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Concise International Chemical Assessment Document 43

ACROLEIN

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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.

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.[1]

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 Coordinator, IPCS, on the selection of chemicals for an IPCS risk assessment based on the following criteria:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, a priority chemical typically

- is of transboundary concern;
- is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- is significantly traded internationally;
- has high production volume;
- has dispersive use.

The Steering Group will also advise IPCS on 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 to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170) (also available at http://www.who.int/pcs/).

CICAD PREPARATION FLOW CHART

Selection of priority chemical, author institution, and agreement on CICAD format

9

Preparation of first draft

9

Primary acceptance review by IPCS and revisions as necessary

9

Selection of review process

9

Peer review

9

Review of the comments and revision of the document

9

Final Review Board: Verification of revisions due to peer review comments, revision, and approval of the document

9

Editing
Approval by Coordinator, IPCS

9

Publication of CICAD on Web and as printed text

Advice from Risk Assessment Steering Group

Criteria of priority:

- there is the probability of exposure; and/or
- there is significant toxicity/ ecotoxicity.

Thus, it is typical of a priority chemical that

- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- the production volume is high;
- the use is dispersive.

Special emphasis is placed on avoiding duplication of effort by WHO and other international organizations.

A prerequisite of the production of a CICAD is the availability of a recent high-quality national/regional risk assessment document = source document. The source document and the CICAD may be produced in parallel. If the source document does not contain an environmental section, this may be produced *de novo*, provided it is not controversial. If no source document is available, IPCS may produce a *de novo* risk assessment document if the cost is justified.

Depending on the complexity and extent of controversy of the issues involved, the steering group may advise on different levels of peer review:

- standard IPCS Contact Points
- above + specialized experts
- above + consultative group

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. At any stage in the international review process, a consultative group may be necessary to address specific areas of the science.

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 acrolein 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 May 1998 (environmental effects) and October 1998 (human health effects) were considered in this review.[1] Information on the nature of the peer review and availability of the source document is presented in Appendix 1. Other reviews that were also consulted include IARC (1979, 1985, 1987, 1995), ATSDR (1990), IPCS (1992, 1996), BUA (1994), US EPA (1996), and EU (1999). 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 Ottawa, Canada, on 29 October – 1 November 2001. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card for acrolein (ICSC 0090), produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

Acrolein (CAS No. 107-02-8) is a clear, colourless liquid with an intensively acrid odour. It is released to the atmosphere as a product of fermentation and ripening processes. It is also emitted by forest fires as a product of incomplete combustion.

In the source country (i.e., Canada), acrolein is used mainly as an aquatic herbicide in irrigation canals and as a microbiocide in produced water during oil exploration. An estimated minimum of 218 tonnes of acrolein is released yearly to the atmosphere from anthropogenic sources involving the combustion of organic matter (i.e., predominantly as a component of vehicle exhaust) or the forest industry. Unquantified amounts are also released from the photo-oxidation of organic pollutants in air. No releases of "non-pesticidal" acrolein to water, sediments, or soils in Canada have been identified.

Acrolein is unlikely to be transported over long distances because of its high reactivity and estimated short half-lives in air and water. It is also unlikely to partition from these compartments to soil or sediments. Acrolein is rapidly metabolized by organisms and does not bioaccumulate. The highest environmental concentrations of acrolein not directly released during its application as a pesticide in the source country (Canada) have been measured in air from urban areas. With the exception of samples taken in the vicinity of pesticidal application, acrolein has not been detected in water, sediment, or soil in the source country (Canada).

Based upon studies conducted primarily in laboratory animals, adverse health effects associated with exposure to acrolein are mostly confined to the tissue of first contact (i.e., the respiratory and gastrointestinal tracts after inhalation and ingestion, respectively) and are concentration related. Studies of the systemic effects of acrolein in humans have not been identified, with available data relevant to the assessment of the potential adverse effects in humans limited primarily to irritation. In humans and experimental species, acrolein is an upper respiratory tract and eye irritant.

Informative epidemiological studies on the long-term effects of acrolein have not been identified. Available data are inadequate to serve as a basis for assessment of the carcinogenicity of acrolein following inhalation. In the more extensive of limited studies concerning the chronic toxicity/carcinogenicity of acrolein following oral exposure in rats and dogs, there have been no increases in the incidence of tumours of any type, although mortality, the cause of which is unclear, was increased in rats and mice. Acrolein is mutagenic *in vitro*, but limited available data do not indicate genotoxic effects in the nasal mucosa (i.e., the site of contact) in rats exposed by inhalation, although *in vitro* studies indicate that acrolein can interact directly with DNA and induce DNA damage. In extensive studies, acrolein did not induce reproductive toxicity in experimental animals following oral administration.

The effects of acrolein have been most extensively investigated following exposure by inhalation. Acrolein is cytotoxic; histopathological effects in the bronchi and/or trachea (including exfoliation, oedema, inflammation, vascular congestion, and haemorrhagic necrosis) have been observed in hamsters, guinea-pigs, and rabbits following single inhalation exposure to acrolein. In short- and long-term inhalation studies conducted in several species (rats, mice, guinea-pigs, hamsters, monkeys, and dogs), at lowest concentrations, effects

[1] New information flagged by the reviewers or obtained in the 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 included.

(degenerative histopathological lesions) have occurred consistently at the site of entry (i.e., the respiratory tract). Effects in other organs have also sometimes been observed, although inconsistently. This is consistent with the results of toxicokinetic studies in rodents and dogs, in which there has been a high degree of retention of inhaled acrolein at the site of contact.

Based on irritant effects at the site of contact in experimental animals, a tolerable concentration for acrolein of 0.4 µg/m^3 in air has been derived. For ingestion, the provisional tolerable concentration is 1.5 µg/litre.

Sample probabilistic estimates of the distribution of time-weighted 24-h concentrations of acrolein in air in the source country (Canada) indicate that between 5% and 10% of the general population is exposed to at least 5 µg/m^3. This is greater than the tolerable concentration.

Indoor air is an important source of exposure, although the relative contribution of various sources therein is unknown. Considerably higher concentrations of acrolein have been reported in tobacco smoke. For the general population, the relative contribution of ambient air to overall exposure to inhaled acrolein is expected to be small, compared with exposure from indoor air. However, for populations residing in the vicinity of locations heavily impacted by vehicular exhaust, ambient air may be an important source of exposure via inhalation.

Although available data are limited, the range of concentrations measured in food in various countries (although highly dependent upon such factors as method of cooking) is within the range of the provisional tolerable concentration for ingestion.

Acute and chronic toxicity data are available for aquatic organisms. Only acute data were identified for terrestrial crop plants. Terrestrial organisms appear less sensitive to acrolein than aquatic organisms. Concentrations of acrolein in the atmosphere of the source country (Canada) are less than the threshold for adverse effects estimated for terrestrial organisms. Exposure of other organisms to non-pesticidal acrolein is considered unlikely, since no sources or detectable concentrations of acrolein have been identified in other compartments.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Acrolein (CAS No. 107-02-8) is also known as acrylaldehyde, allyl aldehyde, acrylic aldehyde, propenal, prop-2-enal, and prop-2-en-1-al. Its molecular formula is $CHOCHCH_2$, and its molecular mass is 56.06. Acrolein's chemical structure is shown in Figure 1.

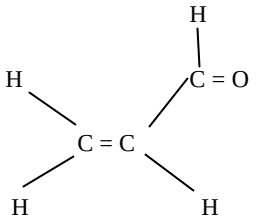


Figure 1: Chemical structure of acrolein.

At room temperature, acrolein is a clear, colourless liquid with an intensively acrid odour. The ranges of values reported for selected physical/chemical properties are presented in Table 1. Additional properties are given in the International Chemical Safety Card (ICSC 0900) reproduced in this document.

Table 1: Physical and chemical properties of acrolein.

Property	Range[a]
Boiling point (°C at 101.3 kPa)	52.1 to 53.5
Vapour pressure (kPa at 20 °C)	29.3 to 36.5
Water solubility (g/litre at 20 °C)	206 to 270
Henry's law constant (Pa·m^3/mol at 20 °C)	0.446 to 19.6
Henry's law constant (dimensionless at 25 °C)	7.8 to 180
log K_{ow}	−1.1 to 1.02
log K_{oc}	−0.219 to 2.43

[a] Includes experimental and calculated values listed in Irwin (1987, 1988), ATSDR (1990), BUA (1994), Eisler (1994), Mackay et al. (1995), US EPA (1996), and EU (1999).

The conversion factor for acrolein in air at 25 °C and 101.3 kPa, used throughout this report, is 1 ppm = 2.29 mg/m^3.[1]

[1] The conversion factor for acrolein in air at 20 °C and 101.3 kPa is 1 ppm = 2.33 mg/m^3 (BUA, 1994).

Table 2: Methods for the determination of acrolein.[a,b]

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Adsorb on sorbent coated with 2-(hydroxymethyl)piperidine on XAD-2; desorb with toluene; analyse for oxazolidine derivative	GC/NSD	2 µg/sample (6.1 µg/m^3)	US OSHA, 1989; Eller, 1994
	Draw air through midget impinger containing acidified DNPH and isooctane; extract DNPH derivative with hexane:dichloromethane (70:30) solution; evaporate to dryness; dissolve in methanol	Reversed-phase HPLC/UV	NR	US EPA, 1988
	Draw air through bubblers in series containing 4-hexyl-resorcinol in an alcoholic trichloroacetic acid solvent medium with mercuric chloride	Colorimetry	22.9 µg/m^3 (10 ppb)[c]	Feldstein et al., 1989a
	Draw air through midget impinger containing 1% sodium bisulfite; react with 4-hexylresorcinol in an alcoholic trichloroacetic acid solvent medium with mercuric chloride	Colorimetry	22.9 µg/m^3 (10 ppb)	Feldstein et al., 1989b
Moist air	Collect in DNPH-impregnated adsorbent tubes (with calcium chloride tubes); extract with acetonitrile	HPLC/UV	0.3 µg/sample (0.01 mg/m^3)	Vainiotalo & Matveinen, 1992
Exhaust gas	Derivatize with *O*-benzyl-hydroxylamine to *O*-benzyloxime; brominate with sulfuric acid, potassium bromate, and potassium bromide; reduce with sodium thiosulfate; extract with diethyl ether	GC/ECD	NR	Nishikawa et al., 1987a
Aqueous solution	Derivatize with *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine	MIMS/EIMS	10 µg/litre (10 ppb)	Choudhury et al., 1992
Rainwater	Derivatize with *O*-methoxylamine to *O*-methyloxime; brominate with sulfuric acid, potassium bromate, and potassium bromide; reduce with sodium thiosulfate; elute with diethyl ether	GC/ECD	0.4 µg/litre	Nishikawa et al., 1987b
Liquid and solid wastes	Purge (inert gas); trap in suitable adsorbent material; desorb as vapour onto packed gas chromatographic column	GC/FID	0.7 µg/litre[d]	US EPA, 1986
Biological samples	Derivatize with DNPH; extract with chloroform, hydrochloric acid; dry with nitrogen; dissolve in methanol	HPLC/UV	1 ng	Boor & Ansari, 1986

[a] From IARC (1995).

[b] Abbreviations used: DNPH = 2,4-dinitrophenylhydrazine; ECD = electron capture detection; FID = flame ionization detection; GC = gas chromatography; HPLC/UV = high-performance liquid chromatography/ultraviolet detection; MIMS/EIMS = membrane introduction mass spectrometry/electron impact mass spectrometry; MS = mass spectrometry; NR = not reported; NSD = nitrogen selective detection.

[c] Note that 1 ppb = 1×10^{-9}.

[d] Practical quantification limits for other matrices: 7 µg/litre for groundwater; 7 µg/kg for low-level soil samples; 350 µg/litre for water-miscible liquid waste samples; 875 µg/kg for high-level soil and sludge samples; 875 µg/litre for non-water-miscible waste samples.

3. ANALYTICAL METHODS

Methods for the determination of acrolein in air, exhaust gas, aqueous solution, rainwater, biological samples, and liquid and solid wastes have been reviewed (IARC, 1995) and are presented in Table 2.

Aldehydes, including acrolein, in environmental samples and in ozonated drinking-water are derivatized with *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine hydrochloride, then identified using gas chromatography and/or mass spectrometry (Le Lacheur et al., 1993). The detection limits of methods involving gas chromatography/electron capture detection and gas chromatography/mass spectrometry with ion-selective monitoring are 3.5 and 16.4 µg/litre, respectively (Glaze et al., 1989).

Personal exposure to acrolein and other airborne aldehydes in emissions is monitored by both passive and active sampling methods. These methods are based on derivatization of the aldehydes with 2,4-dinitrophenylhydrazine (DNPH) during collection. The adsorbent materials are extracted with toluene and analysed by gas chromatography with flame ionization detection (limit of detection 0.05 mg/m^3) (Otson et al., 1993). A limit of detection of acrolein in air of 0.05 µg/m^3 has been determined following sample collection with DNPH-coated silica gel sorbent tubes, elution of acrolein with acetonitrile, and analysis by high-performance liquid chromatography (Dann et al., 1994; T. Dann, personal communication, 1998).

Technical difficulties in the measurement of acrolein in air include possible interference of propionaldehyde-DNPH and acetone-DNPH derivatives with the acrolein-DNPH derivative during gas chromatography or high-performance liquid chromatography and potentially low recovery of acrolein from DNPH-coated silica gel (Risner, 1995).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

Data on sources and emissions from the source country of the national assessment on which this 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

Acrolein is released into the environment as a product of fermentation and ripening processes. It has been identified as a volatile component of essential oils extracted from the wood of oak trees (Slooff et al., 1994). It is also emitted by forest fires as a product of the incomplete combustion of organic matter (Lipari et al., 1984) and produced by photochemical oxidation of hydrocarbons in the atmosphere (Ghilarducci & Tjeerdema, 1995). Quantitative data on the total production of acrolein from natural sources have not been identified.

4.2 Anthropogenic sources

Although uncertain owing to limitations of relevant identified information, estimates of releases of acrolein to the atmosphere in the source country (i.e., Canada) are presented in Table 3. The principal anthropogenic source of emissions into the Canadian environment is estimated to be activities involving the combustion of organic matter. As a product of the incomplete combustion of organic matter, acrolein is released by waste incinerators, furnaces, fireplaces, power plants, burning vegetation (e.g., forest fires), combustion of polyethylene plastics, and the cooking of food. The main combustion source is considered to be gas and diesel motor vehicle emissions. Few data are available for aircraft, railway engines, ships, and other off-road vehicles, but releases from these sources could exceed those of road vehicles (see Table 3).

Acrolein is formed by the reaction and photo-decomposition of other airborne pollutants, such as 1,3-butadiene and allyl chloride (Maldotti et al., 1980; Edney et al., 1986a,b). Forest product manufacturing processes that release volatile organic compounds emit appreciable amounts of acrolein to air (Environment Canada, 1997). The formation of acrolein as a contaminant at 0.4% in the production of vinyl acetate has also

Table 3: Sources and estimated releases of acrolein to air in the sample country (Canada).

Sources	Estimated releases (kg/year)
Natural sources: fermentation, forest fires	Unknown
Road motor vehicles	209 000–2 730 000[a]
Off-road motor vehicles,[b] including aircraft	Unknown, could be greater than road vehicle release
Oriented-strand board (OSB) industry	3 208–25 664[c]
Pulp and paper (kraft) mills	3 747–18 735[d]
Waste incineration	2 435[e]
Coal-based electric power generation plants	467–17 504[f]
Other combustion sources[g]	Unknown
Atmospheric production from other pollutants	Unknown
By-product of vinyl acetate production	Negligible[h]

[a] Estimated based on emissions test data from Howes (1989a,b), BUA (1994), L.A. Graham (personal communication, 1996), and IPCS (1996), multiplied by the estimated 1995 mileage for on-road motor vehicles in Canada (Environment Canada, 1993). This estimate also considers that about 90% of light-duty gas vehicles in Canada have catalytic converters, which reduce emissions (L. King, personal communication, 1998).

[b] These include aircraft, railway and marine vehicles, other off-road motor vehicles, and gas-powered lawnmowers and snow-blowers, most of which are expected to have greater emission rates than on-road vehicles because of a lack of pollution control features (L.A. Graham, personal communication, 1998).

[c] The lower estimate corresponds to the total emissions of acrolein in 1995 reported by two OSB companies responding to the CEPA Section 16 Industrial Survey (Environment Canada, 1997) and one OSB company reporting to the Accelerated Reduction/Elimination of Toxics (ARET) program (ARET Secretariat, 1998). The larger value is the total emission estimated for all 24 such plants in Canada (D. Halliburton, personal communication, 1998), assuming an average emission rate of 1070 kg/year per mill.

[d] The lower estimate corresponds to the total emissions of acrolein in 1995 reported in response to the CEPA Section 16 Industrial Survey by nine Canadian pulp and paper (kraft) mills (Environment Canada, 1997). The larger value is the total emission estimated for all 45 such kraft mills in Canada (D. Halliburton, personal communication, 1998), assuming an average emission rate of 416 kg/year per mill.

[e] Based on the estimated emission rate of acrolein from one municipal incinerator in Ontario (Novamann International, 1997), the nameplate capacity of Canadian hazardous waste incinerators, and the amount of municipal, hazardous, and biomedical waste incinerated in Canada in 1996.

[f] Based on US emission rates (Lipari et al., 1984; Sverdrup et al., 1994), high heating value of fuel, and Canadian coal consumption in 1995 (D. Rose, personal communication, 1998).

[g] Includes prescribed burning, wood-burning furnaces and fire-places, natural gas furnaces, other electric power generation plants, and other industries (e.g., smelters).

