated from brain tissue, presumably via the action of reactive oxygen species generated during acrylonitrile metabolism. Data on dose–response in this regard are limited to animals exposed for 21 days. Moreover, the predicted greater sensitivity of Sprague-Dawley versus Fischer rats to induction of tumours of the brain/spinal cord on the basis of results of shorter-

term studies in which 8-oxodeoxyguanine levels in brain have been determined is not borne out by carcinogenesis bioassays. The origin of this oxidative damage is also unclear.

Also, several aspects of tumour development are characteristic of those induced by compounds that interact directly with DNA. Tumours are systemic and occur at multiple sites in both sexes following both inhalation and ingestion, sometimes at non-toxic doses or concentrations and at periods as early as 7–12 months following onset of exposure. The ratio of benign to malignant tumours is small.

In summary, the mechanism of carcinogenesis of acrylonitrile is unknown. Moreover, available data are insufficient to support a consensus view on a plausible mode of action. There is limited evidence for weak genotoxic potential, insufficient data on acrylonitrile–DNA adducts in the brain, although such adducts can be induced in the liver *in vivo*, and some indication in ongoing studies that oxidative damage, the origin of which is unclear, may play a role.

Effects on the reproductive system in experimental animals (mice) exposed to acrylonitrile are limited to degenerative changes in the seminiferous tubules and associated decreases in sperm counts in a specialized investigation, decreases in sperm motility in an unpublished investigation, for which histopathological results are not yet available, and decreased sperm counts, motility and histopathological changes in an incompletely reported study. In a three-generation study in rats exposed via drinking water, adverse effects on pup survival and viability and lactation indices were attributed to maternal toxicity.

Biologically significant effects in offspring have not been observed at doses that were not toxic to the mothers in developmental studies in rats exposed to acrylonitrile by both inhalation and ingestion. These studies included a recent well-conducted investigation with good characterization of dose–response.

In the few identified investigations of the immunological effects of acrylonitrile, effects on the lung following inhalation and gastrointestinal tract following ingestion have been observed at concentrations and doses at which histopathological effects have also been observed in other investigations.

In recent unpublished studies by inhalation (24 weeks) and ingestion (12 weeks), clinical signs typical of acute acetylcholine-like toxicity and partially reversible reduction in motor and sensory conduction were observed.

3.3.3 Dose–response analyses

3.3.3.1 Effects in humans

In a cross-sectional investigation of workers exposed in acrylic fibre factories to approximately 1 ppm (2.2 mg/m^3) acrylonitrile, there was no consistent evidence of adverse effects based on examination of a wide range of clinical parameters, including liver function tests (Muto *et al*., 1992). Available data in humans are inadequate to serve as a basis for characterization of the concentrations at which acute irritation occurs.

While there has been consistent evidence of a lack of association between exposure to acrylonitrile and cancer of a particular site in recent, well-conducted epidemiological studies, the power of the investigations is insufficient to rule out increases in particularly rare tumours, such as those of the brain. Indeed, the power to detect moderate excesses for some sites (stomach, brain, breast, prostate, lymphatic/hematopoietic) was quite small because of small numbers of deaths.

As a very rough guide to the sensitivity of these studies, the upper 95% confidence limits in the meta-analysis conducted by Collins and

Acquavella (1998) are somewhat informative. For example, for lung cancer, the upper 95% confidence limit on the meta-relative risk (mRR) for 12 studies was 1.1, indicating that a 10% excess could not be excluded; for "highly" exposed workers included in seven of the studies, the upper 95% confidence limit was 1.5, indicating that a 50% excess could not be excluded. Lower confidence limits for these groups, respectively, were 0.8 and 1.0. Interestingly, the upper 95% confidence limit for three studies for which there were estimated parts per million levels of exposure was 1.0, and the lower 95% confidence limit, 0.8.

For the brain, the upper 95% confidence limit on the mRR for 11 studies was 1.5, indicating that a 50% excess could not be excluded; the lower 95% confidence limit was 0.8.

