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## **Concise International Chemical Assessment Document 4**

# METHYL METHACRYLATE

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**Note that the layout and pagination of this pdf file are not identical to the printed CICAD**

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.



World Health Organization  
Geneva, 1998

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (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, 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.

WHO Library Cataloguing in Publication Data

Methyl methacrylate.

(Concise international chemical assessment document ; 4)

1.Methacrylates – toxicity 2.Environmental exposure  
3.Occupational exposure I.International Programme on Chemical  
Safety II.Series

ISBN 92 4 153004 9

(NLM Classification: QV 50)

ISSN 1020-6167

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The Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, Germany, provided financial support for the printing of this publication.

Printed by Wissenschaftliche Verlagsgesellschaft mbH, D-70009 Stuttgart 10

## TABLE OF CONTENTS

	FOREWORD .....	1
1.	EXECUTIVE SUMMARY .....	4
2.	IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES .....	5
3.	ANALYTICAL METHODS .....	5
4.	SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE .....	6
5.	ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION .....	6
6.	ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE .....	6
	6.1 Environmental levels .....	6
	6.2 Human exposure .....	7
7.	COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS .....	9
8.	EFFECTS ON LABORATORY MAMMALS AND <i>IN VITRO</i> TEST SYSTEMS .....	9
	8.1 Single exposure .....	9
	8.2 Irritation and sensitization .....	9
	8.3 Short-term exposure .....	9
	8.4 Long-term exposure .....	10
	8.4.1 Subchronic exposure .....	10
	8.4.2 Chronic exposure and carcinogenicity .....	10
	8.5 Genotoxicity and related end-points .....	15
	8.6 Reproductive and developmental toxicity .....	18
	8.7 Immunological and neurological effects .....	18
9.	EFFECTS ON HUMANS .....	19
	9.1 Case reports .....	19
	9.2 Epidemiological studies .....	19
10.	EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD .....	22
	10.1 Aquatic environment .....	22
	10.2 Terrestrial environment .....	22
11.	EFFECTS EVALUATION .....	23
	11.1 Evaluation of health effects .....	23
	11.1.1 Hazard identification and dose–response assessment .....	23
	11.1.2 Criteria for setting guidance values for methyl methacrylate .....	23
	11.1.3 Sample risk characterization .....	24
	11.2 Evaluation of environmental effects .....	25
12.	PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES .....	25

13.	HUMAN HEALTH PROTECTION AND EMERGENCY ACTION .....	25
13.1	Human health hazards .....	26
13.2	Advice to physicians .....	26
13.3	Health surveillance advice .....	26
13.4	Explosion and fire hazards .....	26
13.4.1	Explosion hazards .....	26
13.4.2	Fire hazards .....	26
13.4.3	Fire-extinguishing agents .....	26
13.5	Storage .....	26
13.6	Transport .....	26
13.7	Spillage .....	26
14.	CURRENT REGULATIONS, GUIDELINES, AND STANDARDS .....	26
	INTERNATIONAL CHEMICAL SAFETY CARD .....	27
	REFERENCES .....	29
	APPENDIX 1 — SOURCE DOCUMENTS .....	33
	APPENDIX 2 — CICAD PEER REVIEW .....	34
	APPENDIX 3 — CICAD FINAL REVIEW BOARD .....	34
	RÉSUMÉ D'ORIENTATION .....	36
	RESUMEN DE ORIENTACIÓN .....	38

## 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 Organisation (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.

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 have undergone 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<sup>1</sup> for advice on the derivation of health-based guidance values.

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<sup>1</sup> 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).

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 the IPCS to inform it of the new information.

## Procedures

The flow chart 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.

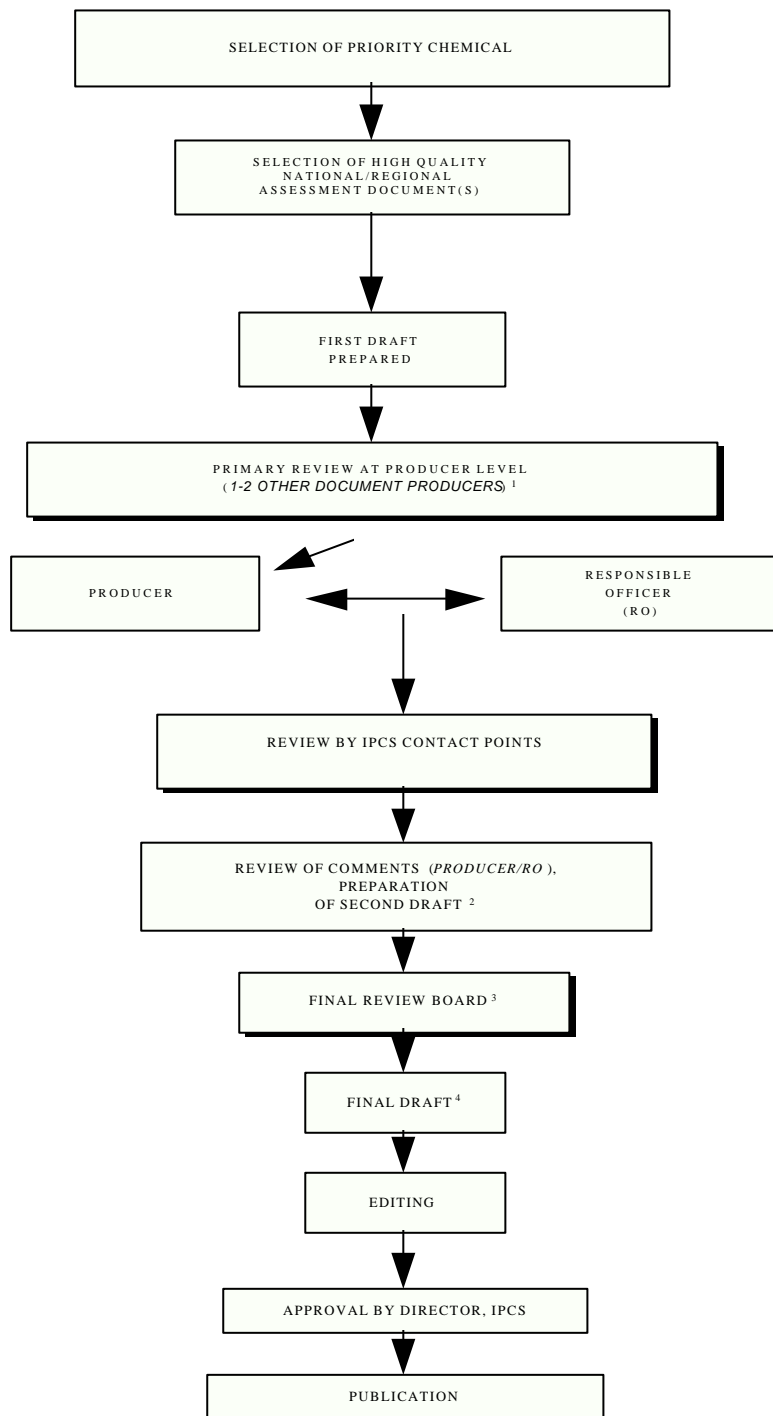
The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes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

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

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.

### CICAD PREPARATION FLOW CHART



1 Revision as necessary.

2 Taking into account the comments from reviewers.

3 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments (6-10 CICADs are usually reviewed at the Final Review Board). In the case of pesticides the role of the Final Review Board is fulfilled by a joint meeting on pesticides.

4 Includes any revisions requested by the Final Review Board.

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 methyl methacrylate was prepared by the Environmental Health Directorate of Health Canada and was based principally on a Government of Canada (1993) review to assess the potential effects on human health of indirect exposure to methyl methacrylate in the general environment as well as the chemical's environmental effects and an International Agency for Research on Cancer review (IARC, 1994) concerning primarily hazard identification for carcinogenicity. Data identified as of March 1992 were considered in the Government of Canada (1993) review and were subsequently updated, based on a comprehensive literature search conducted in September 1995 of on-line databases and the International Register of Potentially Toxic Chemicals. Information on the nature of peer review and the availability of the Government of Canada (1993) and IARC (1994) reviews is presented in Appendix 1. During the peer review phase for this CICAD, additional draft reviews of the United Kingdom Health and Safety Executive (Cary et al., 1995) and the European Union (Draft Assessment on Methyl Methacrylate) and published reviews of ECETOC (1995) and the Finnish Advisory Board of Chemicals (1992) were considered, primarily for identification of relevant additional information for review. Additional information identified during review by Contact Points and consideration by the Final Review Board has also been incorporated. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved for publication at a meeting of the Final Review Board, held in Brussels, Belgium, on 18–20 November 1996. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card for methyl methacrylate (ICSC 0300), produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

Methyl methacrylate (CAS no. 80-62-6) is a volatile synthetic chemical that is used principally in the production of cast acrylic sheet, acrylic emulsions, and moulding and extrusion resins. Polymers and copolymers of methyl methacrylate are also used in waterborne, solvent, and undissolved surface coatings, adhesives, sealants, leather and paper coatings, inks, floor polishes, textile finishes, dental prostheses, surgical bone cements, and leaded acrylic radiation shields and in the preparation of synthetic fingernails and orthotic shoe inserts. The majority of methyl methacrylate is predicted to be emitted to air, with very small amounts being released into water and soil. The persistence of methyl methacrylate in the atmosphere is short, and the chemical is not considered to contribute directly to depletion of the ozone layer. Methyl

methacrylate is not expected to bioconcentrate in the environment, and inhalation from air is likely the primary route of human exposure.

Methyl methacrylate is rapidly absorbed and distributed following inhalation or oral administration to experimental animals. Data on absorption following dermal exposure are limited. In both experimental animals and humans, methyl methacrylate is rapidly metabolized to methacrylic acid. Following inhalation, 16–20% of the chemical is deposited in the upper respiratory tract of rats, where it is primarily metabolized by local tissue esterases.

The acute toxicity of methyl methacrylate is low. Irritation of the skin, eye, and nasal cavity has been observed in rodents and rabbits exposed to relatively high concentrations of methyl methacrylate. The chemical is a mild skin sensitizer in animals. The effect observed most frequently at lowest concentration after repeated inhalation exposure to methyl methacrylate is irritation of the nasal cavity. Effects on the kidney and liver at higher concentrations have also been reported. The lowest reported effect level for inhalation was 410 mg/m<sup>3</sup> in rats exposed to methyl methacrylate for 2 years (based upon inflammatory degeneration of the nasal epithelium); the no-observed-effect level (NOEL) in this investigation was approximately 100 mg/m<sup>3</sup>.