[h] The unintentional production of 2700 kg of acrolein was reported in 1995 by one vinyl acetate producer in the CEPA Section 16 Industrial Survey. Related releases of acrolein are estimated to be negligible, because it is reported that impurities such as acrolein are separated and processed for recovery or disposal (Environment Canada, 1997).

been reported. In this case, acrolein and other impurities are separated and processed for recovery or disposal (Environment Canada, 1997).

Although reported in the mid-1980s in liquid effluents from a limited number of organic chemical manufacturing plants in the source country (i.e., Canada) (King & Sherbin, 1986), releases of acrolein to the aqueous environment were not identified in a survey conducted in the mid-1990s (Environment Canada, 1997). Sources of releases to Canadian waters, sediments, or soils for other than the application of acrolein-based pesticides have, therefore, not been identified. During use as the hydrogen sulfide scavenger, acrolein is assumed to be fully consumed. During its application in petroleum operations (i.e., crude oil exploration and extraction operations at oil wells), the acrolein reacts with sulfides in oil/water mixtures to form a non-hazardous, water-soluble product, which is then re-injected into deep wells (BPCI, 1991). The acrolein used is considered to be completely reacted (I. Viti, personal communication, 1998). Releases are therefore expected to be negligible.

4.3 Production and use

Isolated acrolein is produced in a closed system by heterogeneously catalysed gas-phase oxidation of propene. Acrolein is also produced as a non-isolated intermediate during the manufacture of acrylic acid. Reported values for the annual production (between 1980 and the early 1990s) of isolated acrolein are as follows: USA, 27 000–35 000 tonnes/year; Japan (several sites), 20 000 tonnes/year; European Union (France and Germany, two production sites), 60 000 tonnes/year; Russia, 10 500 tonnes/year (BUA, 1994).

In the European Union, acrolein is produced and used by the chemical industry only, as an intermediate in the production of substances used as animal feed additives, biocides, and leather tanning agents (EU, 1999). In other countries (e.g., Canada, Egypt, Argentina, Australia, and the USA), acrolein is used principally as a broad-band biocide in process water circuits, irrigation canals, cooling water towers, and water treatment basins (BUA, 1994).

The main “non-pesticidal” use of acrolein in the source country (Canada) is as the active ingredient (92%) in a product used by oil companies to scavenge hydrogen sulfide from produced fluids in petroleum operations. This product can also solubilize ferrous sulfide deposits that obstruct wells, tanks, and barrels (BPCI, 1991). Small quantities of acrolein have also been used for research purposes (Environment Canada, 1996a).

Small amounts (2 kg) of acrolein were present in hazardous wastes imported into Canada for treatment or disposal between 1994 and 1997 (Environment Canada, 1994; J. Wittwer, personal communication, 1998). Acrolein has also been identified as an impurity (1%) in imports of acetaldehyde (Environment Canada, 1997).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

Due to its high reactivity, acrolein does not tend to persist in the environment, and its intercompartmental movement is small.

5.1 Air

Acrolein emitted to air reacts primarily with photochemically generated hydroxyl radicals in the troposphere (Ghilarducci & Tjeerdema, 1995). Minor processes include direct photolysis, reaction with nitrate radicals, and reaction with ozone (Atkinson et al., 1987; Haag et al., 1988a; Howard, 1989; BUA, 1994). Acrolein has been detected in rainwater, indicating that it may be removed by wet deposition (Grosjean & Wright, 1983). The calculated atmospheric half-life of acrolein, based on rate constants for hydroxyl radical reaction, is between 3.4 and 33.7 h (Atkinson, 1985; Edney et al., 1986b; Haag et al., 1988a; Howard, 1989; Howard et al., 1991; BUA, 1994). The overall reactivity-based half-life of acrolein in air, as estimated by Mackay et al. (1995), is less than 10 h. Based on these short estimated half-lives, acrolein is not a candidate for long-range atmospheric transport.

5.2 Water

Acrolein is removed from surface water primarily by reversible hydration, biodegradation by acclimatized microorganisms, and volatilization (Bowmer & Higgins, 1976; Tabak et al., 1981; Irwin, 1987; Haag et al., 1988b; Howard, 1989; ATSDR, 1990; Springborn Laboratories, 1993). In groundwater, acrolein is removed by anaerobic biodegradation and hydrolysis (Chou & Spanggord, 1990a). The overall reactivity-based half-life of acrolein in surface water is estimated to be between 30 and 100 h (Mackay et al., 1995). In groundwater, half-lives of 11 days and 336–1344 h (14–56 days) are estimated based on aerobic and anaerobic degradation, respectively (Howard et al., 1991). Observed dissipation half-lives of acrolein applied as a herbicide in irrigation

canals range from 7.3 to 10.2 h (Jacobson & Gresham, 1991a,b,c; Nordone et al., 1996a). The relatively short observed half-lives of acrolein in surface waters make long-range aquatic transport unlikely.

5.3 Sediment

In sediment/water systems, acrolein undergoes hydrolysis, self-oxidation, and biodegradation. Experimental half-lives of 7.6 h and 10 days were determined for aerobic and anaerobic conditions, respectively (Smith et al., 1995). An overall reactivity-based half-life is estimated by Mackay et al. (1995) to be between 100 and 300 h. Because of its low organic carbon/water partition coefficient (K_{oc}) and high water solubility, acrolein is not expected to significantly adsorb to suspended solids or sediments, nor are these suspended solids or sediments expected to significantly absorb acrolein from water (Irwin, 1988; Howard, 1989).

5.4 Soil

In the terrestrial environment, acrolein undergoes biodegradation, hydrolysis, volatilization, and irreversible sorption to soil (Irwin, 1988; Howard, 1989; Chou & Spanggord, 1990b). These processes are expected to significantly decrease the high infiltration rate of acrolein estimated from its low experimental K_{oc} (Irwin, 1988). The overall reactivity-based half-life of acrolein in soil is estimated to be between 30 and 100 h (Mackay et al., 1995).

5.5 Biota

Based on the high water solubility, low octanol/water partition coefficient (K_{ow}), and high reactivity of acrolein, uptake by organisms is predicted to be low. A bioconcentration factor (BCF) of 344 and a half-life of greater than 7 days were reported for acrolein in bluegill (*Lepomis macrochirus*) following exposure to acrolein at a mean concentration of 13 µg/litre for a 28-day period (Barrows et al., 1980). However, these values may be overestimates, as the total ^{14}C measured in the fish may have included metabolites. A lower BCF of 0.6 was estimated using the linear regression equation of Veith et al. (1980) and a log K_{ow} of !0.01 for acrolein. Acrolein was not detected in the tissues of fish and shellfish sampled 1 day after a second exposure to [^{14}C]acrolein in water (0.02 and 0.1 mg/litre for the first and second exposures, respectively) over a 1-week period. The presence of metabolites indicates that these species were able to rapidly metabolize acrolein and its residues (Nordone et al., 1998). Based on these results and the low reported BCFs, acrolein is unlikely to bioaccumulate or bioconcentrate significantly in aquatic organisms (Howard, 1989; ATSDR, 1990; DFO, 1995; Nordone et al., 1996b). Absorption of acrolein by terrestrial plants is poor (WSSA, 1983).

5.6 Environmental partitioning

Fugacity modelling was conducted to characterize key reaction, intercompartment, and advection (movement out of a system) pathways for acrolein 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 Mackay et al. (1995) and summarized here. Values for input parameters were as follows: molecular mass, 56.06; melting point, !86.95 °C; water solubility, 208 g/litre; vapour pressure, 36.5 kPa at 20 °C; log K_{ow}, !0.01; Henry's law constant, 9.8 Pa•m^3/mol; half-life in air, 5 h; half-life in water, 55 h; half-life in soil, 55 h; half-life in sediments, 170 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.

Results of the modelling indicate that acrolein behaves differently depending on the medium to which it is released. Generally, when acrolein is continuously discharged into a specific medium, most of it can be expected to remain in that medium. For example, if discharged into air, almost all of it will exist in the atmosphere, with very small amounts in soil and water. The same applies for discharge to water and soil (Mackay et al., 1995). These predicted distributions suggest that acrolein does not tend to partition from one compartment to another. It could also be possible that when acrolein does partition to another compartment, its persistence in that second compartment is so short that little remains there.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

While data on concentrations in the environment for the source country (i.e., Canada) are emphasized here, levels of acrolein in other countries have been summarized (IPCS, 1992; IARC, 1995; US EPA, 1996). Based on this information, patterns of exposure appear to be similar.

6.1 Environmental levels

6.1.1 Ambient air

Available sampling and analytical methodologies are sufficiently sensitive to detect the presence of acrolein in many samples of ambient (outdoor) air. In urban areas in Canada, mean concentrations of acrolein in 4- or 24-h samples are generally less than 0.2 µg/m^3. Acrolein was detected (detection limit 0.05 µg/m^3) in 1597 (or 57%) of 2816 24-h samples collected between 1989 and 1996 under the National Air Pollution Surveillance (NAPS) programme from rural, suburban, and urban locations (*n* = 15) in five provinces (Environment Canada, 1996b; T. Dann, personal communication, 1998). The mean concentration in all samples was 0.18 µg/m^3. Levels ranged from below the detection limit of 0.05 µg/m^3 up to 2.47 µg/m^3 for seven urban sites. Concentrations ranged up to 1.85 µg/m^3 for two suburban sites and up to 0.33 µg/m^3 for two rural sites considered to be affected by urban areas. The highest mean concentration of acrolein in air measured weekly over any three consecutive months during the NAPS monitoring between 1989 and 1996 was 1.58 µg/m^3. This value was obtained for an urban site during the period of June–August 1994 (Environment Canada, 1996b).

Concentrations of acrolein in ambient air corresponding to the 90th, 95th, and 99th percentiles of the NAPS data set are 0.4 µg/m^3, 0.6 µg/m^3, and 1.1 µg/m^3, respectively. Based on these data, there is some evidence that concentrations of acrolein in ambient air in Canada are increasing at urban and suburban sites.

Acrolein was less frequently detected in ambient air collected at rural sites. Mean concentrations at four rural sites considered to be regionally representative generally did not exceed 0.1 µg/m^3; maximum concentrations were less than 0.5 µg/m^3 in 24-h samples (Environment Canada, 1996b; T. Dann, personal communication, 1998). Concentrations of acrolein in urban and rural areas of Canada are similar to, but generally less than, those in other countries.

6.1.2 Indoor air

In general, concentrations of acrolein in indoor air in Canada are about 2- to 20-fold higher than outdoor levels, although few potential sources of this compound in indoor locations have been identified. Acrolein was detected (detection limit 0.05 µg/m^3) in all 29 indoor air samples collected from homes in Windsor, Ontario, between 1991 and 1992 (Bell et al., 1994a; R.W. Bell, personal communication, 1995). The mean concentration of acrolein in these samples (3.0 µg/m^3) was considerably higher than the mean ambient concentration (0.16 µg/m^3; *n* = 29), with individual values in indoor air ranging from 0.4 to 8.1 µg/m^3. Acrolein was detected (detection limit 0.05 µg/m^3) in 3 of 11 samples of indoor air collected in 1993 from homes in residential and commercial areas of Hamilton, Ontario (R.W. Bell, personal communications, 1996, 1997). The mean concentration was 1.1 µg/m^3, with individual values ranging from <0.05 to 5.4 µg/m^3; acrolein was not detected (detection limit 0.05 µg/m^3) in any of the 11 corresponding samples of ambient air.

There was a general trend of increasing concentrations of acrolein in the indoor air of these homes with increasing concentrations of acetaldehyde and/or formaldehyde. The average concentrations of acrolein in the indoor air of Windsor and Hamilton homes with and without environmental tobacco smoke — i.e., 3.0 µg/m^3 and 2.2 µg/m^3, respectively — provide some support for the hypothesis that cigarette smoking is a source of acrolein in indoor air. Deliveries of acrolein in mainstream smoke from commercial cigarettes purchased in the USA and the United Kingdom ranged from 3 to 260 µg/cigarette (Magin, 1980; Manning et al., 1983; Guerin et al., 1987; Hoffmann et al., 1991; Phillips & Waller, 1991).

Acrolein was detected (detection limit 0.43 µg/m^3) in 3 of 35 samples of indoor air collected in 1997 from randomly selected homes in the Greater Toronto Area at concentrations of 16, 22, and 23 µg/m^3 (Conor Pacific Environmental, 1998). It was not detected (detection limit 0.4 µg/m^3) in any of the 35 samples of outdoor air from these locations. Acrolein was not detected (detection limit 0.43 µg/m^3) in an additional 15 samples of indoor air collected from randomly selected homes in Nova Scotia (*n* = 6) or Alberta (*n* = 15), nor was it detected in the outdoor air at these locations (Conor Pacific Environmental, 1998).

Similar concentrations of acrolein have been measured in indoor air in residential and non-residential locations in other countries (Badré et al., 1978; Weber et al., 1979; Highsmith et al., 1988; Löfroth et al., 1989; CARB, 1991; Sheldon et al., 1992; Lindstrom et al., 1995; Williams et al., 1996). Data from other countries are almost exclusively restricted to environments where there is an active combustion source (e.g., cigarettes, woodstoves and fireplaces, cooking). For example, levels of acrolein in the air in four restaurants were between 11 and 23 µg/m^3 (IPCS, 1992).

6.1.3 Drinking-water

Available quantitative data concerning the levels of acrolein in drinking-water in Canada were limited to two investigations in which acrolein was not detected in raw or treated water supplies.

In monitoring studies conducted between July 1982 and May 1983, acrolein was below the limit of detection (i.e., <0.1 µg/litre) in samples (n = 42) of treated drinking-water collected at 10 municipalities in Ontario (Otson, 1987). In an extensive survey of municipal drinking-water supplies at 150 locations in the four Atlantic provinces conducted between May 1985 and October 1988, acrolein was not detected (detection limit 1.0–2.5 µg/litre) in an unspecified number of samples of raw or treated drinking-water (Environment Canada, 1989a,b,c,d).

In studies conducted in the USA, acrolein was not detected (detection limit 3.5 µg/litre) in an unspecified number of samples of raw and finished drinking-water from three treatment plants surveyed between May and July 1988 (Glaze et al., 1989). In other studies, acrolein was detected (detection limit not reported) in only 2 of 798 samples of well or surface water collected from unspecified locations throughout the USA between 1980 and 1982; the median concentration of acrolein in these samples was <14 µg/litre (Staples et al., 1985).

6.1.4 Surface water

Acrolein was not detected (detection limit 0.1 µg/litre) in 42 raw water samples collected from potable water treatment plants in the Great Lakes region during 1982 and 1983 (Otson, 1987). In 1985, acrolein was detected at concentrations of 6.9 and 7.8 µg/litre (detection limit 5 µg/litre) in liquid effluents from two organic chemical manufacturing plants that discharged into the St. Clair River at Sarnia, Ontario (King & Sherbin, 1986). During 1989 and 1990, however, acrolein was not detected (detection limit 4 µg/litre) in the intake water or effluent of these or 24 other organic chemical manufacturing plants in Ontario (OMEE, 1993).

6.1.5 Sediment and soil

Adequate data on concentrations of acrolein in sediments and soils were not identified.

6.1.6 Food

Acrolein is produced during the cooking or processing of fat-containing foods (Beauchamp et al., 1985; Hirayama et al., 1989; Lane & Smathers, 1991). Concentrations of acrolein ranged from 11.9 to 38.1 µg/g (mean 28.5 µg/g) in samples of five varieties of cooking oil heated to 80 °C and aerated for 20 h (Hirayama et al., 1991). Acrolein was detected in the emissions from four varieties of heated cooking oils in China (Shields et al., 1995) at concentrations ranging from 49 µg/litre (peanut oil) to 392 µg/litre (rapeseed oil). Lane & Smathers (1991) indicated that in addition to the production of acrolein from the frying medium, some ingredients common to commercial batter and breading systems may indirectly lead to the production of acrolein in fried foods.

Acrolein may be generated during the ripening of fruit (Kallio & Linko, 1973; Hayase et al., 1984) and some types of cheese (e.g., Egyptian Domiati, 290–1024 µg/g; Collin et al., 1993). Feron et al. (1991) reported concentrations of acrolein ranging from <0.01 to 0.05 µg/g in fruit and a maximum concentration of 0.59 µg/g in vegetables; however, information concerning the location(s) and date(s) of sample acquisition and the number(s) of samples analysed was not presented. Acrolein has been detected (but not quantified) in cheese, caviar, and lamb (Feron et al., 1991), souring salted pork (Cantoni et al., 1969), raw and cooked poultry (Hrdlicka & Kuca, 1965; Grey & Shrimpton, 1967), cocoa beans and chocolate liquor (Boyd et al., 1965), and molasses (Hrdlicka & Janicek, 1968).

Acrolein may be produced as an unwanted by-product during alcoholic fermentation or during the storage and maturation of alcoholic products (Feron et al., 1991), although available quantitative data are extremely limited. A maximum concentration of 3.8 µg/g was reported for red wine (Feron et al., 1991). Mean concentrations of acrolein in samples of fresh (n = 3) and aged (n = 3) lager from the United Kingdom were 1.6 µg/litre and 5.0 µg/litre, respectively (Greenhoff & Wheeler, 1981), while acrolein was detected in only trace amounts (<10 µg/litre) in an unspecified number of samples of Canadian apple wine purchased at a retail outlet in Ontario (Subden et al., 1986). Acrolein was also detected in non-alcoholic beverages (i.e., coffee and tea), although quantitative data were not presented (Feron et al., 1991).