Moreover, while it has been suggested that the results of the epidemiological studies contrast quantitatively with those of bioassays in animals, meaningful direct comparison of these two types of data is precluded primarily by inadequate information with which to characterize possible relevant sites of cancer in humans (i.e., site concordance between animals and humans) and the relative paucity of data on exposure of workers in the relevant investigations. Results of such comparative exercises can be considered as either consistent or divergent only in the context of full quantitative characterization of the uncertainties related to the assumptions about average exposure, duration or follow-up in the studies of occupationally exposed populations on which they are based.

3.3.3.2 Effects in experimental animals

3.3.3.2.1 Non-neoplastic effects

Inhalation

In the more informative of available short-term inhalation studies, all of which were restricted to single dose levels and examination of a limited range of examined endpoints (Gut *et al*., 1984, 1985), clinical signs and decreases in body and organ weights but no histopathological effects were observed in rats exposed for five days to 280 mg acrylonitrile/m^3.

With the exception of inflammatory changes in the nasal turbinates (Quast *et al*., 1980b), non-neoplastic effects observed in the few conducted chronic inhalation studies were limited to pre-cancerous hyperplastic changes in the central nervous system (Maltoni *et al*., 1977, 1987, 1988; Quast *et al*., 1980b). Inflammatory changes in the nasal turbinates were observed at 80 ppm (176 mg/m^3) (NOEL = 20 ppm; 44 mg/m^3).

In two developmental studies in rats exposed by inhalation, developmental effects (fetotoxic and teratogenic) have not been observed at concentrations that were not toxic to the mothers (Murray *et al*., 1978; Saillenfait *et al*., 1993a). In the investigation in which concentration–response was best characterized (four exposure concentrations and controls with two-fold spacing), the LOEL for maternal toxicity and for fetotoxicity was 55 mg/m^3; the NOEL was 26.4 mg/m^3 (Saillenfait *et al*., 1993a).

In recent studies in rats exposed by inhalation to 25 ppm (55 mg/m^3) and above for 24 weeks, there were partially reversible time- and concentration-dependent reductions in motor and sensory conduction (Gagnaire *et al*., 1998).

Ingestion

In investigations in rats by Szabo *et al*. (1984), effects on non-protein sulphydryl in gastric mucosa have been reported at levels as low as 2 mg/kg-bw per day (drinking water, 60 days). Effects on hepatic glutathione were also observed by these authors at similar doses administered by gavage but not in drinking water (2.8 mg/kg-bw per day, 21 days), although Silver *et al*. (1982) noted only slight biochemical effects but no histopathological effects in the liver at doses up to 70 mg/kg-bw per day (drinking water, 21 days).

Significant increases in proliferation in the forestomach but no changes in the liver or glandular stomach have been observed at 11.7 mg/kg-bw per day (Ghanayem *et al*., 1995, 1997).

Similar to observations in the inhalation studies, non-neoplastic effects observed in the chronic studies in rats exposed by ingestion were limited primarily to pre-cancerous hyperplastic changes in target organs such as the non-glandular stomach (Quast *et al*., 1980a). Other observed effects were limited primarily to increased organ weights, which were not observed consistently within or across the studies.

Consistent effects on the reproductive organs of male or female animals have not been observed in repeated-dose toxicity and carcinogenicity studies conducted to date. In a specialized investigation in CD-1 mice, however, degenerative changes in the seminiferous tubules and associated decreases in sperm counts were observed at 10 mg/kg-bw per day (NOEL, 1 mg/kg-bw per day) (Tandon *et al*., 1988). Although epididymal sperm motility was reduced in a 13-week study with $B6C3F_1$ mice, there was no dose–response and no effect upon sperm density at doses up to 12 mg/kg-bw per day, although histopathological results are not yet available (Southern Research Institute, 1996). In a three-generation study in rats exposed via drinking water (14 and 70 mg/kg-bw per day), adverse effects on pup survival and viability and lactation indices were attributed to maternal toxicity (Litton Bionetics Inc., 1980).