In a well conducted study in rats, there were no developmental effects, although there were decreases in maternal body weight following inhalation of concentrations up to 8315 mg/m<sup>3</sup>. Other available data on developmental toxicity are restricted to results of limited early or poorly documented studies in which fetotoxic effects were observed at concentrations that (where reported) were toxic to the mothers. Available data on reproductive effects of methyl methacrylate are limited. There was no reduction in fertility in a dominant lethal assay in mice exposed to methyl methacrylate concentrations up to 36 900 mg/m<sup>3</sup> and no adverse effects on reproductive organs in repeated-dose studies conducted to date. Available data on the neurotoxicity of methyl methacrylate are limited; impairment of locomotor activity and learning and behavioural and biochemical effects on the brain were observed in rats exposed orally to 500 mg/kg body weight per day for 21 days.

Methyl methacrylate was not carcinogenic in an extensive, well documented 2-year bioassay in rats and mice exposed by inhalation and in additional chronic inhalation studies in rats and hamsters. Although not mutagenic *in vitro* in bacterial systems, methyl methacrylate has been mutagenic and clastogenic in mammalian cells *in vitro*. In *in vivo* studies (primarily by the inhalation route) in which there has been clear evidence

of toxicity within the target tissue, there has been limited evidence of the genotoxicity of methyl methacrylate.

Methyl methacrylate is a mild skin irritant in humans and has the potential to induce skin sensitization in susceptible individuals. Although occupational asthma associated with methyl methacrylate has also been reported, there is no conclusive evidence that methyl methacrylate is a respiratory sensitizer. As a whole, the available epidemiological studies do not provide strong or consistent evidence of a carcinogenic effect of methyl methacrylate on any target organ in humans, nor can it be inferred with any degree of confidence that the possibility of an excess risk has been disproved.

The toxicity of methyl methacrylate to aquatic organisms is low. Although no chronic studies on aquatic organisms were identified, acute tests have been conducted on fish, *Daphnia magna*, and algae. The most sensitive effect was the onset of inhibition of cell multiplication by the green alga *Scenedesmus quadricauda* at 37 mg/litre following 8 days of exposure. The lowest reported 24-hour EC<sub>50</sub> for immobilization in *Daphnia* is 720 mg/litre. The 96-hour LC<sub>50</sub> in juvenile bluegill sunfish (*Lepomis macrochirus*) under flow-through conditions was 191 mg/litre, whereas LC<sub>50</sub> values for durations of 1–24 hours ranged from 420 to 356 mg/litre, respectively. The 96-hour LC<sub>50</sub> for rainbow trout (*Oncorhynchus mykiss*) under flow-through conditions was >79 mg/litre, the highest concentration tested. Sublethal/behavioural responses were noted among the fish at 40 mg/litre.

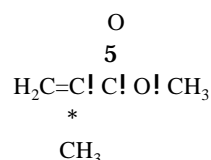
The available studies in humans are considered inadequate as the principal basis for derivation of a guidance value; therefore, in order to provide guidance, a tolerable concentration has been established on the basis of inflammatory degeneration of the nasal epithelium of rats exposed to methyl methacrylate at a concentration of 410 mg/m<sup>3</sup> for 2 years. The NOEL in this investigation was approximately 100 mg/m<sup>3</sup>. Data available to serve as a basis for estimation of indirect exposure in the general environment or consumer exposure are extremely limited. The derived (likely conservative) tolerable concentration of approximately 0.2 mg/m<sup>3</sup> is many orders of magnitude higher than the sample predicted concentrations of methyl methacrylate in ambient air of the general environment. Inhalation exposure predicted from the use of dispersion and oil-based paints containing methyl methacrylate may be up to an order of magnitude higher than the tolerable intake associated with exposure at the level of the tolerable concentration, although it has been reported that in some countries these products are not supplied to the general public. Information on use patterns of these

products in other countries was not identified. Based on a chronic study by the oral route of administration, a tolerable daily intake (TDI) of 1.2 mg/kg body weight per day has been derived.

Although available data on the environmental effects of methyl methacrylate are limited and predicted values in various media are highly uncertain, a wide margin exists between observed effect levels and uncertain predicted environmental concentrations of methyl methacrylate.

## 2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Methyl methacrylate (CAS no. 80-62-6) is a colourless, volatile liquid with an acrid fruity odour. It has a relatively high vapour pressure (4 kPa at 20°C), moderate water solubility (15.8 g/litre), and a low log octanol/water partition coefficient ( $K_{ow} = 1.38$ ) (Government of Canada, 1993). The empirical formula for methyl methacrylate is C<sub>5</sub>H<sub>8</sub>O<sub>2</sub>. The structural formula for methyl methacrylate is given below. Additional physical/chemical properties are presented in the International Chemical Safety Card reproduced in this document.



The purity of commercial methyl methacrylate is typically 99.9%. It contains traces of acidity as methacrylic acid (0.003% max.; specification, 0.005% max.) and water (0.03% max.; specification, 0.05% max.). Inhibitors added for storage and transportation are usually 2–100 ppm methyl ether of hydroquinone and 25–100 ppm hydroquinone, although other phenolic inhibitors, such as dimethyl *tert*-butylphenol, may also be used (IARC, 1994; M. Pemberton, personal communication, 1996).

## 3. ANALYTICAL METHODS

Methods commonly used for the analysis of acrylic compounds include gas chromatography (GC), mass spectrometry (MS), GC/MS, nuclear magnetic resonance, and infrared spectroscopy (Government of Canada, 1993). Methyl methacrylate can be determined

in air by gas chromatography with flame ionization detection; the sample is adsorbed on fused silica (XAD-2 resin) or charcoal coated with 4-*tert*-butylcatechol and desorbed with carbon disulfide or toluene. The estimated limit of detection for this method is 0.01 mg per sample. A detection limit of 0.8 mg/m<sup>3</sup> is obtained with a method involving desorption with 5% isopropanol in carbon disulfide from charcoal (IARC, 1994).

#### **4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE**

Methyl methacrylate is not known to occur naturally (IARC, 1994). It is used principally in the production of cast acrylic sheet, acrylic emulsions, and moulding and extrusion resins (IARC, 1994). Polymers and copolymers of methyl methacrylate are used in waterborne, solvent, and undissolved surface coatings (exterior latex paint based on emulsions containing methyl methacrylate is the surface coating in which it is used most widely). Solvent reducible polymers containing methyl methacrylate are used for industrial finishes, metal and foil coatings, and a variety of overlays for special purposes. Solvent and emulsion polymers containing methyl methacrylate are also used in adhesives, sealants, leather and paper coatings, inks, floor polishes, and textile finishes (IARC, 1994). Methyl methacrylate and polymers of methyl methacrylate are also used for dental prostheses, surgical bone cements, and leaded acrylic radiation shields and in the preparation of synthetic fingernails and orthotic shoe inserts (IARC, 1994).

Global production of methyl methacrylate was estimated to be 1.4 million tonnes in 1988 (IARC, 1994). In the USA and Japan, production of methyl methacrylate ranged from 380 000 to 536 000 t and from 384 000 to 403 000 t, respectively, between 1990 and 1992 (IARC, 1994). Total production volume within the European Union was 447 000 t in 1993 (CEFIC, 1994).

Methyl methacrylate can enter the environment during its transport, bulk storage, and use. Based on data from the US Toxic Chemical Release Inventory, emissions to air, water, and soil from industries in the USA are estimated to be about 0.46% of production.<sup>1</sup>

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<sup>1</sup> Source: Toxic Chemical Release Inventory (TRI), databank produced by the National Library of Medicine and the US Environmental Protection Agency (1989).

Most of the released methyl methacrylate (i.e. 98%) is estimated to be emitted to air, with very small amounts being released into water and soil. Data on emissions of methyl methacrylate in other countries have not been identified. Assuming a production in the USA in 1992 of approximately 500 000 t (IARC, 1994), approximately 2300 t are estimated to have been released to the environment.

#### **5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION**

As methyl methacrylate is highly reactive with hydroxyl radicals, its estimated half-life in the troposphere is short: from <5 hours in summer to a few days in winter at a latitude such as that of Toronto, Canada. The reported photooxidation half-life of methyl methacrylate is 1.1–9.7 hours. Methyl methacrylate is readily polymerized by light and heat but is not expected to photolyze (Government of Canada, 1993).

In neutral or acidic aquatic environments, hydrolysis of methyl methacrylate is not significant. Based upon its measured second-order hydrolysis rate constant of 200 (mol/litre)<sup>-1</sup> h<sup>-1</sup> at 25°C, the hydrolysis half-life of methyl methacrylate is estimated to be 3.9 years at pH 7 and 14.4 days at pH 9 (Howard, 1989).

No data were identified on the rate of volatilization of methyl methacrylate; however, the half-life for evaporation from a river 1 m deep with a 1 m/s current and 3 m/s wind has been calculated as 6.3 hours. Evaporation of methyl methacrylate from soil is expected to be rapid, owing to its high vapour pressure and weak adsorption to soil.

A Level I fugacity model in an evaluative environment predicts the following equilibrium partitioning of methyl methacrylate: air, 86.6%; water, 13.1%; and soil/sediment, <0.4% (Mackay et al., 1995).

Biodegradation contributes significantly to removal of methyl methacrylate from the environment. The aqueous aerobic degradation half-life is estimated to be 1–4 weeks, and the anaerobic degradation half-life is estimated to be 4–16 weeks (Howard, 1989).

Although no studies have been conducted to measure bioconcentration factors for methyl methacrylate, a bioconcentration factor of 3 has been estimated from the log  $K_{ow}$ ; based on this value, methyl methac-

rylate is not expected to bioconcentrate or biomagnify in food-chains (Government of Canada, 1993).

## 6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

### 6.1 Environmental levels

In an analysis of 204 samples of water collected from 14 heavily industrialized river basins in the USA (Ewing & Chian, 1977), methyl methacrylate was detected (detection limit 1.0 : g/litre) only once at a concentration of 10 : g/litre in final tap-water after chlorination in Chicago, Illinois, in 1976. No additional information was provided. Methyl methacrylate was not detected in 24 water samples (limit of determination 0.005–1 : g/litre) or in 24 sediment samples (limit of determination 0.000 11–0.01 : g/g dry weight) taken in Japan in eight locations (harbour or estuarine areas) in 1979 (no further information provided) (S. Tsuda, personal communication, 1996). Methyl methacrylate was not detected (detection limit 0.01 : g/g wet weight) in 30 samples of (edible) shellfish collected from various locations in Atlantic Canada (Environment Canada, 1989). Methyl methacrylate may be present in food as a result of migration of the monomer from food containers made from polymethyl methacrylate (IARC, 1994); for example, concentrations ranged from 180 to 275 ppb (ng/g) in maple syrup that had been packaged in plastic containers (Hollifield et al., 1980). The migration of methyl methacrylate from commercial plastic wrap into 20% ethanol at 25°C was 1 ppm in 1 day and 10 ppm in 90 days. Migration into water and acetic acid was not detected (detection limit 0.05 ppm) (Inoue et al., 1981).