Acrolein is also produced as a thermal degradation product of cellophane and polystyrene thermoplastics used to package foods (Robles, 1968; Zitting & Heinonen, 1980), although data on the extent of migration to packaged food items have not been identified.

Therefore, with the exception of data on heated vegetable oil (Hirayama et al., 1991), the ripening of Egyptian Domiati cheese (Collin et al., 1993), and the reported concentration of 3.8 µg/g for red wine (Feron et

al., 1991), there are no reports of concentrations of acrolein greater than 1 µg/g in any food items.

6.2 Human exposure: environmental

Since adverse health effects of acrolein are primarily confined to the tissue of first contact (i.e., the respiratory and gastrointestinal tracts after inhalation and ingestion, respectively) and are concentration related (see section 8), exposures via inhalation and ingestion have been assessed separately.

Data on levels in food are limited to a small number of foodstuffs from various countries. While concentrations of acrolein as high as 0.1% by weight have been determined on rare occasions in some items, the remainder contained less than 40 µg acrolein/g and, in most cases, less than 1 µg/g. Acrolein has not been detected in two surveys of drinking-water supplies in Ontario and the Atlantic provinces (detection limits <0.1 and 1.0–2.5 µg/litre, respectively).

Available data are sufficient to serve as a basis for development of probabilistic estimates of 24-h time-weighted average concentrations of acrolein in the air to which the general population in Canada is exposed. The assumptions on which these estimates are based and output for two simulations are presented in Table 4. Based on the assumptions underlying these scenarios, between 5% and 10% of the population would be expected to be exposed to a 24-h time-weighted average concentration of acrolein of at least 5 µg/m^3 (Table 4).

Based on limited available data on concentrations of acrolein in mainstream smoke of Canadian cigarettes (Rickert et al., 1980), smokers would be directly exposed to considerably higher concentrations of acrolein.

6.3 Human exposure: occupational

Workers are exposed to acrolein in a wide variety of industrial settings. Data on airborne levels in various occupational environments are summarized in Table 5 (IARC, 1995).

Table 4: Estimation of human exposure to acrolein.

Statistical parameters of distributions of time-weighted average concentrations[a,b,c]	Probabilistic estimates from:	
	Simulation No. 1[d]	Simulation No. 2[e]
25th percentile	0.7 µg/m^3	0.2 µg/m^3
Median	1.7 µg/m^3	0.6 µg/m^3
Mean	2.3 µg/m^3	1.3 µg/m^3
75th percentile	3.6 µg/m^3	1.7 µg/m^3
90th percentile	5.3 µg/m^3	3.7 µg/m^3
95th percentile	5.9 µg/m^3	5.0 µg/m^3

[a] Distributions of 24-h time-weighted average concentrations of acrolein were estimated from distributions of concentrations of acrolein in outdoor air and indoor air, using an assumed normal distribution of time per day spent outdoors (i.e., arithmetic mean of 21 h/day and standard deviation of 1). A mean time spent outdoors of 3 h/day is assumed based on point estimates of time spent indoors and outdoors (EHD, 1997). The distribution of the time spent outdoors is arbitrarily assumed to be normal in shape with an arithmetic standard deviation of 1 h. The estimates were developed using simple random sampling with Crystal Ball® Version 4.0c (Decisioneering, Inc., 1996) and multiple simulations of 10 000 trials.

[b] Concentrations of acrolein in outdoor air were represented by the distribution of 24-h concentrations from the NAPS programme. Acrolein was detected (detection limit 0.05 µg/m^3) in 57% of 2816 samples collected between 1989 and 1996 at 15 rural, suburban, and urban sites in New Brunswick, Nova Scotia, Quebec, Ontario, and British Columbia (T. Dann, personal communication, 1998).

[c] Concentrations of acrolein in indoor air were represented by limited data of the Windsor Air Quality Study and subsequent sampling in Hamilton, Ontario (Bell et al., 1994b; OMEE, 1994; R.W. Bell, personal communications, 1995, 1996, 1997). Acrolein was detected (detection limit 0.05 µg/m^3) in 80% of 40 homes sampled in Windsor and Hamilton between 1991 and 1993. When indoors, it is assumed that the general population is exposed to concentrations of acrolein similar to those in the indoor air of their homes, as there are insufficient data concerning concentrations in other indoor environments.

[d] The distribution of concentrations of acrolein in indoor air used for Simulation No. 1 was the frequency histogram of concentrations in the 40 homes sampled in Windsor and Hamilton, Ontario.

[e] The geometric mean of the data set of concentrations in the 40 homes sampled in Windsor and Hamilton was 0.94 µg/m^3 (geometric standard deviation, 7.07). A lognormal distribution with this geometric mean and standard deviation, truncated at 8.1 µg/m^3 (i.e., the maximum concentration of acrolein measured in the indoor air of homes in the Windsor Air Quality Study), was used to represent the concentrations in indoor air in Simulation No. 2.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Small amounts of acrolein are produced endogenously during the normal intermediary catabolism of various amino acids and polyamines (Alarcon, 1970, 1972, 1976) and during the peroxidation of membrane lipids (Nath et al., 1997). Consistent with the highly reactive nature of acrolein and observed effects being restricted primarily to the initial site of contact following inhalation (i.e., the respiratory tract) (see section 8), available data indicate that the greatest proportion of exogenous inhaled acrolein is retained at the site of exposure, becoming rapidly and irreversibly bound to free protein and non-protein sulfhydryl groups (most notably glutathione; quantitative data were not identified). Based upon kinetic studies in dogs, rats, and ferrets (Egle, 1972; Ben-Jebria et al., 1995; Morris, 1996), the

Table 5: Occupational exposure to acrolein.[a]

Country	No. of plants	Job, task, or industry	No. of samples[b]	Concentration[b] in air (mg/m³)		Reference
				Mean	Range	
Finland (1980–1992)		Various industries, e.g., manufacture of plastics products, pulp, paper, paperboard, metal, glass products, electronic equipment	257 (A and P)	96.9% of measurements <0.25		Finnish Institute of Occupational Health, 1994
Finland	5	Restaurant kitchen	(A)		0.06–0.59	Vainiotalo & Matveinen, 1993
	2	Bakery		0.02		
	1	Food factory		0.01		
Finland	3	Bakery	11 (A)	0.12	<0.03–0.59	Linnainmaa et al., 1990
USA		Bakery	(A)		0.02–0.32 mg/batch	Lane & Smathers, 1991
China		Emission from rapeseed oil		Qualitative identification		Shields et al., 1993
Former USSR		Emission from sunflower oil (160–170 °C)	(A)	#1.1		Ismerov, 1984
Finland	1	Shipyard	82 (A)	0.01–0.07 (median)	0.04–1.4 (maximum)	Engström et al., 1990
Denmark	3	Engine workshops	(A)		ND–0.61	Rietz, 1985
USA		Wildland firefighters	1 (P)		0.05	Materna et al., 1992
USA	1	Truck maintenance shop		0.005		Castle & Smith, 1974
Russian Federation	1	Rubber vulcanization			0.44–1.5	Volkova & Bagdinov, 1969
Russian Federation		Workshop, welding of metals coated with anti-corrosive primers			0.11–1.0	Protsenko et al., 1973
Former Czechoslovakia	1	Pitch cooking plant	10	0.27	0.1–0.6	Mašek, 1982
		Coal coking plant	20	0.05	0.002–0.55	
USA	1	Workshop, repair and service (diesel exhaust)			<0.1	Apol, 1973
Russian Federation		Quarries, exhaust from diesel engines			2.1–7.2	Klochkovskii et al., 1981
Russian Federation	1	Production of acrolein and methyl mercaptopropionic aldehyde	(A)		0.1–8.2	Izmerov, 1984
Russian Federation	1	Press shops in oil seed mills			2–10	IPCS, 1992
Finland	14	Manufacture of thermoplastics (17 different processes)	67 (A)		<0.02	Pfäffli, 1982

[a] From IARC (1995).
[b] Abbreviations used: A = area sample; P = personal air sample (breathing zone); ND = not detected.

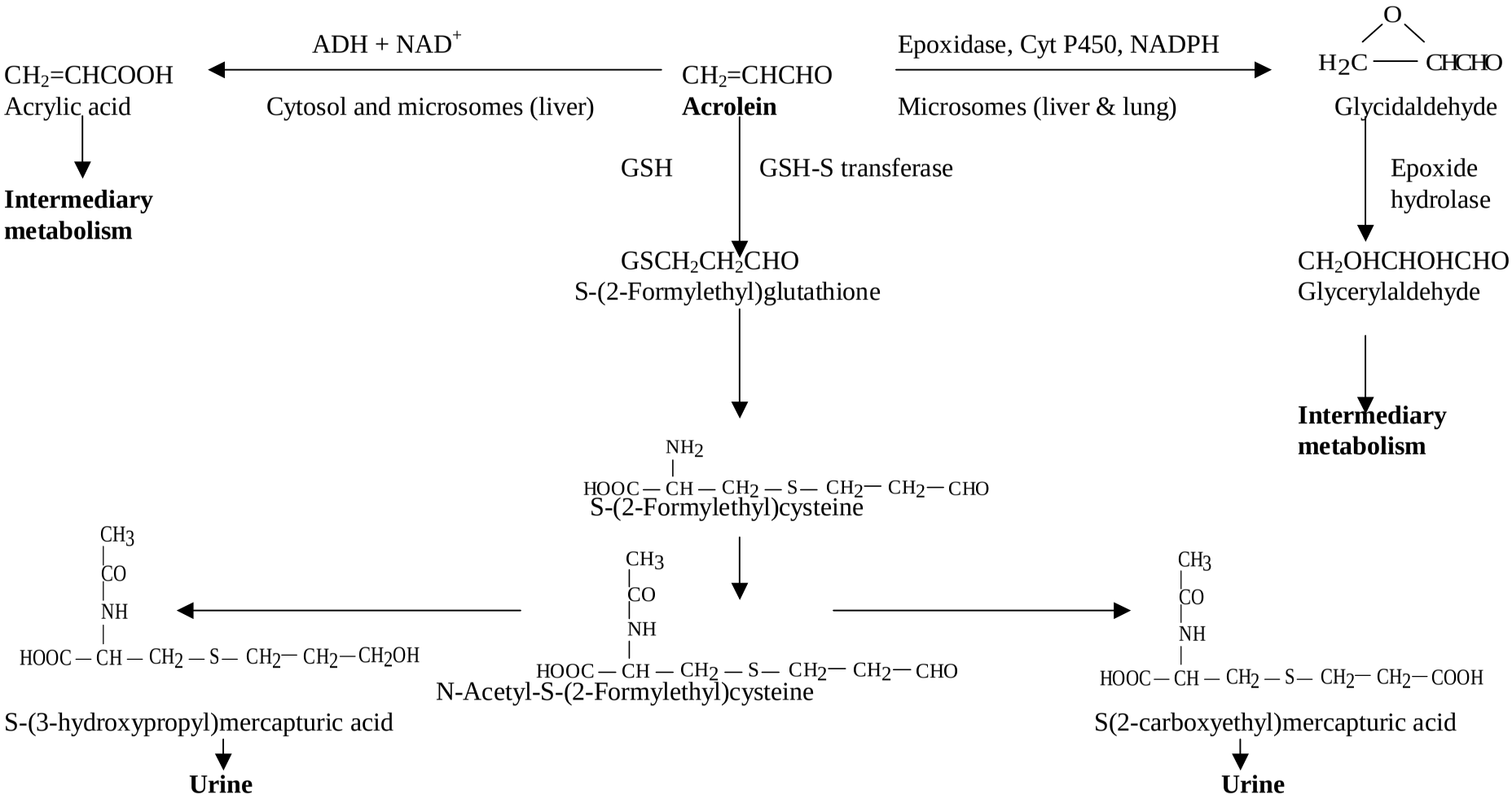
absorption of inhaled acrolein into the systemic circulation is not extensive. No quantitative or qualitative data were identified concerning the absorption of acrolein following oral or dermal exposure. Based on the metabolites most frequently identified in the urine of exposed animals, the predominant pathway for the metabolism of acrolein appears to involve conjugation with glutathione and subsequent conversion to *N*-acetylcysteine compounds (Figure 2).

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

Acrolein is highly acutely toxic, with LC_{50}s for 4- or 6-h inhalation exposures of rats, mice, and hamsters ranging from 18 to 151 mg/m^3 (8 to 66 ppm) and LD_{50}s for oral administration to rats, mice, and hamsters ranging from 7 to 46 mg/kg body weight. Signs of acute

Figure 2: Metabolism of acrolein (Modified from IARC, 1995)



toxicity include irritation of the respiratory and gastrointestinal tracts and central nervous system depression.[1]

Increased respiratory flow resistance and tidal volume and decreased respiratory rate have been observed in guinea-pigs exposed by inhalation to 39 mg acrolein/m^3 (17 ppm) for 1 h (Davis et al., 1967) or to 0.7 or 0.9 mg acrolein/m^3 (0.3 or 0.4 ppm) for 2 h (Murphy et al., 1963; Leikauf, 1992). Reductions in pulmonary resistance, pulmonary compliance, tidal volume, and respiratory rate have been observed among male Swiss mice exposed via tracheal cannula to acrolein vapour at 300 or 600 mg/m^3 for 5 min (Watanabe & Aviado, 1974).

In rats, exposure (nose only) to 0.57 or 1.53 mg acrolein/m^3 (0.25 or 0.67 ppm) for 6 h produced a significant ($P < 0.01$) reduction in glutathione reductase activity in the nasal respiratory epithelium; no histopathological effects or decreases in glutathione content within the nasal passages were observed (Cassee et al., 1996). There have been histopathological effects in the bronchi and/or trachea (including exfoliation, oedema, inflammation, vascular congestion, and haemorrhagic necrosis) in Syrian golden hamsters (Kilburn & McKenzie, 1978), guinea-pigs (Dahlgren et al., 1972; Leikauf, 1992), and New Zealand white rabbits (Beeley et al., 1986) following single exposures to acrolein vapour at concentrations ranging from 2.08 to 1120 mg/m^3 (0.91 to 489 ppm).

Mortality was increased in male F344 rats administered a single intragastric dose of 25 mg acrolein/kg body weight (in saline) (Sakata et al., 1989). Other effects included degenerative changes in the liver (eosinophilic degeneration with microvesicular steatosis), forestomach, and glandular stomach (severe inflammation, haemorrhagic gastritis, multifocal ulceration, fibrin deposition, focal haemorrhage, oedema, and polymorphonuclear leukocyte infiltration); however, no histopathological changes were observed in the urinary bladder, lungs, kidneys, or spleen.

8.2 Irritation and sensitization

Acrolein causes sensory irritation in the upper respiratory tract following inhalation; RD_{50} (the concentration resulting in a 50% reduction in respiratory rate) values of $2.4 mg acrolein/$m^3$ have been reported in rodents (EU, 1999). Based on *in vitro* studies conducted in several animal species (sheep, chickens, cows), acrolein induces a significant reduction (30–100%) in ciliary movement in the upper respiratory tract (BUA, 1994). Acrolein is irritating to the skin of rabbits and the eyes of laboratory animals; 1% solutions of acrolein produced serious eye and skin damage (Albin, 1964; BSC, 1980a,b; BUA, 1994). Although results of the only relevant study identified (i.e., a guinea-pig maximization test reported by Susten & Breitenstein, 1990) were suggestive, due to limitations in the protocol and reporting of results, available data are considered inadequate to allow an assessment of the potential of acrolein to induce sensitization.

8.3 Short- and medium-term exposure

8.3.1 Inhalation

Exposure (nose only) of male Wistar rats (n = 5–6) to 0.57 or 1.53 mg/m^3 (0.25 or 0.67 ppm) acrolein vapour for 6 h/day for 3 days produced concentration-related histopathological changes (including disarrangement, necrosis, thickening, desquamation, and basal cell hyperplasia) in the nasal respiratory/transitional epithelium, but not in the olfactory epithelium (Cassee et al., 1996). **[Lowest-observed-adverse-effect level (LOAEL) = 0.57 mg/m^3 (0.25 ppm)]**

In studies with female rats from Dahl selected lines (one susceptible and one resistant to salt-induced hypertension) exposed via inhalation (whole body) to 0.9, 3.2, or 9.2 mg/m^3 (0.4, 1.4, or 4.0 ppm) acrolein vapour for 6 h/day, 5 days/week, for up to 62 days, slight proliferative histopathological changes were observed in the lungs (including epithelial hyperplasia, squamous metaplasia, and peripheral lymphoid aggregates) of both strains at 0.9 and 3.2 mg/m^3 (0.4 and 1.4 ppm). There were severe histopathological lesions in the lungs (necrosis, oedema, haemorrhage) and trachea (squamous metaplasia) at 9.2 mg acrolein/m^3 (4.0 ppm). No microscopic changes were observed in the nasal turbinates, brain, heart, liver, kidneys, or spleen in either strain 7 days following the last exposure to acrolein (Kutzman et al., 1984). **[LOAEL = 0.9 mg/m^3 (0.4 ppm)]** However, histopathological changes in the nasal passages but not the lungs of rats were reported in a more recent study (Leach et al., 1987) in which male Sprague-Dawley rats were exposed (whole body) to 0.39, 2.45, or 6.82 mg/m^3 (0.17, 1.07, or 2.98 ppm) acrolein vapour for 6 h/day, 5 days/week, for 3 weeks. **[Systemic and site-of-contact effects at 6.82 mg/m^3 (2.98 ppm)**]

Following repeated exposure (whole body) of F344 rats (n = 24 per sex) to 0.9, 3.2, or 9.2 mg/m^3 (0.4, 1.4, or 4.0 ppm) acrolein vapour for 6 h/day, 5 days/week, for up to 62 days, there were no adverse effects at 0.9 mg/m^3 (0.4 ppm). In animals exposed to

[1] For additional detail concerning the acute toxicity of acrolein, refer to the source document (Environment Canada & Health Canada, 2000).