In two studies by the oral route, developmental (including both fetotoxic and teratogenic) effects have not been observed at doses that were not also toxic to the mothers (lowest reported effect level in the mothers, 14 mg/kg-bw per day) (Murray *et al*., 1978; Litton Bionetics Inc., 1980). Reversible biochemical effects on the brain but not functional neurological effects were observed in offspring of rats exposed to 5 mg/kg-bw per day (a dose that did not affect body weight of the dams); dose–response was not investigated in this study (Mehrotra *et al*., 1988).

Clinical signs resembling those associated with acute acetylcholine toxicity were observed in a recently completed study in rats exposed by gavage to 12.5 mg/kg-bw per day and above for 12 weeks (Gagnaire *et al*., 1998).

3.3.3.2.2 Cancer

Cancer is considered the critical endpoint for quantitation of dose–response for risk characterization for acrylonitrile. This is based on the observation of tumours at non-toxic doses or concentrations in chronic studies at levels less than those that have induced effects in (limited) repeated-dose toxicity studies and identified investigations of neurological, reproductive and developmental effects. Moreover, there is evidence for weak genotoxic potential, and data are insufficient to support a plausible mode of action for acrylonitrile-induced carcinogenesis other than through direct interaction with DNA.

There is no reason to believe that carcinogenesis is unique to the rat, although there may be quantitative differences between experimental animals and humans, based on metabolic studies. Indeed, physiologically based pharmacokinetic modelling predicts that concentrations of cyanoethylene oxide in the brains of humans would be considerably greater than those in rats exposed to similar concentrations of acrylonitrile, although increases in brain cancer have not been observed in epidemiological studies with limited power to detect excesses of this rare tumour.

In carcinogenesis assays conducted in various strains of rats exposed via inhalation or ingestion (most of which are early unpublished studies), the incidences of astrocytomas of the central nervous system, Zymbal gland tumours and tumours of the non-glandular forestomach have increased most consistently following

exposure to acrylonitrile. Increases in the incidence of tumours of the tongue, mammary gland and intestine have been observed less consistently, and those of the skin and liver in a single study.

Of the tumours increased in incidence most consistently, astrocytomas occurred at highest incidence consistently across studies; the other two tumours observed most often were confined to organs not present in humans (i.e., Zymbal gland, forestomach), for which incidence was less. This was confirmed, through calculation, in a screening exercise, of Tumorigenic Concentrations/Tumorigenic Doses (TC_{05}s/TD_{05}s) for each of the tumours presented in Section 2.4.3.4, based on incidences presented by U.S. EPA (1983)[8] and Johnston and Rock (1990).[9] The only possible exception in studies by most relevant media of administration was the incidence of tumours of the non-glandular stomach in the drinking water assay of Quast *et al*. (1980a). However, it was not possible to confirm the incidences on which these calculations were based upon examination of data in the original study report due to discrepancies within the critical table (i.e., the number of animals in which tumours were reported in the five categories for the non-glandular stomach, combined, was greater than the total number of animals examined); there was also a discrepancy between the content of this table (Table 22) and data presented in the Appendix (Table A-21). Moreover, the tumours that occurred at highest incidence are not consistent with the results of other studies, and they have therefore not been further addressed here.

Quantitative estimates presented herein are limited to the tumours that occurred at highest incidence (i.e., astrocytomas of the central nervous system) in bioassays for which media of intake are most relevant to exposure in the general environment — i.e., inhalation and drinking water. Of the few inhalation bioassays identified, the study by Quast *et al*. (1980b) is considered most suitable for quantitation of cancer potency, although it is limited by the fact that there were only two dose levels and controls. Group sizes were large (n = 100 per sex per group), however, and animals were exposed for two years. In other identified inhalation bioassays, group sizes were small and/or exposure periods short (Maltoni *et al*., 1977, 1987, 1988).