In view of the limited available monitoring data, estimates of the fate and concentrations of methyl methacrylate in the Canadian environment were generated by a Level III fugacity model (Mackay & Paterson, 1981, 1982, 1991; Mackay et al., 1985) developed for southern Ontario, incorporating data on the physical and chemical properties of the chemical (Government of Canada, 1993), transformation half-lives (Howard et al., 1991), and proportion of production in the USA emitted to environmental media (see section 4) applied to the volume imported into Canada. Methyl methacrylate is not produced in Canada; approximately 22 000 t are imported (CPI, 1989). The model assumed emissions of 95% to air, 4.5% to water, and 0.5% to soil. The estimated relative proportions of methyl methacrylate predicted for air, water, soil, and sediment at

steady state were 26.6%, 60.8%, 12.6%, and 0.03%, respectively. The amount of methyl methacrylate estimated to partition to fish was negligible. The relatively longer half-life for methyl methacrylate in water compared with air accounts for the higher estimated relative proportion predicted for the water compartment. Although such models are useful primarily for identification of the relative proportions of exposure from various media rather than for quantitative estimates of concentrations, the latter are presented here primarily as a baseline for comparison with measured concentrations. It should also be noted that such predicted values will vary in different countries depending upon production and releases of methyl methacrylate. The average concentrations estimated on the basis of the model were  $2.44 \times 10^{-4}$  : g/m<sup>3</sup> in air, 0.13 ng/litre in surface water,  $1.2 \times 10^{-6}$  : g/g in soil,  $8.7 \times 10^{-8}$  : g/g in sediment, and  $1.5 \times 10^{-7}$  : g/g in fish (Government of Canada, 1993).

### 6.2 Human exposure

Examples of estimated indirect exposure in the general environment and during use of consumer products are presented here. Levels determined in various occupational settings are also summarized. Estimates of indirect exposure in the general environment are based in Canada owing to the availability of relevant data for input; however, predicted levels will vary considerably as a function of production and use patterns in various countries. Consumer exposure estimates are based on data on the percent composition of methyl methacrylate in products provided by European manufacturers. Levels in occupational environments are those reported from various countries. Countries are strongly encouraged, however, to estimate exposure on the basis of local data, possibly in a manner similar to that outlined here.

Adequate data on measured concentrations of methyl methacrylate in air, drinking-water, foodstuffs, and soil have not been identified; indeed, they are limited to non-detectable values in a limited number of small surveys. Although predicted concentrations in environmental media based on fugacity modelling are uncertain, they are helpful in estimating proportions of exposure from various media. Based on a daily inhalation volume for adults of 22 m<sup>3</sup>, a mean body weight for males and females of 64 kg, and a predicted concentration (by fugacity modelling; see section 6.1) of methyl methacrylate in ambient air in Canada of  $2.44 \times 10^{-4}$  : g/m<sup>3</sup>, the estimated intake of methyl methacrylate from air for the general population represents approximately 97% of the total intake from air, drinking-water, fish, and soil. Based on a daily volume of water consumption for

adults of 1.4 litres, a mean body weight of 64 kg, and a predicted concentration of methyl methacrylate in surface water in Canada of 0.13 ng/litre (see section 6.1), the estimated intake of methyl methacrylate from drinking-water for the general population represents approximately 3.3% of total intake. Available data were inadequate to estimate the intake of methyl methacrylate from food, with the exception of intake from fish. Based on a daily amount of fish ingested for adults of 23 g/day, a mean body weight for adults of 64 kg, and the predicted concentration of methyl methacrylate in fish in Canada of  $1.5 \times 10^{17}$  : g/g (see section 6.1), the estimated intake of methyl methacrylate from fish represents 0.06% of total intake. Based on a daily amount of soil ingested for adults of 20 mg, a mean body weight for adults of 64 kg, and a predicted concentration of methyl methacrylate in soil in Canada of  $1.2 \times 10^{-6}$  : g/g (see section 6.1), the estimated intake of methyl methacrylate from soil, as a proportion of total intake, is negligible (0.0004%). Therefore, based on predicted concentrations in the Canadian environment, the overwhelmingly principal source of indirect exposure to methyl methacrylate for most of the general population is air.

Inhalation exposure to methyl methacrylate from the use of consumer products containing methyl methacrylate (e.g. dispersion paints and oil-based paints) was modelled using the US EPA Screening Consumers Inhalation Exposure Software (SCIES) computer model. All scenarios were based on the assumption that the percent composition of methyl methacrylate-based polymers in formulations of dispersion paints, varnishes, or lacquers is 15%, although residual monomer content is much less (European Union Draft Assessment on Methyl Methacrylate), and that 100% is absorbed. Although it has been reported that in some countries these products are not supplied to the general public, information on use patterns of these products in other countries was not available.

For the use of dispersion paints, the standard default values of the SCIES model were assumed for the following parameters: frequency of use, six events per year; mass of product, 13.6 kg; room size, 40 m<sup>3</sup>; duration of use, 4.9 hours; house air exchange rate, 0.2 room air exchanges per hour; and user inhalation rate, 1.3 m<sup>3</sup>/hour. The vapour pressure of methyl methacrylate was considered to be 38.4 torr (5.12 kPa) (Howard, 1989). Resulting estimated consumer exposure from inhalation was in the range of 10–100 mg/kg body weight per day. However, as the residual methyl methacrylate monomer content in dispersion paints is specified to be 0.1% (ECETOC, 1995), consumer exposure to methyl methacrylate would fall within the range of 10–100 : g/kg body weight per day.

For the estimation of consumer exposure from the use of oil-based (solvent-based) paints, the standard default values of the SCIES model were assumed as above, with the exception of the following parameters, for which default values were: mass of product, 6.71 kg; and duration of use, 3.2 hours. The vapour pressure of methyl methacrylate and absorption were the same as those for the scenario mentioned above. The resulting estimated consumer exposure from inhalation was again in the range of 10–100 mg/kg body weight per day. However, as the residual methyl methacrylate monomer content in solvent-based paints is assumed to be 1.5% by the producer (European Union Draft Assessment on Methyl Methacrylate), consumer exposure to methyl methacrylate would fall within the range of 100–1000 : g/kg body weight per day.

Occupations in which there is potential exposure to methyl methacrylate include those in the medical, dental, and beauty professions, such as chemical process operators, surgeons and surgical assistants, operating room nurses, dental technicians and hygienists, and beauty technicians applying synthetic fingernails (IARC, 1994). Exposure to methyl methacrylate in the workplace could be substantially greater than that in the general environment. Based on experience in the United Kingdom, for example, long-term personal exposures during monomer production average about 2 ppm (8.2 mg/m<sup>3</sup>) and are less than 60 ppm (246 mg/m<sup>3</sup>) (Cary et al., 1995). In open system industries such as cast sheet production, long-term exposures are higher, averaging 22.2 ppm (91 mg/m<sup>3</sup>) and ranging from 0.5 to 165 ppm (2–677 mg/m<sup>3</sup>). For various end uses of methyl methacrylate, including aerospace manufacture, plastics processing, and artificial teeth production, the mean long-term value for personal exposure was 13.4 ppm (55 mg/m<sup>3</sup>), with a range of 0.8–109 ppm (3.3–447 mg/m<sup>3</sup>). In medical and dental applications, peak concentrations up to 374 ppm (1533 mg/m<sup>3</sup>) have been recorded, although short-term time-weighted-average exposures are likely to be less than 100 ppm (410 mg/m<sup>3</sup>).

Mean levels (time period often unspecified) of methyl methacrylate in the air of various chemical manufacturing and processing plants (located in Europe, the USA, Canada, Russia, Japan, and China) vary widely, ranging from not detectable (detection limit not reported) to 1500 mg/m<sup>3</sup> (CEFIC, 1993; Mizunuma et al., 1993; IARC, 1994; M. Baril, personal communication, 1996). Peak values as high as 7900 mg/m<sup>3</sup> have been reported for some manufacturing facilities (M. Baril, personal communication, 1996). Mean concentrations of methyl methacrylate in the air of dental clinics and dental laboratories (in the USA, Norway, Denmark, and the United Kingdom) have ranged from not detectable

(detection limit not reported) to 273 mg/m<sup>3</sup> during denture prosthesis manufacture and repair (IARC, 1994). Mean concentrations of methyl methacrylate in the air of beauty salons (in the USA) have ranged from 21.7 to 87.5 mg/m<sup>3</sup> during the application of artificial fingernails (IARC, 1994). It should be noted that in some cases these values reflect shorter-term peak exposures rather than time-weighted averages. Elevated levels (above 1500 mg/m<sup>3</sup>) during floor coating with methyl methacrylate-containing resins have been reported, although these levels were measured during activities that normally do not cover a full shift; hence, time-weighted-average concentrations would be less.<sup>1</sup>

## 7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Methyl methacrylate is rapidly absorbed and distributed following inhalation or oral administration to rats. On the basis of available data, methyl methacrylate appears to be rapidly metabolized to methacrylic acid, which is subsequently converted to carbon dioxide via the tricarboxylic acid cycle in both experimental animals and humans. Adequate studies on the dermal absorption of methyl methacrylate were not identified. Methyl methacrylate is rapidly eliminated, primarily via the lungs in expired air. After oral or intravenous administration to rats, approximately 65% of the dose was exhaled in the expired air as <sup>14</sup>CO<sub>2</sub> within 2 hours (Bratt & Hathway, 1977). Lesser amounts are eliminated in the urine, and an even smaller fraction in the faeces. Owing to its rapid metabolism and excretion, there appears to be little potential for accumulation of methyl methacrylate within tissues (Government of Canada, 1993; ECETOC, 1995).

Deposition in the surgically isolated upper respiratory tract of urethane-anaesthetized male F344 rats exposed to methyl methacrylate at 90, 437, or 2262 mg/m<sup>3</sup> under cyclic flow conditions was 16–20% (Morris & Frederick, 1995). Deposition was 3% less on average in the unidirectional flow groups than in the cyclic flow groups. Deposition was less efficient at the high than at the low and middle concentrations, although the

mechanism is unknown. (The deposition efficiency of inhaled methacrylic acid under similar conditions was much greater, averaging 95% under unidirectional flow.) Pretreatment with a carboxylesterase inhibitor (bis-nitrophenylphosphate) decreased uptake of methyl methacrylate by one-third, suggesting that methyl methacrylate is hydrolysed by carboxylesterase in nasal tissues and that such metabolism serves to enhance its deposition efficiency. Methyl methacrylate decreased nasal non-protein content by approximately 25% at the highest concentration, but not at lower concentrations. Nasal non-protein content was not decreased by exposure to methacrylic acid even at delivered dose rates twofold more than that for methyl methacrylate, suggesting that this effect is attributable to the ester itself and not to the acid metabolite (Morris & Frederick, 1995).

