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Concise International Chemical Assessment Document 39

ACRYLONITRILE

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The International Programme on Chemical Safety (IPCS), established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170 for advice on the derivation of health-based guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Co-ordinator, IPCS, on the selection of chemicals for an IPCS risk assessment, the appropriate form of the document (i.e., EHC or CICAD), and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS and one or more experienced authors of criteria documents to ensure that it meets the specified criteria for CICADs.

The draft is then sent to an international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers’ comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers’ comments.

1 Taking into account the comments from reviewers.
2 The second draft of documents is submitted to the Final Review Board together with the reviewers’ comments.
3 Includes any revisions requested by the Final Review Board.
A consultative group may be necessary to advise on specific issues in the risk assessment document.

The CICAD Final Review Board has several important functions:

– to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
– to verify that the peer reviewers’ comments have been addressed appropriately;
– to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
– to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.
1. EXECUTIVE SUMMARY

This CICAD on acrylonitrile was prepared jointly by the Environmental Health Directorate of Health Canada and the Commercial Chemicals Evaluation Branch of Environment Canada based on documentation prepared concurrently as part of the Priority Substances Program under the Canadian Environmental Protection Act (CEPA). The objective of assessments on Priority Substances under CEPA is to assess potential effects of indirect exposure in the general environment on human health as well as environmental effects. Data identified as of the end of 31 May 1998 (environmental effects) and April 1998¹ (human health effects) were considered in this review. Other reviews that were also consulted include US EPA (1980, 1985), IPCS (1983), ATSDR (1990), IARC (1999), and EC (2000). Information on the nature of the peer review and availability of the source document (Environment Canada & Health Canada, 2000) is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Geneva, Switzerland, on 8–12 January 2001. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card on acrylonitrile (ICSC 0092), produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

Acrylonitrile (CAS No. 107-13-1) is a volatile, flammable, water-soluble liquid at room temperature. The large majority of acrylonitrile in Canada is used as a feedstock or chemical aid in the production of nitrile-butadiene rubber and in acrylonitrile-butadiene-styrene and styrene-acrylonitrile polymers. Estimated world capacity in 1993 was about 4 million tonnes. Major areas of production are the European Union (>1.25 million tonnes per year), the USA (approximately 1.5 million tonnes per year), and Japan (approximately 0.6 million tonnes per year).

Acrylonitrile is released into the environment primarily from chemical production and the chemical and plastic products industries (>95% in the sample country). There are no known natural sources.

¹ New information flagged by the reviewers or obtained in a literature search conducted prior to the Final Review Board meeting has been scoped to indicate its likely impact on the essential conclusions of this assessment, primarily to establish priority for its consideration in an update. More recent information not critical to the hazard characterization or exposure–response analysis, considered by reviewers to add to informational content, has been added.

Acrylonitrile is distributed largely to the environmental compartments to which it is principally released (i.e., air or water), with movement to soil, sediment, or biota being limited; reaction and advection are the major removal mechanisms. In limited surveys in the country on which the sample risk characterization is based (i.e., Canada), acrylonitrile has been detected in the general environment only in the vicinity of industrial sources.

Occupational exposure to acrylonitrile occurs during production and its use in the manufacture of other products; potential for exposure is greater in the latter case, where the compound may not be as easily contained. Based on recent data for countries in the European Union, time-weighted-average (TWA) exposures are #1.45 ppm (#1 mg/m³) during production and #1.01 ppm (#2.2 mg/m³) in various end uses.

Acrylonitrile is rapidly absorbed via all routes of exposure and distributed throughout examined tissues. There is little potential for significant accumulation in any organ, with most of the compound being excreted primarily as metabolites in the urine within the first 24–48 h following administration. Available data are consistent with conjugation to glutathione being the major detoxification pathway, while oxidation to 2-cyanoethylene oxide is considered an activation pathway.

Available data from studies in animals indicate that acrylonitrile is a skin, respiratory, and severe eye irritant. Acrylonitrile may cause allergic contact dermatitis, but the available data are inadequate to assess its sensitization potency. With the exception of developmental toxicity, for which effects (fetotoxic and teratogenic) have not been observed at concentrations that were not toxic to the mothers, available data on other non-neoplastic effects in experimental animals are inadequate to characterize exposure–response. In the few studies in human populations in which non-neoplastic effects of acrylonitrile have been systematically investigated, only acute dermal irritation has been reported consistently.

Based on studies in animals, cancer is the critical end-point 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. In almost all adequate bioassays, there have been reported increases in astrocytomas of the brain and spinal cord, which are rarely observed spontaneously; 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 multigeneration reproductive study at 45 weeks.

Increases in cancer incidence have not been consistently observed in available epidemiological studies. However, the meaningful quantitative comparison of the results of these investigations with those of studies in animals is precluded by inadequate data on mode of induction of brain tumours, relative paucity of data on exposure of workers in the relevant investigations, and the wide range of the confidence limits on the standardized mortality ratios for cancers of possible interest in the epidemiological studies.

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, while the metabolite, cyanoethylene oxide, is mutagenic. Although direct evidence is not available, based on available data, it is reasonable to assume that induction of tumours by acrylonitrile involves direct interaction with genetic material. The weight of evidence for other potential modes of induction of tumours is inadequate. Acrylonitrile or its epoxide can react with macromolecules.

Cancer is considered the critical end-point for quantification of exposure–response for risk characterization for acrylonitrile. The lowest tumorigenic concentration (TCS, the concentration that causes a 5% increase in tumour incidence over background) (human equivalent value) was 2.7 ppm (6.0 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. This equates to a unit risk of $8.3 \times 10^{-3}$ per mg/m$^3$.

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 the margins between carcinogenic potency and limited available data on predicted and measured concentrations of acrylonitrile primarily in the vicinity of point sources in the sample risk characterization, risks in the vicinity of industrial point sources are $>10^{-5}$.

In the sample environmental risk characterization, levels in treated industrial wastewaters are less than the estimated no-effects value (ENEV) for the most sensitive aquatic organism, and predicted maximum levels (near a chemical industry processing plant) are less than the ENEV for the most sensitive terrestrial organism.

## 2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Acrylonitrile is also known as acrylic acid nitrile, acrylon, carbacryl, cyanoethylene, fumigrain, propene-nitrile, 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, $\text{C}_3\text{H}_3\text{N}$, and its relative molecular mass, 53.06. The molecular structure of acrylonitrile is presented in Figure 1.

![Chemical structure of acrylonitrile.](image)

**Fig. 1:** Chemical structure of acrylonitrile.

The physical and chemical properties of acrylonitrile are presented in Table 1. At room temperature, acrylonitrile is a volatile, flammable, colourless liquid with a weakly pungent odour (IPCS, 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/litre 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 (IPCS, 1983). Hence, it is stored accordingly, often as an acrylonitrile–water formulation that acts as a polymerization inhibitor (Kirk et al., 1983). Spontaneous polymerization during storage and transport can also be prevented by the addition of an inhibitor, typically hydroquinone methyl ether (NICNAS, 2000).

## 3. ANALYTICAL METHODS

The most common method for analysis of acrylonitrile is gas chromatography. Method S156 of the US National Institute for Occupational Safety and Health (NIOSH, 1978, 1994) specifies sampling with activated charcoal sorption tubes, rinsing with methanol, and subsequent analysis by gas chromatography with a nitrogen–phosphorus detector. The working range of this method is 0.5–31 ppm (1–68 mg/m$^3$) for a 15-litre sample. The estimated limit of detection is 0.02 ppm.
### Table 1: Physical and chemical properties of acrylonitrile.

<table>
<thead>
<tr>
<th>Property</th>
<th>Mean (range)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density at 20 °C (g/litre)</td>
<td>806</td>
<td>American Cyanamid Co., 1959</td>
</tr>
<tr>
<td>Melting point (°C)</td>
<td>83.55</td>
<td>Riddick et al., 1986; Budavari et al., 1989</td>
</tr>
<tr>
<td>Boiling point (°C)</td>
<td>77.3</td>
<td>Langvardt, 1985; Howard, 1989</td>
</tr>
<tr>
<td>Water solubility at 25 °C (g/litre)</td>
<td>75.1</td>
<td>Martin, 1961; Spencer, 1981; Langvardt, 1985; Howard, 1989; DMER &amp; AEL, 1996</td>
</tr>
<tr>
<td>Solubility</td>
<td>Miscible with most organic solvents</td>
<td>American Cyanamid Co., 1959</td>
</tr>
<tr>
<td>Vapour pressure at 25 °C (kPa)</td>
<td>11 (11–15.6)</td>
<td>Groet et al., 1974; Riddick et al., 1986; Banerjee et al., 1990; BG-Chemie, 1990; Mackay et al., 1995</td>
</tr>
<tr>
<td>Henry’s law constant(^{b}) at 25 °C (Pa m(^3)/mol)</td>
<td>11 (8.92–11.14)</td>
<td>Mabey et al., 1982; Howard, 1989; Mackay et al., 1995</td>
</tr>
<tr>
<td>Log organic carbon/water partition coefficient (log (K_{oc}))</td>
<td>1.06 (1.09 to 1.1)</td>
<td>Koch &amp; Nagel, 1988; Walton et al., 1992</td>
</tr>
<tr>
<td>Log octanol/water partition coefficient (log (K_{ow}))</td>
<td>0.25 (0.92 to 1.2)</td>
<td>Collander, 1951; Pratesi et al., 1979; Veith et al., 1980; Tonogai et al., 1982; Tanii &amp; Hashimoto, 1984; Sangster, 1989; DMER &amp; AEL, 1996</td>
</tr>
<tr>
<td>Log bioconcentration factor (log BCF) in fish</td>
<td>0.48–1.68</td>
<td>Barrows et al., 1980; Lech et al., 1995</td>
</tr>
<tr>
<td>Half-life ((t_{1/2}))</td>
<td></td>
<td>Callahan et al., 1979; Cupitt, 1980; Atkinson, 1985; DMER &amp; AEL, 1996</td>
</tr>
<tr>
<td>air (h)</td>
<td>55 or 96 (4–189)</td>
<td>Atkinson et al., 1992</td>
</tr>
<tr>
<td>water (h)</td>
<td>170 (30–552)</td>
<td>Going et al., 1979; Howard et al., 1991</td>
</tr>
<tr>
<td>soil (h)</td>
<td>170 (30–552)</td>
<td>Howard et al., 1991</td>
</tr>
<tr>
<td>sediment (h)</td>
<td>550</td>
<td>DMER &amp; AEL, 1996</td>
</tr>
</tbody>
</table>

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

\(^{b}\) Vapour pressure (at given temperature) \(\times\) molar mass/water solubility (at same temperature).

\(^{c}\) No specific sediment value was found in the literature; this is based on the assumption of slower reactivity compared with soils (DMER & AEL, 1996).

(0.04 mg/m\(^3\)). The US Occupational Safety and Health Administration specifies a similar method of sampling with charcoal tubes, desorption with acetone, and subsequent analysis with gas chromatography using a nitrogen–phosphorus detector. The detection limit for this method is 0.01 ppm (0.026 mg/m\(^3\)) (OSHA, 1982, 1990). Health and Safety Executive (1993, 2000) specifies additional methods using porous polymer adsorption tubes and thermal desorption with gas chromatographic analysis.

A method has been developed for monitoring of exposure to acrylonitrile by determination of the adduct, \(N\)-(2-cyanoethyl)valine, formed in the reaction of acrylonitrile with the \(N\)-terminal group of haemoglobin (Bergmark et al., 1993; Osterman-Golkar et al., 1994; Tavares et al., 1996). The method is based on a modified Edman procedure and detection with selected ion monitoring by gas chromatography–mass spectrometry. The limit of detection is about 0.1–1 pmol/g globin (Tavares et al., 1996; Licea Perez et al., 1999).

### 4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

Data on sources and emissions primarily from the source country of the national assessment on which the CICAD is based (i.e., Canada) are presented here as an example. Sources and patterns of emissions in other countries are expected to be similar, although quantitative values may vary.

#### 4.1 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).

4.2 Anthropogenic sources

The total release of acrylonitrile in Canada in 1996 was 19.1 tonnes (97.3% to air and 2.7% to water) (Environment Canada, 1997). The major source of releases was the organic chemicals industry (97.4%) (namely, the chemicals and chemical products industries and the plastic products industries), while municipal wastewater treatment facilities accounted for 2.6% of releases. Although accounting for at most 1% of the releases to air from chemical industries in Canada, incineration of sewage sludge represents another potential source of acrylonitrile release to air. Use of acrylonitrile polymers as conditioners for wastewater treatment is another potential source, although this is also considered to be minor in relation to industrial sources in Canada.

There is also potential for long-range transport of acrylonitrile (up to 2000 km from its source) based on its half-life in air of between 55 and 96 h (see Table 1).

Acrylonitrile has also been used in some countries as a pesticide. Its registration as a fumigant for stored grain in Canada ceased in 1976 (J. Ballantine, personal communication, 1997).

Environmental tobacco smoke is a potentially important source of acrylonitrile indoors (Miller et al., 1998).

4.3 Production and use

World production of acrylonitrile exceeded 3.2 million tonnes in 1988, with later production increasing slowly (IARC, 1999). The estimated world capacity in 1991 was 4.2 million tonnes, while world demand in 1993 was 3.846 million tonnes (PCI, 1994). Major areas of production are the European Union (>1.25 million tonnes per year), the USA (approximately 1.5 million tonnes per year), and Japan (approximately 0.6 million tonnes per year). The large majority of acrylonitrile is used as a feedstock or chemical aid in the production of nitrile-butadiene rubber (68% of 1994 imports in the sample country) and in acrylonitrile-butadiene-styrene and styrene-acrylonitrile polymers (30% of 1994 imports in the sample country).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

5.1 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; US DHHS, 1990; Bunce, 1996). The atmospheric half-life, based on hydroxyl radical reaction rate constants, is calculated to be between 4 and 189 h (Callahan et al., 1979; Cupitt, 1980; Edney et al., 1982; Howard, 1989; Grosjean, 1990b; Kelly et al., 1994.). Modelling of environmental partitioning (section 5.5) is based on a mean half-life for acrylonitrile in air of 55 h.

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).