Among the bioassays in which acrylonitrile was administered in drinking water (Bio/Dynamics Inc., 1980a,b; Quast *et al*., 1980a; Gallagher *et al*., 1988),[10] characterization of dose–response was best in Bio/Dynamics Inc. (1980b). In this investigation, there were five doses and controls with good dose spacing and optimum characterization of dose–response, including lower, non-toxic doses. Group sizes were large (n = 100). Group sizes were smaller in other bioassays (Gallagher *et al*., 1988), or dose spacing was poor (Bio/Dynamics Inc., 1980a). Although group sizes were smaller and doses higher, TD_{05}s based on the investigation of Quast *et al*. (1980a) are also included, since incidence was increased at more doses (three rather than two in Bio/Dynamics Inc., 1980b).

The tumour incidences and resulting TD_{05}s/TC_{05}s for benign and malignant tumours (combined) of the central nervous system (astrocytomas) for the Quast *et al*. (1980b) inhalation study and the Bio/Dynamics Inc. (1980b) and Quast *et al*. (1980a) drinking water bioassays modelled using the multistage model (GLOBAL 82) are presented in Tables 5, 6 and 7. Degrees of freedom, parameter estimates and nature of any adjustments for mortality or period of exposure are also presented therein. Benign and malignant tumours have been combined owing to the observed clear progression,

[8] Incidence was based on benign and malignant tumours (combined), with no adjustment for early mortality.
[9] Incidence was based on malignant tumours, excluding animals dying or sacrificed before or at six months.
[10] For reasons mentioned in Section 2.4.3.4.1, including limitations of histopathological analysis, data on tumour incidence in Bigner *et al*. (1986) are considered inadequate for quantitation of dose–response.

although, as indicated in the tables, numbers of benign lesions included in the incidences on which these calculations were based are small; exclusion of the benign tumours would result in only slightly higher values of the TD_{05}s/TC_{05}s. In all cases, incidences have been adjusted to exclude animals dying before six months (i.e., prior to observation of the first tumours). For comparison, TC_{05}s developed on the basis of incidences reported by TERA (1997) for male rats for the Quast *et al*. (1980b) inhalation bioassay adjusted to exclude animals dying before approximately 10 months are also included.

With respect to appropriate scaling of the TD_{05}s/TC_{05}s, those for inhalation have been adjusted to reflect differences in inhalation volumes and body weights between humans and exposed animals. The TC_{05}s were multiplied by:

$$(0.11\ m^3 \text{ per day}/0.35 \text{ kg-bw}) \times (70 \text{ kg-bw}/23\ m^3 \text{ per day})$$

where 0.11 m^3 per day is the breathing rate of a rat, 0.35 kg-bw is the body weight of a rat, 23 m^3 per day is the breathing rate of a human and 70 kg-bw is the body weight of a human. The estimates of carcinogenic potency for ingestion were not scaled on the basis of body surface area, as the carcinogenicity of acrylonitrile appears to be due to a metabolite rather than to the parent compound.

The physiologically based pharmacokinetic model, once completed, holds considerable promise as a more suitable basis for scaling of TD_{05}s/TC_{05}s. Alternatively, it might be suitable as a basis for scaling of estimated exposures with which the TD_{05}s/TC_{05}s are compared.

Tumorigenic potencies developed in this manner for ingestion and inhalation are similar.

3.3.4 Human health risk characterization

Although limited, available data are consistent with air being the principal medium of exposure of the general population to acrylonitrile; intake from other media is likely to be negligible in comparison. Moreover, with the exception of air in the vicinity of industrial point sources, acrylonitrile has seldom been detected in samples of ambient air, indoor air or drinking water. This is consistent with lack of identification of non-point sources. On this basis, the focus of the human health risk characterization is populations exposed through air in the vicinity of industrial point sources. Moreover, the vast majority of acrylonitrile (>97%) is released to air.

For compounds such as acrylonitrile, where data are insufficient to support a consensus view on a plausible mode of action for induction of tumours by other than direct interaction with genetic material, estimates of exposure are compared with quantitative estimates of cancer potency (Exposure Potency Index) to characterize risk and provide guidance in establishing priorities for further action (i.e., analysis of options to reduce exposure) under CEPA.