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

### 8.1 Single exposure

The acute toxicity of methyl methacrylate is consistently low, although unconfirmed effects on the lungs were reported at relatively low concentrations in one study of poor design (Raje et al., 1985). The 4-hour LC<sub>50</sub>s for methyl methacrylate in rats ranged from 3750 to 7093 ppm (15 375–29 080 mg/m<sup>3</sup>). The oral LD<sub>50</sub>s ranged from 5.0 ml/kg body weight (4.7 g/kg body weight) in dogs to 10.0 ml/kg body weight (9.44 g/kg body weight) in rats (Government of Canada, 1993).

### 8.2 Irritation and sensitization

Irritation of the skin, eye, and mucosa of the respiratory tract has been observed in rodents and rabbits exposed to relatively high concentrations of methyl methacrylate (dermal application of approximately 2–38 g/kg body weight; inhalation of 100–17 600 ppm [410–72 160 mg/m<sup>3</sup>]; or instillation of approximately 0.1 ml into the cornea) (Spealman et al., 1945; Castellino & Colicchio, 1969; Rohm & Haas, 1982; Raje et al., 1985; Kanerva & Verkkala, 1986; NTP, 1986; Ouyang et al., 1990).

The weight of evidence is that methyl methacrylate is a skin sensitizer in animals (Cary et al., 1995; ECETOC, 1995).

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<sup>1</sup> Source: Excerpts from the (1995) BIA file provided by BG Chemie containing measurement data of occupational exposures to methyl methacrylate in industry and trade. Communication to Bundesinstitut für Gesundheitlichen Verbraucherschutz und Veterinarmedizin (BgVV).

### **8.3 Short-term exposure**

Death, decreases in body weight, changes in respiration rate, increases in level of blood urea nitrogen, and pulmonary damage were observed after exposure to high concentrations in short-term repeated-dose studies in rats and mice in which inhaled concentrations of methyl methacrylate ranged up to 5000 ppm (20 500 mg/m<sup>3</sup>) (Government of Canada, 1993). Cardiovascular effects (irregular ECG, changes in blood pressure) were also observed in rats exposed to undocumented concentrations of vaporized methyl methacrylate for 20 minutes/day for 21 or 42 days in a limited study (Blanchet et al., 1982).

In short-term studies, mice were more susceptible than rats, with effects on the respiratory tract (redness and swelling of the nasal region) observed after exposure to 500 ppm (2050 mg/m<sup>3</sup>; the lowest tested concentration in the study) for 10 days (NTP, 1986). No systemic histopathological effects were observed after inhalation of concentrations up to 5000 ppm (20 500 mg/m<sup>3</sup>).

### **8.4 Long-term exposure**

The protocols and results of available long-term studies on methyl methacrylate are summarized in Table 1.

#### **8.4.1 Subchronic exposure**

In most subchronic studies conducted to date, rats and mice have been exposed to methyl methacrylate by inhalation. Effects observed most commonly in these investigations were decreases in body weight gain and irritation of the skin, nasal cavity, and eye at high concentrations (generally 500 ppm [2050 mg/m<sup>3</sup>]) (Rohm & Haas, 1977; NTP, 1986). At higher concentrations, other effects, such as renal cortical necrosis and tubular degeneration (rats and mice) and hepatic necrosis (mice), have also been reported (Tansy et al., 1980a; NTP, 1986; Deichmann-Gruebler & Read, undated).

On the basis of decreases in final mean body weight and squamous metaplasia at the site of entry (i.e. nasal epithelium), the lowest reported NOEL and lowest-observed-effect level (LOEL) in a subchronic inhalation bioassay in which several concentration levels were administered were 250 and 500 ppm (1025 and 2050 mg/m<sup>3</sup>), respectively, in mice exposed to methyl methacrylate for 64 days or 14 weeks (Rohm & Haas, 1977; NTP, 1986). Except for effects at the site of entry, histopathological changes have not been observed in the two most extensive subchronic bioassays in rats

exposed to methyl methacrylate for 65 days or 14 weeks, at concentrations up to 1000 ppm (4100 mg/m<sup>3</sup>) (Rohm & Haas, 1977; NTP, 1986).

In less extensive and less well documented studies conducted by Tansy et al. (1976, 1980a,b), effects on the trachea and some indications of liver damage in rats were observed at the only tested concentration of 116 ppm (476 mg/m<sup>3</sup>), administered for 7 hours/day for 3 or 6 months, although the statistical significance of the pulmonary changes was not specified, and similar effects were observed in some of the sham-exposed control animals. In a supplementary study, there was weak evidence of an effect on liver function (barbiturate sleeping time) in male rats administered "intermittent daily exposures" of 100 ppm (410 mg/m<sup>3</sup>) methyl methacrylate for a total of 160 hours (Tansy et al., 1980b). Initial reports of reduced fat deposits after exposure for 3 months were not confirmed in later studies of similar protocol by the same investigators (Tansy et al., 1980a,b).

#### **8.4.2 Chronic exposure and carcinogenicity**

In the few studies identified in which the chronic toxicity and carcinogenicity of methyl methacrylate were investigated, the observed effects were, in general, similar to those reported in short-term and subchronic studies and included inflammation and epithelial hyperplasia of the nasal cavity and degeneration of the olfactory sensory epithelium. Based on the results of a well documented inhalation study in F344/N rats and B6C3F<sub>1</sub> mice reported by the NTP (1986) and Chan et al. (1988), there was no evidence of carcinogenicity of methyl methacrylate for groups of 50 male F344/N rats and 50 male and 50 female B6C3F<sub>1</sub> mice exposed to 500 or 1000 ppm (2050 or 4100 mg/m<sup>3</sup>) and groups of 50 female rats exposed to 250 or 500 ppm (1025 or 2050 mg/m<sup>3</sup>) for 2 years. Based on inflammation and degeneration of the olfactory epithelium in the nasal cavity (accompanied by variable atrophy of the nerve bundles in the submucosa and, in the most severely affected areas, replacement of sensory neuroepithelial cells with respiratory epithelium) and minimal increases in the numbers of alveolar macrophages in the nasal cavity at all dose levels, the LOEL in rats was considered to be 250 ppm (1025 mg/m<sup>3</sup>). In mice, the LOEL was considered to be 500 ppm (2050 mg/m<sup>3</sup>) on the basis of lower mean body weights in exposed animals and localized histopathological effects at the site of entry (including inflammation and degeneration of the olfactory epithelium).

In earlier studies conducted for Rohm & Haas (1979a,b), no treatment-related increases in tumour incidence occurred in either groups of 56 male and 56 female golden hamsters or groups of 70 male and 70

**Table 1: Summary of effect levels in long-term studies.**

Species	Study design	Effects	Effect levels	Comments	Reference
<b>INHALATION</b>					
Rats, Sprague-Dawley, 50 males per group	Exposed to 0 or 116 ppm (476 mg/m <sup>3</sup> ) methyl methacrylate, 8 hours/day, for 5 days/week. Approximately half of the rats in each group were sacrificed after 3 months; blood and tissue samples were taken. The remainder of the rats were exposed for 6 months.	Rats exposed for 3 months lacked visceral and subcutaneous fat deposits, had significantly lower body, lung, and spleen weights, and had significantly higher mean serum alkaline phosphatase concentration. Rats exposed for 6 months had less subcutaneous fat, significantly lower mean body weights, popliteal fat pad weights, and mean intestinal transit time, and significantly higher mean alkaline phosphatase and inorganic phosphate concentrations compared with controls.	Effects at 116 ppm (476 mg/m <sup>3</sup> )	One dose group only	Tansy et al., 1976
Rats, Sprague-Dawley, 23 males per group	Exposure to 0 or 116 ppm (476 mg/m <sup>3</sup> ) methyl methacrylate, 5 days/week, averaging 7 hours/day, for 542 hours (3 months). Excretion studies in nine rats from each group; histopathological examinations of heart, lung, kidneys, spleen, stomach, small bowel, liver, and adrenal.	Exposed rats had significantly lower total bilirubin and higher total cholesterol levels; possible liver damage in the exposed group, but details not reported.	Effects at 116 ppm (476 mg/m <sup>3</sup> )	One dose group only	Tansy et al., 1980a
Rats, Sprague-Dawley, 23 males per group for 3 months and unspecified number for	Exposure to 0 or 116 ppm (476 mg/m <sup>3</sup> ) methyl methacrylate, 7 hours/day, 5 days/week, for 3 or 6 months. Histopathological examinations of heart, lung, kidneys, spleen, stomach, small bowel, liver, and adrenal.	Mild lung damage in some of the rats exposed for 3 and 6 months and the sham-exposed controls. Rats exposed for 6 months had damaged tracheal mucosa. The epithelium was denuded of cilia, and the cellular covering of 6 months microvilli was reduced in rats exposed for 3 months.	Effects at 116 ppm (476 mg/m <sup>3</sup> )	One dose group only; statistical significance not reported; similar effects in sham-exposed controls	Tansy et al., 1980b
Rats, F344, 10 per sex per group	Exposure to 0, 63, 125, 250, 500, or 1000 ppm (0, 258, 512, 1025, 2050, or 4100 mg/m <sup>3</sup> ) methyl methacrylate, 6 hrs/day, for 65 days. Complete gross pathological and histopathological examinations.	Some clinical signs and one death each in groups exposed to 63 ppm and controls, but not dose-related.	NOEL = 1000 ppm (4100 mg/m <sup>3</sup> )		Rohm & Haas, 1977
Rats, F344/N, 10 per sex group	Inhalation of 0, 63, 125, 250, 500, or 1000 ppm (0, 258, 512, 1025, 2050, or 4100 mg/m <sup>3</sup> ) methyl methacrylate, 6 hours/day, 5 days/week, for 14 weeks (65 exposures). Histological examinations were conducted of an unspecified range of tissues from all high-dose and control rats, those that died before the end of the study, and some of the rats from the other groups.	No methyl methacrylate-related effects.	NOEL = 1000 ppm (4100 per mg/m <sup>3</sup> )		NTP, 1986