5.2 Water

Acrylonitrile in water can be biodegraded by acclimatized microorganisms or volatilized (Going et al., 1979). In water, half-lives of 30–552 h are estimated based on aqueous aerobic biodegradation (Ludzack et al., 1961; Going et al., 1979; Howard et al., 1991). Modelling of environmental partitioning (section 5.5) is based on a mean half-life for acrylonitrile in water of 170 h (7 days). 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 criteria of 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 & Kincannon, 1983; Freeman & Schroy, 1984; Watson, 1993).
5.3 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 2 days (Donberg et al., 1992). Similar breakdown by microbial populations present in sediment is likely (DMER & AEL, 1996; EC, 2000). Results of experimental studies (Zhang et al., 1990) or soil sorption coefficients calculated by quantitative structure–activity relationships (Koch & Nagel, 1988; Walton et al., 1992) or based on water solubility (Kenaga, 1980) indicate little potential for adsorption of acrylonitrile to soil or sediments.

A half-life of acrylonitrile in soil of 6–7 days has been reported (Howard et al., 1991; Donberg et al., 1992) (see Table 1). Based on biodegradability and the soil partition coefficient (EC, 1996), the half-life of acrylonitrile in soil was classified in the category of 300 days (EC, 2000). Modelling of environmental partitioning (section 5.5) is based on a mean half-life for acrylonitrile in soil of 170 h (7 days). The half-life in the oxic zone of sediment can be assumed to be similar.

5.4 Biota

Bioaccumulation of acrylonitrile is not anticipated, given experimentally derived values of the octanol/water partition coefficient (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 & Hashimoto, 1984; Sangster, 1989) and a log bioconcentration factor (log BCF) of 0 calculated from the water solubility of acrylonitrile (EC, 2000).

Log BCF values were 0.48–1.68 in 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 be an overestimate, due to uptake of $^{14}$C-labelled degradation products in addition to acrylonitrile and to cyanoethylation of macromolecules (EC, 2000).

5.5 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 Mackay & Paterson (1991). Assumptions, input parameters, and results are presented in DMER & AEL (1996) and summarized here. Values for input parameters were as follows: molecular mass, 53.06 g/mol; water solubility, 75.5 g/litre; vapour pressure, 11.0 kPa; log $K_{ow}$, 0.25; Henry’s law constant, 11 Pa$m^2$/mol; half-life in air, 55 h; half-life in water, 170 h; half-life in soil, 170 h; half-life in sediments, 550 h. Modelling was based on an assumed default emission rate of 1000 kg/h 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.

Modelling indicates that when acrylonitrile is continuously discharged into a specific medium, most of it (84–97%) can be expected to be present in that medium (DMER & AEL, 1996). More specifically, Level III fugacity modelling by DMER & AEL (1996) predicts that:

• when 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 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; and

• when 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.

Owing to the paucity of data on concentrations of acrylonitrile in environmental media, fugacity modelling with version 4 of the ChemCAN3 model (Mackay et al., 1995) was also conducted with the conservative assumption that all known releases in 1996 (Environment Canada, 1997) in Canada occurred in southern Ontario. Release to air was considered to be approximately 19 tonnes per year, with simultaneous release to water of 0.53 tonnes per year. 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 (4, 55, and 189 h) under summer, winter, and year-round conditions. Modelling predicted distribution primarily to air (41.9–78.1%) and water (21.6–57.9%).
6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Data on concentrations in the environment primarily from the source country of the national assessment on which the CICAD is based (i.e., Canada) are presented here as a basis for the sample risk characterization. Patterns of exposure in other countries are expected to be similar, although quantitative values may vary. Detection of acrylonitrile in the general environment is restricted primarily to the vicinity of industrial sources.

6.1 Environmental levels

6.1.1 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 (H. Michelin, personal communication, 1999). Predicted concentrations at 11, 25, 41, and 1432 m from the stacks under the assumption that inversion occurs just above stack height and the plume is therefore forced to the ground were 6.6, 2.2, 0.4, and 0.1 µg/m³. Predicted concentrations at 11, 35, 41, and 3508 m under the assumption of close to stable or neutral atmospheric conditions were 9.3, 2.9, 0.6, and 0.1 µg/m³. Accuracy testing indicates that the model may overpredict actual values by as much as 2 orders of magnitude.

In six samples taken on 2 different days in the vicinity of a nitrile-butadiene rubber production plant in Sarnia, Ontario, 5 m outside the company fence line, 2 m above ground, and directly downwind of the stacks, acrylonitrile was not detected (detection limit 52.9 µg/litre) (B. Sparks, personal communication, 1997; M. Wright, personal communication, 1998).

Levels of acrylonitrile in ambient air sampled for 6 days near a chemical manufacturing plant in Cobourg, Ontario, ranged from 0.12 to 0.28 µg/m³. Measurements from stacks of the facility in 1993 ranged from <251 to 100763 µg/m³ (Ortech Corporation, 1994). The concentration at point of impingement estimated on the basis of dispersion modelling of these data was 1.62 µg/m³.

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/m³. In this study, the maximum and only detectable concentration of acrylonitrile was 1.9 µg/m³ in one sample (OMOE, 1992a).

Levels of acrylonitrile were <0.64 µg/m³ in all seven samples of ambient air taken in the industrialized area of Windsor, Ontario, in August 1991 (Ng & 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/m³) in any sample analysed (Bell et al., 1991).

Air samples were collected within the inhalation zone by a personal unit for 1–2 h while the participants were commuting to and from work (n = 19) and while they were 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/m³) in any sample analysed. Acrylonitrile was also not detected (detection limit 0.9 µg/m³) 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 while the participants were at a barbecue, and the fourth was an overall composite sample of the afternoon and morning commutes and the overnight residential indoor air (Bell et al., 1991).

6.1.2 Indoor air

Environmental tobacco smoke appears to be a source of acrylonitrile in indoor air (California Air Resources Board, 1994).

Acrylonitrile was not detected in samples collected overnight (duration up to 16 h) from June to August 1990 in four different residences near Toronto, Ontario (detection limit 0.9 µg/m³) (Bell et al., 1991).

6.1.3 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/litre).

Of the effluents sampled from five companies using acrylonitrile and discharging to the environment in 1989–1990 in Ontario, the compound was detected in 12 of 256 samples (OMOE, 1993). Daily concentrations ranged from 0.7 to 3941 µg/litre; annual site averages ranged from 2.7 to 320 µg/litre. Intake water at the 26 organic chemical manufacturing plants sampled over the same period did not contain detectable amounts of acrylonitrile (207 samples; detection limit 4.2 µg/litre) (OMOE, 1992b). Biological treatment reactors have recently been introduced for two of the five companies.
with remaining commercial activity involving acrylonitrile, and levels from both sites are below 4.2 µg/litre (Y. Hamdy, personal communication, 1998).

In a large study of Canadian municipal water supplies in 1982–1983, 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/litre) (Otson, 1987). Acrylonitrile was not detected (detection limit 2.1 µg/litre) in groundwater samples downgradient of a wastewater treatment pond at an Ontario chemical industry site (Environment Canada, 1997).

6.1.4 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/litre) in only one sample of treated water in Nova Scotia in June 1988 (detection limit 0.5–1.0 µg/litre) (Environment Canada, 1989a,b,c,d).

Acrylonitrile was not identified in treated (or raw) water at facilities near the Great Lakes in 1982–1983 \((n=42);\) detection limit 5 µg/litre during the initial sampling and <1 µg/litre during later sampling after the technique was modified over three sampling periods (Otson, 1987). Analyses were by gas chromatography–mass spectrometry.

6.1.5 Soil and sediment

Significant concentrations of acrylonitrile are not expected in soil or sediment based on the release patterns and the environmental partitioning, behaviour, and fate of the substance (section 5.3).

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 (G. Dinwoodie, personal communication, 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, 1997).

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

6.1.6 Food

Acrylonitrile may potentially be introduced into foodstuffs from acrylonitrile-based polymers used in food packaging. Page & 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.

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 & Charbonneau, 1985).

6.1.7 Multimedia study

In a multimedia study carried out for Health Canada (Conor Pacific Environmental & 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-h period. Acrylonitrile was not detected in air (detection limit 1.36 µg/m³), water (detection limit 0.7 ng/ml), beverages (detection limit 1.8 ng/ml), or food (detection limit 0.5 ng/g).

6.2 Human exposure: environmental

Point estimates of average daily intake (per kilogram body weight) were developed for the sample country (i.e., Canada), based on the few monitoring data available and reference values for body weight, inhalation volume, and amounts of food and drinking-water consumed daily by six age groups (Environment Canada & Health Canada, 2000). Similar estimates were developed based on the results of the ChemCAN3 fugacity modelling (Environment Canada & Health Canada, 2000). In view of the limitations of the data on which these estimates are based, however (i.e., lack of detection of acrylonitrile in most media in which it was monitored or fugacity modelling), these estimates are primarily useful as a basis for identification of principal routes and media of exposure.

Although it is uncertain, based on this limited information, air (ambient and indoor) is likely the principal medium of exposure. 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 5.5). On the basis of the estimates derived above, 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. Data presented above (see section 6.1.1) on concentrations in the vicinity of point sources indicate that populations in the area might be exposed to levels of acrylonitrile in the range of tenths of \( \mu g/m^3 \) (Ng & Karellas, 1994; Ortech Corporation, 1994). Additional data from the USA indicate that levels vary considerably in the vicinity of various point sources (Health Canada, 2000).

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

6.3 Human exposure: occupational

Exposure to acrylonitrile may occur during its production and its use in the manufacture of other products; potential for exposure is greatest in factories where acrylonitrile is used to make other products, where it may not be as easily contained (Sax, 1989). IARC (1999) indicates that approximately 35,000 workers in Europe and as many as 80,000 workers in the USA are potentially exposed to acrylonitrile. These individuals include acrylic resin makers, synthetic organic chemists, pesticide workers, and rubber, synthetic fibre, and textile makers. The primary routes of potential exposure in the occupational environment are inhalation and dermal.

Based on data collected in 1995 for countries in the European Union (EC, 2000), 8-h time-weighted-average (TWA) exposures for production and various end uses were as follows: production, \( \#1 \).45 ppm (1 mg/m\(^3\)); fibre, \( \#1 \).01 ppm (\#2.2 mg/m\(^3\)); latex, \( \#1 \).10 ppm (\#2.2 mg/m\(^3\)); acrylonitrile-butadiene-styrene polymer, \( \#1 \).40 ppm (\#0.88 mg/m\(^3\)); and acrylamide, \( \#1 \).20 ppm (\#0.44 mg/m\(^3\)).

For six European producers of acrylonitrile, average personal monitoring levels at the workplace varied from <0.12 to 0.49 ppm (<0.26 to 1.1 mg/m\(^3\)); the maximum recorded level was 5.5 ppm (12.1 mg/m\(^3\)). For production of acrylonitrile fibres, the average personal monitoring levels were from <0.26 to 0.43 ppm (<0.57 to 0.95 mg/m\(^3\)), with a maximum value of 3.6 ppm (7.9 mg/m\(^3\)). For production of acrylonitrile-butadiene-styrene polymers, the average levels for personal monitoring were 0.08–0.3 ppm (0.18–0.66 mg/m\(^3\)), with a maximum recorded value of 8.6 ppm (19.0 mg/m\(^3\)). The higher levels in use were consistent with production of acrylonitrile being initially in a closed system, while manufacture of, for example, acrylonitrile-butadiene-styrene polymers is carried out in a partially closed system, with local exhaust ventilation and emission (EC, 2000).

Recent information on the occupational exposure scenario for Australia (NICNAS, 2000) correlates well with the above data. Australia imports approximately 2000 tonnes of acrylonitrile per year, 70% of which is used for the manufacture of styrene-acrylonitrile polymer, which is further compounded into plastic resins. The remainder is used in the manufacture of latex polymers (polymers dispersed in water) for adhesive and coating applications. Of 187 breathing-zone air samples collected in 1991–1999 during normal operations, 68% were <0.1 ppm (<0.22 mg/m\(^3\)), 95% <0.5 ppm (<1.1 mg/m\(^3\)), and 97% <1 ppm (<2.2 mg/m\(^3\)), expressed as 8-h TWAs. Personal exposure levels were slightly higher in latex than in styrene-acrylonitrile polymer and plastic resin manufacturing plants.

Surveys of full-shift personal exposures in four US acrylonitrile production plants have also been reported (Zey et al., 1989, 1990a,b; Zey & McCammon, 1990). Mean 8-h TWA personal exposures for monomer production operators were 1.1 ppm (2.4 mg/m\(^3\)) or less from about 1978 to 1986, with some individual TWA levels up to 37 ppm (82 mg/m\(^3\)). In three of these plants, levels for maintenance employees averaged below 0.3 ppm (0.7 mg/m\(^3\)), but in one plant, the average TWA exposure for these workers was 1 ppm (2.2 mg/m\(^3\)). Average 8-h TWA exposures for loaders of acrylonitrile into tank trucks, rail cars, or barges varied from 0.5 to 5.8 ppm (1.1 to 12.8 mg/m\(^3\)). For some of the higher values for production and maintenance workers and loaders in these plants, respirator use was noted. Although there were several changes introduced to reduce exposure levels, no trends over the years were noted.

In three US fibre plants for which data for full-shift personal samples were available between the years 1977 and 1986, the average 8-h TWA exposures were between 0.3 and 1.5 ppm (0.7 and 3.3 mg/m\(^3\)), based on nearly 3000 individual samples. The dope (viscous pre-fibre solution) and spinning operators had exposures averaging 0.4–0.9 ppm (0.9–2.0 mg/m\(^3\)). The lower exposure occurred in the plant that dried the polymer before the spinning operation, resulting in a lower monomer content in the polymer. The other plant had a continuous wet operation without the drying stage. Exposure of maintenance workers averaged 0.2 ppm (0.4 mg/m\(^3\)). Tank farm operators, who are also likely to unload acrylonitrile monomer from trucks, rail cars, or barges, had homogeneous exposure levels (0.5 ppm [1.1 mg/m\(^3\)]) across plants (IARC, 1999).