3.2 mg/m^3 (1.4 ppm), there were biochemical (i.e., increased collagen) and histopathological changes in the lungs compared with unexposed controls. Effects observed following exposure to 9.2 mg acrolein/m^3 (4.0 ppm) included increased mortality in males and histopathological changes in the trachea and lungs. Data on other systemic effects and histopathology in the nasal passages were not presented in these reports (Kutzman et al., 1985; Costa et al., 1986); however, in an original report of this study (Kutzman, 1981), fluctuations in the incidence of submucosal lymphoid aggregates within the nasal turbinate were noted. In animals exposed to 0, 0.9, 3.2, or 9.2 mg acrolein/m^3 (0, 0.4, 1.4, or 4.0 ppm), the incidence (statistical evaluation not presented) of submucosal lymphoid aggregates within the nasal turbinate was 1/8, 3/8, 2/7, and 3/5, respectively. **[Lowest-observed-effect level (LOEL) = 0.9 mg/m^3 (0.4 ppm)]**

Repeated inhalation exposure (whole body) of Sprague-Dawley rats, Princeton or Hartley guinea-pigs, male squirrel monkeys, and very small groups of male beagle dogs to 1.6 or 8.5 mg/m^3 (0.7 or 3.7 ppm) acrolein vapour for 8 h/day, 5 days/week, for 6 weeks produced histopathological inflammatory changes and mild emphysema in the lungs of all species (most notably in dogs and monkeys) at 1.6 mg/m^3 (0.7 ppm) (Lyon et al., 1970). Exposure to 8.5 mg acrolein/m^3 (3.7 ppm) produced mortality in monkeys, clinical signs of toxicity in dogs and monkeys, significantly ($P < 0.005$) reduced body weights in rats, and exposure-related histopathological effects in the trachea (squamous metaplasia and basal cell hyperplasia) of dogs and monkeys and in the lungs (necrotizing bronchitis, bronchiolitis with squamous metaplasia) of monkeys.

Subchronic studies of the toxicity of inhaled acrolein are limited to two investigations in which survival, growth, urinary and haematological parameters, serum biochemistry, and histopathology were examined in several species (Lyon et al., 1970; Feron et al., 1978). In one study, Wistar rats, Dutch rabbits, and Syrian golden hamsters were exposed to 0.9, 3.2, or 11.2 mg/m^3 (0.4, 1.4, or 4.9 ppm) acrolein vapour for 6 h/day, 5 days/week, for 13 weeks (Feron et al., 1978). In rats, the frequency and severity of histopathological effects within the nasal passages were concentration dependent; exposure to 0.9 mg acrolein/m^3 (0.4 ppm) produced only a slight reduction in relative heart weight and histopathological lesions in the nasal passages of one animal, while exposure to 11.2 mg acrolein/m^3 (4.9 ppm) increased mortality, as well as producing moderate to severe histopathological changes in the nasal passages, larynx, trachea, bronchi, and lungs. In hamsters, exposure to 3.2 mg acrolein/m^3 (1.4 ppm) produced slight inflammatory changes in the nasal passages, while exposure to 11.2 mg acrolein/m^3 (4.9 ppm) produced slight to severe histopathological changes in the nasal passages, larynx, and trachea. In rabbits, slight to moderate histopathological changes in the nasal passages, trachea, bronchi, and lungs were observed only in animals exposed to 11.2 mg acrolein/m^3 (4.9 ppm) (Feron et al., 1978).

The continuous inhalation of 0.50, 2.3, or 4.1 mg acrolein/m^3 (0.22, 1.0, or 1.8 ppm) by groups of Sprague-Dawley rats (n = 15 per sex), Princeton or Hartley guinea-pigs (n = 15 per sex), male beagle dogs (n = 2–4), and male squirrel monkeys (n = 9–17) for 90 days produced exposure-related histopathological lesions in dogs (lungs, spleen, and thyroid) at the lowest concentration tested, 0.50 mg/m^3 (0.22 ppm). Histopathological changes in the lung, trachea, liver, and/or kidney (in all species) were observed at higher concentrations; however, effects in the nasal passages were not assessed (Lyon et al., 1970). Systemic effects (which are not well characterized) have not been consistently observed at lowest concentrations and thus are not considered critical. **[LOAEL (dogs) = 0.50 mg/m^3 (0.22 ppm)]**

8.3.2 Ingestion

Uncertainty concerning the doses administered and lack of clear exposure-related effects on survival, behaviour, body weight, organ weights, haematological parameters, or stomach histopathology limit the usefulness, in the characterization of effects, of early short- and medium-term toxicological studies in which rats were administered drinking-water containing acrolein (Newell, 1958). In a study in which only a limited number of endpoints was assessed, the oral administration (by gavage) of 4.6–9.0 mg acrolein/kg body weight per day (at concentrations ranging from 0.46 to 0.90 mg/ml) for 14 consecutive days to male and female CD-1 mice had no dose-related effect upon mortality or weight gain, although there was a clear increase in the occurrence of white thickening of the gastric mucosa in the high-dose groups (BSC, 1983).

In a 13-week study, acrolein was administered by oral gavage in a 5% aqueous solution of methylcellulose to Fischer 344 rats at concentrations of 0.15, 0.25, 0.5, 1.0, or 2.0 mg/ml (0.75, 1.25, 2.5, 5.0, or 10.0 mg/kg body weight per day) and to B6C3F$_1$ mice at concentrations of 0.125, 0.25, 0.5, 1.0, or 2.0 mg/ml (1.25, 2.5, 5.0, 10.0, or 20.0 mg/kg body weight per day) (NTP, 1998). In a preliminary report of the results, histopathological lesions in the stomach (including haemorrhage, necrosis, and inflammation of the glandular stomach and forestomach and squamous epithelial hyperplasia of the forestomach) were observed in rats receiving $0.25 mg acrolein/ml and in mice receiving $0.125 mg acrolein/ml (i.e., in 1/10 males at the lowest concentration);

however, the incidence and statistical significance of these lesions were either poorly reported or not presented. Systemic effects in rats (increased liver weights) and mice (increased liver and kidney weights) were observed at doses $2.5 mg acrolein/kg body weight per day (NTP, 1998). **[No-observed-effect level (NOEL) (rats) = 0.75 mg/kg body weight per day (0.15 mg/ml); LOEL (mice) = 1.25 mg/kg body weight per day (0.125 mg/ml)]**

8.3.3 Dermal exposure

Erythema, oedema, and histopathological changes in the skin (hyperkeratosis, acanthosis, parakeratosis) have been observed in male and female New Zealand white rabbits exposed dermally to acrolein (7, 21, or 63 mg/kg body weight; concentrations of 3.5, 10.5, and 31.5 mg/ml) for 6 h/day, 5 days/week, for 3 weeks (BSC, 1982a).

8.4 Long-term exposure and carcinogenicity

Identified data concerning the chronic toxicity/carcinogenicity of acrolein following the inhalation exposure of laboratory species are restricted to the results of two limited studies. In one study in which groups of Syrian golden hamsters (18 animals per sex) were exposed (whole body) to 0 or 9.2 mg/m^3 (0 or 4.0 ppm) acrolein vapour for 7 h/day, 5 days/week, for 52 weeks (Feron & Kruysse, 1977), followed by a 29-week recovery period, exposure to acrolein produced variable (statistically significant) reductions in body weight among males ($P < 0.01$ to $P < 0.05$) and females ($P < 0.001$ to $P < 0.05$), an increase ($P < 0.05$) in relative lung weights and a reduction ($P < 0.05$) in relative liver weights in females, as well as slight to moderate histopathological effects in the anterior portion of the nasal passages. No exposure-related tumours were observed among animals exposed to acrolein; however, this study is limited by the relatively short exposure period, small group sizes, and single exposure concentration.

Limited exposure (1 h/day) of small numbers ($n = 20$) of female Sprague-Dawley rats to a single concentration (18 mg/m^3; 8 ppm) of acrolein for up to 18 months had no apparent adverse effects on body weight, lung weight, or histopathology in major tissues and organs (including nasal fossae, larynx, trachea, and lungs) (LeBouffant et al., 1980).

Available data concerning the chronic toxicity/carcinogenicity of acrolein following oral exposure include three bioassays in which a wide range of endpoints was examined in Sprague-Dawley rats (Parent et al., 1992a), CD-1 mice (Parent et al., 1991), and beagle dogs (Parent et al., 1992b) and an earlier study in male F344 rats, in which only mortality and histopathology in selected tissues were examined (Lijinsky & Reuber, 1987).

In a study in which Sprague-Dawley rats were administered (by oral gavage) 0.05, 0.5, or 2.5 mg acrolein/kg body weight per day (solutions were prepared fresh daily in deionized water at concentrations of 0.005, 0.05, and 0.25 mg/ml) for up to 102 weeks, there was an unspecified reduction ($P < 0.05$) in serum creatinine phosphokinase levels among both sexes at all levels of exposure. There was also a (dose-related) increase in mortality among males ($P = 0.003$) at 0.5 and 2.5 mg acrolein/kg body weight per day during the first year only and in females ($P < 0.001$) at 0.5 and 2.5 mg/kg body weight per day throughout the entire exposure period (Parent et al., 1992a). The cause of the increased mortality was not specified, and adverse effects other than those noted here were not observed. Exposure-related histopathological effects were not observed; examinations were conducted on all major tissues and organs (including oesophagus, stomach, and intestines) from animals in the control and high-dose groups and in animals found dead or sacrificed moribund, although only the stomachs of some animals sacrificed after 13 weeks were examined histopathologically. After the first year of the study, survival in the mid- and high-dose male rats was reduced compared with the controls; however, survival appeared to be higher among males exposed to acrolein (at all dose levels) during the second year of exposure than in controls. No statistical evaluation of this apparent increase in survival in the acrolein-exposed male rats was presented. Although histopathological effects in the stomach were not observed in rats exposed to acrolein in this investigation, such changes have been noted in other adequate subchronic oral studies conducted with Fischer 344 rats (NTP, 1998), in which the time-point of histopathological analysis was similar to one of those included in this study by Parent et al. (1992a).

Similarly, no apparent dose-related effects on clinical or haematological parameters, organ weight, gross pathology, or histopathology were observed when CD-1 mice were administered (by oral gavage) 0.5, 2.0, or 4.5 mg acrolein/kg body weight per day (solutions were prepared fresh daily in deionized water at concentrations of 0.05, 0.20, and 0.45 mg/ml) for 18 months (Parent et al., 1991). Administration of 4.5 mg acrolein/kg body weight per day produced effects in male mice only, which included a significant ($P # 0.05$) reduction in growth (approximately 5%) and a significant ($P # 0.05$) increase in mortality throughout the entire study period, the cause of which was not specified.

Notably, survival was higher in the low- and mid-dose males throughout the entire exposure period than in unexposed controls; no statistical evaluation of this apparent increase in survival in treated male mice was presented. Once again, although there was an absence of histopathological effects in the stomachs of mice exposed to acrolein in this study, such changes have been observed in other adequate subchronic oral studies (NTP, 1998) conducted with $B6C3F_1$ mice.

In studies of small groups (n = 20) of male F344 rats receiving drinking-water containing 0, 100, 250, or 625 mg acrolein/litre (0, 14, 36, or 89 mg/kg body weight per day)[1] for 5 days/week for up to 124 weeks or male and female rats receiving drinking-water containing 0 or 625 mg acrolein/litre (0 or 89 mg/kg body weight per day) for up to 104 weeks, exposure to acrolein had no significant effect on mortality in either sex or on histopathology (including the forestomach, peritoneum, and colon) in male rats (Lijinsky & Reuber, 1987). Female rats receiving drinking-water containing 625 mg acrolein/litre (89 mg/kg body weight per day) had a marginal increase in the incidence of adrenal cortical adenomas (5/20, P = 0.091) and in the combined incidence of adrenal cortical adenomas and "hyperplastic nodules" (7/20, P = 0.022) compared with unexposed controls (Lijinsky & Reuber, 1987). However, no additional details were provided. Re-examination of slides prepared from tissue blocks derived from the Lijinsky & Reuber (1987) study revealed no evidence of acrolein-induced carcinogenesis in the adrenal glands of female rats (Parent et al., 1992a). It should be noted that there was no indication in the Lijinsky & Reuber (1987) study that precautions had been taken to control the instability of acrolein in water or prevent the likely volatilization of acrolein; therefore, the doses that the animals received were likely considerably less than the nominal doses indicated above. Indeed, the highest dose at which non-neoplastic effects were not observed is considerably greater than reported LD_{50}s.

Non-neoplastic effects in dogs administered up to 2.0 mg acrolein/kg body weight per day, 7 days a week for up to 53 weeks, were limited to transient (dose-dependent) vomiting at all levels of exposure, which decreased over time (suggesting that animals developed tolerance to acrolein), and (persistent) significant (P < 0.05) alterations in serum biochemical parameters (including reduced total protein [up to 17%], albumin [up to 19%], and calcium [up to 7%]) in animals at the highest dose (Parent et al., 1992b).

[1] Calculated based on the average amount of water consumed (0.05 litre/day) by rats weighing 350 g (Health Canada, 1994; Meek et al., 1994).

There were no increases in diethylnitrosamine-induced respiratory tract tumours in hamsters exposed simultaneously to acrolein, and there was only limited evidence of an enhancing effect on carcinogenesis induced by benzo[a]pyrene (Feron & Kruysse, 1977). Cohen et al. (1992) reported an increased incidence of urinary bladder papillomas in rats administered acrolein by intraperitoneal injection (in water) followed by uracil in the diet, compared with controls administered water by intraperitoneal injection followed by uracil.

8.5 Genotoxicity and related end-points

In the absence of cytotoxicity, acrolein induces gene mutations in both bacteria (with or without metabolic activation) (Hemminki et al., 1980; Lijinsky & Andrews, 1980; Hales, 1982; Lutz et al., 1982; Haworth et al., 1983; Marnett et al., 1985; Foiles et al., 1989; Parent et al., 1996) and mammalian cells in culture (Smith et al., 1990), as well as structural chromosomal aberrations in Chinese hamster ovary (CHO) cells (Au et al., 1980) and sister chromatid exchanges in CHO cells (Au et al., 1980; Galloway et al., 1987) and cultured human lymphocytes (Wilmer et al., 1986). The mode of induction of the genotoxicity of acrolein appears to involve the induction of DNA damage. Acrolein binds to DNA, forms DNA–protein cross-links (Grafstrom et al., 1988), and induces DNA single strand breaks in human fibroblasts (Dypbukt et al., 1993) and bronchial epithelial cells (Grafstrom et al., 1988). In human fibroblasts, acrolein induces mutations at the HPRT locus in DNA repair-deficient cells from xeroderma pigmentosum patients but not in normal cells (Curren et al., 1988), supporting DNA damage as the primary mechanism for acrolein-induced mutagenesis. The results of *in vitro* studies suggest that intracellular glutathione (or other free sulfhydryl groups) may protect against the DNA-damaging effects of acrolein (Eisenbrand et al., 1995).

Although the results of *in vitro* studies indicate that acrolein can react directly with DNA and proteins to form stable adducts, an increased formation of DNA–protein cross-links was not observed in the nasal mucosa of male F344 rats exposed *in vivo* (by inhalation) to 5 mg acrolein/m^3 (2 ppm) for 6 h (Lam et al., 1985).

Although less relevant to the assessment of genotoxicity at the site of initial contact (i.e., where critical effects occur), *in vivo* studies of the genotoxicity of acrolein at systemic sites are not extensive. In a dominant lethal study in male ICR/Ha Swiss mice, acrolein (administered by intraperitoneal injection) at doses up to 2.2 mg/kg body weight had no effect upon the numbers of pregnancies, implants, or fetal deaths (Epstein et al., 1972). Increases in the frequency of chromosomal aberrations in peripheral blood lymphocytes or bone

marrow cells were not observed in studies in which F344 rats were exposed (by inhalation) to concentrations up to 9.2 mg acrolein/m^3 (4.0 ppm) for 6 h/day, 5 days/week, for 62 days (Kutzman, 1981) or in which Sprague-Dawley rats were administered (by intraperitoneal injection) single doses of up to 4.1 mg acrolein/kg body weight (BSC, 1982b), respectively.

8.6 Reproductive toxicity

Identified *in vivo* studies (using physiologically relevant routes of exposure) on the developmental/ reproductive toxicity of acrolein conducted by oral gavage include a two-generation reproduction study in rats (Parent et al., 1992c) and developmental toxicity studies in rabbits (Parent et al., 1993), rats (BSC, 1982c,d), and mice (BSC, 1982c,d), while studies in which animals were exposed via inhalation are limited to the results of a single-generation reproductive study in rats (Bouley et al., 1976). On the basis of these investigations, effects generally at the site of contact (e.g., gastric lesions) in the parental generation have been limiting (i.e., adverse effects have been confined primarily to the parental generation, although in studies involving non-physiological routes of administration, feto/embryotoxic and teratogenic effects have been observed).

In the most extensive reproductive bioassay identified, reproductive function (including mating performance, fertility indices, duration of gestation, pup viability and body weight, lactation indices, and maternal and pup behaviour) was assessed in two generations of rats administered acrolein by gastric intubation (Parent et al., 1992c). Sprague-Dawley rats (F_0) were administered (by gavage) 1.0, 3.0, or 6.0 mg acrolein/kg body weight per day (solutions prepared daily in deionized water at concentrations of 0.2, 0.6, and 1.2 mg/ml) for 70 days and throughout a 21-day mating period (females only). A statistically significant ($P < 0.01$) reduction in body weight in F_0 males and females and gastric lesions (i.e., erosion of the glandular mucosa and hyperplasia/hyperkeratosis of the forestomach) in F_0 and F_1 females were also observed in animals receiving 3.0 mg acrolein/kg body weight per day (0.6 mg/ml).