**Table 1: cont'd**

Species	Study design	Effects	Effect levels	Comments	Reference
Rats, F344/N, 10 per sex per group	Exposure to 0, 500, 1000, 2000, 3000, or 5000 ppm (0, 2050, 4100, 8200, 12 300, or 20 500 mg/m <sup>3</sup> ) methyl methacrylate, 6 hours/day, 5 days/week, for 14 weeks (65 exposures). Histological examinations were performed on the controls, the two highest dose groups, and rats that died before the end of the study. Tissues from the nasal turbinates, larynx, trachea, lungs, and brain for all rats exposed at 1000 ppm and survivors of the 2000 ppm groups were also examined histopathologically.	At 1000 ppm, a low incidence of mild effects on the brain and nasal turbinates in females was observed. At 2000-5000 ppm, death, effects on body weight, and lesions of nasal turbinates and brain were observed; changes in spleen were observed at 3000 ppm and above. Also, follicular atrophy of the spleen in 4/10 males, bone marrow atrophy in 8/10 males (5000 ppm exposure group), and cerebellar congestion and penducle haemorrhage in the females exposed to 3000 and 5000 ppm that died early. At 5000 ppm, listlessness, nasal and serous ocular discharge, and prostration during the first 2 days, nasal cavity inflammation with necrosis and loss of epithelium, follicular atrophy of the spleen, and bone marrow atrophy in the males. Cerebellar congestion and penducle haemorrhage in the early-death females exposed to 3000 and 5000 ppm, and malacia and gliosis in 5/9 females exposed to 2000 ppm and 1/8 females exposed to 1000 ppm.	LOEL = 1000 ppm (4100 mg/m <sup>3</sup> ) NOEL = 500 ppm (2050 mg/m <sup>3</sup> )		NTP, 1986
Rats, albino F344, 70 per sex per group	Exposure to 0, 25, 100, or 400 ppm (0, 102.5, 410, or 1640 mg/m <sup>3</sup> ) methyl methacrylate, 6 hours/day, 5 days/week, for up to 104 weeks. Histopathological examination of a wide range of tissues from controls and high-dose groups, as well as selected tissues from other dose groups (ovaries or testes and nasal turbinates).  A re-examination of the nasal tissues from the rats of the Rohm & Haas (1979a) study was conducted. The review consisted of microscopic examination of nasal tissue from at least 10% of randomly selected rats from each group, and the slides evaluated included the original study slides plus slides from tissue sections taken deeper into the block.	Decreased body weights; slight increase in the incidence of mild rhinitis in the nasal mucosal lining of the turbinates. The re-examination revealed that rats exposed to 100 or 400 ppm methyl methacrylate had exposure-related and concentration-dependent microscopic changes in the olfactory epithelium lining the dorsal meatus in the anterior region of the nasal cavity. The microscopic changes consisted of degeneration/atrophy of the olfactory epithelium and underlying Bowman's glands, hyperplasia of basal (reserve) cells, replacement of olfactory epithelium by ciliated (respiratory-like) epithelium, and inflammation of the mucosa and/or submucosa. The squamous epithelium of the nasal cavity was not affected. The lesions tended to be bilateral in distribution in rats exposed to both 100 and 400 ppm methyl methacrylate. A small nasal polypoid adenoma was observed in one male from both the 100 and 400 ppm exposure groups.	NOEL = 25 ppm (102.5 mg/m <sup>3</sup> ) LOEL = 100 ppm (410 mg/m <sup>3</sup> )		Rohm & Haas, 1979a; Lomax, 1992; Lomax et al., 1997
Rats, F344/N, 50 per sex per group	Rats exposed to methyl methacrylate at 0, 2050, or 4100 mg/m <sup>3</sup> (males) or 0, 1025, or 2050 mg/m <sup>3</sup> (females), 6 hours/day, 5 days/week, for 102 weeks. Histological examination of a comprehensive range of tissues.	Inflammation and degeneration of the olfactory epithelium (accompanied by variable atrophy of the nerve bundles in the submucosa and, in the most severely affected areas, replacement of sensory neuroepithelial cells with respiratory epithelium) and minimal increases in the numbers of alveolar macrophages in the nasal cavity at all dose levels. The incidence of focal or multifocal fibrosis of the lung was increased in the females exposed to 2050 mg/m <sup>3</sup> .	LOEL = 250 ppm (1025 mg/m <sup>3</sup> )		NTP, 1986; Chan et al., 1988

**Table 1: cont'd**

Species	Study design	Effects	Effect levels	Comments	Reference
Rats, Fischer 344, male and female (number not specified).	Exposure to 0, 25, 100, or 400 ppm (0, 102.5, 410, or 1640 mg/m <sup>3</sup> ) methyl methacrylate, 6 hours/day, 5 days/week, for 24 months. Evaluation of haemograms, clinical chemistries, and urine, as well as gross histopathological examination.	Mild rhinitis was observed (dose level not specified)		Abstract only	Smith et al., 1979
Mice, B6C3F1, 10 per sex per group	Exposure to 0, 63, 125, 250, 500, or 1000 ppm (0, 258, 512, 1025, 2050, or 4100 mg/m <sup>3</sup> ) methyl methacrylate, 6 hours/day, 5 days/week, for 14 weeks (64 exposures). Histological examination of an unspecified range of tissues in all mice of the highest-dose and control groups, all animals that died before the end of the study, and some mice in the other groups.	Final mean body weight of the highest-dose males was 7% lower than controls.	NOEL = 500 ppm (2050 mg/m <sup>3</sup> ) LOEL = 1000 ppm (4100 mg/m <sup>3</sup> )		NTP, 1986
Mice, B6C3F1, 10 per sex per group	Exposure to 0, 63, 125, 250, 500, or 1000 ppm (0, 258, 512, 1025, 2050, or 4100 mg/m <sup>3</sup> ) methyl methacrylate, 6 hours/day, for 64 days. Complete gross pathological and histopathological examinations.	Some clinical signs and one death in the group exposed to 500 ppm, but not dose-related. Body weights of males receiving the two highest doses were significantly decreased during weeks 11-13 (500 ppm) and weeks 6, 11, and 12 (1000 ppm). In female mice, the total body weight changes were statistically significantly lower in animals exposed to 500 ppm but not to 1000 ppm.	NOEL = 250 ppm (1025 mg/m <sup>3</sup> ) LOEL = 500 ppm (2050 mg/m <sup>3</sup> )		Rohm & Haas, 1977
Mice, B6C3F1, 10 per sex per group	Exposure to 0, 500, 1000, 2000, 3000, or 5000 ppm (0, 2050, 4100, 8200, 12 300, or 20 500 mg/m <sup>3</sup> )methyl methacrylate, 6 hours/day, 5 days/week, for 14 weeks. Histological examinations of tissues from the major organs of all mice in the highest-dose and control groups and mice that died before the end of the study, of the lung and nasal turbinates of the males and the nasal membranes of all females in the 2000 and 3000 ppm groups, and of the liver of the males in the 2000 ppm group. At 1000 ppm, the nasal turbinates from both sexes and brain from the males were also histologically examined.	The final mean body weights of all groups of exposed mice were lower than controls. Deaths at 2000 ppm and above. Renal cortical necrosis, cortical tubular degeneration and/or focal mineralization, nasal cavity inflammation with necrosis, and loss of olfactory epithelium at 2000-5000 ppm in males and extensive liver necrosis in males exposed to 5000 ppm. Inflammation of the nasal turbinates in females exposed to 2000 ppm and above. Metaplasia of the nasal epithelium in all exposed mice.	LOEL = 500 ppm (2050 mg/m <sup>3</sup> )		NTP, 1986
Mice, B6C3F1, 50 per sex per group	Exposure to 0, 2050, or 4100 mg/m <sup>3</sup> methyl methacrylate, 6 hours/day, 5 days/week, for 102 weeks. Histological examination of a comprehensive range of tissues.	Decrease in mean body weights; localized histopathological effects (inflammation and degeneration of the olfactory epithelium) in the nasal epithelium.	LOEL = 500 ppm (2050mg/m <sup>3</sup> )		NTP, 1986; Chan et al., 1988
Golden hamsters, 56 per sex per group	Exposure to 0, 25, 100, or 400 ppm (0, 102.5, 410, or 1640 mg/m <sup>3</sup> ) methyl methacrylate, 6 hours/day, 5 days/week, for 18 months. Haematological analysis and gross and microscopic examination of a comprehensive range of tissues.	Decreased body weights; increased mortality.	LOEL = 400 ppm (1640 mg/m <sup>3</sup> ) NOEL = 100 ppm (410 mg/m <sup>3</sup> )		Rohm & Haas, 1979b

**Table 1: cont'd**

Species	Study design	Effects	Effect levels	Comments	Reference
Golden hamsters, male and female (number not specified)	Exposure to 0, 25, 100, or 400 ppm (0, 102.5, 410, or 1640 mg/m <sup>3</sup> ) methyl methacrylate, 6 hours/day, 5 days/week, for 18 months. Evaluation of haemograms, clinical chemistries, and urine, as well as gross histopathological examination.	No exposure-related toxic effects were observed.	NOEL = 400 ppm (1640 mg/m <sup>3</sup> )	Abstract only	Smith et al., 1979
Dogs, beagles, 6 per group, sex unspecified	Exposure to 0, 100, or 400 ppm (0, 410, or 1640 mg/m <sup>3</sup> ) methyl methacrylate vapour, 6 hours/day, 5 days/week, for 3 months. Each dog had an external iliac artery catheter. Two dogs from each group sacrificed at the end of the 3-month period; remaining dogs observed for another month.	No significant differences in systolic and diastolic blood pressure, ECG, heart and respiratory rates, haematology, clinical chemistries, and urinalysis; histopathological examination of the major organs was unremarkable.	NOEL = 400 ppm (1640 mg/m <sup>3</sup> )		Tansy & Drees, 1979
Dogs, beagles, male (number not specified)	Exposure to 0, 100, or 400 ppm (0, 410, or 1640 mg/m <sup>3</sup> ) methyl methacrylate vapour, 6 mg/m <sup>3</sup> hours/day, 5 days/week, for 3 months. Gross and histopathological evaluations in addition to evaluation of haemograms, clinical chemistries and urine, ECGs, and blood pressure.	No exposure-related toxic effects were observed.	NOEL = 400 ppm (1640 mg/m <sup>3</sup> )	Abstract only	Smith et al., 1979
<b>INGESTION</b>					
Rats (sex and strain unspecified, groups of 5)	Ingestion of 0, 1, 3, or 5 ml/kg body weight (0, 0.9, 2.8, or 4.7 mg/kg body weight) orally by gavage, every second day for 70 days. Urine samples from rats of all groups were periodically collected and examined for blood. Histopathological examinations unspecified.	Rats in mid-dose group did not gain as much weight as those in low-dose group; animals in high-dose group died before the 4th treatment. All high-dose rats had distended bladders filled with blood; a moderate degree of cellular degeneration in the liver, but without necrosis or fibrosis; renal effects (haemorrhages in the tubules, marked hyperaemia, and degeneration of the tubular epithelium).	NOAEL = 3 ml/kg body weight (2832 mg/kg body weight)	Small group sizes; histopathological examination unspecified	Deichmann-Gruebler & Read, undated
Rats, Wistar, 25 per sex per group	Ingestion of 0, 6, 60, or 2000 ppm (mg/litre) (equivalent to 0, 0.4, 4, and 121 mg/kg body weight per day) for males; and 0, 0.5, 5, and 146 mg/kg body weight per day for females) methyl methacrylate in drinking-water for 2 years. (Groups received 6 and 60 ppm for 5 months, then the concentrations were increased to 7 and 70 ppm for the remainder of the 2 years.) Histopathological examination of a wide range of tissues from mid- and high-dose groups. Limited haematological and urine analyses conducted.	Increase in relative kidney weight in females only.	NOEL = 60 ppm (5 mg/kg body weight per day) NOAEL = 2000 ppm (146 mg/kg body weight per day)		Borzelleca et al., 1964
Dogs, beagles, 2 per sex per group	Ingestion of 0, 10, 100, or 1000 ppm (mg/kg) methyl methacrylate in corn oil in the diet (high dose gradually increased to 1500 ppm [equivalent to about 38 mg/kg body weight per day] at week 9) for 2 years. Histopathological examination of a wide range of tissues. Limited haematological and urine analyses conducted.	No treatment-related effects.	NOEL = 1500 ppm (38 mg/kg body weight per day)	Extremely small number of animals	Borzelleca et al., 1964

female albino F344 rats exposed to 0, 25, 100, or 400 ppm (0, 102.5, 410, or 1640 mg/m<sup>3</sup>) methyl methacrylate 6 hours/day, 5 days/week, for 18 months and 2 years, respectively. At the highest concentration, body weight decreased significantly in both species, mortality increased in hamsters, and the incidence of mild rhinitis in the nasal mucosa increased slightly in rats.