Haemoglobin adduct measurement is an extremely sensitive method for monitoring exposure to acrylo-
nitrile. The level of N-(2-cyanoethyl)valine reflects exposure during a 4-month period (i.e., the life span of the erythrocytes) prior to blood sampling. Licea Pérez et al. (1999) reported levels of 0.76 ± 0.36 pmol/g globin in 18 non-smokers (who claimed that they were not exposed to environmental tobacco smoke). Adduct levels in smokers range from 8 to a few hundred pmol/g globin and are related to cigarette consumption. Adduct levels in 10 smoking mothers (92.5–373 pmol/g globin) and their newborns (34.6–211 pmol/g globin) were strongly correlated and demonstrated that transplacental transfer of acrylonitrile occurs (Tavares et al., 1996). Adduct levels ranging from 20 to 66 000 pmol/g have been observed in occupationally exposed workers (Bergmark et al., 1993; Tavares et al., 1996; Thier et al., 1999). Polymorphism with respect to the glutathione transferases GSTTI and GSTMI had little effect on adduct levels (Thier et al., 1999; Fennell et al., 2000).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Based on studies conducted primarily in laboratory animals, acrylonitrile is rapidly absorbed by all routes of administration and distributed throughout examined tissues. In inhalation studies with volunteers, 50% of acrylonitrile was absorbed (Jakubowski et al., 1987). 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 h following administration (Kedderis et al., 1993a; Burka et al., 1994).

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 (Langvardt et al., 1980; Geiger et al., 1983; Fennell et al., 1991; Kedderis et al., 1993a) (Figure 2). Oxidative metabolism of acrylonitrile leads to the formation of 2-cyanoethylene oxide, which is either conjugated with glutathione (Fennell & Sumner, 1994; Kedderis et al., 1995) to form a series of metabolites including cyanide and thiocyanate or directly hydrolysed by epoxide hydrolase (Borak, 1992; Kim et al., 1993). Recent data indicate that cytochrome P4502E1 is the sole P-450 catalysing the oxidation of acrylonitrile (Sumner et al., 1999).

Available data 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 (Lambotte-Vandepaepe et al., 1985; Tardif et al., 1987). 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 (Kedderis et al., 1993b).

Liver microsomes from rats, mice, and humans produced 2-cyanoethylene oxide at a greater rate than lung or brain microsomes, indicating that the liver is the major site of formation in vivo of 2-cyanoethylene oxide (Roberts et al., 1989; Kedderis & 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 & Batra, 1993). Studies with inhibitory antibodies in human hepatic microsomes indicate that the 2E1 isoform of cytochrome P-450 is primarily involved in epoxidation of acrylonitrile (Guengerich et al., 1991; Kedderis et al., 1993c).

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 & Held, 1998). Research is in progress to determine partition coefficients for other human tissues.

1 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.
Figure 2 Metabolic pathway of acrylonitrile (IARC, 1999)

- **H₂C = CH - CN** (Acrylonitrile) → GS - CH₂CH₂CN → COOH
- **H₂C - CH - CN** (2-Cyanoethylene oxide) → GS - CH₂CH₂CN → HOCCH₂ - S - CH₂CH₂CN → HOOCCH₂ - S - CH₂CH₂CN
- Glutathione S-transferase
- Cytochrome P450
- N-Acetyl-S-(2-cyanoethyl)cysteine
- S-(2-Cyanoethyl)thioacetic acid
- N-Acetyl-S-(2-hydroxyethyl)cysteine
- N-Acetyl-S-(2-carboxymethyl)cysteine
- Thiodiglycolic acid
8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

8.1 Single exposure

The acute toxicity of acrylonitrile is relatively high, with 4-h LC₅₀ ranging from 140 to 410 ppm (300 to 900 mg/m³) (Knobloch et al., 1971, 1972) and oral LD₅₀ ranging from 25 to 186 mg/kg body weight (Maltoni et al., 1987). Dermal LD₅₀ values for various species were in the range of 148–693 mg/kg body weight, with the rat being most sensitive (BUA, 1995). Signs of acute toxicity include respiratory tract irritation and central nervous system dysfunction, resembling cyanide poisoning. Superficial necrosis of the liver and haemorrhagic gastritis of the forestomach have also been observed following acute exposure (Silver et al., 1982).

Acrylonitrile-induced neurotoxicity following acute exposure via inhalation or ingestion 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, diarrhoea, and gastric secretion. These effects are maximal within 1 h of dosing. The second phase of toxicity is delayed by 4 h or more and includes signs of central nervous system disturbance, such as trembling, ataxia, convulsions, and respiratory failure (TERA, 1997).

8.2 Irritation and sensitization

Available data indicate that acrylonitrile is a skin, respiratory, and severe eye irritant. It induces skin sensitization in guinea-pigs, but available data are inadequate to assess its sensitization potency.

8.2.1 Skin irritancy

Identified data on irritancy to the skin are restricted to three studies in which acrylonitrile was applied to the shaved skin of rabbits (McOmie, 1949; Zeller et al., 1969; Vernon et al., 1990). In early periods following administration (e.g., 15 min), slight local vasodilation and oedema were observed; at longer periods (20 h), effects were more severe, with necrosis reported.

8.2.2 Eye irritancy

Identified investigations of eye irritancy are restricted to principally early unpublished studies (McOmie, 1949; BASF, 1963; Zeller et al., 1969; DuPont, 1975). Results of these investigations were consistent with those reported in the most recent study conducted by DuPont (1975), in which 0.1 ml of undiluted acrylonitrile was placed in the right conjunctival sac of each of two albino rabbits. After 20 s, the treated eye of one rabbit was washed with tap water for 1 min. Acrylonitrile produced moderate corneal opacity, moderate iritis, and severe conjunctival irritation in the unwashed treated eye. In the washed eye, there was slight temporary corneal opacity, transient, moderate iritic congestion, and moderate conjunctival irritation. These effects were not completely reversible in the unwashed eye; by washing the eye, the effects were considerably lessened, as was the duration of these ocular effects.

8.2.3 Respiratory tract irritancy

While not examined directly, in repeated-dose toxicity studies, there has been evidence of irritant effects on the upper respiratory tract, including nasal discharge in rats acutely exposed (Food and Drug Research Laboratories, 1985) and rhinitis and hyperplastic changes in the nasal mucosa following chronic exposure (Quast et al., 1980b).

8.2.4 Sensitization

In a guinea-pig maximization test, animals challenged with 0.5% and 1.0% acrylonitrile had a 95% positive sensitization rate. Exposure to 0.2% on challenge caused an 80% sensitization rate (Koopmans & Daamen, 1989).

8.3 Short-term exposure

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 130 ppm (280 mg/m³) acrylonitrile (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 content in gastric mucosa and hyperplasia in the adrenal cortex have been reported at levels as low as 2 mg/kg body weight 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 body weight 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 body weight 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 body weight (Ghanayem et al., 1995, 1997).

Gastric lesions in the rat have been accompanied by a decrease of gastric reduced glutathione concentration. It has been suggested that depletion and/or inactivation of critical endogenous sulfhydryl groups cause configurational changes of cholinergic receptors and increase agonist binding affinity, which may lead to gastric mucosal erosion (Ghanayem et al., 1985; Ghanayem & Ahmed, 1986).

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 (Szabo et al., 1983).

8.4 Medium-term exposure

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 National Toxicology Program (NTP) gavage study in mice. Lack of validation and inadequate detail limit the utility of these studies for hazard evaluation or characterization of dose–response.

8.5 Long-term exposure and carcinogenicity

Data on effects of long-term exposure to acrylonitrile are currently restricted to those conducted in rats, although an NTP bioassay in mice is under way (NTP, 1998). 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 on page 18 in section 8.5.2).

8.5.1 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/m³) acrylonitrile 6 h/day, 5 days/week, for 2 years. Non-neoplastic histopathological changes related to the treatment were present 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 (44 mg/m³), and this dose is considered as a no-observed-effect level (NOEL) for inflammatory changes in the nasal turbinates. There was an early onset of chronic renal disease in the group exposed to 20 ppm (44 mg/m³) based upon histopathological examination. The renal effect was not apparent at the high dose because of early mortality. The chronic renal disease, which is commonly observed in older rats of this strain, was considered a secondary effect caused by increased water intake, although there was no pair-fed control study, and clinical analyses were inadequate to confirm the cause. In males, mortality at 80 ppm (176 mg/m³) was consistently and significantly increased from days 211–240 to the end of the experiment. Similar findings were noted for females beginning at days 361–390.

In both sexes, there was an increase in the combined incidence of malignant and benign tumours of the brain and spinal cord (Table 2) 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).

Although Maltoni et al. (1977) reported an increased incidence of tumours in the mammary gland, forestomach, and skin in Sprague-Dawley rats exposed to up to 40 ppm (88 mg/m³) for 52 weeks, low concentrations of acrylonitrile, short exposure time, and small group size (n = 30) limit the sensitivity of the study. In a follow-up study (Maltoni et al., 1987, 1988), 54 female Sprague-Dawley rat breeders and offspring were administered 60 ppm (132 mg/m³) by inhalation for 4–7 h/day, 5 days/week. The breeders and some of the offspring were exposed for 104 weeks, and 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. The incidence of various tumours was

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### 8.5.2 Drinking-water

Quast et al. (1980a) administered acrylonitrile in drinking-water to Sprague-Dawley rats for 2 years at dose levels of 0, 35, 100, or 300 mg/litre. 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 mg/litre. In the brain of females, there was a significantly increased incidence of focal gliosis and perivascular cuffing in the 35 and 100 mg/litre groups. Tumours (including astrocytomas) were observed as early as 7–12 months in females in the high-dose group; in other dose groups, tumours 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 3).

In a study conducted by Bio/Dynamics Inc. (1980a), Sprague-Dawley rats were administered acrylonitrile at dose levels of 0, 1, or 100 mg/litre in drinking-water for 19 and 22 months. Non-neoplastic effects included increased weight of kidney and testes. The concentration of 1 mg/litre can be considered as a NOEL and 100 mg/litre 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. In high-dose females, astrocytoma of the brain and carcinoma of the Zymbal gland were increased. At the high dose, there was an increased cumulative incidence of astrocytoma of the brain, carci-

Table 2: Quantitative estimates of carcinogenic potency, derived for tumour incidences reported in an inhalation bioassay with Sprague-Dawley rats

<table>
<thead>
<tr>
<th>Animal data</th>
<th>Parameter estimates</th>
<th>Human equivalent values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 6 months</td>
<td>control</td>
<td>0/98</td>
</tr>
<tr>
<td></td>
<td>44 mg/m\text{3} (20 ppm)</td>
<td>497 (4 astrocytoma)</td>
</tr>
<tr>
<td></td>
<td>176 mg/m\text{3} (80 ppm)</td>
<td>22/98 (15 astrocytoma, 7 benign)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 10 months (TERA, 1997)</td>
<td>control</td>
<td>0/97</td>
</tr>
<tr>
<td></td>
<td>44 mg/m\text{3} (20 ppm)</td>
<td>4/93</td>
</tr>
<tr>
<td></td>
<td>176 mg/m\text{3} (80 ppm)</td>
<td>15/83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 6 months</td>
<td>control</td>
<td>0/99</td>
</tr>
<tr>
<td></td>
<td>44 mg/m\text{3} (20 ppm)</td>
<td>8/100 (4 astrocytoma, 4 benign)</td>
</tr>
<tr>
<td></td>
<td>176 mg/m\text{3} (80 ppm)</td>
<td>21/99 (17 astrocytoma, 4 benign)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 6 months (TERA, 1997)</td>
<td>control</td>
<td>0/99</td>
</tr>
<tr>
<td></td>
<td>44 mg/m\text{3} (20 ppm)</td>
<td>8/99</td>
</tr>
<tr>
<td></td>
<td>176 mg/m\text{3} (80 ppm)</td>
<td>21/99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\* From Quast et al. (1980b).
\* For this study, the resulting TC\text{eq}s were multiplied by [(6 h/day)/(24 h/day)] × [(5 days/week)/(7 days/week)] to adjust for intermittent to continuous exposure.
\* 95% LCL = lower 95% confidence limit.
\* To scale from rats to humans, the TC\text{eq}s were multiplied by [(0.11 m\text{3}/day)/(0.35 kg body weight)] × [(70 kg body weight)/(23 m\text{3}/day)], where 0.11 m\text{3}/day is the breathing rate of a rat, 0.35 kg body weight is the body weight of a rat, 23 m\text{3}/day is the breathing rate of a human, and 70 kg body weight is the body weight of a human.
\* These incidence data could not be verified in an examination of mortality data in Quast et al. (1980b).
noma of the Zymbal gland, and papilloma/carcinoma of the stomach in both sexes. 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. Dose spacing was poor in this study.

These results are consistent with those of a second bioassay by Bio/Dynamics Inc. (1980b), in which exposure–response was better characterized. Fischer 344 rats (200 per sex, control group; 100 per sex per dose group) were administered acrylonitrile in drinking-water for approximately 2 years. The dose levels were 0, 1, 3, 10, 30, and 100 mg acrylonitrile/litre (0, 0.1, 0.3, 0.8, 2.5, and 8.4 mg/kg body weight per day for males and 0, 0.1, 0.4, 1.3, 3.7, and 10.9 mg/kg body weight per day for females, as reported by US 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 primarily 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 haemoglobin, haematocrit, 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 mg/litre, but body weight was comparable to that in controls. The LOAEL is considered 100 mg/litre, the lowest-observed-effect level (LOEL), 30 mg/litre, and the NOEL for non-carcinogenic effects, 10 mg/litre. In both males and females, the incidences of astrocytoma of the brain (Table 4) and 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 mg acrylonitrile/litre (0, 14, or 70 mg/kg body weight per day; Health Canada, 1994) was administered in drinking-water to breeders (F1) and the offspring of Charles River Sprague-Dawley rats (Litton Bionetics Inc., 1980). Rats of the F1 generation in the high-exposure group had a significantly increased incidence of astrocytomas and Zymbal gland tumours. For control, low-exposure, and high-exposure groups, the incidence of astrocytoma 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 mg acrylonitrile/litre in drinking-water (0, 14, and 70 mg/kg body weight 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 mg acrylonitrile/litre. 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 mg/litre. 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 mg/litre 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. Based on histopathological examination of 215 animals in the 500 mg/litre group, there were 49 primary brain tumours, which were difficult to classify. 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 were poorly presented). Other end-points 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 mg/litre (approximately 0, 2.8, 14, and 70 mg/kg body weight per day; Health Canada, 1994) to male Sprague-Dawley rats (20 per group) for 2 years. There was no survival in the 500 mg/litre exposure group at 2 years. Ingestion of acrylonitrile at

1 “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).
Table 3: Quantitative estimates of carcinogenic potency, derived for tumour incidences reported in a drinking-water bioassay with Sprague-Dawley rats