8.7 Neurotoxicity and effects on the immune system

Limited data on neurotoxicity indicate a lack of morphological changes in the tracheal or pulmonary nerves of rats exposed by inhalation to up to 570 mg acrolein/m^3 (249 ppm) for 10 min (Springall et al., 1990), no histopathological changes in the nerve cells of the nasal olfactory epithelium of mice exposed by inhalation to 3.9 mg acrolein/m^3 (1.7 ppm) for 6 h/day for 5 days (Buckley et al., 1984), and no behavioural effects in rats exposed by inhalation to up to 9.2 mg acrolein/m^3 (4.0 ppm) for 6 h/day, 5 days/week, for up to 62 days (Kutzman et al., 1984).

The direct effects of acrolein on the immune system (including host resistance, pulmonary bacterial clearance, antibody responsiveness, lymphocyte blastogenesis, and respiratory damage) have been investigated in *in vivo* studies conducted with rats (Bouley et al., 1976; Sherwood et al., 1986; Leach et al., 1987) and mice (Jakab, 1977; Astry & Jakab, 1983; Aranyi et al., 1986) exposed via inhalation. Immunological effects (i.e., reduced pulmonary bacterial clearance) have been observed in mice exposed to concentrations of acrolein as low as 0.23 mg/m^3 (i.e., 0.10 ppm for 3 h/day for 5 days; single administered concentration) (Aranyi et al., 1986), although effects have been transient in long-term studies. Transient effects on immunological parameters and decreased splenic weight have been observed in rats exposed to higher concentrations of acrolein.

8.8 Mechanisms of toxicity / mode of action

Due to its highly reactive nature, acrolein can bind rapidly (both enzymatically and non-enzymatically) with cellular components. Many of the toxicological effects of acrolein may be due to the saturation of protective cellular mechanisms (most notably glutathione) and subsequent reaction with critical sulfhydryl groups in proteins and peptides (Gurtoo et al., 1981; Marinello et al., 1984). In rats, inhalation of acrolein at levels ranging from 0.2 to 39 mg/m^3 (0.1 to 17 ppm) produces a concentration-dependent reduction in non-protein sulfhydryl groups in the respiratory tract, but not in the liver (McNulty et al., 1984; Lam et al., 1985; Heck et al., 1986; Walk & Haussmann, 1989). Some studies have revealed that pretreatment with compounds containing free sulfhydryl groups (e.g., cysteine) is protective against the acute lethality of acrolein (Sprince et al., 1979; Gurtoo et al., 1981). Similarly, the studies of Eisenbrand et al. (1995) suggest that intracellular glutathione (or other free sulfhydryl groups) may protect against the DNA-damaging effects of acrolein. Although there have been some suggestions that the toxic effects of acrolein may be mediated, at least in part, through mechanisms involving acrolein–glutathione conjugates (Mitchell & Petersen, 1989; Horvath et al., 1992; Ramu et al., 1996), available data remain inconclusive. In one study, acrolein and its glutathione adduct, glutathionyl-propionaldehyde, induced oxygen radical formation (Adams & Klaidman, 1993).

The nature of responses associated with exposure to acrolein is qualitatively similar to that of other

aldehydes. Acrolein is, however, the most irritating of these compounds. The pattern of observed irritancy of acrolein at the site of contact and the results of *in vitro* studies indicating that it can react directly with DNA and proteins to form stable adducts are findings similar to those for other aldehydes (such as formaldehyde) that have been carcinogenic to the respiratory system in sensitive inhalation bioassays. Although the exact mechanism is unknown, induction of tumours by these aldehydes (notably formaldehyde) is considered to be a function of both regenerative proliferative response and DNA–protein cross-linking at the site of contact.

The limited available data indicate, however, that the pattern of DNA–protein cross-linking and proliferative response induced by acrolein differs from that of acetaldehyde and formaldehyde. For acetaldehyde, at the concentrations at which tumours are observed (1350 mg/m^3 [750 ppm]), there are increases in DNA–protein cross-links in the respiratory and olfactory mucosa of rats but no increase in proliferation (Cassee et al., 1996). For formaldehyde, at the lower concentrations at which tumours are observed (7 mg/m^3 [6 ppm]), there are increases in DNA–protein cross-links and proliferation in the nasal respiratory (but not olfactory) epithelium (Casanova et al., 1994).

Moreover, available data are inadequate to assess whether acrolein is carcinogenic or interacts directly with DNA at the site of contact following inhalation, although *in vitro* studies have demonstrated that acrolein can react directly with DNA to form adducts and induce DNA damage. While there was no increase in DNA–protein cross-links in the nasal mucosa of Wistar rats exposed (by inhalation) to a single concentration of 5 mg acrolein/m^3 (2 ppm) alone, acrolein enhanced the formation of formaldehyde-induced DNA–protein cross-links (Lam et al., 1986). It is possible that the lack of observation of DNA–protein cross-links at the site of exposure at the single dose administered in studies conducted to date (Lam et al., 1985) might be attributable to preferential binding to sulfhydryl-containing nucleophiles (such as glutathione). Moreover, it appears that the cytotoxicity of acrolein at low concentrations associated with the saturation of protective mechanisms (namely glutathione) may be the crucial determinant in the toxicity of this compound at the site of exposure.

Increases in cell proliferation have been observed in the nasal respiratory epithelium (but not olfactory epithelium) of Wistar rats following single (Roemer et al., 1993) or repeated exposure (Cassee et al., 1996) (by inhalation) to relatively low concentrations (0.5 mg/m^3 [0.2 ppm] or greater) of acrolein, although data in this regard are also not completely consistent.

9. EFFECTS ON HUMANS

Acrolein is an upper respiratory tract and eye irritant in humans. The threshold concentration for the perception of acrolein vapour may be as low as 0.07 mg/m^3 (Sinkuvene, 1970), while the odour recognition threshold may be as low as 0.48 mg/m^3 (Leonardos et al., 1969). Sensory ocular irritation has been observed at concentrations that were reported to be as low as 0.13 mg acrolein/m^3 (calculated value) (Darley et al., 1960), while nasal (sensory) irritation has been reported following exposure to concentrations as low as 0.34 mg/m^3 (Weber-Tschopp et al., 1977). Respiratory rate was reduced in male volunteers exposed to concentrations as low as 0.69 mg/m^3 for 40 min (Weber-Tschopp et al., 1977). Inhalation of concentrations as low as 0.6 mg acrolein/m^3 may cause respiratory effects, including coughing, nasal irritation, chest pain, and difficulty breathing (Kirk et al., 1991). Most individuals cannot tolerate exposure to concentrations of acrolein in air of 5 mg/m^3 or higher for more than 2 min, while exposure to concentrations above 20 mg/m^3 may be lethal (Einhorn, 1975; Kirk et al., 1991).

Effects including weakness, nausea, vomiting, diarrhoea, severe respiratory and ocular irritation, shortness of breath, bronchitis, pulmonary oedema, unconsciousness, and death have been observed upon accidental exposure (by inhalation or ingestion) to acrolein. Direct dermal or ocular contact with liquid acrolein can produce severe skin or eye injury, including necrosis, oedema, erythema, dermatitis, and follicular pharyngitis (ITII, 1975; Beauchamp et al., 1985; Kirk et al., 1991; Bronstein & Sullivan, 1992; Rorison & McPherson, 1992). Effects following the ingestion or inhalation of acrolein have been consistently observed at the site of contact (i.e., stomach or respiratory tract) (Champeux et al., 1966; Gosselin et al., 1979; Schielke, 1987; Mahut et al., 1996).

In patch tests conducted with volunteers, no dermal irritation was observed following exposure to 0.01% or 0.1% acrolein; however, positive reactions (i.e., severe oedema with bullae and erythema) were observed in 6 of 48 individuals exposed to 1.0% acrolein, while more severe effects (including bullae, necrosis, inflammatory cell infiltration, and papillary oedema) were observed in 8 of 8 subjects exposed to 10% acrolein (Lacroix et al., 1976).

In a nested case–referent study among employees of chemical manufacturing companies, Ott et al. (1989) assessed the relationship between mortality from non-Hodgkin's lymphoma (52 cases), lymphocytic leukaemia (18 cases), non-lymphocytic leukaemia (39 cases), and

multiple myeloma (20 cases) and exposure to 21 different chemicals, including acrolein. The odds ratio for being a case of non-Hodgkin's lymphoma and having exposure to acrolein was 2.6 (two exposed cases), that for non-lymphocytic leukaemia 2.6 (three exposed cases), and that for multiple myeloma 1.7 (one exposed case). None of the odds ratios was statistically significant (details of statistical analysis and confidence intervals not presented); this study was limited by the small number of cases, lack of reporting of statistical analyses, and limited characterization of exposure to acrolein (and concomitant exposure to other chemicals).

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

The toxicity of acrolein to aquatic organisms has been extensively studied, while the data set on the toxicity of acrolein to terrestrial organisms is more limited. A brief summary of effects is presented below, with an emphasis on the most sensitive end-points for aquatic and terrestrial organisms.

10.1 Aquatic organisms

Acrolein is acutely toxic to aquatic organisms. Its toxicity in the aquatic environment has been extensively studied as a result of its use as an aquatic herbicide in irrigation canals.

The frog *Xenopus laevis* tadpole is the most sensitive aquatic species tested, with a 96-h LC_{50} of 7 µg/litre (Holcombe et al., 1987). Short-term LC_{50}s for freshwater fish range from 14 to 250 µg/litre. For marine fish, LC_{50}s of 56–240 µg/litre have been reported (Holcombe et al., 1987; Eisler, 1994; EU, 1999). Invertebrates have a range of sensitivity to acrolein similar to that of fish (US EPA, 1978; Eisler, 1994). The water flea *Daphnia magna* is the most sensitive invertebrate, with a 48-h LC_{50} ranging from 22 to 93 µg/litre (EU, 1999). Microbes are also sensitive to acrolein. Under closed static conditions, the 2-h growth EC_{50} for the bacterium *Proteus vulgaris* was 20 µg/litre (Eisler, 1994).

According to many field trials on the efficiency of acrolein as a pesticide, most submerged aquatic weeds and algae are sensitive (BPCI, 1994). The most sensitive species identified is the alga *Scenedesmus subspicatus*, which has a 72-h EC_{50} (biomass) of 26 µg/litre, a 72-h EC_{50} (growth rate) of 61 µg/litre, and a no-observed-effect concentration (NOEC) of 10 µg/litre (EU, 1999). When acrolein is used to clear unwanted vegetation from irrigation canals, its effective dose range is 1–15 mg/litre over an exposure period of 0.25–8 h (BPCI, 1997). Most terrestrial crop plants can tolerate irrigation water containing 25 mg acrolein/litre without damage (Ferguson et al., 1961).

Few chronic toxicity studies are available for aquatic organisms. Acrolein was toxic to the fathead minnow (*Pimephales promelas*) following a 60-day exposure to 21.8 µg/litre (Macek et al., 1976). The survival of the F_1 fathead minnow was significantly reduced at 42 µg/litre; the NOEL for F_1 survival was estimated to be 11 µg/litre. In a 64-day exposure of the zooplankton *Daphnia magna*, 100% mortality occurred in the F_2 generation at 42.7 µg/litre. The NOEC for survival was estimated to be 16.9 µg/litre (Macek et al., 1976). In another study, a subchronic 14-day NOEC of 1800 µg/litre was derived for the mollusc *Dreissena polymorpha* (EU, 1999).

In many of the aquatic studies, the exposure solutions were periodically replenished via static renewal. In other cases, the organisms were exposed in a flow-through design to a continually renewed solution of acrolein. Dose–response relationships were frequently based on nominal concentrations of acrolein because of the ready volatilization and degradation of acrolein in aqueous solutions. The actual concentrations to which the organisms were exposed, particularly in the case of static renewal bioassays, may have been lower than reported. As a result, many of the existing data may underestimate the toxicity of acrolein to aquatic organisms.

10.2 Terrestrial organisms

The data on toxicity relevant for terrestrial wildlife are limited to studies on laboratory mammals and a few acute studies on crop plants. Data indicate that terrestrial organisms are less sensitive than aquatic organisms to single exposures to acrolein (Eisler, 1994).

There have been no tests on wild terrestrial animals; effects on laboratory animals are presented in section 8. In chickens (*Gallus* sp.), there was tracheal damage at concentrations of 113–454 mg acrolein/m^3 for up to 27 days (Denine et al., 1971). With oral exposure to acrolein, the LD_{50} for mallards (*Anas platyrhynchos*) is 9.1 mg/kg body weight, and treatment levels as low as 3.3 mg/kg body weight produce signs of intoxication, such as regurgitation, ataxia, imbalance, and withdrawal (Hudson et al., 1984). The 4-h LC_{50} for the fruitfly *Drosophila melanogaster*, which is the only invertebrate tested, exceeded 4606 mg/litre following exposure to an aqueous solution of acrolein on a petri dish (Comendador et al., 1989).

The data on toxicity of acrolein in air to terrestrial plants are limited to three acute studies on crop plants. Smog-like leaf damage was observed for seven species exposed to concentrations of acrolein ranging from 233 to 4700 µg/m^3 (Haagen-Smit et al., 1952; Darley et al., 1960; Masaru et al., 1976). The most sensitive plant tested was alfalfa (*Medicago sativa*), which developed speckled surface necrosis (percentage effect not given) after a 9-h exposure to 233 µg acrolein/m^3, the lowest concentration tested in a study by Haagen-Smit et al. (1952). This concentration corresponded to a NOEC for the four other species of crop plants tested in that study (sugar beet, *Beta* sp.; endive, *Cichorium endivia*; spinach, *Spinacia oleracea*; oats, *Avena* sp.). The method of exposure involved the vaporization of liquid acrolein continuously injected into a fumigation chamber (Haagen-Smit et al., 1952). In a study of the Easter lily (*Lilium longiflorum*) seed, there was a complete inhibition of pollen tube elongation following a 5-h exposure to 910 µg acrolein/m^3 (Masaru et al., 1976). Pinto beans (*Phaseolus* sp.) exposed to 4700 µg acrolein/m^3 in air for 1.2 h exhibited 10% surface damage (Darley et al., 1960).

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and exposure–response assessment

11.1.1.1 Effects in humans

Data relevant to the assessment of the potential adverse effects of exposure to acrolein in humans are limited primarily to irritation. In early clinical studies of small numbers of volunteers exposed for short periods, ocular and nasal sensory irritation were reported at acrolein concentrations as low as 0.13 mg/m^3 (Darley et al., 1960) and 0.34 mg/m^3 (Weber-Tschopp et al., 1977), respectively, while respiratory rate was reduced at concentrations as low as 0.69 mg/m^3 (Weber-Tschopp et al., 1977). The single identified epidemiological study (Ott et al., 1989) is inadequate to serve as a basis for assessment of the carcinogenicity of acrolein.

Because of the limited nature of data in humans, hazard characterization and dose–response analysis for acrolein are based primarily on studies in animals.

11.1.1.2 Effects in experimental animals

Acrolein is highly acutely toxic, inducing irritation of the respiratory and gastrointestinal tracts and central nervous system depression. Acrolein is also irritating to the skin following dermal exposure. Available data suggest that acrolein may induce skin sensitization in experimental species, although these data are currently under review.

The effects of acrolein following exposure by inhalation have been most extensively investigated. Acrolein is cytotoxic; in short-, medium-, and long-term inhalation studies conducted in several species (rats, mice, guinea-pigs, hamsters, monkeys, and dogs), at lowest concentrations, effects (degenerative histopathological lesions) have occurred consistently at the site of entry (i.e., the respiratory tract). Effects in other organs have also sometimes been observed, although inconsistently. This is consistent with the results of toxicokinetic studies in rodents and dogs, in which there has been a high degree of retention of inhaled acrolein at the site of contact.

In primarily early repeated-exposure inhalation studies, in which examination of the respiratory tract was often not complete, species-related differences in sensitivity to acrolein have been observed, with adverse effects on the respiratory tract of dogs, monkeys, and rats at lowest concentrations (i.e., $\geq$0.50 mg/m^3 [0.22 ppm]) (Lyon et al., 1970; Feron et al., 1978; Cassee et al., 1996). With some exceptions, and although histopathological examination was, in some cases, restricted to one area of the respiratory tract, the pattern of lesions among species is generally similar to that observed for other aldehydes. Effects in rats are primarily confined to the nasal passages at lower concentrations but are observed in the more distal airways at higher concentrations, whereas effects in hamsters and guinea-pigs are observed primarily in the bronchi and/or trachea.

Based on short-, medium-, and long-term studies in a range of species, consistent with observations for inhalation, non-neoplastic histopathological effects (i.e., gastric lesions) are observed at the portal of entry in rodents following repeated ingestion of acrolein (Newell, 1958; BSC, 1983; NTP, 1998). In other studies, effects including mortality, the cause of which is uncertain (in rats and mice), reduced body weight gain (in mice), and alterations in serum biochemical parameters (in rats and dogs) have also been observed (Parent et al., 1991, 1992a,b). Ulcerative gastric lesions have also been observed in rats and rabbits following repeated oral administration of acrolein in developmental/reproductive toxicity studies (Parent et al., 1992c, 1993).

Following dermal exposure, in a single identified study, acrolein induced irritation and histopathological changes in the skin of rabbits (BSC, 1982a).