A histopathological review of the nasal tissues from the rats in the above-mentioned Rohm & Haas (1979a) study was commissioned by the US Methacrylate Producers Association (Lomax, 1992; Lomax et al., 1997). The review consisted of microscopic examination of nasal tissue from at least 10% of randomly selected rats from each group, and the slides evaluated included the original study slides plus slides from tissue sections taken deeper into the block. The tissues from male and female rats that had been exposed to 25 ppm (102.5 mg/m<sup>3</sup>) methyl methacrylate for 2 years were morphologically similar to those of controls. Rats exposed to 100 or 400 ppm (410 or 1640 mg/m<sup>3</sup>) methyl methacrylate had exposure-related and concentration-dependent microscopic changes in the olfactory epithelium lining the dorsal meatus in the anterior region of the nasal cavity. The microscopic changes consisted of degeneration/atrophy of the olfactory epithelium and underlying Bowman's glands, hyperplasia of basal (reserve) cells, replacement of olfactory epithelium by ciliated (respiratory-like) epithelium, and inflammation of the mucosa and/or submucosa (Lomax et al., 1997). Changes in the respiratory epithelium were observed only at the high concentration (400 ppm [1640 mg/m<sup>3</sup>]) and were limited to hyperplasia of the submucosal gland and/or goblet cells in the anterior region of the nasal cavity. The squamous epithelium of the nasal cavity was not affected. The lesions tended to be bilateral in distribution in rats exposed to both 100 and 400 ppm (410 and 1640 mg/m<sup>3</sup>) methyl methacrylate. A small nasal polypoid adenoma was observed in one male from both the 100 and 400 ppm (410 and 1640 mg/m<sup>3</sup>) exposure groups. Based on this re-examination, the NOEL and LOEL are considered to be 25 ppm (102.5 mg/m<sup>3</sup>) and 100 ppm (410 mg/m<sup>3</sup>), respectively.

Data available on the effects of methyl methacrylate following ingestion are limited. In an early study (Borzelleca et al., 1964) in which organ to body weight ratios were determined and histopathological examination of a wide range of tissues as well as limited haematological and urine analyses were conducted, the relative kidney weight was increased in a small group of female rats ( $n = 25$ ) exposed to 2000 ppm (mg/litre) methyl methacrylate in drinking-water for 2 years. This effect was not observed in the males, and histopathological examination revealed no damage. The authors also reported a decrease in fluid consumption in rats exposed

to 2000 ppm. The no-observed-adverse-effect level (NOAEL) was therefore considered to be 2000 ppm (equivalent to a dose of about 146 mg/kg body weight per day for females and 121 mg/kg body weight per day for males, based on intake and body weight data presented by the authors). There were no treatment-related effects, based upon gross or histopathological examination, in extremely small groups of beagle dogs ( $n = 2$ ) exposed to concentrations of up to 1500 ppm (mg/kg) methyl methacrylate (equivalent to a dose of about 38 mg/kg body weight per day) in their feed for 2 years (Borzelleca et al., 1964).

## 8.5 Genotoxicity and related end-points

Results of available genotoxicity studies on methyl methacrylate are summarized in Table 2. In a number of well conducted *in vitro* studies with precautions taken to limit evaporation, methyl methacrylate was not mutagenic in *Salmonella typhimurium* with or without metabolic activation. In a single study (Poss et al., 1979), results were positive at clearly cytotoxic concentrations in the presence of metabolic activation in a poorly validated forward mutation assay in *S. typhimurium* TM677; results were negative in the absence of metabolic activation.

Methyl methacrylate has been mutagenic and clastogenic in mammalian cells in culture. It induced gene mutation in mouse lymphoma L5178Y cells without metabolic activation in five investigations and was positive with metabolic activation in all of the three investigations in which it was examined. Results for chromosomal aberrations and micronucleus formation were also positive in this cell line without metabolic activation at concentrations at which there was poor cell survival (Doerr et al., 1989). An increase in chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells has also been observed in the presence and absence of metabolic activation in assays conducted in two laboratories (NTP, 1986; Anderson et al., 1990).

In *in vivo* studies conducted to date, there has been limited evidence of genotoxicity. In an early study in which rats were exposed to methyl methacrylate as either a single 2-hour exposure or for 5 hours/day for 5 days at concentrations up to 9000 ppm (36 900 mg/m<sup>3</sup>), there were small but significant increases in chromosomal aberrations in bone marrow cells from rats exposed to the highest concentration in the multiple-exposure study (Anderson & Richardson, 1976). Although of questionable biological significance, small increases in gaps were also noted at the two highest concentrations. In a follow-up study with a larger number of intermediate dose levels, there were significant increases in

**Table 2: Genetic effects (adapted from IARC, 1994).**

Test system	End-point	Dose <sup>a</sup> (LED/HID)	Results <sup>b</sup>		Reference
			Without exogenous metabolic system	With exogenous metabolic system	
Salmonella typhimurium TM677	Forward mutation	5000	-	+	Poss et al., 1979
Salmonella typhimurium TA100	Reverse mutation	500	-	-	Lijinsky & Andrews, 1980
		5000	-	-	Hachitani et al., 1981
		2300	-	-	Waegemaekers & Bensink, 1984
		5000	-	-	Zeiger et al., 1987
Salmonella typhimurium TA1535	Reverse mutation	25 mg/plate	-	-	Schweikl et al., 1994
		500	-	-	Lijinsky & Andrews, 1980
		2300	-	-	Hachitani et al., 1981
Salmonella typhimurium TA1537	Reverse mutation	5000	-	-	Waegemaekers & Bensink, 1984
		1700	-	-	Zeiger et al., 1987
		500	-	-	Lijinsky & Andrews, 1980
		2300	-	-	Hachitani et al., 1981
Salmonella typhimurium TA1538	Reverse mutation	5000	-	-	Waegemaekers & Bensink, 1984
		500	-	-	Lijinsky & Andrews, 1980
		2300	-	-	Hachitani et al., 1981
Salmonella typhimurium TA98	Reverse mutation	5000	-	-	Waegemaekers & Bensink, 1984
		2300	-	-	Hachitani et al., 1981
		500	-	-	Lijinsky & Andrews, 1980
		25 mg/plate	-	-	Schweikl et al., 1994
Salmonella typhimurium TA97	Reverse mutation	1700	-	-	Zeiger et al., 1987
Salmonella typhimurium TA97a		25 mg/plate	-	-	Schweikl et al., 1994
Salmonella typhimurium TA102		25 mg/plate	-	-	Schweikl et al., 1994
Salmonella typhimurium TA104		25 mg/plate	-	-	Schweikl et al., 1994

Table 2, continued		Dose <sup>a</sup> (LED/HID)	Results <sup>b</sup>		Reference
Test system	End-point		Without exogenous metabolic system	With exogenous metabolic system	
Mouse lymphoma L5178Y cells in vitro	Gene mutation (tk locus)	2200	+	0	Doerr et al., 1989
		2000	+	0	Moore et al., 1988
		250		+	Myhr et al., 1990
		500	+		Myhr et al., 1990
		500	+	+	Dearfield et al., 1991
		117.5 (0.125 µl/ml)	+	+	NTP, 1986
Mouse lymphoma L5178Y cells in vitro	Micronucleus formation	2200	(+)	0	Doerr et al., 1989
Chinese hamster ovary cells in vitro	Sister chromatid exchange	16	+	+	Anderson et al., 1990
		750	+		NTP, 1986
		500		+	NTP, 1986
Chinese hamster ovary cells in vitro	Chromosomal aberrations	1600	+	(+)	Anderson et al., 1990
		5000		+ <sup>c</sup>	NTP, 1986
		1600	+ <sup>c</sup>		NTP, 1986
Mouse lymphoma L5178Y cells in vitro	Chromosomal aberrations	2200	(+)	0	Doerr et al., 1989
Human lymphocytes in vitro	Sister chromatid exchange	0.1	?	0	Cannas et al., 1987
Mouse bone marrow cells in vivo	Micronucleus formation	≤4.52 g/kg bodyweight x 1 p.o. <sup>d</sup>	-		Hachitani et al., 1981
		1.13 g/kg body weight x 4 p.o. <sup>d</sup>	-		Hachitani et al., 1981
Rat bone marrow cells in vivo	Chromosomal aberrations	36 900 mg/m <sup>3</sup> , 2 hour x 1 inhal.	-		Anderson & Richardson, 1976
		36900 mg/m <sup>3</sup> , 5 h/day, 5 d inhal.	+		Anderson & Richardson, 1976
		4100 mg/m <sup>3</sup> , 2 hour x 1 inhal.	Equivocal		Anderson et al., 1979
		4100 mg/m <sup>3</sup> , 5 h/day, 5 d inhal.	Equivocal		Anderson et al., 1979
Male mice in vivo	Dominant lethal assay	<36900 mg/m <sup>3</sup> , 6 h/day, 5 d inhal.	-		Anderson & Hodge, 1976

<sup>a</sup> In vitro tests, µg/ml; in vivo tests, mg/kg body weight; LED = lowest effective dose; HID = highest ineffective dose. <sup>b</sup> +, positive; (+), weak positive; -, negative; 0, not tested; ?, inconclusive (variable response within several experiments within an adequate study). Negative results of an additional in vivo micronucleus assay in mice do not contribute to an assessment of the weight of evidence of genotoxicity owing to inadequate dose levels (Jensen et al., 1991). Available data in the published accounts were inadequate to permit an assessment of the mixed results of two additional studies in which chromosomal aberrations in bone marrow cells of rats were examined following intraperitoneal administration (Fedyukovich et al., 1988; Fedyukovich & Egorova, 1991). <sup>c</sup> 5% of cells affected without exogenous metabolic system; 30% of cells affected with exogenous metabolic system. <sup>d</sup> No toxicity in target tissue. p.o. = per os.

chromosomal aberrations following both single and repeated exposures (Anderson et al., 1979); although there was no clear dose–response, the pattern of effect may have been attributable to chemically induced cell cycle delay (Anderson et al., 1979). The maximum concentration tested in the follow-up study (1000 ppm [4100 mg/m<sup>3</sup>]) caused significant reductions in the mitotic activity in the bone marrow of all exposed animals. Results were negative in a well conducted dominant lethal assay in which mice were exposed to concentrations of methyl methacrylate up to 9000 ppm (36 900 mg/m<sup>3</sup>) 6 hours/day for 5 days (Anderson & Hodge, 1976).