<table>
<thead>
<tr>
<th>Dose</th>
<th>Incidence</th>
<th>Parameter estimates</th>
<th>Human equivalent values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TD_{0.05} = 0.84 mg/kg body weight per day</td>
<td>TD_{0.05c} = 0.56 mg/kg body weight per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95% LCL = 0.68 mg/kg body weight per day</td>
<td>95% LCL = 0.44 mg/kg body weight per day</td>
</tr>
</tbody>
</table>

| Males: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 6 months | control | 3.4 mg/kg body weight per day (35 ppm) | 21.2 mg/kg body weight 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_{0.05} = 0.84 mg/kg body weight per day | 95% LCL = 0.68 mg/kg body weight per day | Chi-square = 3.68 | Degrees of freedom = 2 | P-value = 0.16 |
| Females: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 6 months | control | 4.4 mg/kg body weight per day (35 ppm) | 10.8 mg/kg body weight per day (100 ppm) | [25.0 mg/kg body weight 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_{0.05c} = 0.56 mg/kg body weight per day | 95% LCL = 0.44 mg/kg body weight per day | Chi-square = 4.77 | Degrees of freedom = 1 | P-value = 0.08 |

a From Quast et al. (1980a).
b 95% LCL = lower 95% confidence limit.
c 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.
Table 4: Quantitative estimates of carcinogenic potency, derived for tumour incidences reported in a drinking-water bioassay with F344 rats

<table>
<thead>
<tr>
<th>Animal data</th>
<th>Dose</th>
<th>Incidence</th>
<th>Parameter estimates</th>
<th>Human equivalent values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males: Nervous system,</td>
<td>control</td>
<td>5/182 (3 astrocytoma, 2 benign)</td>
<td>TD$_{05}^a$ = 1.8 mg/kg body weight per day</td>
<td>TD$_{05}^a$ = 2.3 mg/kg body weight per day</td>
</tr>
<tr>
<td>combined incidence, astrocytoma and focal gliosis, excluding animals dying or sacrificed before 6 months</td>
<td>0.08 mg/kg body weight per day (1 ppm)</td>
<td>2/90 (2 astrocytoma)</td>
<td>95% LCL$^c$ = 1.2 mg/kg body weight per day</td>
<td>95% LCL$^c$ = 1.6 mg/kg body weight per day</td>
</tr>
<tr>
<td>0.25 mg/kg body weight per day (3 ppm)</td>
<td>1/89 (1 astrocytoma)</td>
<td>Chi-square = 3.0</td>
<td>Degrees of freedom = 3</td>
<td></td>
</tr>
<tr>
<td>0.84 mg/kg body weight per day (10 ppm)</td>
<td>2/90 (2 astrocytoma)</td>
<td>Degrees of freedom = 3</td>
<td>P-value = 0.39</td>
<td></td>
</tr>
<tr>
<td>2.49 mg/kg body weight per day (30 ppm)</td>
<td>10/89 (10 astrocytoma)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.37 mg/kg body weight per day (100 ppm)</td>
<td>22/90 (21 astrocytoma, 1 benign)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females: Brain and/or spinal cord, benign and malignant; excluding animals dying or sacrificed before 6 months</td>
<td>control</td>
<td>1/178 (1 astrocytoma)</td>
<td>TD$_{05}^a$ = 2.0 mg/kg body weight per day</td>
<td>TD$_{05}^a$ = 2.3 mg/kg body weight per day</td>
</tr>
<tr>
<td>0.10 mg/kg body weight per day (1 ppm)</td>
<td>1/90 (1 astrocytoma)</td>
<td>95% LCL$^c$ = 1.2 mg/kg body weight per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.40 mg/kg body weight per day (3 ppm)</td>
<td>2/90 (2 astrocytoma)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.30 mg/kg body weight per day (10 ppm)</td>
<td>5/88 (4 astrocytoma, 1 benign)</td>
<td>Chi-square = 1.8</td>
<td>Degrees of freedom = 3</td>
<td></td>
</tr>
<tr>
<td>3.70 mg/kg body weight per day (30 ppm)</td>
<td>6/90 (6 astrocytoma)</td>
<td>Degrees of freedom = 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.90 mg/kg body weight per day (100 ppm)</td>
<td>26/90 (24 astrocytoma, 2 benign)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^b$ The experimental length for this study was 23 months for females and 26 months for males, so the resulting TD$_{05}^a$s for males were multiplied by $(26 \text{ months}/24 \text{ months}) \times (26 \text{ months}/24 \text{ months})^2$, 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.
$^c$ 95% LCL = lower 95% confidence limit.
concentrations up to and including 100 mg/litre did not increase mortality. There was a significant increase in Zymbal gland tumours at 500 mg/litre (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.

### 8.5.3 Gavage

Groups of 100 male and female Sprague-Dawley rats were exposed in a Bio/Dynamics Inc. (1980c) study to acrylonitrile in water by intubation at 0, 0.1, or 10 mg/kg body weight per day for 20 months. The non-neoplastic effects in the high-dose group included higher mortality (both sexes), decreased body weight (males), and increased relative liver weight (males). The dose of 10 mg/kg body weight per day is a LOAEL, based upon decreased body weight and increased liver to body weight ratio in males, with 0.1 mg/kg body weight being the NOEL. In both sexes 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.

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 body weight per day, 3 days/week for 52 weeks. In females, the incidence of mammary gland carcinomas was 7/75 and 4/40 in control and exposed groups, respectively; the incidence of forestomach epithelial tumours was 0/75 and 4/40 in control and exposed groups, respectively. 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 contribution of the study to characterization of exposure–response.

### 8.6 Genotoxicity and related end-points

#### 8.6.1 In vitro studies

In the *Salmonella* assay, acrylonitrile has induced reverse mutations in strains TA1535 (Lijinsky & Andrews, 1980), TA1535, and TA100 (Zeiger & 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 in Chinese hamster V79 cells (Lee & Webber, 1985). In several studies, acrylonitrile was positive at the TK locus in mouse lymphoma L5178 TK+/- cells, either with or without rat S9 (Amacher & Turner, 1985; Lee & Webber, 1985; Myhr et al., 1985; Oberly et al., 1985), and in mouse lymphoma P388F cells with metabolic activation (Anderson & Cross, 1985). It was also mutagenic at the TK locus in human lymphoblasts with metabolic activation (Crespi et al., 1985; Recio & 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 & Sofuni, 1985). Results for sister chromatid exchanges in Chinese hamster ovary cells and human lymphocytes both with and without metabolic activation are mixed (Brat & Williams, 1982; Perocchi et al., 1985; Natarajan et al., 1985; Obe et al., 1985; Chang et al., 1990).

Results of *in vitro* assays for DNA single strand breaks (Bradley, 1985; Lakhansky & Hendricks, 1985; Bjorge et al., 1996) and DNA repair (unscheduled DNA synthesis) (Perocchi et al., 1982; Glauert et al., 1985; Martin & Campbell, 1985; Probst & Hill, 1985; Williams et al., 1985; Butterworth et al., 1992) 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 (Lawrence & McGregor, 1985; Matthews et al., 1985; Sanner & Rivedal, 1985; Abernethy & Boreiko, 1987; Yuan & Wong, 1991).

Binding of 2-cyanoethylene oxide to nucleic acids has also been reported in *in vitro* studies at high concentrations (Hogy & Guengerich, 1986; Solomon & Segal, 1989; Solomon et al., 1993; Yates et al., 1993, 1994). The formation of acrylonitrile–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 & Guengerich, 1986; Solomon & 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 alklylation by acrylonitrile 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); although there was no glutathione S-transferase activity in cytosol preparations from human liver exposed to acrylonitrile, there was some activity for 2-cyanoethylene oxide (Guengerich et al., 1981).

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1 Yates et al. (1994) also reported single and double strand breaks in plasmid DNA incubated with 2-cyanoethylene oxide.
8.6.2 In vivo studies

Limitations of the few in vivo studies conducted in which the genotoxicity of acrylonitrile has been investigated preclude definitive conclusions. Data from these studies are also inadequate for characterization of dose–response for comparison between studies or with the cancer bioassays.

Exposure to acrylonitrile in drinking-water resulted in increased frequency of mutants at the hprt locus in splenic T-cells (Walker & Walker, 1997). Five female F344 rats were exposed to 0, 33, 100, or 500 mg/litre (0, 8, 21, or 76 mg/kg body weight per day; Health Canada, 1994) in drinking-water for up to 4 weeks and serially sacrificed throughout exposure and up to 8 weeks post-exposure. At 4 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 & Ahmed, 1980), NMRI (Leonard et al., 1981), and C57B1/6 (Sharief et al., 1986) mice and a collaborative study following exposure by multiple routes 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 & 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 & Guengerich, 1986). In these studies, however, unscheduled DNA synthesis was measured by liquid scintillation counting to determine \[^3H\]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 spermatoctyes were negative when \[^3H\]thymidine uptake in individual cells was determined by autoradiography, which eliminates replicating cells from the analysis (Butterworth et al., 1992).

Urinary excretion of 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 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 body weight intraperitoneally, 7-(2-oxoethyl)-guanine adducts were detected in liver (Hogy & 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 body weight by subcutaneous injection (Prokopczyk et al., 1988). In contrast, in three studies from one laboratory, exposure of SD rats to 46.5 mg \[^14C\]acrylonitrile/kg body weight (50 µCi/kg body weight) resulted in apparent binding of radioactivity to DNA from liver, stomach, brain (Farooqui & 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 h following treatment.

It is not clear why acrylonitrile–DNA binding was detected in the brain in these studies and not in those by Hogy & 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 & 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, however, 7-oxoethylguanine and cyanoethyl adducts are of little consequence in the induction of acrylonitrile-induced brain tumours. Indeed, investigation of the role of cyanohydroxyethylguanine and other adducts in the induction of these tumours seems warranted.

8.7 Reproductive 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 exposed by gavage, however, degenerative changes in the seminiferous tubules and associated decreases in sperm counts were observed at 10 mg/kg body weight per day (NOEL = 1 mg/kg body weight per day) (Tandon et al., 1988). Although epididymal sperm motility was reduced in a 13-week study with B6C3F<sub>1</sub> mice, there was no dose–response and no effect upon sperm density at doses up to 12 mg/kg body weight 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 body weight 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., 1993). In the investigation in which concentration–response was best characterized (four exposure concentrations and controls with 2-fold spacing: 0, 12, 25, 50, and 100 ppm [0, 26.4, 55, 110, and 220 mg/m³]), the LOEL for maternal toxicity and for fetotoxicity was 25 ppm (55 mg/m³); the NOEL was 12 ppm (26.4 mg/m³) (Saillenfait et al., 1993).

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 was 14 mg/kg body weight 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 body weight 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).

8.8 Neurological effects and effects on the immune system

In recently published studies in rats exposed by inhalation to 25 ppm (55 mg/m³) 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. The effects on the lungs included an increase in the level of procoagulant activity in alveolar macrophages (Bhooma et al., 1992). The effects on the gastrointestinal tract consisted of an increase in the number of IgA-producing cells in the duodenum, jejunum, and ileum, an increase in the number of cells in S-phase in the duodenum and ileum, and a decrease in the response of splenocytes to mitogens (Hamada et al., 1998).

8.9 Mode of action

8.9.1 Cancer

Results of the few identified investigations in which the relative potency of acrylonitrile was compared with that of cyanoethylene oxide are consistent with the oxidative pathway of metabolism being critical in genotoxicity. In an assay with two strains of S. typhimurium, cyanoethylene oxide was mutagenic without activation, whereas acrylonitrile required activation (Cerna et al., 1981). In one study, cyanoethylene oxide was approximately 15-fold more mutagenic than acrylonitrile at the TK locus in cultured human lymphoblastoid cells (Recio & 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, cyanoethylene oxide alkylates DNA much more readily than acrylonitrile (Guengerich et al., 1981; Solomon et al., 1984, 1993).

Data on the binding of acrylonitrile to DNA are presented in section 8.6. However, available data are inadequate to implicate a particular adduct in the induction of acrylonitrile-induced brain tumours.

There are some suggestions from in vitro studies reported as abstracts that free radicals (OH, O₂, H₂O₂ and hydrogen peroxide 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 et al., 1996; Ahmed & Nouraldeen, 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 mg acrylonitrile/litre in drinking-water for 2 weeks. End-points 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-κB (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 brain of male Sprague-Dawley rats exposed to 3, 30, or 300 mg acrylonitrile/litre in drinking-water for 3 weeks.) Reactive oxygen species were increased 4-fold in brain. Levels of 8-hydroxy-2-deoxyguanosine were increased 3-fold in the brain. Activation of NF-κB was also observed in the brain.

In recently conducted studies, levels of 8-oxodeoxyguanosine 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):

# In male Sprague-Dawley rats exposed for 21 days to 0, 3, 30, or 300 mg/litre, there was a significant increase in 8-oxodeoxyguanosine in brain nuclear DNA at the two highest doses. In the liver, nuclear DNA 8-oxodeoxyguanosine concentrations were significantly increased at the two highest doses (Whysner et al., 1998a). 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 mg acrylonitrile/litre (3.4 mg/kg body weight per day) and higher for 2 years (Quast et al., 1980a).

# In male F344 rats exposed for 21 days to 0, 1, 3, 10, 30, or 100 mg/litre, there were no significant differences between groups for 8-oxodeoxyguanosine in the brain (Whysner et al., 1998a).

# In male Sprague-Dawley rats exposed for up to 94 days to 0 or 100 mg/litre, concentrations of 8-oxodeoxyguanosine in the brain were significantly increased after 3, 10, and 94 days of exposure (Whysner et al., 1998a). In the 2-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 mg/litre (8.5 mg/kg body weight per day).

The end-point for which changes were consistently observed in male Sprague-Dawley rats was the induction of oxidative DNA damage, including the accumulation of 8-oxodeoxyguanosine 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).

### 8.9.2 Neurotoxicity

Neurotoxicity following inhalation by male Sprague-Dawley rats of 0, 25, 50, or 100 ppm (0, 55, 110, or 220 mg/m³) acrylonitrile for 6 h/day, 5 days/week, for 24 weeks, followed by 8 weeks of recovery, was reported by Gagnaire et al. (1998). Body weight at the high dose was significantly reduced throughout exposure. Clinical observations at the mid and high doses included wet fur and hypersalivation during exposure. The authors noted that signs were similar to those associated with acute acetylcholine-like toxicity. There were time- and concentration-dependent reductions in motor conduction velocity, sensory conduction velocity, and amplitude of sensory action potential in tail nerve, which were partially reversible after 8 weeks of recovery (LOEL = 25 ppm [55 mg/m³]). The protocol did not include histological examination.