The lowest TC_{05} (human equivalent value) was 6 mg/m^3 for the combined incidence of benign and malignant tumours of the brain and/or spinal cord in female rats exposed by inhalation; the lower 95% confidence limit was 4.5 mg/m^3 (Table 5) (Quast *et al*., 1980b). The margins between carcinogenic potency and limited available data on predicted and measured concentrations of acrylonitrile primarily in the vicinity of point sources in Canada are presented in the table below. On this basis, priority for investigation of options to reduce exposure in the vicinity of industrial point sources is considered to be high. It should be noted, however, that populations residing in the vicinity of sources would likely be exposed to lower concentrations, in view of the proximity of many of these predicted and measured values to the stacks, and monitoring in residential areas in the vicinity of point sources is desirable.

Concentration of acrylonitrile (Reference)	Potency (Table 5)	Margin between potency and concentration Exposure Potency Index	Priority for further action (Health Canada, 1994)
Vicinity of sources			
9.3 µg/m^3, concentration predicted by dispersion modelling, 11 m from stack at industrial site in Ontario (Table 4)	TC_{05} = 6000 µg/m^3	650	high
		16×10^{-4}	
	95% LCL[1] = 4500 µg/m^3	480	high
		21×10^{-4}	
2.9 µg/m^3, concentration predicted by dispersion modelling, 35 m from stack at industrial site in Ontario (Table 4)	TC_{05} = 6000 µg/m^3	2100	high
		4.8×10^{-4}	
	95% LCL = 4500 µg/m^3	1550	high
		6.4×10^{-4}	
0.6 µg/m^3, concentration predicted by dispersion modelling, 41 m from stack at industrial site in Ontario (Table 4)	TC_{05} = 6000 µg/m^3	10 000	moderate
		1×10^{-4}	
	95% LCL = 4500 µg/m^3	7500	moderate
		1.3×10^{-4}	
0.1 µg/m^3, concentration predicted by dispersion modelling, 3508 m from stack at industrial site in Ontario (Table 4)	TC_{05} = 6000 µg/m^3	60 000	moderate
		0.2×10^{-4}	
	95% LCL = 4500 µg/m^3	45 000	moderate
		0.2×10^{-4}	
<52.9 µg/m^3, sampling at the site of nitrile-butadiene rubber production in Sarnia in 1997, 5 m from company fence line, 2 m above ground, downwind (Sparks, 1997; Wright, 1998)	TC_{05} = 6000 µg/m^3	110	high
		8.8×10^{-3}	
	95% LCL = 4500 µg/m^3	85	high
		1.2×10^{-2}	
0.12 µg/m^3, lowest concentration measured in ambient air sampled for six days near a chemical manufacturing plant in Cobourg, Ontario (Ortech, 1994)	TC_{05} = 6000 µg/m^3	50 000	moderate
		2×10^{-5}	
	95% LCL = 4500 µg/m^3	38 000	moderate
		2.7×10^{-5}	

Concentration of acrylonitrile (Reference)	Potency (Table 5)	Margin between potency and concentration: Exposure Potency Index	Priority for further action (Health Canada, 1994)
0.28 µg/m^3, highest concentration measured in ambient air sampled for six days near a chemical manufacturing plant in Cobourg, Ontario (Ortech, 1994)	TC_{05} = 6000 µg/m^3	21 000	moderate
		4.7×10^{-5}	
	95% LCL = 4500 µg/m^3	16 000	moderate
		6.2×10^{-5}	
<251 µg/m^3, lowest concentration measured at stack of chemical manufacturing plant in Cobourg, Ontario, in 1993 (Ortech, 1994)[2]	TC_{05} = 6000 µg/m^3	0.04183 (4.2×10^{-2})	high
		24	
	95% LCL = 4500 µg/m^3	0.05577 (5.6×10^{-2})	high
		18	
Ambient air			
1.9 µg/m^3, maximum (and only detectable) concentration measured in 11 samples at six urban stations in Ontario in 1990 (OMOE, 1992a,c)[3]	TC_{05} = 6000 µg/m^3	3200	high
		3.2×10^{-4}	
	95% LCL = 4500 µg/m^3	2400	high
		4.2×10^{-4}	
<0.64 µg/m^3, seven samples in industrialized area of Windsor, Ontario, in 1991 (Ng and Karellas, 1994)	TC_{05} = 6000 µg/m^3	9400	moderate
		1.1×10^{-4}	
	95% LCL = 4500 µg/m^3	7000	moderate
		1.4×10^{-4}	