No significant increase in the incidence of micronuclei was observed in the bone marrow of mice following a single administration of methyl methacrylate by gavage at doses up to 4.52 g/kg body weight or in an additional investigation with one dose group that was exposed to 1.13 g/kg body weight per day for 4 days; however, cells were harvested at one time point (24 hours) only, and there was no evidence of toxicity in the target tissue (Hachitani et al., 1981). Negative results of an additional *in vivo* micronucleus assay in mice do not contribute to an assessment of the weight of evidence of genotoxicity owing to inadequate dose levels (Jensen et al., 1991). Available data in the published accounts were inadequate to allow the assessment of the mixed results of two additional studies in which chromosomal aberrations in bone marrow cells of rats were examined following intraperitoneal administration of methyl methacrylate (Fedyukovich et al., 1988; Fedyukovich & Egorova, 1991).

Although not mutagenic in bacterial systems *in vitro*, methyl methacrylate has induced mutation and chromosomal aberrations in mammalian cells *in vitro*. In *in vivo* inhalation studies in which there has been clear evidence of toxicity within the target tissue, there has been limited evidence of genotoxicity of methyl methacrylate.

## **8.6 Reproductive and developmental toxicity**

In a well conducted study in CrI:CDBR rats, there was no embryotoxicity or fetotoxicity and no increase in the incidence of malformations or variations following exposure for 6 hours/day on days 6–15 of gestation to concentrations of methyl methacrylate that ranged from 99 to 2028 ppm (406–8315 mg/m<sup>3</sup>; NOEL = 8315 mg/m<sup>3</sup>). However, there were treatment-related effects on maternal body weight at all concentrations (Solomon et al., 1993). In an earlier study in which pregnant ICR mice were exposed to 1330 ppm (5450 mg/m<sup>3</sup>) methyl methacrylate for 2 hours twice daily during days 6–15 of pregnancy, there were no developmental effects.

Maternal toxicity was not addressed in the report (McLaughlin et al., 1978).

In a study reported only in the form of an abstract, a number of effects, including intrauterine deaths, an increase in the number of fetuses with vascular pathology, and an increase in the frequency of “functional immaturity,” were observed in the offspring of rat dams exposed to concentrations of methyl methacrylate as low as 0.01 mg/m<sup>3</sup> (Farmakovskaya & Tikhomirov, 1993). The information presented in the published account of this study is inadequate to permit assessment of the protocol and results.

In early studies, developmental effects, including decreases in fetal weights, embryo–fetal deaths, and skeletal abnormalities, were observed in rats following inhalation of concentrations of methyl methacrylate that were toxic to the dams (Hodge & Palmer, 1977; Nicholas et al., 1979). Similar effects were reported in studies in mice in which maternal toxicity was not addressed (Tansy, 1975) and in studies in rats in which the protocol and results were not well documented (Luo et al., 1986).

Data on reproductive effects are limited to a dominant lethal assay and examination of gonads in repeated-dose toxicity studies. There was no reduction in fertility as measured by the number and percentage of successful matings each week or the percentage of female mice that become pregnant in a dominant lethal assay in mice exposed to 100, 1000, or 9000 ppm (410, 4100, or 36 900 mg/m<sup>3</sup>) methyl methacrylate by inhalation for 6 hours/day for 5 days (Anderson & Hodge, 1976).

Adverse effects on the reproductive organs of experimental animals have not been observed in repeated-dose studies in animals exposed to methyl methacrylate (see sections 8.3 and 8.4).

## **8.7 Immunological and neurological effects**

In a study in which the leukocyte migration inhibition method was employed to determine if methyl methacrylate was potentially a causative agent in denture stomatitis, three groups of five albino rabbits of both sexes were injected intramuscularly with 1 ml of methyl methacrylate on days 1, 5, and 14 (Zafiroopoulos et al., 1985). On the 36th day, blood was drawn to test the inhibition of leukocyte migration. The results indicated that methyl methacrylate was a specific antigen that was capable of inducing cellular immune reaction.

Methyl methacrylate markedly impaired locomotor activity and learning while significantly increasing aggressive behaviour in male rats orally administered the

chemical at 500 mg/kg body weight for 21 days (Husain et al., 1985). There was an overall increase in levels of biogenic amine in the pons-medulla and hippocampus. Levels of noradrenaline in the cerebral cortex and 5-hydroxytryptamine in the mid-brain and the hypothalamus were increased, whereas there was a slight decrease in dopamine levels in the corpus striatum (Husain et al., 1985). In a separate study under the same experimental conditions, a significant increase in cholesterol (26%) and triglycerides (65%) and a slight decrease in the total phospholipid content of the sciatic nerve were noted (Husain et al., 1989).

In a study investigating the neurotoxic effects of acrylamide, no evidence of neurotoxicity (evaluated as observation of ataxia) or enhancement of acrylamide neuropathy was observed in male rats fed a diet containing 18 800 ppm (mg/kg) methyl methacrylate for 5 weeks (the intake of methyl methacrylate was estimated to be 410 mg/day) (Edwards, 1975). Other limited studies that have been identified do not contribute to our understanding of the neurotoxicity of methyl methacrylate (Innes & Tansy, 1981; Wynkoop et al., 1982; Kanerva & Verkkala, 1986).

## 9. EFFECTS ON HUMANS

Data on effects of methyl methacrylate on humans are informative primarily with respect to irritation and sensitization (for exposure both dermally and by inhalation), respiratory effects, and carcinogenicity; however, in cross-sectional epidemiological studies conducted to date, effects on the nervous (Seppalainen & Rajaniemi, 1984; Schwartz et al., 1989) and cardiac (Cromer & Kronoveter, 1976; NIOSH, 1976) systems have also been examined.

Hypotension, changes in pulse rate, and cardiac arrest have been reported following bone replacement surgery with polymethyl methacrylate cemented prostheses; however, the significance of these observations with respect to methyl methacrylate exposure is questionable owing to lack of correlation between peak plasma concentrations of methyl methacrylate and reported effects and the absence of similar effects in younger patients (Government of Canada, 1993; Cary et al., 1995; ECETOC, 1995).

### 9.1 Case reports

There are reports of skin irritation and sensitization in human volunteers and in patients suspected of occupational sensitization to acrylates from exposure to

dental materials or anaerobic sealants (Spealman et al., 1945; Estlander et al., 1984; Kassis et al., 1984; Rajaniemi & Tola, 1985; Conde-Salazar et al., 1988; Kanerva et al., 1988, 1989; Farli et al., 1990; Guerra et al., 1993). Occupational asthma associated with methyl methacrylate has also been reported (Lozewicz et al., 1985; Pickering et al., 1986, 1993); however, there is no conclusive evidence that methyl methacrylate is a respiratory sensitizer, and the possibility of a non-specific response due to respiratory tract irritation cannot be excluded.

### 9.2 Epidemiological studies

Protocols and results of cross-sectional studies in which respiratory effects of methyl methacrylate have been investigated in occupationally exposed populations are presented in Table 3. For example, in a study in which smoking was taken into account, an increase in the prevalence of chronic cough (as evaluated by questionnaire) was observed in a small group of workers ( $n = 40$ ) exposed exclusively to methyl methacrylate for at least 5 years in two factories (mean atmospheric levels of methyl methacrylate in the two factories were 18.5 and 21.6 ppm [75.8 and 88.6 mg/m<sup>3</sup>]) compared with controls engaged in similar job categories, but without exposure to methyl methacrylate (Marez et al., 1993). Spirometric values did not differ before the work shift, but two of nine parameters decreased during the work shift. Information concerning exposure to other respiratory irritants was not provided; although increased cough and mild airway resistance correlated with exposure to methyl methacrylate, peak versus mean exposures were not examined. In other studies in which there was some quantitative information on exposure, results have varied, with effects on respiratory function being observed in some cases at mean concentrations as low as 11 mg/m<sup>3</sup> (Jedrychowski, 1982) and no effects in other investigations at time-weighted-average concentrations up to 40–50 ppm (164–205 mg/m<sup>3</sup>) (Cromer & Kronoveter, 1976; NIOSH, 1976; Röhm, 1994). It is difficult, however, to draw meaningful conclusions concerning levels of exposure that induced effects in these studies, as there was little attempt to assess mean versus peak exposures. Moreover, interpretation of several of the investigations is complicated by concomitant exposure of the examined populations to other substances. In other investigations reported to date, quantitative data on exposure of workers to methyl methacrylate were not included (Andrews et al., 1979; Schwartz et al., 1989). An additional cross-sectional study of the prevalence of disorders of smell in methyl methacrylate-exposed workers is under way (A. Muttray, personal communication, 1997).