### 9. EFFECTS ON 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 skin sensitizer, the latter based on patch testing of workers (Balda, 1975; Bakker et al., 1991; EC, 2000; Chu & Sun, 2001).

In the few studies in which non-neoplastic effects of acrylonitrile have been systematically investigated, only acute dermal irritation has been reported consistently. In a cross-sectional investigation of workers exposed in acrylic fibre factories to approximately 1 ppm (2.2 mg/m³), 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 dermal irritation, consistent with observations in another cohort of acrylic fibre manufacturing workers (Kaneko & 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 & 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 & 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 fulfills, even in part, traditional criteria for causality in epidemiological studies.

BENN & OSBORNE (1998) reported results of a historical cohort study carried out in 2763 workers. Vital status was traced from 1978 through 1991, and follow-up was virtually complete. Only for lung cancer was there any indication of excess risk, and that was in the more highly exposed jobs and among the very young; however, based upon detailed analyses, there was no consistent support for the hypothesis of a causal relationship between exposure to acrylonitrile and lung cancer. Limited information on exposure levels, questionable quality of source records of work histories, and use of national rather than local rates for computing standardized mortality ratios (SMRs) compromise the inferences that can be drawn.

SWAEN ET AL. (1998) conducted a historical cohort study in 2842 workers occupationally exposed to acrylonitrile. Extensive industrial hygiene assessments were conducted to quantify past exposure to acrylonitrile. The follow-up between 1979 and 1995 was 99.6% complete; in 99.3% of cases, the cause of death could be ascertained. selected cause-specific SMRs in the exposed cohort were as follows: lung, 109.8 (95% confidence interval [CI] = 81–146, number of observed cases [Obs] = 47); colon, 126.0 (95% CI = 58–239, Obs = 9); leukaemia, 266.7 (95% CI = 54–390, Obs = 5); prostate, 83.3 (95% CI = 22–213, Obs = 4); bladder, 97.9 (95% CI = 20–286, Obs = 3); brain, 173.9 (95% CI = 64–378, Obs = 6). Some of these results are suggestive of excess risks, but the evidence of excess for any specific type of cancer is not strong. The data appear to have been well collected and analysed, and follow-up was good. While this is a reasonably large study, the power to detect dose–response relationships is still limited. Smoking was not considered.

The largest and most statistically powerful 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. Estimates of exposure to acrylonitrile were based on information from production procedures at the plants, interviews with management and labour, monitoring data from the companies, and monitoring conducted by the investigators specifically for the study. Vital status was successfully determined for 96% of the cohort. There was a total of 545 369 person-years of follow-up, of which one-third was in unexposed workers. This study had the most extensive exposure assessment protocol and the most extensive data on smoking. The mortality follow-up was complete, and the observation period was lengthy. There was a small (non-significant) excess of lung cancer in the highest quintile of cumulative exposure (relative risk = 1.5; 95% CI = 0.9–2.4), but no exposure–response trend. The exposure categories were as follows:

- 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/haematopoietic) because of small numbers of expected deaths.

WOOD ET AL. (1998) reported a historical cohort mortality and cancer incidence study in 2559 workers who had been occupationally exposed to acrylonitrile. There was a total of 75 009 person-years of mortality observation among the study subjects. There were no significantly elevated SMRs for specific cancer sites. This study was carried out in a company with good-quality information on work practices and industrial hygiene, complete work records, and good follow-up for mortality and cancer incidence. The latter is a unique advantage of this data set. The data appear to have been well collected and analysed. Limitations include the lack of data on workers’ race and smoking habits. Based upon a comparison with US rates, there was a 40% all-cause deficit and 34% cancer deficit seen in the Waynesboro cohort, which suggests a lack of reporting of cause of death. While this is a reasonably large study, power to detect dose–response relationships is still limited. While considerable effort was made to gather exposure data, there was no monitoring of acrylonitrile before 1975, and data for early years were inferred. An additional strength of this study is the number of person-years at the high level of exposure.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

The toxicity of acrylonitrile has been examined in a wide range of aquatic organisms, while the data set on the toxicity of acrylonitrile to terrestrial organisms is more limited.

10.1 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 require-
ments of OECD or similar test guideline protocols, and volatility was often not adequately addressed (Environment Canada, 1998). Below, a brief summary of the key studies carried out in general compliance with current OECD testing protocols and/or where concentrations were measured or could be adequately adjusted is presented. Primary studies selected include those where concentrations have been measured in static or static-renewal tests or flow-through tests with five turnovers per day (Henderson et al., 1961; Bailey et al., 1985; V. Nabholz, personal communication, 1998).

T.D. Sabourin (personal communication, 1987) determined the ratio of flow-through to static concentrations at the 96-h period to be 0.23. Therefore, studies with 96-h end-points can be adjusted by multiplying the reported concentration by 0.23, although the evidence provided by these studies is considered secondary. Tests done under static conditions or those with nominal concentrations only at a time period different from 96 h 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; Analytical BioChemistry Laboratories, 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 end-points was examined, including survival, growth, respiration, and mobility at exposure durations ranging from 24 to 840 h (1–35 days). The remainder of the studies (i.e., where there was no replication of doses or other limitations such as lack of aeration) were considered as supporting evidence only.

The 96-h LC_{50} for freshwater fish range from 10 to 20 mg/litre (nominal) (Henderson et al., 1961; Analytical BioChemistry Laboratories, 1980b; Zhang et al., 1996). Reported 48-h LC_{50} range between 14.3 and 33.5 mg/litre. At 840 h, the LC_{50} for fathead minnow (*Pimephales promelas*) was 0.89 mg/litre (Analytical BioChemistry Laboratories, 1980a).

Based on the primary evidence, the most sensitive aquatic end-point was that for long-term 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 end-point was foreleg growth, where the lower and upper chronic limits around the 28-day EC_{50} were 0.4 mg/litre and 0.8 mg/litre, respectively. The 96-h and 48-h EC_{50} for immobility were 11.59 mg/litre and 14.22 mg/litre, respectively.

The effect of acrylonitrile on the growth (length and wet weight) and mortality of the early life stage (<18-h-old eggs) of the fathead minnow (Analytical BioChemistry Laboratories, 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 end-point in the study was the 840-h (35-day) lowest-observed-effect concentration (LOEC) for weight (20% reduction in wet weight) at 0.44 mg/litre; the corresponding no-observed-effect concentration (NOEC) was 0.34 mg/litre. For mortality, the 840-h NOEC (LC_{15}) was 0.44 mg/litre, and the LOEC (LC_{50}) was 0.86 mg/litre.

Henderson et al. (1961) reported mortality of fathead minnow exposed to acrylonitrile in a flow-through system in which solutions were renewed every 100 min. Test durations were 24, 48, 72, and 96 h and 5, 10, 15, 20, 25, and 30 days (720 h). Effects ranged from the 24-h LC_{50} of 33.5 mg/litre through decreasing concentrations to the most sensitive end-point in the study, the 720-h LC_{50} at 2.6 mg/litre.

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

Bailey et al. (1985) examined the effect of acrylonitrile on the mortality of bluegill (*Lepomis macrochirus*) in a flow-through system with measured concentrations. The 96-h LC_{50} was 9.3 mg/litre.

In addition to primary studies with adequate flow-through or measured concentrations, 96-h 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 (T.D. Sabourin, personal communication, 1987; V. Nabholz, personal communication, 1998). Based on this method, the adjusted 96-h LC_{50}s ranged from 1.18 to 5.4 mg/litre. The lowest 96-h LC_{50} of 1.18 mg/litre was that for grass carp (*Ctenopharyngodon idella*) (Zhang et al., 1996).

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

Ninety-six-hour tests in 7 of 14 invertebrate and 1 of 1 freshwater plant species can be adjusted to provide secondary evidence. Based on the secondary information, which must be interpreted with caution, it appears that, overall, invertebrates are more sensitive to acrylo-
Acrylonitrile

nitrile than vertebrates, although this was not discussed further by the authors. Effects in invertebrates range from the 96-h LC$_{50}$ of 0.16 mg/litre (adjusted concentration 0.04 mg/litre) in the pond snail (*Lymnaea stagnalis*) (Erben & Beader, 1983) to the 96-h immobility EC$_{50}$ at 17.94 mg/litre (adjusted concentration 4.1 mg/litre) in the common stream snail (*Lymnaea plicatula*) (Zhang et al., 1996).

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

### 10.2 Terrestrial organisms

Data on the toxicity of acrylonitrile to terrestrial vertebrate wildlife or avian species were not identified; those from mammalian toxicity studies are reviewed in section 8. Studies reviewed below are limited to those on insect species exposed to acrylonitrile in air.

In nine studies conducted on 13 insect species — including pulse beetle (*Callosobruchus chinensis*), rice weevil (*Sitophilus oryzae*), lesser grain borer (*Rhyzopertha dominica*), granary weevil (*Sitophilus granarius*), saw-toothed grain beetle (*Oryzaephilus surinamensis*), red flour beetle (*Tribolium castaneum*), confused flour beetle (*Tribolium confusum*), Mediterranean fruit fly (*Ceratitis capitata*), Oriental fruit fly (*Bactrocera dorsalis*), and honey bee (*Apis mellifera*) — short- and long-term exposure via fumigation with acrylonitrile affected survival, reproduction, and enzyme activity (Environment Canada, 1998). LC$_{50}$s in insects ranged from 0.107 to 36.7 mg/litre, with 10% of the LC$_{50}$ values in insects reported by Rajendran & Muthu (1998). Solutions were renewed every 24 h, with five test concentrations, 10 fronds per concentration, and four replicates. The 96-h growth inhibition EC$_{50}$ was 6.25 mg/litre (adjusted EC$_{50}$ is 1.44 mg/litre).

In mammalian species, the 24-h LC$_{50}$ is 1.44 mg/litre (1.07 × 10$^3$ µg/m$^3$) (95% CI = 0.094–0.122 mg/litre air) (Adu & Muthu, 1996). Solutions were renewed every 24 h, with five test concentrations, 10 fronds per concentration, and four replicates. The 96-h growth inhibition EC$_{50}$ was 6.25 mg/litre (adjusted EC$_{50}$ is 1.44 mg/litre).

Rajendran & Muthu (1981a) reported that for adults and pupae of rice weevil (*Sitophilus oryzae L.*) exposed to the LC$_{50}$ of 0.40 mg/litre air (4.0 × 10$^3$ µg/m$^3$) for 8 h, there was a 50% decrease in the number of progeny.

Of the knockdown times reported for insects, the most sensitive organisms were rice weevil (*Sitophilus oryzae L.*) adults, for which exposure to 1–1.5 mg/litre air (1–1.5 × 10$^3$ µg/m$^3$) for 4 h resulted in 100% mortality (Rajendran & Muthu, 1977).

Of phosphorylase, trehalase, and acetylcholinesterase enzymes involved in carbohydrate and energy metabolism, phosphorylase was the most susceptible. There was no detectable activity (100% decrease) of this enzyme at a concentration of 1.05 mg/litre air (1.05 × 10$^3$ µg/m$^3$) in adult red flour beetle (*Tribolium castaneum*), which survived exposure to the LC$_{50}$ of 0.79 mg/litre (7.9 × 10$^3$ µg/m$^3$) (Rajendran & Muthu, 1981b).

### 10.3 Microorganisms

There is considerable evidence of the effectiveness of acrylonitrile in industrial wastewater treatment systems (e.g., Biox reactors). Wyatt & Knowles (1995a,b) demonstrated that complex mixtures of microorganisms under different dilution rates and a combination of batch and continuous culture can 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/litre are not 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 & Stack, 1955). *Nocardia rhodochrous* can degrade acrylonitrile in a more limited manner, based on its use as a nitrogen rather than carbon source (DiGeronimo & Antoine, 1976).

Kincannon et al. (1983) reported almost complete biodegradation, with 99.9% and 99.1% removal of acrylonitrile after 8 h in batch reactors and 2 days in complete mixture activated sludge, respectively. Initial concentrations of acrylonitrile were 110 and 152 mg/litre, respectively; effluent concentrations post-treatment were 1.0 mg/litre after 8 h and <0.05 mg/litre after 2 days, respectively. In the batch reactor, biodegradation accounted for 75% and stripping accounted for 25% of removal of acrylonitrile. In the activated sludge system, biodegradation was responsible for 100% of the removal.

Tabak et al. (1980) reported 100% biodegradation within 7 days in a static screening flask test method.
when microbial inoculum from a sewage treatment plant was mixed with 5 and 10 mg acrylonitrile/litre.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification

11.1.1.1 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 (Balda, 1975; Bakker et al., 1991; Chu & Sun, 2001).

In the few studies in which non-neoplastic effects of acrylonitrile have been systematically 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.

11.1.1.2 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 resembling cholinergic overstimulation and the second being central nervous system dysfunction, resembling cyanide poisoning. Superficial necrosis of the liver and haemorrhagic gastritis of the forestomach have also been observed following single 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 end-points, 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 end-points, 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 haematological 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, haematological 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). In the most sensitive bioassays, a range of tumours (both benign and malignant) has 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 end-points 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 end-points that cannot be discounted. Limitations of the in vivo investigations also

\[1\] A carcinogenesis study in mice exposed to acrylonitrile by gavage is under way (NTP, 1998).
preclude their meaningful contribution to the weight of evidence of 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. The role of mutagenesis and the primary mutagenic lesion induced by acrylonitrile in acrylonitrile-induced carcinogenesis is 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., cyano-hydroxyethyl 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. However, on the basis of available data, tumours are likely induced by a mode involving direct interaction with DNA. 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. Available data in support of this latter hypothesis as a plausible pathway for induction of acrylonitrile-associated tumours are inadequate. There is no hypothesized sequence of events for which there are data to serve as a basis for assessment of the weight of evidence against traditional criteria of causality such as consistency, strength, specificity, dose–response, temporal patterns, biological plausibility, and coherence.

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 with exposure by gavage, decreases in sperm motility in an unpublished 13-week investigation with exposure by gavage, 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 on the gastrointestinal tract following ingestion have been observed at concentrations and doses at which histopathological effects have also been observed in other investigations.

In recent 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 (Gagnaire et al., 1998).