[1] 95% LCL = lower 95% confidence limit.
[2] Based on the concentration of 100 763 µg/m^3 measured at the stack, priority for further action is high.
[3] The detection limit was 0.0003 µg/m^3. The Exposure Potency Index would indicate a low priority for further action.

3.3.5 *Uncertainties and degree of confidence in human health risk characterization*

There is a high degree of uncertainty in the quantitative estimates of intake of acrylonitrile in ambient and indoor air for the general population owing to the paucity of relevant monitoring data and lack of detection in most studies. However, there is a fair degree of certainty that air is the principal medium of exposure based on the limited monitoring data, which is supported by information on the physical/chemical properties of the compound and intakes estimated on the basis of levels in various media predicted by fugacity modelling.

There is a high degree of uncertainty in the estimates of intake of acrylonitrile in food, since estimates were based on a small number of samples of foodstuffs packaged in acrylonitrile-based plastic containers taken in the early 1980s in Canada. Since acrylonitrile-based polymers are not used in Canada to any great extent in direct food contact application, intake in these foodstuffs is likely overestimated. This is offset to some extent by the assumption of zero for concentrations in all other foodstuffs. Since food is likely a minor medium of exposure, this uncertainty does not impact greatly on overall confidence in the estimates of exposure.

There is a high degree of certainty that drinking water contributes only negligible amounts of acrylonitrile to overall exposure, based on lack of detection in a large, sensitive survey.

Although there are recent data on concentrations of acrylonitrile in the vicinity of point sources in Canada (both monitored and modelled), the available studies are limited in scope. Studies were conducted over short periods, at few locations, with no indication of proximity to local populations. The estimates near the largest source were based on air dispersion modelling in which chemical transformations are treated to a limited extent and acrylonitrile is considered to be in the aerosol state and released at a maximal emission rate. Predicted values were, however, supported to some extent by monitoring data in the vicinity of another point source. Available data indicate that levels of acrylonitrile 0.2–5 km from various point sources in the United States range over three orders of magnitude (<0.1–325 $\mu g/m^3$); maximal averages ranged over two orders of magnitude (0.3–84 $\mu g/m^3$) (see Table 6.3.3 in the supporting documentation).

The overall degree of confidence in the population exposure estimates is, therefore, low, owing primarily to the paucity of current representative monitoring data for the likely principal medium of exposure of the general population in Canada (air). There is some degree of assurance, though, that based on the lack of identification of non-point sources and due to the lack of detection in ambient air in small surveys with sensitive methodology, investigations of options to reduce exposure should be limited to the vicinity of point sources.

The degree of confidence in the database on toxicity of acrylonitrile is moderate. The carcinogenicity of acrylonitrile in humans has been investigated in well-conducted recent studies of four relatively large cohorts of occupationally exposed workers. While this epidemiological database is extensive in comparison to that available for many other compounds, the power of the studies was insufficient to detect moderate excesses for some sites. Available data are also insufficient to provide meaningful direct comparison with the results of quantitative dose–response analyses based on bioassays in animals due to inadequate information with which to characterize possible relevant sites of cancer in humans (i.e., site concordance between animals and humans) and the relative paucity of data on exposure of workers in the relevant investigations.

The database on non-cancer toxicity in laboratory animals is limited, being restricted to primarily early unpublished carcinogenesis bioassays in which few non-cancer endpoints

were examined, a few more recent investigations of specialized endpoints such as neurotoxicity or more recent repeated-dose toxicity studies for which full accounts are not yet available. Although there are a relatively large number of bioassays, the database on carcinogenicity of acrylonitrile is limited primarily to early unpublished investigations in one species; a bioassay in mice, however, is currently under way.