Available data are inadequate to serve as a basis for assessment of the carcinogenicity of acrolein following inhalation. Tumours have not been observed in the two relevant identified studies in rats and Syrian golden hamsters. However, these investigations were limited by small group sizes, limited exposure periods, and single dose levels (Feron & Kruysse, 1977; LeBouffant et al., 1980).

Available data concerning the chronic toxicity/carcinogenicity of acrolein following oral exposure include three bioassays in which a wide range of endpoints was examined following administration in Sprague-Dawley rats (Parent et al., 1992a), CD-1 mice (Parent et al., 1991), and beagle dogs (Parent et al., 1992b) and an earlier study in male F344 rats in which only mortality and histopathology in selected tissues were examined (Lijinsky & Reuber, 1987). In the more extensive of these studies, there have been no increases in the incidence of tumours of any type, although mortality, the cause of which is unclear, was increased in rats and mice (Parent et al., 1991, 1992a).

Reproductive/developmental studies include a one-generation reproductive study in rats exposed by inhalation (Bouley et al., 1976); for ingestion, there is a two-generation reproductive study in rats (Parent et al., 1992c) and developmental toxicity studies in rabbits (Parent et al., 1993), rats (BSC, 1982c,d), and mice (BSC, 1982c,d), all conducted by oral gavage. In these studies, effects have generally been confined to the site of contact in the parental generation.

Based on the limited number of investigations identified to date, immunological effects (i.e., reduced pulmonary bacterial clearance) have been observed at concentrations that are similar to those that have induced respiratory tract damage (Aranyi et al., 1986).

Acrolein is mutagenic *in vitro*, inducing gene mutations in both bacteria and mammalian cells in culture, as well as structural chromosomal aberrations in CHO cells and sister chromatid exchanges in CHO cells and cultured human lymphocytes. Acrolein binds to DNA, forms DNA–protein cross-links, and induces DNA single strand breaks in human fibroblasts and bronchial epithelial cells. In human fibroblasts, acrolein induces mutations at the HPRT locus in DNA repair-deficient cells from xeroderma pigmentosum patients, supporting DNA damage as the primary mechanism for acrolein-induced mutagenesis.

In the single relevant study identified, there was no increase in DNA–protein cross-links in the nasal mucosa of Wistar rats exposed by inhalation to a single concentration of acrolein (Lam et al., 1986). Although less relevant to the assessment of genotoxicity at the site of initial contact (i.e., where critical effects occur), *in vivo* studies of the genotoxicity of acrolein at systemic sites are not extensive, and results have been negative (Epstein et al., 1972; Kutzman, 1981; BSC, 1982b).

Available data are considered inadequate to allow an assessment of whether acrolein is carcinogenic or interacts directly with DNA at the site of contact following inhalation, although *in vitro* studies indicate that acrolein can interact directly with DNA and induce DNA damage. In view of the inadequacy of the identified inhalation carcinogenicity bioassays conducted to date, the documented genotoxicity of acrolein *in vitro*, and the paucity of data on genotoxicity at the site of contact *in vivo*, the carcinogenic potential of this substance cannot be ruled out, and further studies are desirable.

11.1.2 Criteria for setting tolerable intakes/concentrations or guidance values

11.1.2.1 Inhalation

In inhalation studies conducted in several species, the respiratory tract has consistently been affected at lowest concentrations, with similar effects noted in the critical studies, although with some variation in sensitivity and principal site among species. In identified short-term investigations, degenerative changes were observed in the nasal respiratory epithelium of rats exposed (by inhalation) to 0.57 mg acrolein/m^3 (0.25 ppm) (Cassee et al., 1996). Degenerative changes in the nasal olfactory epithelium, trachea, bronchi, and/or lungs were noted at higher concentrations (i.e., $\geq$0.9 mg/m^3 or $\geq$0.4 ppm) in several species (Lyon et al., 1970; Buckley et al., 1984; Kutzman et al., 1984, 1985; Leach et al., 1987). In subchronic inhalation studies in several species, dogs were most sensitive, with histopathological changes in the lungs (nasal passages were not assessed) observed following continuous exposure to 0.50 mg/m^3 (0.22 ppm), considered to be the LOAEL (Lyon et al., 1970). In rats exposed to 3.2 mg/m^3 (1.4 ppm), there were moderate histopathological changes in the nasal passages and a significant reduction in growth (Feron et al., 1978). Exposure–response has not been well characterized in the two identified limited chronic inhalation studies, in both of which rodents were exposed to a single concentration of acrolein (Feron & Kruysse, 1977; LeBouffant et al., 1980). In these investigations, non-neoplastic lesions in the nasal passages of hamsters were observed at 9.2 mg/m^3 (4.0 ppm).

Since non-neoplastic effects in the respiratory tract of experimental animals are considered critical, a tolerable concentration (TC) for acrolein has been derived on the basis of a benchmark concentration (BMC) in rats, one of the most sensitive species, divided by an

Table 6: Benchmark concentrations for acrolein using a multistage model.

Lesion[a]	Incidence (at 0, 0.58, 1.56 mg/m³)	BMC_{05} (mg/m³)	$BMCL_{05}$ (mg/m³)	P^2	df	*P*-value
Disarrangement, necrosis, thickening, and desquamation of the respiratory/ transitional epithelium	0/19, 1/5, 3/6	0.14	0.06	0	0	1
Basal cell hyperplasia and/or increased mitotic figures in the respiratory/transitional epithelium	0/19, 0/5, 4/6	0.68	0.13	0	0	1

[a] Moderate and severe histopathological changes in nasal passages of rats exposed (6 h/day) for 3 days (Cassee et al., 1996).

uncertainty factor. However, since no single study is clearly superior as a basis for characterization of concentration–response, several values have been developed for comparison. Despite differences in the anatomy and physiology of the respiratory tract in experimental animals and humans, respiratory tract defence mechanisms are similar. In addition, the limited available data indicate that there is sensory irritation (nasal and ocular) in humans exposed to low concentrations of acrolein vapour. Thus, it is reasonable to assume that the response of the human respiratory tract mucosa to acrolein will be qualitatively similar to that of experimental species, although there may be quantitative differences due to oro-nasal breathing patterns and larger surface area in humans compared with rodents; available data are inadequate, however, to quantitatively account for this variation.

There are two short-term inhalation studies in rats for which information was sufficient to derive BMCs[1] — namely, the 3-day study by Cassee et al. (1996) and the 62-day study of Kutzman et al. (1985). Effects were observed at lowest levels by Cassee et al. (1996); moreover, this was one of the few studies in which histopathological effects in both the upper and lower respiratory tract were examined. However, the number of administered concentrations was limited to two in addition to controls in this study; moreover, the number of animals examined in each of the exposed groups was small (5–6 in exposed and 19 in control). Therefore, TCs have been developed on the basis of both a BMC and an effect level in the most sensitive investigation (i.e., Cassee et al., 1996). The BMC from the Cassee et al. (1996) study is compared with a BMC reported by Kutzman et al. (1985), who used three administered concentrations and controls in their investigation. The TCs are compared with that which might be derived based on a LOAEL in dogs (Lyon et al., 1970), another sensitive species for which available information is insufficient to develop a BMC.

For many types of effects, studies of short duration are not preferred as the basis for development of TCs. However, the investigation by Cassee et al. (1996) is the most sensitive of the inhalation studies in which the incidence of histopathological changes in the respiratory tract of experimental species has been reported. Although the data were derived from a short-term study, the type of degenerative changes observed in the nasal epithelium of male Wistar rats in this study was not dissimilar to those observed in longer-term bioassays conducted at similar concentrations in the same strain of rats (Feron et al., 1978) and in hamsters (Feron & Kruysse, 1977). Thus, BMCs for non-neoplastic effects have been calculated for degeneration in the nasal respiratory epithelium of male Wistar rats exposed (by inhalation) to acrolein for 3 days, based on data from the critical study for characterization of concentration–response discussed above (Cassee et al., 1996). The critical data are presented in Table 6. Analyses were limited to "moderate to severe" changes for those end-points for which data were considered adequate to characterize exposure–response.[2] These were lesions where there were adequate data on incidence for two concentrations and controls: namely, "basal cell hyperplasia and/or increased mitotic figures in the respiratory/transitional epithelium" and "disarrangement, necrosis, thickening, and desquamation of the respiratory/transitional epithelium." On this basis, the BMC_{05} (the concentration associated with a 5% increase in the incidence of lesions in the nasal respiratory epithelium) for male Wistar rats for the most sensitive of these end-points, modelled using THRESH (Howe, 1995), is 0.14 mg/m^3 (Figure 3). This was based on moderate to severe disarrangement, necrosis, thickening, and desquamation. The lower 95% confidence limit for this value ($BMCL_{05}$) is 0.06 mg/m^3. For comparative purposes, the lowest BMC_{05} for lesions in the nasal turbinates reported by Kutzman (1981) and Kutzman et al. (1985) was 0.76 mg/m^3 (0.33 ppm) ($BMCL_{05}$ = 0.27 mg/m^3 [0.12 ppm]).

[1] All attempts were made to access original data to serve as the basis for BMCs for critical studies.

[2] Where there was downturning or levelling at 100% of the dose–response curve, data were considered inadequate.

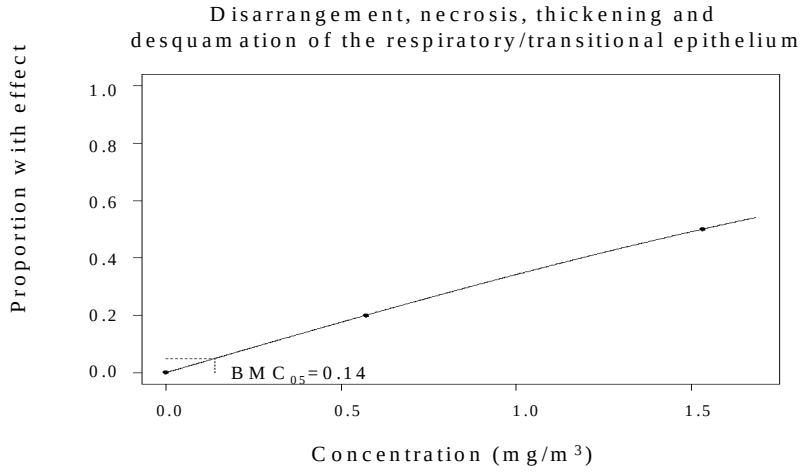


Figure 3: Benchmark concentration for acrolein (not adjusted for continuous exposure).

A TC has been developed on the basis of the BMC_{05} for non-neoplastic lesions in the nasal respiratory epithelium of rats as follows:

$$TC = \frac{0.14\ mg/m^3}{100} \times \frac{6}{24}$$

$$= 0.000\ 35\ mg/m^3$$

$$\approx 0.4\ \mu g/m^3$$

where:

- $0.14\ mg/m^3$ is the concentration estimated to be associated with a 5% increase in disarrangement, necrosis, thickening, desquamation, and hyperplasia in the nasal respiratory epithelium of rats exposed (by inhalation) to acrolein for 3 days (Cassee et al., 1996). The lower 95% confidence limit ($0.06\ mg/m^3$) was not utilized[1] because of the instability in the data, attributable primarily to small group sizes;
- 6/24 is the adjustment of intermittent (6 h/day) to continuous exposure. There are no data that provide direct evidence as to whether such an adjustment is suitable for acrolein, although it is likely that lesions would be more severe with continuous exposure; and
- 100 is the uncertainty factor (×10 for interspecies variation, ×10 for intraspecies variation). Available data are inadequate to further address toxicokinetic and toxicodynamic aspects of components of uncertainty with values derived on the basis of compound-specific data, and guidance is not explicit, currently (WHO, 1994), on more generalized replacement of the kinetic component of default for interspecies and within-human variability for site-of-contact effects related to delivered concentration. Also, consistent with data on respiratory irritation induced by other aldehydes and no indication for acrolein that severity of the critical effects increases with duration of exposure, an additional uncertainty factor to address the use of a short-term study as the basis for the TC is considered inappropriate. No additional quantitative element has been included to address limitations of the database, such as the lack of an adequate carcinogenesis bioassay via the inhalation route, since a TC that is based on critical effects at the site of entry is likely to be protective for systemic effects (including teratogenicity). While further studies of the potential relative roles of cytotoxicity, cell proliferation, and DNA–protein cross-links observed *in vitro* are desirable, chronic studies via ingestion are available. Moreover, the TC is considered to be conservative in view of the fact that reductions in glutathione content have been observed in another strain of rats at concentrations less than the levels at which adverse effects have been observed in the study deemed critical here (McNulty et al., 1984; Cassee et al., 1996).

A TC derived on the basis of the LOAEL in this study (incorporating an additional factor of 10 for use of

[1] A TC based on the $BMCL_{05}$ would be $0.2\ \mu g/m^3$.

a LOAEL instead of a NOAEL) would be slightly lower (0.1 μg/m^3).

This TC is also considered to be protective based on a LOAEL of 0.50 mg/m^3 (0.22 ppm) for non-neoplastic lesions in the lung (emphysema, congestion, and focal vacuolation) of dogs exposed continuously in the subchronic inhalation study by Lyon et al. (1970). Based on the application of an uncertainty factor of 1000 (×10 for interspecies variation, ×10 for intraspecies variation, ×10 for use of a LOAEL rather than a NOEL), the resulting value (i.e., 0.5 μg/m^3) is similar to 0.1 and 0.4 μg/m^3.

On the basis of limited available data in human studies, the TCs derived above (0.1–0.5 μg/m^3) are 2 or 3 orders of magnitude lower than the thresholds for odour perception (i.e., 70 μg/m^3) (Sinkuvene, 1970) and sensory irritation (i.e., 130 μg/m^3) (Darley et al., 1960), respectively. Quantitative data on respiratory (versus sensory) irritation in humans are inadequate to allow conclusions concerning exposure–response to be drawn.

11.1.2.2 Ingestion

Owing to uncertainties about the doses received by the animals exposed in drinking-water (due to the volatility and instability of acrolein in water), early studies are not informative in characterization of dose–response for effects of acrolein following ingestion (Newell, 1958; Lijinsky & Reuber, 1987), and results of the remaining studies are not consistent with respect to the nature of the effects observed at lowest doses or concentrations, possibly due to the very low doses administered. In subchronic studies in rats and mice administered acrolein by gavage in solutions of methylcellulose (NTP, 1998), lesions in the stomach (including hyperplasia of the forestomach and necrosis, inflammation, and haemorrhage of the glandular stomach and forestomach) were observed at doses as low as 1.25 mg acrolein/kg body weight per day (administered concentrations of 0.25 mg/ml in rats and 0.125 mg/ml in mice). In mice exposed to higher concentrations by gavage in drinking-water for 14 days, based on examination of a limited range of end-points, effects were limited to thickening of the squamous portion of the glandular mucosa at 5.8 mg/kg body weight per day and above (administered concentration, 0.58 mg/ml) (BSC, 1983). In contrast, in chronic studies in which acrolein was administered by gavage in water to rats and mice at doses up to 2.5 mg/kg body weight per day (administered concentration, 0.25 mg/ml) and 4.5 mg/kg body weight per day (administered concentration, 0.45 mg/ml), respectively, observed effects were limited to increased mortality, the cause of which was unclear (Parent et al., 1991, 1992a); in a reproductive study in rats by the same investigators (Parent et al., 1992c), however, erosion of the glandular stomach and hyperplasia/hyperkeratosis of the forestomach were observed at lowest doses (3.0 mg/kg body weight per day; administered concentration, 0.6 mg/ml). In chronic studies in which dogs were administered gelatin capsules containing acrolein (Parent et al., 1992b), alterations in serum biochemical parameters and (transient) clinical signs of toxicity were observed at 2.0 mg acrolein/kg body weight per day (considered to be the NOAEL). The reasons for these variations in results are unclear but have been suggested to be due to the variations in vehicles or, potentially, the development of tolerance in longer-term investigations. Available data are inconsistent with the latter hypothesis, however, in that lesions in the stomach were not noted at the 90-day interim sacrifice in the chronic study in rats (Parent et al., 1992a); without systematic investigation of the progression of lesions, available data are inadequate to allow any conclusions in this regard to be drawn.

Based on available data, it seems likely that effects at the site of contact following ingestion of acrolein will be limiting; moreover, the most sensitive study in rats and mice (NTP, 1998) is most informative in characterization of dose– and concentration–response in this regard. While effects were noted at administered concentrations of 0.25 mg/ml (rats) and 0.125 mg/ml (in 1/10 male mice), there were no effects in rats at 0.15 mg/ml (NTP, 1998). This latter value corresponded to a dose of 0.75 mg/kg body weight per day. Since the effects at the site of contact are more likely related to administered concentration than dose, a TC based on administered concentration is derived here and the corresponding dose on a body weight basis presented for comparison.

A provisional[1] TC has been developed on the basis of the NOEL for non-neoplastic lesions in the gastrointestinal tract of rats as follows:

$$TC = \frac{0.15 \text{ mg/ml}}{100}$$

$$= 0.0015 \text{ mg/ml}$$

$$= 1.5 \text{ μg/ml (corresponding to 7.5 μg/kg body weight per day)}$$

where:

[1] This value is considered provisional because it is based on preliminary results of the 13-week NTP (1998) study. Derivation of the provisional TC on the basis of the LOEL in mice of 0.125 mg/ml (based on non-neoplastic lesions in the gastrointestinal tract in 1/10 males) would be similar to that derived based on the NOEL of 0.15 mg/ml in rats.