11.1.2 Dose–response analyses

11.1.2.1 Effects in humans

In a cross-sectional investigation of workers exposed in acrylic fibre factories to approximately 1 ppm (2.2 mg/m³) acrylonitrile, there was no consistent evidence of adverse effects based on examination of a wide
effects observed in the few conducted long-term nasal turbinates (Quast et al., 1980b), non-neoplastic to 130 ppm (280 mg/m³). Logical effects were observed in rats exposed for 5 days (Quast et al., 1980b). Inflammatory changes in the nasal turbinates were observed at 80 ppm (176 mg/m³). The NOEL for changes in nasal turbinates is 20 ppm (44 mg/m³); it is likely that secondary renal effects would be present at this concentration. At high dose levels, survival was also decreased, prior to the appearance of the first tumour (Quast et al., 1980b).

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., 1993). In the investigation in which concentration–response was best characterized (four exposure concentrations and controls with 2-fold spacing), the LOEL for maternal toxicity and for fetotoxicity was 25 ppm (55 mg/m³); the NOEL was 12 ppm (26.4 mg/m³) (Saillenfait et al., 1993).

In recent studies in rats exposed by inhalation to 25 ppm (55 mg/m³) and above for 24 weeks, there were partially reversible time- and concentration-dependent marginal reductions in motor and sensory conduction (Gagnaire et al., 1998).

2) 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 body weight 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 body weight 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 body weight 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 body weight per day (Ghanayem et al., 1995, 1997).

Similar to observations in the inhalation studies, non-neoplastic effects observed in the long-term 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

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.

There has been no consistent evidence of an association between exposure to acrylonitrile and cancer of any specific site in recent studies of four cohorts. However, a non-significant excess of lung cancer was noted in the most highly exposed quintile in the statistically most powerful investigation. A large deficit in cancer in one cohort in comparison with national rates also suggests an underreporting of cause of death.

It has been suggested that the results of the epidemiological studies contrast quantitatively with those of bioassays in animals. However, meaningful direct comparison of these two types of data is precluded primarily by inadequate data on mode of induction as a basis to characterize possible relevant sites of cancer in humans (i.e., site concordance between animals and humans), the relative paucity of data on exposure of workers in the relevant investigations, and the wide range of the confidence limits on the SMRs for cancers of possible interest in the epidemiological studies. (For example, the upper 95% confidence limit on the SMRs for brain cancer in the only recent cohort study in which it was reported [Swain et al., 1998] was 378, indicating that an almost 400% excess could not be excluded; the lower 95% confidence limit was 64.)

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/haematopoietic) was quite small because of small numbers of expected deaths.

11.1.2.2 Effects in experimental animals

11.1.2.2.1 Non-neoplastic effects

1) 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 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 5 days to 130 ppm (280 mg/m³) acrylonitrile.

With the exception of inflammatory changes in the nasal turbinates (Quast et al., 1980b), non-neoplastic effects observed in the few conducted long-term
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 body weight per day (NOEL = 1 mg/kg body weight per day) (Tandon et al., 1988). Although epididymal sperm motility was reduced in a 13-week study with B6C3F1 mice, there was no dose–response and no effect upon sperm density at doses up to 12 mg/kg body weight 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 body weight 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 was 14 mg/kg body weight 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 body weight 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 body weight per day and above for 12 weeks (Gagnaire et al., 1998).

11.1.2.2.2 Cancer

Cancer is considered the critical end-point for quantification of dose–response for risk characterization for acrylonitrile. This is based on the observation of tumours at non-toxic doses or concentrations in long-term 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 (Kedderis et al., 1996), 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. 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 quantification 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 2 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.,
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, tumorigenic doses \((\text{TD}_{0.05}, \text{the dose that causes a 5% increase in tumour incidence over background})\) 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 \(\text{TD}_{0.05}/\text{TC}_{0.05}\) 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 2, 3, and 4. 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, 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 \(\text{TD}_{0.05}/\text{TC}_{0.05}\). In all cases, incidences have been adjusted to exclude animals dying before 6 months (i.e., prior to observation of the first tumours). For comparison, \(\text{TC}_{0.05}\) 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 \(\text{TD}_{0.05}/\text{TC}_{0.05}\), those for inhalation have been adjusted to reflect differences in inhalation volumes and body weights between humans and exposed animals. The \(\text{TC}_{0.05}\) were multiplied by:

\[
\left(\frac{0.11 \text{ m}^3/\text{day}}{0.35 \text{ kg body weight}}\right) \times \left(\frac{70 \text{ kg body weight}}{23 \text{ m}^3/\text{day}}\right)
\]

where 0.11 m\(^3\)/day is the breathing rate of a rat, 0.35 kg body weight is the body weight of a rat, 23 m\(^3\)/day is the breathing rate of a human, and 70 kg body weight 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.

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

### 11.1.3 Sample 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 sample 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. However, should there be specific cases where ingestion may represent a significant source of exposure (e.g., during spills), the tumorigenic doses presented in Tables 3 and 4 may be informative in making judgements about risk as a basis for management.

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1 For reasons mentioned in section 8.5.1, including limitations of histopathological analysis, data on tumour incidence in Bigner et al. (1986) are considered inadequate for quantification of dose–response.
For compounds such as acrylonitrile, where data are insufficient to support a consensus view on a plausible mode of action for induction of tumors by other than direct interaction with genetic material, estimates of exposure are compared with quantitative estimates of cancer potency to characterize risk. The lowest TC_{50} (human equivalent value) was 2.7 ppm (6.0 mg/m³) for the combined incidence of benign and malignant tumors of the brain and/or spinal cord in female rats exposed by inhalation; the lower 95% confidence limit was 2.0 ppm (4.5 mg/m³) (Quast et al., 1980b; Table 2). This equates to a unit risk of 8.3 × 10⁻⁶ per mg/m³. The margins between carcinogenic potency and limited available data on predicted and measured concentrations of acrylonitrile primarily in the vicinity of point sources in the sample country (i.e., Canada) are presented in Table 5. On this basis, risks in the vicinity of industrial point are >10⁻³. 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.

Of the reported values for occupational exposure to acrylonitrile (section 6.3), the highest average level of exposure was 5.8 ppm (12.8 mg/m³) for loaders in a US acrylonitrile production plant (IARC, 1999). This concentration is approximately 2 times more than the lowest TC_{50} (human equivalent value) of 2.7 ppm (6.0 mg/m³) derived above for a continuous (24 h/day, 7 days/week), lifelong exposure.

### Table 5: The margins between carcinogenic potency and limited available data on predicted and measured concentrations of acrylonitrile

<table>
<thead>
<tr>
<th>Concentration of acrylonitrile (Reference)</th>
<th>Potency (Table 2)</th>
<th>Margin between potency and concentration</th>
<th>Category of equivalent low-dose risk estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vicinity of sources</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.3 µg/m³, concentration predicted by dispersion modelling, 11 m from stack at industrial site in Ontario</td>
<td>TC_{50} = 6000 µg/m³</td>
<td>650</td>
<td>(&gt;10⁻³)</td>
</tr>
<tr>
<td></td>
<td>95% LCL = 4500 µg/m³</td>
<td>480</td>
<td>(&gt;10⁻³)</td>
</tr>
<tr>
<td>2.9 µg/m³, concentration predicted by dispersion modelling, 35 m from stack at industrial site in Ontario</td>
<td>TC_{50} = 6000 µg/m³</td>
<td>2100</td>
<td>(&gt;10⁻³)</td>
</tr>
<tr>
<td></td>
<td>95% LCL = 4500 µg/m³</td>
<td>1550</td>
<td>(&gt;10⁻³)</td>
</tr>
<tr>
<td>0.6 µg/m³, concentration predicted by dispersion modelling, 41 m from stack at industrial site in Ontario</td>
<td>TC_{50} = 6000 µg/m³</td>
<td>10 000</td>
<td>(10⁻² to 10⁻³)</td>
</tr>
<tr>
<td></td>
<td>95% LCL = 4500 µg/m³</td>
<td>7500</td>
<td>(10⁻² to 10⁻³)</td>
</tr>
<tr>
<td>0.1 µg/m³, concentration predicted by dispersion modelling, 3508 m from stack at industrial site in Ontario</td>
<td>TC_{50} = 6000 µg/m³</td>
<td>60 000</td>
<td>(10⁻² to 10⁻³)</td>
</tr>
<tr>
<td></td>
<td>95% LCL = 4500 µg/m³</td>
<td>45 000</td>
<td>(10⁻² to 10⁻³)</td>
</tr>
<tr>
<td>&lt;52.9 µg/m³, sampling at the site of nitrile-butadiene rubber production in Sarnia in 1997, 5 m from company fence line, 2 m above ground, downwind (B. Sparks, personal communication, 1997; M. Wright, personal communication, 1998)</td>
<td>TC_{50} = 6000 µg/m³</td>
<td>110</td>
<td>(&gt;10⁻³)</td>
</tr>
<tr>
<td></td>
<td>95% LCL = 4500 µg/m³</td>
<td>85</td>
<td>(&gt;10⁻³)</td>
</tr>
<tr>
<td>0.12 µg/m³, lowest concentration measured in ambient air sampled for 6 days near a chemical manufacturing plant in Cobourg, Ontario (Ortech Corporation, 1994)</td>
<td>TC_{50} = 6000 µg/m³</td>
<td>50 000</td>
<td>(10⁻² to 10⁻³)</td>
</tr>
<tr>
<td></td>
<td>95% LCL = 4500 µg/m³</td>
<td>38 000</td>
<td>(10⁻² to 10⁻³)</td>
</tr>
<tr>
<td>0.28 µg/m³, highest concentration measured in ambient air sampled for 6 days near a chemical manufacturing plant in Cobourg, Ontario (Ortech Corporation, 1994)</td>
<td>TC_{50} = 6000 µg/m³</td>
<td>21 000</td>
<td>(10⁻² to 10⁻³)</td>
</tr>
<tr>
<td></td>
<td>95% LCL = 4500 µg/m³</td>
<td>16 000</td>
<td>(10⁻² to 10⁻³)</td>
</tr>
<tr>
<td>&lt;251 µg/m³, lowest concentration measured at stack of chemical manufacturing plant in Cobourg, Ontario, in 1993 (Ortech Corporation, 1994)</td>
<td>TC_{50} = 6000 µg/m³</td>
<td>24</td>
<td>(&gt;10⁻³)</td>
</tr>
<tr>
<td></td>
<td>95% LCL = 4500 µg/m³</td>
<td>18</td>
<td>(&gt;10⁻³)</td>
</tr>
<tr>
<td><strong>Ambient air</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.9 µg/m³, maximum (and only detectable) concentration measured in 11 samples at six urban stations in Ontario in 1990 (OMOE, 1992a,b)</td>
<td>TC_{50} = 6000 µg/m³</td>
<td>3200</td>
<td>(&gt;10⁻³)</td>
</tr>
<tr>
<td></td>
<td>95% LCL = 4500 µg/m³</td>
<td>2400</td>
<td>(&gt;10⁻³)</td>
</tr>
<tr>
<td>&lt;0.64 µg/m³, seven samples in industrialized area of Windsor, Ontario, in 1991 (Ng &amp; Karellas, 1994)</td>
<td>TC_{50} = 6000 µg/m³</td>
<td>9400</td>
<td>(10⁻² to 10⁻³)</td>
</tr>
<tr>
<td></td>
<td>95% LCL = 4500 µg/m³</td>
<td>7000</td>
<td>(10⁻² to 10⁻³)</td>
</tr>
</tbody>
</table>

a 95% LCL = lower 95% confidence limit.

b Based on the concentration of 100 763 µg/m³ measured at the stack, risk category is high.

c Compound not detected in majority of samples. The detection limit was 0.0003 µg/m³. Risk category for most samples is low.
11.1.4 Uncertainties and degree of confidence in human health risk characterization

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 with 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 end-points were examined, a few more recent investigations of specialized end-points 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 $TD_{50}/TC_{50}$ 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 ($TC_{50}$ of 6.0 versus 8.9 mg/m$^3$). These values were also up to 2-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 $TC_{50}$ for the combined incidence of benign and malignant tumours of the brain and/or spinal cord in female rats was 4.5 mg/m$^3$, compared with the maximum likelihood estimate of 6.0 mg/m$^3$.

11.2 Evaluation of environmental effects

11.2.1 Assessment end-points

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.

11.2.1.1 Aquatic end-points

Data on aquatic toxicity are available for a variety of plants, invertebrates, fish, and amphibians. Identified sensitive end-points include growth inhibition in aquatic plants (Zhang et al., 1996), mortality in pond snails (Erben & Beader, 1983), mortality and reduced growth in fish (Henderson et al., 1961; Analytical BioChemistry Laboratories, 1980a), and reduction in growth of frogs (Zhang et al., 1996).

11.2.1.2 Terrestrial end-points

Data on terrestrial toxicity are available for invertebrates (particularly grain insect pests) as well as from mammalian toxicology. Identified sensitive end-points via fumigation or inhalation routes of exposure include mortality of insect eggs (Adu & Muthu, 1985), decreased number of insect offspring (Rajendran & Muthu, 1981a), maternal and fetal toxicity in rats (Saillenfait et al., 1993), and histopathological changes in the nasal turbinates in rats (Quast et al., 1980b).

11.2.2 Sample environmental risk characterization

First-tier (i.e., “hyperconservative”) analyses are presented below; since resulting quotients were less than one, higher-tier analyses were not conducted.

11.2.2.1 Aquatic organisms

Environmental exposure to acrylonitrile is expected to be greatest near point sources. In general, releases to water (all fresh water in the sample country) are low (0.529 tonnes, or 2.7% of all releases). Recently determined levels in effluent are very low, below the
Acrylonitrile

detection limit of 0.0042 mg/litre. Therefore, the value 0.0042 mg/litre will be used as the estimated exposure value (EEV) in the hyperconservative analysis for aquatic organisms.

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

For a hyperconservative analysis, the estimated no-effects value (ENEV) is derived by dividing this CTV by an application 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/litre.

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

\[
\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}} = \frac{0.0042 \text{ mg/litre}}{0.04 \text{ mg/litre}} = 0.1
\]

Since the hyperconservative quotient is less than 1, it is unlikely that acrylonitrile causes adverse effects on populations of aquatic organisms in the country on which the sample environmental risk characterization is based (i.e., Canada).

11.2.2.2 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/m³ (H. Michelin, personal communication, 1999) at an 11-m distance from an industrial stack.

For the exposure of terrestrial organisms to acrylonitrile in air, the CTV is the LOEL of 55 mg/m³, causing decreased maternal weight and fetal toxicity in rats exposed for 9 days during gestation (Saillenfait et al., 1993). 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. (1993) reported that none of these effects were observed at 26.4 mg/m³. 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 data set. As a result, the ENEV is 0.55 mg/m³ (550 µg/m³).