Based on information acquired to date on the kinetics and metabolism of acrylonitrile, a physiologically based pharmacokinetic model, once completed, holds promise as a more suitable basis for scaling of TD_{05}s/TC_{05}s than the default assumption about relative inhalation volumes and body weights.

Tumorigenic potencies for inhalation based on the combined incidence of benign and malignant tumours of the brain and/or spinal cord in female rats were 1.4 times less than for these tumours in males in the same study (TC_{05} of 6 versus 8.9 mg/m^3). These values were also up to two-fold less than those for tumours at other sites in both sexes in the critical study (i.e., Quast *et al*., 1980b). The lower 95% confidence limit on the TC_{05} for the combined incidence of benign and malignant tumours of the brain and/or spinal cord in female rats was 4.5 mg/m^3 versus the maximum likelihood estimate of 6 mg/m^3.

3.4 Conclusions

CEPA 1999 64(a): Based on available data, it has been concluded that acrylonitrile is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity.

CEPA 1999 64(b): Based on available data, it has been concluded that acrylonitrile is not entering the environment in a quantity or concentration or under conditions that constitute or that may constitute a danger to the environment on which life depends.

CEPA 1999 64(c): Available data are insufficient to support a consensus view on a plausible mode of action for induction of tumours by acrylonitrile by other than direct interaction with genetic material. On this basis, it has been concluded that acrylonitrile does enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health, and acrylonitrile is considered to be "toxic" as defined in Paragraph 64(c) of CEPA 1999. This approach is consistent with the objective that exposure to compounds for which induction of cancer through direct interaction with genetic material cannot be ruled out be reduced wherever possible and obviates the need to establish an arbitrary *de minimis* level of risk for the determination of "toxic" under CEPA 1999. On the basis of worst-case estimates, priority for investigation of options to reduce exposure in the vicinity of industrial point sources is considered to be high.

Overall conclusion: Based on critical assessment of relevant information, acrylonitrile is considered to be "toxic" as defined in Section 64 of CEPA 1999.

3.5 Considerations for follow-up (further action)

Based on comparison of worst-case estimates of exposure in air in the vicinity of industrial sources with the tumorigenic potency, it is recommended that options to reduce exposure to acrylonitrile in the vicinity of industrial point sources be investigated. It is also recommended that there be additional investigation of the magnitude of exposure of populations in the vicinity of industrial point sources as a basis for risk management.

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APPENDIX A SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA

Environmental assessment

Data relevant to the assessment of whether acrylonitrile is "toxic" to the environment under CEPA were identified from existing review documents, published reference texts and on-line searches of the following databases for the period 1980–1996: Aqualine (Water Research Centre, Buckinghamshire), ARET (Accelerated Reduction/Elimination of Toxics, Environment Canada), ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts), BIODEG (Syracuse Research Corp.), BIOLOG, BIOSIS (Biosciences Information Services), Business Opportunities Sourcing System, CAB (Commonwealth Agriculture Bureaux), Canadian Research Index (Microlog: CRI, Government Publications/Micromedia Ltd.), Catalogue of Environmental Data in Atlantic Canada (Environment Canada, Atlantic Region), CCINFO, CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources), Chemfate (Syracuse Research Corp.), ChemINFO (Canadian Centre for Occupational Health and Safety), CHRIS (Chemical Hazard Release Information System), CPI Profile (Camford Information Services), Current Contents (Institute for Scientific Information), Datalog (Syracuse Research Corp.), Domestic Substances List (Environment Canada), ELIAS (Environmental Library Integrated Automated System, Environment Canada library), ENVIRODAT (Environment Canada), Enviroline (R.R. Bowker Publishing Co.), Environmental Abstracts, Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara), Envirosource (Environment Canada), GEOREF (Geo Reference Information System, American Geological Institute), HCA, HSBD (Hazardous Substances Data Bank, U.S. National Library of Medicine), ICAR (Inventory of Canadian Agricultural Research, Canadian Agri-food Research Council), IRL, IRPTC (International Register of Potentially Toxic Chemicals, Geneva), Life Sciences (Cambridge Scientific Abstracts), MSDS (Material Safety Data Sheets, Canadian Centre for Occupational Health and Safety), NATES (National Analysis of Trends in Emergencies System, Environment Canada), National Emission Inventory (Canadian Chemical Producers Association), NPRI (National Pollutant Release Inventory, Environment Canada), National Registry of Toxic Chemical Residues (National Wildlife Research Centre, Environment Canada), Northern Info Network, NTIS (National Technical Information Service, U.S. Department of Commerce), Pesticide Registrant Survey (Environment Canada and Agriculture Canada), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine), REPEN (*Répertoire informatisé des bases de données environnementales sur le Fleuve Saint-Laurent*, Environment Canada, Quebec Region), RRETC (River Road Environmental Technology Centre monitoring data), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute of Occupational Safety and Health), Statistics Canada Import/Export Merchandise Trade Vols. I–II, Synopsis Northern Contaminants Program, Toxline (U.S. National Library of Medicine), TRI87-94 (Toxic Chemical Release Inventory, Office of Toxic Substances, U.S. Environmental Protection Agency), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency), USEPA-ECOTOX (including AQUIRE; U.S. Environmental Protection Agency), USEPA-National Catalog (U.S. Environmental Protection Agency), WASTEINFO (Waste Management Information Bureau, American Energy Agency).

Several databases or surveys were evaluated to quantify releases. These included the National Pollutant Release Inventory (NPRI), the Accelerated Reduction/Elimination of Toxics (ARET) database, the Canadian Chemical Producers Association Responsible Care® Initiative database, and the emissions modelling data of Shen and Minns (1997). A survey of Canadian industry was carried out under authority of Section 16 of CEPA (Environment Canada, 1997c). Companies were required to provide information on uses, releases, environmental concentrations, effects or other data on acrylonitrile available to them if they met the trigger quantity of 1000 kg acrylonitrile per year. Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the environmental effects of acrylonitrile. Data obtained after May 31, 1998, were not considered in this assessment unless they were critical data received during the 60-day public review of the report (June 26 to August 24, 1999).

Health assessment

Data relevant to the assessment of whether acrylonitrile is "toxic" to human health obtained after April 1998 have not been included.

Data relevant to environmental exposure to acrylonitrile under CEPA were identified in review documents and on-line searches of commercial and governmental databases. The following databases were searched: AQUAREF (Inland Waters Directorate, Environment Canada), CISTIMON (Canadian Institute of Scientific and Technical Information collection, National Research Council of Canada), ELIAS (Environmental Library Integrated Automated System, Environment Canada library), EMBASE (on-line version of Excerpta Medica, Elsevier Science), Enviroline (R.R. Bowker Publishing Co.), Environmental Bibliography (Environmental Study Institute, International Academy at Santa Barbara), Medline (U.S. National Library of Medicine), Microlog (Canadian Research Index, Government Publications, Micromedia Ltd.), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine). Numerous provincial officials and industry associations were contacted between 1996 and 1998 for monitoring data relevant to exposure.

Data relevant to the toxicity of acrylonitrile were identified in review documents prepared by the U.S. Environmental Protection Agency (U.S. EPA, 1983, 1985) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1990) and in on-line searches of commercial and governmental databases. The following databases were searched: CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources), DART (Developmental and Reproductive Toxicology, U.S. National Library of Medicine), EMIC (Environmental Mutagen Information Center database, Oak Ridge National Laboratory), GENE-TOX (Genetic Toxicology, Office of Toxic Substances, U.S. Environmental Protection Agency), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine), IRIS (Integrated Risk Information System, U.S. Environmental Protection Agency), NTIS (National Technical Information Service, U.S. Department of Commerce), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health), Toxline (U.S. National Library of Medicine).