- 0.15 mg/ml is the NOEL for effects on the gastrointestinal tract (hyperplasia of the forestomach and necrosis, inflammation, and haemorrhage of the glandular stomach and forestomach) in rats exposed for 13 weeks to acrolein by gavage in a 5% solution of methylcellulose (NTP, 1998). Although it was considered that the dog (Parent et al., 1992b) might be a more appropriate model for humans, due to its lack of forestomach, or that the TC could be based on the higher effect level in the glandular stomach of rats, in view of the nature of the effect, which relates to reactivity of the compound at the site of first contact, the more conservative effect level utilized here was selected; and

- 100 is the uncertainty factor (×10 for interspecies variation, ×10 for intraspecies variation). In view of the fact that there appears to be no indication that severity of the critical effects increases with duration of exposure (i.e., the type of degenerative changes observed in the glandular stomach and forestomach of rats or mice following short-term exposure to acrolein [BSC, 1983; Parent et al., 1992c] was not dissimilar to that observed in longer-term bioassays conducted at similar concentrations in the same species [NTP, 1998]), an additional uncertainty factor to address the use of a subchronic study as the basis for the TC is considered inappropriate.

This TC is considered to be conservative in view of the fact that the critical concentration is based on a study in which administration was by gavage in a 5% solution of methylcellulose.

11.1.3 Sample risk characterization

Based on relatively extensive data on concentrations in ambient air for the source country of this CICAD (i.e., Canada), the population appears to be exposed routinely to concentrations of airborne acrolein that are higher than the TC (for inhalation) of 0.1–0.5 µg/m^3. Indeed, mean, median, and the 95th percentiles for distributions of 24-h time-weighted average concentrations of acrolein in Canada exceed these values by up to 10-fold.

In addition, the range of concentrations in food measured in other countries (although dependent upon such factors as method of cooking) is within the range of the provisional TC for ingestion (1 µg/g versus 1.5 µg/ml, assuming a density of 1 g/ml).

11.1.4 Uncertainties in the evaluation of health risks

Since estimates of exposure are provided in the CICAD only as an example as a basis for the sample risk characterization, the focus in this section is on uncertainties associated with characterization of hazard and exposure–response analyses.

The degree of confidence in the database on toxicity that serves as the basis for the development of the TCs for inhalation and ingestion is moderate, although there is a relatively high degree of certainty that critical effects are those that occur at the site of entry. There are few relevant studies in humans, restricted primarily to early investigations of subjective reports of sensory irritation, and none in which histopathological changes in the upper respiratory tract have been examined following exposure to acrolein for comparison with the results of studies in animals. Confidence in the notion of the possible development of tolerance to the effects of acrolein following repeated exposure is low, owing to the lack of reliable data. The derived TCs for inhalation are highly conservative, compared with the limited data from studies in humans, where signs of nasal and ocular sensory irritation have been observed at levels as low as 130 µg acrolein/m^3. The carcinogenicity of inhaled acrolein has not been adequately investigated and warrants further study, although it is possible, based primarily on data for other aldehydes, that concentrations developed to protect against irritant effects at the site of contact may also be protective for possible carcinogenicity.

The degree of confidence in the provisional TC for ingestion will be increased by confirmation in more detailed reports of the preliminary results of the 13-week NTP (1998) study.

11.2 Evaluation of environmental effects

11.2.1 Assessment end-points

Based on its physical/chemical properties, acrolein is unlikely to partition out of air when released into that medium. Non-pesticidal sources in water, sediment, and soil have not been identified, and acrolein is degraded in these media. Lack of focus on these media is also supported by air monitoring data in Canada and the lack of detectable concentrations of acrolein in water, sediment, and soil. Acrolein does not bioaccumulate in organisms. Therefore, the assessment of acrolein will focus on terrestrial organisms exposed to air in urban areas.

Selected assessment end-points for terrestrial biota are reductions in the growth, survival, or reproduction of terrestrial plants and animals due to exposure to acrolein. Small animals, such as deer mice or songbirds, are likely

Table 7: Summary of the environmental risk analysis.

Exposure scenario	EEV (µg/m³)	CTV (µg/m³)	Application factor	ENEV (µg/m³)	Quotient
Single / Plant	2.47	233	10	23	0.11
Single / Animals	2.47	570	10	57	0.04
Long-term / Plant	1.58	233	100	2.33	0.68
Long-term / Animals	1.58	570	10	57	0.03

to have the highest exposure because of their rapid respiration rate and high metabolism.

The most sensitive measured end-point identified for terrestrial plants is the acute effect of acrolein on the survival of the alfalfa plant. Both single and long-term exposure scenarios are based on this end-point because of the lack of chronic toxicity data on plants. The most sensitive measured end-point identified for terrestrial animals is the short-term effect of acrolein on rats exposed via inhalation, which is the basis for both single and long-term exposure scenarios.

11.2.2 Sample environmental risk characterization

For each end-point, an estimated exposure value (EEV) is selected and an estimated no-effects value (ENEV) is determined by dividing a critical toxicity value (CTV) by an application factor. A quotient (EEV/ENEV) is calculated for each of the assessment end-points in order to determine whether there is potential ecological risk in the source country (Canada) (summarized in Table 7).

Acrolein is released from natural and anthropogenic sources in Canada. Acrolein from non-pesticidal sources is released predominantly to air. The largest source appears to be exhaust from diesel and gasoline motor vehicles. Since acrolein is not persistent in air, environmental effects are expected to be greatest in urban areas where traffic volume is high and continuous. This is supported by monitoring data on concentrations of acrolein in ambient air in the sample country (Canada).

11.2.2.1 Single exposure of terrestrial plants and animals

The highest concentration of acrolein reported for ambient air in seven urban sites in Canada between 1989 and 1996 is 2.47 µg/m^3. It will be considered as the EEV in the analysis of single exposure scenarios for terrestrial plants and animals.

11.2.2.1.1 Terrestrial plants

For single exposure of terrestrial plants to acrolein in air, the CTV is 233 µg/m^3, based on a 9-h exposure concentration causing speckled surface necrosis in the alfalfa plant (Haagen-Smit et al., 1952). This value was selected from a data set composed of three acute toxicity studies conducted on seven species of crop plants representing monocots and dicots at two life stages.

The ENEV for terrestrial plants is derived by dividing the CTV by an application factor of 10. This factor accounts for the uncertainty surrounding the conversion of a lowest-observed-effect concentration (LOEC) to a long-term no-effects value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity. As a result, the ENEV is 23 µg/m^3.

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

$$= \frac{2.47\ \mu g/m^3}{23\ \mu g/m^3}$$

$$\therefore 0.11$$

Since the quotient is less than 1, it is unlikely that acrolein emissions cause acute adverse effects on terrestrial plants in the sample country (Canada).

11.2.2.1.2 Terrestrial animals

For single exposure of terrestrial animals to acrolein in air, the CTV is 570 µg/m^3, based on the LOAEL for exposure of the rat via inhalation for 6 h/day for 3 days (Cassee et al., 1996). The exposure caused an increase in cell proliferation and histopathological changes in the nasal respiratory epithelium. Since non-neoplastic effects in the respiratory tract of experimental animals are considered critical, this study represents the most sensitive inhalation study reported (see section 11.1.2.1). This CTV was selected as the lowest short-term effects concentration from a large data set composed of more than 10 studies conducted on six species of laboratory mammals and one species of domestic fowl.

The ENEV is derived by dividing the CTV by an application factor of 10. This factor accounts for the uncertainty surrounding the conversion of a LOAEL to a no-effects value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity. As a result, the ENEV is 57 µg/m^3.

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}} = \frac{2.47\ \mu g/m^3}{57\ \mu g/m^3} \approx 0.04$$

Since the quotient is less than 1, it is unlikely that acrolein emissions cause acute adverse effects on terrestrial animals in the sample country (Canada).

11.2.2.2 Long-term exposure of terrestrial plants and animals

The highest mean concentration of acrolein in air measured weekly over any 3 consecutive months during the monitoring of 15 Canadian sites between 1989 and 1996 is 1.58 µg/m^3. This value was obtained for an urban site (Environment Canada, 1996b). This value will be used as the EEV in the analysis of long-term exposure scenarios for terrestrial plants and animals. A 3-month mean was selected for the chronic EEV because it corresponds to an appropriate long-term exposure period relative to the life span of test organisms.

11.2.2.2.1 Terrestrial plants

For long-term exposure of terrestrial plants to acrolein in air, the CTV is 233 µg/m^3, based on a 9-h exposure concentration causing speckled surface necrosis in the alfalfa plant (Haagen-Smit et al., 1952). This value was selected from a data set composed of three acute toxicity studies conducted on seven species of crop plants representing monocots and dicots at two life stages.

The ENEV is derived by dividing the CTV by an application factor of 100. This factor accounts for the uncertainty surrounding the conversion of an acute LOEC to a long-term no-effects value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity. As a result, the ENEV is 2.33 µg/m^3.

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}} = \frac{1.58\ \mu g/m^3}{2.33\ \mu g/m^3} \approx 0.68$$

Since the quotient is less than 1, it is unlikely that acrolein emissions will cause adverse effects on populations of terrestrial plants in the sample country (Canada).

11.2.2.2.2 Terrestrial animals

For long-term exposure of terrestrial animals to acrolein in air, the Cassee et al. (1996) study is also the basis for the ENEV. In this assessment, the respiratory tract is considered to be the most sensitive site in mammals for acrolein, as indicated in the study by Cassee et al. (1996). Therefore, the CTV is 570 µg/m^3, based on the LOAEL for exposure of the rat via inhalation for 6 h/day for 3 days. This CTV value for the rat is selected from a large data set composed of more than 10 studies conducted on six species of laboratory animals.

The ENEV is derived by dividing the CTV by an application factor of 10. This factor accounts for the uncertainty surrounding the extrapolation from a LOAEL to a no-effects value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity. The concentration of acrolein at the site of contact is the critical effect concentration, not the total cumulative dose, which would be observed only over a longer exposure period. Therefore, for derivation of the ENEV for long-term exposure, an additional application factor to account for the "less than long-term" exposure period has not been incorporated. The choice of application factor is consistent with other environmental risk assessments in protecting against population-level effects. The resulting ENEV is 57 µg/m^3.

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}} = \frac{1.58\ \mu g/m^3}{57\ \mu g/m^3} \approx 0.03$$

Since the quotient is less than 1, it is unlikely that acrolein emissions will cause adverse effects on populations of terrestrial animals in the sample country (Canada).

11.2.3 Uncertainties in the evaluation of environmental risks

Since estimates of exposure are provided in this CICAD only as an example as a basis for the sample risk characterization, the focus in this section is on uncertainties associated with characterization of hazard.

Regarding effects of acrolein on terrestrial organisms, uncertainty inevitably surrounds the extrapolation from available toxicity data to potential ecosystem effects. While the toxicity data set for plants includes monocot and dicot species, it does not contain data on coniferous species, which are often particularly sensitive to air pollution. Also, the extent to which surface necrosis of the alfalfa plant translates into long-term ecological damage is not known. The toxicity data set for animals, composed of studies on herbivores and carnivores, is more extensive. However, no data were found for small bird species such as songbirds, which are considered to be more sensitive than small mammals (L. Brownlee, personal communication, 1997). It is also not known to what extent the physiological effects observed in the rat are representative of long-term ecological damage. To counter these uncertainties, appropriate application factors were used in the environmental risk analysis to derive ENEVs.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

IARC (1979, 1985, 1995) has concluded that acrolein is not classifiable as to its carcinogenicity to humans (Group 3). This is based on inadequate evidence in humans and in experimental animals for the carcinogenicity of acrolein.

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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 acrolein 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 acrolein were prepared by staff of Health Canada and Environment Canada. H. Hirtle, Health Canada, assisted in the preparation of the draft CICAD through inclusion of additional relevant information.

Environmental sections of the assessment report and the supporting documentation (Environment Canada, 1998) were reviewed externally by C. Jacobs (Degussa AG, Germany), R. Parent (Consultox Ltd.), G. Rawn (Fisheries and Oceans Canada), S. Semeniuk (E.B. Eddy Forest Products Ltd.), N. Tolson (Pest Management Regulatory Agency), and J. van Koten (The Netherlands' National Institute of Public Health and the Environment).

Sections of the assessment report and supporting documentation on genotoxicity were reviewed by D. Blakey of the Environmental and Occupational Toxicology Division of Health Canada. Sections of the supporting documentation pertaining to human health were reviewed externally by R. Parent (Consultox Ltd.) and W.F. Mayr and S. Jacobi (both from Degussa AG), primarily to address adequacy of coverage. 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 16 November 1998 in Cincinnati, Ohio:

M. Aardema, Procter & Gamble
J. Christopher, California Environmental Protection Agency
M. Dourson, TERA
M. Friedman, private consultant
M. Gargas, ChemRisk Division of McLaren/Hart
H. Heck, The Chemical Industry Institute of Toxicology (written comments)
G. Leikauf, University of Cincinnati
M. Moore, US Environmental Protection Agency
R. Tardiff, The Sapphire Group, Inc.
V. Vu, US Environmental Protection Agency
V. Walker, New York State Department of Health

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on acrolein 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:

M. Baril, International Programme on Chemical Safety/ Institut de Recherche en Santé et en Sécurité du Travail du Québec, Montreal, Quebec, Canada

R. Benson, Drinking Water Program, US Environmental Protection Agency, Denver, CO, USA

R. Cary, Health and Safety Executive, Bootle, Merseyside, United Kingdom

R. Chhabra, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA

J. Curless, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

H. Gibb, National Centre for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

M. Greenberg, National Center for Environmental Assessment, US Environmental Protection Agency, Research Triangle Park, NC, USA

R.F. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV), Berlin, Germany

C. Hiremath, National Center for Environmental Assessment, US Environmental Protection Agency, Research Triangle Park, NC, USA

H. Nagy, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

K. Ziegler-Skylakakis, European Commission, Luxembourg

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Ottawa, Canada,
29 October – 1 November 2001

Members

Mr R. Cary, Health and Safety Executive, Merseyside, United Kingdom

Dr T. Chakrabarti, National Environmental Engineering Research Institute, Nehru Marg, India

Dr R. Chhabra, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA (*teleconference participant*)

Dr B.-H. Chen, School of Public Health, Fudan University (formerly Shanghai Medical University), Shanghai, China

Dr C. De Rosa, Agency for Toxic Substances and Disease Registry, Department of Health and Human Services, Atlanta, GA, USA (*Chairman*)

Dr S. Dobson, Centre for Ecology and Hydrology, Huntingdon, Cambridgeshire, United Kingdom (*Vice-Chairman*)

Dr O. Faroon, Agency for Toxic Substances and Disease Registry, Department of Health and Human Services, Atlanta, GA, USA

Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Ms R. Gomes, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario, Canada

Dr M. Gulumian, National Centre for Occupational Health, Johannesburg, South Africa

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany

Dr A. Hirose, National Institute of Health Sciences, Tokyo, Japan

Mr P. Howe, Centre for Ecology and Hydrology, Huntingdon, Cambridgeshire, United Kingdom (*Co-Rapporteur*)

Dr J. Kielhorn, Fraunhofer Institute of Toxicology and Aerosol Research, Hanover, Germany (*Co-Rapporteur*)

Dr S.-H. Lee, College of Medicine, The Catholic University of Korea, Seoul, Korea

Ms B. Meek, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario, Canada

Dr J.A. Menezes Filho, Faculty of Pharmacy, Federal University of Bahia, Salvador, Bahia, Brazil

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ACROLEIN

0090
March 2001

CAS No: 107-02-8
RTECS No: AS1050000
UN No: 1092
EC No: 605-008-00-3

2-Propenal
Acrylic aldehyde
2-Propen-1-al
CH_2=CHCHO
Molecular mass: 56.06

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Highly flammable.	NO open flames, NO sparks, and NO smoking. See Chemical Dangers.	Alcohol-resistant foam. Powder. Carbon dioxide.
EXPLOSION	Vapour/air mixtures are explosive. Risk of fire and explosion on mixing with alkalis, acids or strong oxidants.	Closed system, ventilation, explosion-proof electrical equipment and lighting. Use non-sparking handtools.	In case of fire: keep drums, etc., cool by spraying with water. Combat fire from a sheltered position.
EXPOSURE		**STRICT HYGIENE!**	**IN ALL CASES CONSULT A DOCTOR!**
Inhalation	Burning sensation. Cough. Laboured breathing. Shortness of breath. Sore throat. Nausea. Symptoms may be delayed (see Notes).	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Half-upright position. Refer for medical attention.
Skin	Redness. Pain. Blisters. Skin burns.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Redness. Pain. Severe deep burns.	Face shield, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Burning sensation in the throat and chest. Convulsions. Nausea.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Do NOT induce vomiting. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING	
Evacuate danger area! Remove all ignition sources. Consult an expert! Collect leaking liquid in covered containers. Absorb remaining liquid in sand or inert absorbent and remove to safe place. Do NOT let this chemical enter the environment. Chemical protection suit including self-contained breathing apparatus.	F Symbol T+ Symbol R: 11-25-26-34 S: (1/2-)3/9/14-26-36/37/39-38-45 UN Hazard Class: 6.1 UN Subsidiary Risks: 3 UN Pack Group: I	Unbreakable packaging; put breakable packaging into closed unbreakable container. Do not transport with food and feedstuffs. Marine pollutant.

EMERGENCY RESPONSE	STORAGE
Transport Emergency Card: TEC (R)-118 NFPA Code: H 3; F 3; R 3	Fireproof. Separated from strong oxidants, strong bases, strong acids, food and feedstuffs. Cool. Ventilation along the floor. Store only if stabilized.