The hyperconservative quotient is calculated by dividing the EEV of 9.3 µg/m³ 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 1, it is unlikely that acrylonitrile causes adverse effects on populations of terrestrial organisms in the country on which the sample environmental risk characterization is based (i.e., Canada).

11.2.2.3 Discussion of uncertainty

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 focused 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.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

IARC (1999) classified acrylonitrile in Group 2B ("possibly carcinogenic to humans"), based on inadequate evidence in humans but adequate evidence in experimental animals.
In the WHO Air Quality Guidelines for Europe, it was concluded that owing to its carcinogenicity in animals and limited evidence of carcinogenicity in humans (at that time), acrylonitrile was considered as if it were a human carcinogen, and a unit risk value of $2 \times 10^{-5}$ per µg/m$^3$ was calculated on the basis of an early epidemiological study and an inhalation study in rats (WHO, 1987).

**REFERENCES**


Baida BR (1975) [Acrylonitrile as a contact allergen.] Hautartz, 26:599–601 (in German).


Bigner DD, Bigner SH, Burger PC, Shelburne JD, Friedman HS (1986) Primary brain tumors in Fischer 344 rats chronically exposed to acrylonitrile in their drinking water. Food and chemical toxicology, 24:129–137.


BUA (1995) Acrylonitrile. Frankfurt am Main, German Chemical Society, GDCh Advisory Committee on Existing Chemicals of Environmental Relevance (BUA Report 142).


DuPont (1975) Unpublished study performed in the Haskell Laboratory [cited in EC, 2000].


Environment Canada (1997) Results of the CEPA Section 16 Notice respecting the second Priority Substances List and di(2-ethylhexyl) phthalate. Hull, Quebec, Environment Canada, Commercial Chemicals Evaluation Branch, Use Patterns Section.
Acrylonitrile


Ortec Corporation (1994) Ambient air monitoring. A report submitted by Ortec Corporation to G.E. Plastics Canada Ltd. 39 pp. plus four appendices (Report No. 94-T62-P6994-CI); submitted by G.E. Plastics Canada Ltd. to Use Patterns Section, Environment Canada (Dossier No. 294, 3 July 1997).


Acrylonitrile


Quast JF, Wade CE, Humiston CG, Carreon RM, Hermann EA, Park CN, Schwetz BA (1980a) A two-year toxicity and oncogenicity study with acrylonitrile incorporated in the drinking water of rats. Midland, MI, Dow Chemical USA, Health and Environmental Sciences, Toxicology Research Laboratory (TSCATS Accession No. 48306; Document I.D. No. 88-920003736; Microfiche No. OTS0540235).

Quast JF, Schuetz DJ, Balmer MF, Gushow TS, Park CN, McKenna MJ (1980b) A two-year toxicity and oncogenicity study with acrylonitrile following inhalation exposure of rats. Midland, MI, Dow Chemical USA, Health and Environmental Sciences, Toxicology Research Laboratory (TSCATS Accession No. 45647; Document I.D. No. 88-920002471; Microfiche No. OTS0537281).


Zey JN, McCammon C (1990) *Industrial hygiene survey at Sterling Chemicals, Inc., Texas City Plant, Texas City, Texas*. Cincinnati, OH, National Institute for Occupational Safety and Health (Report No. 84.20.10) [cited in IARC, 1999].


APPENDIX 1 — SOURCE DOCUMENT

Environment Canada & Health Canada (2000)

Copies of the Canadian Environmental Protection Act Priority Substances List assessment report (Environment Canada & Health Canada, 2000) and unpublished supporting documentation for acrylonitrile may be obtained from:

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

or

Environmental Health Centre
Health Canada
Address Locator: 0801A
Tunney’s Pasture
Ottawa, Ontario
Canada K1A 0L2

Initial drafts of the supporting documentation and assessment report for acrylonitrile were prepared by staff of Health Canada and Environment Canada. The health-related sections of the supporting documentation and the assessment report were based in part upon a review of the epidemiological data, prepared under contract by J. Siemiatycki of the Institut Armand-Frappier.

H. Hirtle contributed additional information in the preparation of the draft CICAD.

Environmental sections of the assessment report were reviewed externally by W. Broadworth (G.E. Plastics Canada), N. Karellas (Ontario Ministry of the Environment), R. Keefe (Imperial Oil), A. Kerr (Bayer-Rubber Division), J. Murray (AN Group, Inc.), V. Nabholz (US Environmental Protection Agency), J. Pellerin (Université du Québec à Rimouski), J. Soule (DuPont Canada), and A. Tomlin (Agriculture and Agri-Food Canada).

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, MO; B. Ghanayem, National Institute of Environmental Health Sciences, Research Triangle Park, NC; G.L. Kedderis, Chemical Industry Institute of Toxicology, Research Triangle Park, NC; N. Krivanek, E.I. du Pont de Nemours & Co., Newark, DE; D. Strother, BP Chemicals Inc., Cleveland, OH; and J. Whysner, American Health Foundation, Valhalla, NY.

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 17 November 1998, in Cincinnati, OH:

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, US Environmental Protection Agency
V. Walker, New York State Department of Health
APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on acrylonitrile was sent for review to institutions and organizations identified by IPCS after contact with IPCS national contact points and Participating Institutions, as well as to identified experts. Comments were received from:

A. Aitio, International Programme on Chemical Safety, World Health Organization, Switzerland
M. Baril, International Programme on Chemical Safety/Institut de Recherche en Santé et en Sécurité du Travail du Québec, Canada
D.L. Bayliss, National Center for Environmental Assessment, US Environmental Protection Agency, USA
R. Benson, Drinking Water Program, US Environmental Protection Agency, USA
R. Cary, Health and Safety Executive, United Kingdom
R. Chhabra, National Institute of Environmental Health Sciences, National Institutes of Health, USA
H.B.S. Conacher, Bureau of Chemical Safety, Health Canada, Canada
C. Elliott-Minty, Health and Safety Executive, United Kingdom
H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, USA
R. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Germany
C. Hiremath, National Center for Environmental Assessment, US Environmental Protection Agency, USA
S. Kristensen, National Industrial Chemicals Notification and Assessment Scheme, Australia
J.F. Murray, AN Group, Inc., USA
H. Nagy, National Institute of Occupational Safety and Health, USA
S. Tarkowski, Nofer Institute for Occupational Medicine, Poland
W.F. ten Berge, DSM Corporate Safety and Environment, The Netherlands
K. Ziegler-Skylakakis, Commission of the European Communities/European Union

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Geneva, Switzerland, 8–12 January 2001

Members

Dr A.E. Ahmed, Molecular Toxicology Laboratory, Department of Pathology, University of Texas Medical Branch, Galveston, TX, USA
Mr R. Cary, Health and Safety Executive, Merseyside, United Kingdom (Chairperson)
Dr R.S. Chhabra, General Toxicology Group, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA
Dr S. Czerczak, Department of Scientific Information, Nofer Institute of Occupational Medicine, Lodz, Poland
Dr S. Dobson, Centre for Ecology and Hydrology, Cambridgeshire, United Kingdom
Dr O.M. Faroon, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA
Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA
Dr R.F. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany
Dr A. Hirose, Division of Risk Assessment, National Institute of Health Sciences, Tokyo, Japan
Dr P.D. Howe, Centre for Ecology and Hydrology, Cambridgeshire, United Kingdom (Rapporteur)
Dr D. Lison, Industrial Toxicology and Occupational Medicine Unit, Université Catholique de Louvain, Brussels, Belgium
Dr R. Liteplo, Existing Substances Division, Bureau of Chemical Hazards, Health Canada, Ottawa, Ontario, Canada
Dr I. Mangelsdorf, Chemical Risk Assessment, Fraunhofer Institute of Toxicology and Aerosol Research, Hanover, Germany
Ms M.E. Meek, Existing Substances Division, Safe Environments Program, Health Canada, Ottawa, Ontario, Canada (Vice-Chairperson)
Dr S. Osterman-Golkar, Department of Molecular Genome Research, Stockholm University, Stockholm, Sweden
Dr J. Sekizawa, Division of Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan
Dr S. Soliman, Department of Pesticide Chemistry, Faculty of Agriculture, Alexandria University, El-Shatby, Alexandria, Egypt
Dr M. Sweeney, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, USA
Professor M. van den Berg, Environmental Sciences and Toxicology, Institute for Risk Assessment Sciences, University of Utrecht, Utrecht, The Netherlands
Observers

Dr W.F. ten Berge, DSM Corporate Safety and Environment, Heerlen, The Netherlands

Dr K. Ziegler-Skylakakis, Commission of the European Communities, Luxembourg

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr Y. Hayashi, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr P.G. Jenkins, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr M. Younes, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland
# ACRYLONITRILE

**CAS No:** 107-13-1  
**RTECS No:** AT5250000  
**UN No:** 1093  
**EC No:** 608-003-00-4

<table>
<thead>
<tr>
<th>TYPES OF HAZARD/EXPOSURE</th>
<th>ACUTE HAZARDS/SYMPTOMS</th>
<th>PREVENTION</th>
<th>FIRST AID/FIRE FIGHTING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRE</strong></td>
<td>Highly flammable. Gives off irritating or toxic fumes (or gases) in a fire.</td>
<td>NO open flames, NO sparks, and NO smoking. NO contact with strong bases and strong acids.</td>
<td>Powder, alcohol-resistant foam, water spray, carbon dioxide.</td>
</tr>
<tr>
<td><strong>EXPLOSION</strong></td>
<td>Vapour/air mixtures are explosive. Risk of fire and explosion on contact with strong base(s) and strong acid(s).</td>
<td>Closed system, ventilation, explosion-proof electrical equipment and lighting. Use non-sparking handtools.</td>
<td>In case of fire: keep drums, etc., cool by spraying with water.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXPOSURE</th>
<th>AVOID ALL CONTACT!</th>
<th>IN ALL CASES CONSULT A DOCTOR!</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td>MAY BE ABSORBED! Redness. Pain. Blisters. (Further see Inhalation).</td>
<td>Protective gloves. Protective clothing.</td>
</tr>
<tr>
<td><strong>Eyes</strong></td>
<td>Redness. Pain.</td>
<td>Safety goggles, or eye protection in combination with breathing protection.</td>
</tr>
<tr>
<td><strong>Ingestion</strong></td>
<td>Abdominal pain. Vomiting. (Further see Inhalation).</td>
<td>Do not eat, drink, or smoke during work. Wash hands before eating.</td>
</tr>
</tbody>
</table>

## SPILLAGE DISPOSAL
Evacuate danger area! Consult an expert! Ventilation. Collect leaking liquid in covered containers. Absorb remaining liquid in sand or inert absorbent and remove to safe place. Do NOT wash away into sewer. Do NOT let this chemical enter the environment. Chemical protection suit including self-contained breathing apparatus.

**F Symbol**  
**T Symbol**  
**N Symbol**  
**R:** 45-11-23/24/25-37/38-41-43-51/53  
**S:** 9-16-53-45-61  
**Note:** D and E  
**UN Hazard Class:** 3  
**UN Subsidiary Risks:** 6.1  
**UN Pack Group:** I  

## PACKAGING & LABELLING
Unbreakable packaging; put breakable packaging into closed unbreakable container. Do not transport with food and feedstuffs.

## EMERGENCY RESPONSE
**Transport Emergency Card:** TEC (R)-61  
NFPA Code: H 4; F 3; R 2  
Fireproof. Separated from strong oxidants, strong bases, food and feedstuffs. Cool. Keep in the dark. Ventilation along the floor. Store only if stabilized.

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission  
© IPCS 2000  
SEE IMPORTANT INFORMATION ON THE BACK.
### IMPORTANT DATA

#### Physical State; Appearance
COLOURLESS OR PALE YELLOW LIQUID, WITH PUNGENT ODOUR.

#### Physical dangers
The vapour is heavier than air and may travel along the ground; distant ignition possible.

#### Chemical dangers
The substance polymerizes due to heating or under the influence of light and bases, causing fire and explosion hazard. The substance decomposes on heating producing toxic fumes including hydrogen cyanide, nitrogen oxides. Reacts violently with strong acids, and strong oxidants. Attacks plastics and rubber.

#### Occupational exposure limits
TLV: (as TWA) 2 ppm; skin A3 (ACGIH 2000).

### PHYSICAL PROPERTIES

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling point</td>
<td>77°C</td>
</tr>
<tr>
<td>Melting point</td>
<td>-84°C</td>
</tr>
<tr>
<td>Relative density (water = 1)</td>
<td>0.8</td>
</tr>
<tr>
<td>Solubility in water, g/100 ml at 20°C</td>
<td>7</td>
</tr>
<tr>
<td>Vapour pressure, kPa at 20°C</td>
<td>11.0</td>
</tr>
<tr>
<td>Relative vapour density (air = 1)</td>
<td>1.8</td>
</tr>
<tr>
<td>Relative density of the vapour/air-mixture at 20°C (air = 1)</td>
<td>1.05</td>
</tr>
<tr>
<td>Flash point</td>
<td>-1°C c.c.</td>
</tr>
<tr>
<td>Auto-ignition temperature</td>
<td>481°C</td>
</tr>
<tr>
<td>Explosive limits, vol% in air</td>
<td>3.0-17.0</td>
</tr>
<tr>
<td>Octanol/water partition coefficient as log Pow</td>
<td>0.25</td>
</tr>
</tbody>
</table>

### ENVIRONMENTAL DATA

The substance is harmful to aquatic organisms.

### NOTES

Depending on the degree of exposure, periodic medical examination is suggested. Exposure to the substance will result in cyanide formation. Also consult ICSC of a cyanide salt, such as 0671. Specific treatment is necessary in case of poisoning with this substance; the appropriate means with instructions must be available. The odour warning when the exposure limit value is exceeded is insufficient. Rinse contaminated clothes (fire hazard) with plenty of water.

### ADDITIONAL INFORMATION

#### Routes of exposure
The substance can be absorbed into the body by inhalation of its vapour, through the skin and by ingestion.

#### Inhalation risk
A harmful contamination of the air can be reached very quickly on evaporation of this substance at 20°C.

#### Effects of short-term exposure
The substance and the vapour is irritating to the eyes, the skin and the respiratory tract. The substance may cause effects on the central nervous system. Exposure far above the OEL may result in death. The effects may be delayed. See Notes. Medical observation is indicated.

#### Effects of long-term or repeated exposure
Repeated or prolonged contact may cause skin sensitization. The substance may have effects on the central nervous system and liver. This substance is possibly carcinogenic to humans.
Résumé d'Orientation


L’acrylonitrile (No CAS 107-13-1) se présente, à la température ambiante, sous la forme d’un liquide volatile, inflammable et soluble dans l’eau. Au Canada, ce composé est utilisé en majeure partie comme produit de départ ou adjuvant chimique dans la fabrication des élastomères nitrile-butadiène et des copolymères acrylonitrile-butadiène-styrène et acrylonitrile-styrène. On estime que la capacité de production mondiale était d’environ 4 millions de tonnes en 1993. Les principales zones de production sont l’Union européenne (>1,25 millions de tonnes par an), les États-Unis (environ 1,5 millions de tonnes par an) et le Japon (environ 0,6 millions de tonnes par an).

Ce sont principalement les unités de production ou d’autres industries chimiques ou plasturgiques qui sont susceptibles d’en libérer dans l’environnement (plus de 95 % dans le pays témoin). On ne lui connaît pas de sources naturelles. L’acrylonitrile est largement répandu dans les compartiments de l’environnement où il est déversé (c’est-à-dire l’air ou l’eau), son mouvement vers le sol, les sédiments et les biotes étant limité. Il est principalement éliminé par réaction chimique et advection. Les enquêtes limitées effectuées dans le pays choisi pour la caractérisation du risque dans l’environnement général (le Canada) n’ont permis de trouver de l’acrylonitrile qu’à proximité d’installations industrielles.

L’exposition professionnelle à l’acrylonitrile est liée à sa production et à son utilisation pour la fabrication d’autres produits. C’est d’ailleurs dans ce dernier cas que le risque est le plus important en raison des difficultés de confinement. Selon des données récentes relatives aux pays de l’Union européenne, l’exposition moyenne pondérée par rapport au temps est #1,45 ppm (1 mg/m³) au cours de la production et #1,01 ppm (2,2 mg/m³) pour diverses utilisations en bout de chaîne.

L’acrylonitrile est rapidement absorbé par toutes les voies d’exposition et il se répartit dans l’ensemble des tissus examinés. Il n’y a guère de possibilité d’accumulation dans un organe quelconque, le composé étant excrété, principalement sous forme de métabolites, dans les 24 à 48 h suivant l’administration. Selon les données disponibles, la principale voie métabolique de détoxication est une conjugaison avec le glutathion, l’oxydation en oxyde de 2-cyanoéthylène étant considérée comme une voie d’activation.

Les données fournies par l’expérimentation animale indiquent que l’acrylonitrile est fortement irritant pour la peau, les yeux et les voies respiratoires. Il peut provoquer une dermatite allergique de contact, mais on ne possède pas suffisamment de données pour évaluer son pouvoir sensibilisateur. À l’exception des effets toxiques sur le développement (effets foetoxiques et tératogènes), qui ne s’observent d’ailleurs pas aux doses non toxiques pour la mère, les données disponibles concernant les autres effets non néoplasiques révélés par l’expérimentation animale ne sont pas suffisantes pour permettre de caractériser la relation dose-réponse. Lors des quelques études au cours desquelles on a systématiquement recherché la présence d’effets non néo-

1 Les nouvelles données notées par les auteurs et obtenues par un dépouillement de la littérature effectué avant la réunion du Comité d’évaluation finale ont été examinées compte tenu de leur influence probable sur les conclusions essentielles de la présente évaluation, le but étant avant tout d’établir si leur prise en compte serait prioritaire lors d’une prochaine mise à jour. Les auteurs ayant estimé qu’elles apportaient des éléments d’information supplémentaires, on a ajouté des données plus récentes encore que non essentielles pour la caractérisation des dangers ou l’analyse des relations dose-réponse.
plasiques, seuls des cas d’irritation cutanée aiguë ont été régulièrement observés.

Compte tenu des résultats obtenus sur l’animal, c’est le cancer qui constitue le point d’aboutissement toxicologique majeur de l’action de l’acrylonitrile chez l’Homme. Après inhalation ou ingestion, on observe chez le rat toute une variété de tumeurs touchant notamment le système nerveux central (encéphale et moelle épinière), le conduit auditif, les voies digestives et les glandes mammaires. La plupart des tests biologiques correctement effectués révèlent une augmentation des astrocytomes cérébraux et médullaires, néoplasmes qui se produisent rarement de façon spontanée; ces tumeurs s’observent régulièrement avec une incidence très élevée dans toutes les études. L’augmentation constatée est statistiquement significative et il existe une nette relation dose-réponse. On a quelquefois observé des tumeurs à des doses ou concentrations non toxiques et dès les 7 à 12 mois suivant le début de l’exposition. On en a également observé au bout de 45 semaines dans la progéniture exposée lors d’une étude toxicologique sur la reproduction portant sur plusieurs générations.

Toutes les études épidémiologiques disponibles n’ont pas mis systématiquement en évidence une augmentation des cancers. Cependant il est impossible de procéder à une comparaison quantitative valable entre ces résultats et ceux de l’expérimentation animale, car on ne possède pas suffisamment d’informations sur le mode d’induction des tumeurs cérébrales, les données sur l’exposition des travailleurs lors des enquêtes en question sont relativement maigres et les limites de confiance des SMR (taux comparatifs de mortalité) qui ressortent des études épidémiologiques pour des cancers pouvant être pris en considération présentent une forte dispersion.

Si, en ce qui concerne la gênotoxicité, les nombreuses études portant sur l’examen d’effets très variés tant in vitro, avec ou sans activation métabolique, qu’ in vivo chez la souris et le rat, donnent des résultats mitigés pour l’acrylonitrile, son métabolite, l’oxyde de 2-cyanoéthylène, est par contre clairement mutagène. Même si les résultats disponibles ne fournissent pas de preuve directe, on peut raisonnablement penser que l’action cancérogène de l’acrylonitrile est due à une interaction avec le matériel génétique. En ce qui concerne les autres modes d’induction tumorigale possibles, les données sont insuffisantes. L’acrylonitrile et son époxyde peuvent réagir avec les macromolécules.

On estime que le cancer constitue l’effet toxique essentiel à prendre en considération pour la quantification de la relation dose-réponse en vue de la caractérisation du risque. La concentration tumorigène la plus faible (la CT_{105}, c’est-à-dire la concentration qui provoque une augmentation de 5 % de l’incidence tumorigale par rapport à l’incidence normale) (valeur équivalente pour l’Homme) a été trouvée égale à 2,7 ppm (6,0 mg/m^3) pour l’incidence combinée des tumeurs cérébrales ou médullaires bénignes ou malignes chez le rat et la souris exposés par la voie respiratoire. Cela correspond à un risque unitaire de 8,3 × 10^{-3} par mg/m^3.

Bien que limitées, les données montrent que c’est principalement par l’air que la population générale est exposée à l’acrylonitrile; l’absorption à partir d’autres milieux est négligeable en comparaison. La caractérisation du risque pour l’Homme est centrée sur les populations vivant à proximité de sources industrielles d’acrylonitrile. Compte tenu de la marge qui existe, dans la caractérisation du risque type, entre les données concernant le pouvoir cancérogène du composé et celles, limitées, dont on dispose au sujet des concentrations calculées et mesurées, notamment au voisinage des sources d’émission ponctuelles, on estime que le risque sur ces sites est >10^{-5}.

S’agissant de la caractérisation du risque environnemental type, la concentration dans les eaux résiduaires industrielles après traitement est inférieure à la valeur estimative à effet nul (ENEV) pour l’organisme aquatique le plus sensible et la concentration maximale calculée (à proximité d’une usine chimique) est inférieure à l’ENEV pour l’organisme terrestre le plus sensible.
RESUMEN DE ORIENTACIÓN


El acrilonitrilo (CAS N° 107-13-1) es un líquido volátil, inflamable, soluble en agua a temperatura ambiente. La inmensa mayoría del acrilonitrilo se utiliza en el Canadá como materia prima o coadyuvante químico en la producción de caucho de nitrilo-butadieno y en el Canadá como materia prima o coadyuvante químico en el medio ambiente. La inmensa mayoría del acrilonitrilo se utiliza (es decir, aire o agua), siendo el desplazamiento hacia el suelo, los sedimentos o la biota limitado; los principales mecanismos de eliminación son la reacción y la advección. En estudios limitados en el país en el cual se basa la caracterización del riesgo de muestra (es decir, el Canadá), se ha detectado acrilonitrilo en el medio ambiente general sólo en las cercanías de fuentes industriales.

La exposición al acrilonitrilo en el lugar de trabajo se produce durante su producción y utilización en la fabricación de otros productos; el mayor potencial se da en el segundo caso, donde el compuesto puede no ser fácil de contener. Según datos recientes para los países de la Unión Europea, la exposición media ponderada por el tiempo es 0,45 ppm (1 mg/m³) durante la producción y 0,01 ppm (2,2 mg/m³) en diversos usos finales.

El acrilonitrilo se absorbe con rapidez por todas las vías de exposición y se distribuye en todos los tejidos examinados. Es poco probable que se acumule de manera significativa en un órgano determinado, excretándose la mayor parte del compuesto en la orina, principalmente como metabolitos, en las primeras 24-48 horas después de la administración. Los datos disponibles coinciden en indicar que la conjugación con el glutatión es la principal vía de desintoxicación, mientras que la oxidación a óxido de 2-cianoetileno se considera una vía de activación.

Los datos disponibles de estudios en animales indican que el acrilonitrilo es un irritante cutáneo, respiratorio y ocular grave. Puede provocar dermatitis alérgica por contacto, pero no se dispone de datos adecuados para evaluar su capacidad de sensibilización. Con la excepción de la toxicidad en el desarrollo, para la cual no se han observado efectos (fetotóxicos y teratógenos) a concentraciones que no eran tóxicas para las madres, los datos disponibles sobre otros efectos no neoplásicos en animales de experimentación no son suficientes para caracterizar la exposición-respuesta. En un pequeño número de estudios en poblaciones humanas en los que se han investigado de manera sistemática los efectos no neoplásicos del acrilonitrilo, sólo se ha notificado la presencia continuada de irritación cutánea aguda.

1 Se ha incluido nueva información destacada por los examinadores y obtenida en una búsqueda bibliográfica realizada antes de la reunión de la Junta de Evaluación Final para señalar sus probables repercusiones en las conclusiones esenciales de esta evaluación principalmente con objeto de establecer la prioridad para su examen en una actualización. Se ha añadido información más reciente, no esencial para la caracterización del peligro o el análisis de la exposición-respuesta, que a juicio de los examinadores aumentaba su valor informativo.
De los estudios en animales cabe deducir que el cáncer es el efecto final crítico del acrilonitrilo para la salud humana. Se ha observado de manera constante una serie de tumores en ratas - en particular del sistema nervioso central (cerebro y/o médula espinal), el conducto auditivo, el tracto gastrointestinal y las glándulas mamarias - tras la ingestión o la inhalación. En casi todas las biovaloraciones adecuadas se ha notificado un mayor número de astrocitomas del cerebro y la médula espinal, que raramente se observan de forma espontánea, correspondiendo siempre a éstos la incidencia más alta en todos los estudios. El aumento ha sido estadísticamente significativo y se han observado tendencias claras de dosis-respuesta. Se han notificado a veces tumores con dosis o concentraciones no tóxicas y ya a los 7-12 meses del comienzo de la exposición. Se han detectado asimismo tumores en crías expuestas en un estudio de reproducción multigeneracional a las 45 semanas.

En los estudios epidemiológicos disponibles no se ha observado de manera constante un aumento de la aparición de cáncer. Sin embargo, no se puede realizar una comparación cuantitativa válida de los resultados de estas investigaciones con los obtenidos en estudios en animales, debido a la falta de datos adecuados sobre el mecanismo de inducción de tumores cerebrales, la relativa escasez de datos sobre la exposición de los trabajadores en las investigaciones pertinentes y el amplio intervalo de los límites de confianza para las razones normalizadas de mortalidad en los casos de cáncer de posible interés en los estudios epidemiológicos.

En numerosos estudios sobre la genotoxicidad del acrilonitrilo con un examen de un amplio espectro de efectos finales, tanto in vitro, con activación metabólica y sin ella, como in vivo, en ratones y ratas, los resultados han sido bastante variables, mientras que su metabolito, el óxido de cianoetileno, es mutagénico. Aunque no hay pruebas directas, según los datos disponibles, es razonable suponer que la inducción de tumores por el acrilonitrilo está relacionada con la interacción directa con material genético. El valor probatorio para otros posibles mecanismos de inducción de tumores es insuficiente. El acrilonitrilo o su epóxido pueden reaccionar con macromoléculas.

El cáncer se considera el efecto final crítico para la cuantificación de la exposición-respuesta en la caracterización del riesgo del acrilonitrilo. La concentración inductora de tumores más baja (CT(5%)) concentración que produce un aumento del 5% en la incidencia de tumores sobre el nivel basal) (valor equivalente humano) fue de 2,7 ppm (6,0 mg/m³) para la incidencia combinada de tumores benignos y malignos del cerebro y/o la médula espinal en ratas expuestas por inhalación. Esto equivale a un riesgo unitario de $8,3 \times 10^{-3}$ por mg/m³.

Aunque limitados, los datos disponibles son compatibles con el hecho de que el aire es el principal medio de exposición de la población general al acrilonitrilo; la ingesta a partir de otros medios probablemente es insignificante en comparación. El objetivo principal de la caracterización del riesgo para la salud humana es la población expuesta mediante el aire en las proximidades de fuentes industriales. Basándose en las márgenes entre la potencia carcinogénica y los limitados datos disponibles sobre las concentraciones de acrilonitrilo previstas y medidas principalmente en las cercanías de fuentes puntuales en la caracterización del riesgo de muestra, los riesgos en estos lugares son $>10^{-5}$.

En la caracterización del riesgo de muestra para el medio ambiente, los niveles en las aguas residuales tratadas son inferiores al valor sin efectos estimados (ENEV) para el organismo acuático más sensible y los niveles máximos pronosticados (cerca de una fábrica de elaboración de la industria química) son inferiores al ENEV para el organismo terrestre más sensible.
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3,3'-Dichlorobenzidine (No. 2, 1998)
1,2-Dichloroethane (No. 1, 1998)
2,2-Dichloro-1,1,1-trifluoroethane (HCFC-123) (No. 23, 2000)
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