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance
YELLOW TO COLOURLESS 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 can form explosive peroxides. The substance may polymerize with fire and explosion hazard. Upon heating, toxic fumes are formed. Reacts with strong acids, strong bases and strong oxidants, causing fire and explosion hazard.

Occupational exposure limits
TLV (as ceiling values): 0.1 ppm; (skin, A4) (ACGIH 2000).

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
Tear drawing. The substance is severely irritating to the eyes, the skin and the respiratory tract. Inhalation of this substance at high levels may cause lung oedema (see Notes). The effects may be delayed. Medical observation is indicated.

PHYSICAL PROPERTIES

Boiling point: 53°C
Melting point: -88°C
Relative density (water = 1): 0.8
Solubility in water, g/100 ml at 20°C: 20
Vapour pressure, kPa at 20°C: 29
Relative vapour density (air = 1): 1.9
Relative density of the vapour/air-mixture at 20°C (air = 1): 1.2
Flash point: -26°C c.c. Auto-ignition temperature: 234°C
Explosive limits, vol% in air: 2.8-31
Octanol/water partition coefficient as log Pow: 0.9

ENVIRONMENTAL DATA

The substance is very toxic to aquatic organisms.

NOTES

The symptoms of lung oedema often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential. Immediate administration of an appropriate spray, by a doctor or a person authorized by him/her, should be considered. An added stabilizer or inhibitor can influence the toxicological properties of this substance, consult an expert. The odour warning when the exposure limit value is exceeded is insufficient. Check for peroxides prior to distillation; render harmless if positive.

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Ce CICAD sur l'acroléine a été préparé conjointement par la Direction de l'Hygiène du milieu de Santé Canada et par la Direction de l'Evaluation des produits chimiques commerciaux d'Environnement Canada, sur la base d'une documentation rédigée simultanément dans le cadre du Programme d'évaluation des produits chimiques prioritaires prévu par la *Loi canadienne sur la protection de l'environnement* (LCPE). Les évaluations sanitaires des substances prioritaires effectuées en application de cette loi portent sur les effets que pourraient avoir ces produits sur la santé humaine en cas d'exposition indirecte dans l'environnement général ainsi que sur leurs effets sur l'environnement lui-même. La présente mise au point prend en compte les données sur les effets environnmentaux jusqu'à fin mai 1998 et les données sur les effets sanitaires jusqu'à octobre 1998.[1] L'appendice 1 donne des informations sur la nature de l'examen par des pairs et sur les sources documentaires. D'autres études ont également été utilisées, à savoir celles du CIRC/IARC (1979, 1985, 1987, 1995), celle de l'ATSDR (1990), celles de l'IPCS/PISC (1992, 1996), ainsi que celles du BUA (1994), de l'US EPA (1996, *Agence américaine pour la protection de l'environnement*) et de l'Union européenne (1999). Des renseignements sur l'examen par des pairs du présent CICAD sont donnés à l'appendice 2. Ce CICAD a été adopté en tant qu'évaluation internationale lors de la réunion du Comité d'évaluation finale qui s'est tenue à Ottawa (Canada) du 29 octobre au 1er novembre 2001. La liste des participants à cette réunion figure à l'appendice 3. La fiche internationale sur la sécurité chimique (ICSC 0090) de l'acroléine, établie par le Programme international sur la sécurité chimique (IPCS, 1993), est également reproduite dans le présent document.

L'acroléine (No CAS 107-02-8) se présente sous la forme d'un liquide limpide à l'odeur âcre très marquée. Il se dégage dans l'atmosphère lors de processus naturels tels que la fermentation et le mûrissement. Il est également libéré lors de feux de forêt produisant une combustion incomplète.

Dans le pays d'où proviennent les données (le Canada), l'acroléine est principalement utilisée comme herbicide aquatique dans les canaux d'irrigation et comme microbicide pour le traitement de l'eau produite lors de la recherche des gisements de pétrole. On estime qu'au moins 218 tonnes d'acroléine sont libérées chaque année dans l'atmosphère par suite d'activités humaines comportant la combustion de matières organiques (en fait, essentiellement en tant que constituant des gaz d'échappement des véhicules à moteur) ou qui sont en rapport avec l'exploitation forestière. L'oxydation photochimique de certains polluants atmosphériques libère également de l'acroléine dans une proportion qui reste indéterminée. On n'a pas mis en évidence au Canada de libération d'acroléine dans les eaux, les sédiments ou les sols dont l'origine ne puisse être imputée à l'épandage de pesticides.

Il est peu probable que l'acroléine puisse être transportée sur de grandes distances du fait de sa forte réactivité et de la brièveté de sa demi-vie dans l'eau et l'atmosphère. Elle ne devrait pas non plus passer de ces deux compartiments dans le sol ou dans les sédiments. L'acroléine est rapidement métabolisée et ne subit pas de bioaccumulation. Dans le pays d'origine des données (Canada), c'est dans l'air des zones urbaines que l'on a mesuré les concentrations environnementales d'acroléine les plus élevées qui ne résultent pas de la libération directe de ce composé lors de son utilisation comme pesticide. On n'a pas décelé dans ce pays la présence d'acroléine dans les eaux, les sédiments ou le sol, sauf dans des échantillons prélevés à proximité des lieux d'épandage du produit à titre de pesticide.

Selon des études principalement effectuées sur des animaux de laboratoire, les effets nocifs d'une exposition à l'acroléine sont en majeure partie limités aux tissus qui subissent le premier contact (c'est-à-dire les voies respiratoires ou digestives selon que le produit a été inhalé ou ingéré) et ils dépendent de la concentration. On n'a pas relevé d'études consacrées à l'action générale de l'acroléine sur l'organisme humain, les données utilisables pour une évaluation des effets indésirables potentiels de ce composé chez l'Homme se limitant principalement à son action irritante. Chez l'Homme comme chez les espèces utilisées dans l'expérimentation animale, l'acroléine se comporte en effet comme un irritant des voies respiratoires supérieures et de la muqueuse oculaire.

On n'a pas non plus connaissance d'études épidémiologiques informatives sur les effets à long terme de l'acroléine. Les données existantes sont insuffisantes pour servir de base à une évaluation de la cancérogénicité de ce composé après inhalation. Les plus complètes des études limitées dont on dispose au sujet de la toxicité

[1] Les nouvelles données notées par les auteurs ou 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 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.

chronique ou de la cancérogénicité de l'acroléine portent sur des rats et des chiens exposés à ce produit par la voie orale. Elles ne font ressortir aucune augmentation des tumeurs de quelque nature que ce soit, en dépit d'une certaine mortalité observée chez des rats et des souris sans que la cause en soit véritablement connue. Le composé se révèle mutagène *in vitro*, mais les données limitées que l'on possède n'indiquent pas la présence d'effets génotoxiques au niveau de la muqueuse nasale (c'est-à-dire au point de contact) chez des rats exposés par la voie respiratoire. Il reste que selon ce type d'études, l'acroléine est capable de réagir directement sur l'ADN et de l'endommager. Des études très complètes ont montré que l'acroléine n'avait pas d'effets toxiques sur la reproduction après administration par voie orale à des animaux de laboratoire.

C'est après exposition par la voie respiratoire que les effets de l'acroléine ont été le plus largement étudiés. L'acroléine est cytotoxique; des effets histopathologiques au niveau des bronches et de la trachée (desquamation, oedème, inflammation, congestion des vaisseaux et nécrose hémorragique) ont été observés chez des hamsters, des cobayes et des lapins après une seule exposition par inhalation. Lors d'études d'inhalation à court et à long terme effectuées sur plusieurs espèces (rats, souris, cobayes, hamsters, singes et chiens), on a constaté aux concentrations les plus faibles, des effets consistant en lésions histopathologiques dégénératives au niveau de la porte d'entrée, c'est-à-dire des voies respiratoires. Des effets ont parfois été observés au niveau d'autres organes, mais pas de façon constante. Ces observations concordent avec les résultats des études toxicocinétiques effectuées sur des rongeurs et des chiens, selon lesquels après exposition, l'acroléine inhalée est retenue dans une forte proportion au point de contact.

En se basant sur les effets irritants observés au point de contact chez les animaux de laboratoire, on a fixé à 0,4 µg/m^3 la concentration d'acroléine tolérable dans l'air. Dans le cas d'une ingestion, la concentration tolérable est fixée provisoirement à 1,5 µg/litre.

Selon des estimations probabilistes représentatives de la distribution des concentrations atmosphériques d'acroléine en valeur pondérée par rapport au temps sur 24 h, qui ont été effectuées dans le pays d'origine des données (Canada), une proportion comprise entre 5 et 10 % de la population est exposée à une concentration d'acroléine d'au moins 5 µg/m^3, c'est-à-dire à une concentration supérieure à la valeur tolérable.

L'air intérieur est à l'origine d'une exposition importante, mais la part respective des diverses sources de pollution est inconnue. Des concentrations beaucoup plus fortes d'acroléine ont été relevées dans la fumée de tabac. En ce qui concerne la population dans son ensemble, la contribution relative de l'air ambiant à l'exposition globale devrait être faible par rapport à celle de l'air intérieur. Toutefois, dans le cas des populations qui résident à proximité de zones fortement polluées par les gaz d'échappement de véhicules à moteur, l'air ambiant peut être à l'origine d'une importante exposition par la voie respiratoire.

Bien que les données disponibles soient limitées, on estime que les concentrations relevées dans les produits alimentaires de divers pays (qui sont toutefois fortement tributaires de facteurs tels que le mode de cuisson) sont de l'ordre de la dose tolérable provisoire relative à l'ingestion.

On dispose de données relatives à la toxicité aiguë et chronique de l'acroléine pour les organismes aquatiques. Dans le cas des plantes vivrières terrestres, on ne dispose que de données sur la toxicité aiguë. Les organismes terrestres se révèlent moins sensibles à l'acroléine que les organismes aquatiques. Dans le pays d'origine des données (le Canada), la concentration atmosphérique de l'acroléine est inférieure au seuil estimatif d'apparition d'effets indésirables chez les organismes terrestres. On juge par ailleurs improbable l'exposition d'autres organismes à l'acroléine en dehors de son utilisation comme pesticide, car on n'a trouvé ni acroléine en concentrations décelables ni sources d'acroléine dans d'autres compartiments du milieu.

RESUMEN DE ORIENTACIÓN

Este CICAD sobre la acroleína, preparado conjuntamente por la Dirección de Higiene del Medio del Ministerio de Sanidad del Canadá y la División de Evaluación de Productos Químicos Comerciales del Ministerio de Medio Ambiente del Canadá, se basó en la documentación preparada al mismo tiempo como parte del Programa de Sustancias Prioritarias en el marco de la *Ley Canadiense de Protección del Medio Ambiente* (CEPA). Las evaluaciones de sustancias prioritarias previstas en la CEPA tienen por objeto valorar los efectos potenciales para la salud humana de la exposición indirecta en el medio ambiente general, así como los efectos ecológicos. En este examen se analizaron los datos identificados hasta el final de mayo de 1998 (efectos ecológicos) y octubre de 1998 (efectos en la salud humana).[1] La información relativa al carácter del examen colegiado y la disponibilidad del documento original figuran en el apéndice 1. También se consultaron otros exámenes, entre ellos los del CIIC (1979, 1985, 1987, 1995), ATSDR (1990), IPCS (1992, 1996), BUA (1994), US EPA (1996) y UE (1999). La información sobre el examen colegiado de este CICAD aparece en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final celebrada en Ottawa (Canadá) del 29 de octubre al 1 de noviembre de 2001. La lista de participantes en esta reunión figura en el apéndice 3. La Ficha internacional de seguridad química (ICSC 0090) para la acroleína, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en este documento.

La acroleína (CAS Nº 107-02-8) es un líquido incoloro transparente con un intenso olor acre. Se libera a la atmósfera como producto de los procesos de fermentación y maduración. También se desprende en los incendios forestales como producto de la combustión incompleta.

En el país de origen (es decir, el Canadá), la acroleína se utiliza principalmente como herbicida acuático en canales de riego y como microbicida en el agua extraída durante las prospecciones petrolíferas. Se estima que cada año se liberan en la atmósfera como mínimo 218 toneladas de acroleína de fuentes humanas como consecuencia de la combustión de materia orgánica (es decir, fundamentalmente como componente de los gases de escape de los vehículos) o la de las actividades de la industria forestal. También se liberan cantidades no cuantificadas a partir de la fotooxidación de contaminantes orgánicos presentes en el aire. No se han identificado emisiones de acroleína «no plaguicida» al agua, los sedimentos o el suelo en el Canadá.

Es poco probable que la acroleína recorra largas distancias, debido a su alta reactividad y a su breve semivida estimada en el aire y el agua. También es poco probable su desplazamiento al suelo o los sedimentos a partir de estos compartimentos. Los organismos metabolizan con rapidez la acroleína y no se produce bioacumulación. Las concentraciones más altas en el medio de acroleína no liberada directamente durante su aplicación como plaguicida en el país de origen (Canadá) se han medido en el aire de zonas urbanas. Con la excepción de las muestras obtenidas en lugares próximos a puntos de aplicación de plaguicidas, no se ha detectado acroleína en el agua, los sedimentos o el suelo en el país de origen (Canadá).

Sobre la base de los estudios realizados fundamentalmente en animales de laboratorio, los efectos adversos en la salud asociados a la exposición a la acroleína se limitan sobre todo al tejido del primer contacto (es decir, los tractos respiratorio y gastrointestinal tras la inhalación y la ingestión, respectivamente) y están en relación con su concentración. No se han encontrado estudios de los efectos sistémicos de la acroleína en las personas, limitándose los datos disponibles de interés a la evaluación de los efectos adversos potenciales, en particular la irritación. En las personas y en los animales de experimentación, la acroleína se comporta como irritante de las vías respiratorias superiores y de los ojos.

No se han encontrado estudios epidemiológicos informativos sobre los efectos a largo plazo de la acroleína. Los datos disponibles son insuficientes para realizar una evaluación de la carcinogenicidad de la acroleína tras la inhalación. En el más amplio de los limitados estudios relativos a la toxicidad crónica/carcinogenicidad de la acroleína tras la exposición oral de ratas y perros, no se observó un aumento de la incidencia de tumores de ningún tipo, aunque en ratas y ratones aumentó la mortalidad, no se sabe por qué motivo. La acroleína es mutagénica *in vitro*, pero los limitados datos disponibles no indican que tenga efectos genotóxicos en la mucosa nasal (es decir, el lugar de contacto) de ratas expuestas por inhalación, aunque los estudios *in vitro* ponen de manifiesto que la acroleína

[1] Se ha incluido nueva información destacada por los examinadores u 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 decisiva para la caracterización del riesgo o el análisis de la exposición-respuesta, que a juicio de los examinadores aumentaba el contenido informativo.

puede actuar directamente sobre el ADN y dañarlo. En estudios amplios no se observó toxicidad reproductiva tras la administración oral de acroleína a animales de experimentación.

Se han investigado más ampliamente los efectos de la acroleína tras la exposición por inhalación. La acroleína es citotóxica; se han detectado efectos histopatológicos en los bronquios y/o la tráquea (en particular, exfoliación, edema, inflamación, congestión vascular y necrosis hemorrágica) en hámsteres, cobayas y conejos tras una exposición única a ella por inhalación. En estudios de inhalación breves y prolongados realizados en varias especies (ratas, ratones, cobayas, hámsteres, monos y perros) se observaron siempre efectos con las concentraciones más bajas (lesiones histopatológicas degenerativas) en el lugar de entrada (es decir, el tracto respiratorio). También se han detectado a veces efectos en otros órganos, aunque no de manera uniforme. Esto está en consonancia con los resultados de los estudios toxicocinéticos en roedores y perros, en los cuales se ha registrado un elevado grado de retención de la acroleína inhalada en el lugar de contacto.

A partir de los efectos irritantes en el lugar de contacto en animales de experimentación se ha calculado una concentración tolerable para la acroleína de 0,4 µg/m^3 en el aire. Para la ingestión, la concentración tolerable provisional es de 1,5 µg/litro.

Las estimaciones probabilistas de muestras de la distribución ponderada por el tiempo de 24 horas de concentraciones de acroleína en el aire en el país de origen (Canadá) indican que entre el 5% y el 10% de la población general está expuesta como mínimo a 5 µg/m^3, concentración superior a la tolerable.

El aire de los espacios cerrados es una fuente importante de exposición, aunque no se conoce la contribución relativa de las diversas fuentes implicadas. Se han notificado concentraciones considerablemente más altas de acroleína en el humo del tabaco. Para la población general, cabe suponer que la contribución relativa del aire ambiente a la exposición global a la acroleína por inhalación es baja, en comparación con la registrada en el aire de los espacios cerrados. Sin embargo, para las poblaciones que residen cerca de lugares fuertemente afectados por los gases de escape de los vehículos, el aire ambiente puede ser una fuente importante de exposición por inhalación.

Aunque los datos disponibles son limitados, las concentraciones medidas en los alimentos en diversos países (si bien dependen en gran medida de factores como el método de cocción) entran dentro del margen de concentraciones tolerables provisionales para la ingestión.

Se dispone de datos sobre la toxicidad aguda y crónica para los organismos acuáticos. En cuanto a las plantas cultivadas terrestres, sólo se encontraron datos relativos a la toxicidad aguda. Los organismos terrestres parecen menos sensibles a la acroleína que los acuáticos. Las concentraciones de acroleína en la atmósfera del país de origen (Canadá) son inferiores al umbral para los efectos adversos estimados en los organismos terrestres. Se considera poco probable la exposición de otros organismos a acroleína no plaguicida, puesto que no se han identificado fuentes o concentraciones detectables de acroleína en otros compartimentos.

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