**Table 3: Cross-sectional epidemiological studies - respiratory effects**

Protocol	Results	Reference
<p>Study population composed of 40 workers from two factories who were exposed to methyl methacrylate for &gt;5 years and 45 controls engaged in similar job categories but without exposure to methyl methacrylate. Mean atmospheric concentrations of methyl methacrylate at the two factories were 18.5 ppm (75.9 mg/m<sup>3</sup>) (range 9-32 ppm [36.9-131.2 mg/m<sup>3</sup>]) and 21.6 ppm (88.6 mg/m<sup>3</sup>) (range 11.9-38.5 ppm [48.8-157.9 mg/m<sup>3</sup>]). Smoking history and information on the presence of respiratory symptoms were gathered by means of a questionnaire. Respiratory measurements (maximum expiratory flow volume [MEFV], forced vital capacity [FVC], forced expiratory volume [FEV]) were performed by means of a spirometer: one before the working shift, and the second in the last 2 hours of the 8-hour shift.</p>	<p>An increase in the prevalence of chronic cough was observed in exposed workers compared with controls (p = 0.04). This difference remained significant after adjustment for smoking (p = 0.03). Airway resistance increased during the 8-hour work shift in workers exposed to methyl methacrylate (as measured by MEF<sub>50</sub> [p = 0.04] and MEF<sub>50</sub>/MEF [p = 0.0]). The obstruction was mild, and forced expiratory volume in one second (FEV<sub>1</sub>) did not decrease during the work shift.</p>	Marez et al., 1993
<p>Ninety-one exposed and 43 non-exposed workers were evaluated at five plants manufacturing polymethyl methacrylate sheets. For exposed workers, 8-hour time-weighted-average concentrations of methyl methacrylate were between 4 and 49 ppm (16.4-200.9 mg/m<sup>3</sup>). Evaluation of chronic effects was conducted through an extensive questionnaire, a comparison of mean blood pressure values with predicted values from the 1971-1972 US National Health Survey, and results of pulmonary function tests, haemoglobin and white blood cell counts, urinalysis, and blood chemistry.</p>	<p>No significant differences were observed for respiratory function, chronic liver and gastrointestinal effects, skin and allergic problems, blood pressure and pulse rate, white blood cell count, and haemoglobin values. The only parameters for which effects were observed were serum glucose, blood urea nitrogen, cholesterol, albumin, and total bilirubin values, although the implication of these effects remains unclear. Although not statistically significant, the data also "suggested possible alterations in skin and nervous system symptomatology, urinalysis findings, and serum triglycerides."</p>	Cromer & Kronoveter, 1976
<p>Employees of the Rohm &amp; Haas Co. (which manufactures acrylic acid, acrylates, and methacrylates) - 618 males and 113 females (mean age 42.9 years), out of the total number of 909 short- and long-term employees - were asked to complete a University of Pennsylvania Smell Identification Test (UPSIT) and questionnaires on job histories as well as personal and medical information. Employees were grouped into four exposure categories: no significant chemical exposures (n = 319), exposure to other chemicals (n = 193), exposure to low levels of acrylate/methacrylate (n = 164), and exposure to higher levels of acrylate/methacrylate (n = 55). In a nested case-control study, 77 workers who scored below the 10th percentile in their age group on the UPSIT were matched with controls (scored at or above the 50th percentile). Exposure was classified in terms of whether workers had been exposed to methyl methacrylate for at least 6 weeks, the total time of employment at the plant, and a cumulative exposure score - a semi-quantitative index of lifetime exposure to the acrylates - for each worker.</p>	<p>Upon cross-sectional analysis, when the age, ethnic group, and smoking status were considered, the mean UPSIT scores in the four exposure groups did not differ. For the "no significant chemical exposures," "exposure to other chemicals," "exposure to low levels of acrylate/methacrylate," and "exposure to higher levels of acrylate/methacrylate" groups, the scores were 37.8, 37.4, 37.0, and 37.6, respectively. Based on logistic regression analysis, adjusting for multiple confounders, in the nested case-control study, the odds ratios for the association of UPSIT score with exposure to methyl methacrylate for all workers was 2.8 (95% CI 1.1-7.0) and for those who never smoked was 13.5 (95% CI 2.1-87.6); the crude odds ratios were 2.0 and 6.0, respectively. There was a dose-response relationship between olfactory dysfunction and the cumulative exposure. The odds ratios increased with the cumulative exposure scores, except for a decrease in the highest exposure category. The olfactory dysfunction may be reversible, as the odds ratios decreased with the length of time since the last exposure.</p>	Schwartz et al., 1989

**Table 3: Continued**

Protocol	Results	Reference
<p>Four hundred and fifty-four males from a plant (Plant A) producing styrene and methyl methacrylate were compared with 683 males from a plant producing carbon derivatives who served as controls (jobs were similar in both plants, but there was no exposure to styrene or methyl methacrylate in the latter plant). Standardized interviews on chest symptoms, measured heights, lung function tests, and examinations for chronic bronchitis and asthmatic syndrome were conducted. The workers were divided into the following groups: non-smokers, ex-smokers, and current smokers. Styrene and methyl methacrylate concentrations were determined in 18 workplaces in Plant A. For methyl methacrylate, the mean concentration in Plant A was 11 mg/m<sup>3</sup>.</p>	<p>There was a non-significantly lower occurrence of bronchitis and/or asthma in the exposed (17.8%) compared with the control (19.5%) group. There was no significant difference in the incidence of chronic chest symptoms between the two groups. However, the frequency of lung obstruction was over twice as high in the exposed workers (45.4% vs 18.0%); this percentage was higher for smokers than for non-smokers (20.9% vs 13.6%). Within the exposed group, the occurrence of lung obstruction in smokers and in non-smokers did not differ significantly. Fifty-six per cent of the controls and 76% of the exposed workers with lung obstruction did not have any chronic chest symptoms. The lung function of the exposed group was significantly poorer than that of the controls; the effects were slightly worse among smokers in both groups. The relative risk of lung obstruction (compared with non exposed ex- and non-smokers) was 1.7 for non-exposed smokers, 4.7 for exposed ex- and non-smokers, and 5.5 for exposed smokers.</p>	Jedrychowski, 1982
<p>Five hundred and two dental students (who handled methyl methacrylate in their laboratories) completed self-administered multiple-choice questionnaires concerning their past histories and any symptoms (not specified) associated with activities in the lab. Spirometric tests were performed before and after exposure to unreported amounts of methyl methacrylate for 77 students who had allergic rhinitis, smoked, or had symptoms upon usual exposure.</p>	<p>In exposed students, 6% reported respiratory symptoms associated with exposure to methyl methacrylate (88% had histories of asthma or allergic rhinitis), and 5% when using high-speed drills. Among the 77 students who underwent spirometric tests, there was no significant change in symptoms or spirometry.</p>	Andrews et al., 1979
<p>A study of 91 exposed and 43 non-exposed workers from five methyl methacrylate cast sheet manufacturing plants in the USA. The survey included a medical questionnaire, measurement of clinical symptoms, blood pressure, and pulse rate, testing of pulmonary function and blood chemistry, urinalysis, and white blood cell counts. Based on 8-hour time-weighted-average exposures to methyl methacrylate, workers were divided into five categories: &lt;5 ppm (20.5 mg/m<sup>3</sup>) (n = 13), 5-25 ppm (20.5-102.5 mg/m<sup>3</sup>) (n = 20), 25-50 ppm (102.5-205 mg/m<sup>3</sup>) (n = 33), no current exposure but past exposure &gt;1 year (n = 25), and the control group with no exposure (n = 43). The ages and smoking histories of exposure groups were not matched very well because of the low number of volunteers.</p>	<p>Some significant differences in terms of coughing and expectoration, but these were likely due to differences in smoking habits. When smoking histories were taken into consideration, there was no significant change in pulmonary function among the exposure groups. No significant differences in blood pressure or in white blood cell count were found. There were several significant differences in the blood chemistry tests of the "no current exposure" group, but this was likely due to the fact that they were significantly older than the controls.</p>	NIOSH, 1976
<p>A cross-sectional study involving 211 workers at a polymethyl methacrylate sheet producing factory in Germany. The study report period was 1991-1993. Working areas were classified into the following exposure ranges: 3-10 ppm (12.3-41 mg/m<sup>3</sup>), 10-20 ppm (41-82 mg/m<sup>3</sup>), 20-30 ppm (82-123 mg/m<sup>3</sup>), and 30-40 ppm (123-164 mg/m<sup>3</sup>) (8-hour time-weighted averages; ranges represent geometric means). The numbers of persons in each exposure group were 7, 128, 20, and 56, respectively. The examination of the workers consisted of a self-administered questionnaire (concerning lifestyle, occupation, and medical history, with emphasis on complaints of nose, throat, and respiratory system failures and allergic reactions, including skin and asthmatic reactions) as well as a visual examination of the nasal cavity.</p>	<p>There were no significant respiratory effects associated with exposure in any of the groups. There were some observations of eye and respiratory tract irritation, which were reported to be transient and were limited to short-term exposures (5-15 minutes in duration) at concentrations exceeding 100 ppm (410 mg/m<sup>3</sup>).</p>	Röhm, 1994

Owing to an excess of mortality from colon cancer observed in early investigations in exposed workers, several historical cohort studies have been conducted to examine the mortality rate from cancer of the colon or rectum among male workers employed at two plastics manufacturing plants in Bristol, Pennsylvania, and Knoxville, Tennessee (DeFonso & Maher, 1981, 1986; Maher & DeFonso, 1987a,b; Walker et al., 1991). An additional cohort study of workers at a small number of polymethyl methacrylate sheet production factories in the United Kingdom has also been identified (Tomenson & Bonner, 1994; Cary et al., 1995); however, documentation available at this time is inadequate for evaluation. In the most recent and extensive follow-up by Walker et al. (1991) in the above-mentioned plastics manufacturing plants, data were reanalysed as a function of the period of employment of the workers. In this investigation, the two cohorts were composed of 10 482 men who had worked during the period 1933–1982 in the Bristol plant and 3381 men hired between 1943 and 1982 in the Knoxville plant. The population of workers at the Bristol plant was further divided into an early cohort (men employed at some time between 1933 and 1945, inclusive) and late cohort (1946–1982, inclusive). The early cohort worked in conditions that are thought to have involved high exposures to the vapour phase of ethyl acrylate and methyl methacrylate monomer, as well as to a variety of volatile by-products of the ethyl acrylate/methyl methacrylate polymerization process.

In the two cohorts with later dates of first hire (Knoxville and late Bristol), there was no excess mortality due to cancer of the colon or rectum. In the early (Bristol) cohort, there was an apparent excess of deaths due to colon cancer (38 cases observed overall in those persons who accumulated a dose of >0 units, compared with an expected number of 25.4). Although the highest risk was in the subgroup of workers with the highest cumulative exposure, there was no trend of increasing risk with increasing exposure after allowing for a long latency period. There was no systematic pattern of excess risk of cancer at any other site. For respiratory cancer, however, there was a significantly high standardized mortality ratio (of 1.44) in the Knoxville cohort, with no excess in either of the Bristol cohorts. Owing to the large number of statistical estimates in this study and the absence of a clear dose–response trend, the association of methyl methacrylate with respiratory cancer is unclear. The apparent excess may have been due to statistical fluctuation or to confounding by other occupational exposures in the environment at the time.

Collins et al. (1989) reported a limited study of a much smaller cohort of workers exposed for considerably shorter periods to methyl methacrylate at two plants that either manufactured methyl methacrylate or used methyl methacrylate in other product manufacture between 1951 and 1983. There was no excess mortality for any type of cancer examined (Collins et al., 1989). There was a very

weak indication of an excess of rectal cancer (two cases in exposed workers with the expected number much less than 1.0) and weak to moderate indication of an excess risk of lung cancer (odds ratios of 4–5) in a population-based study of a small number of workers exposed to methyl methacrylate in Montreal, Canada (Siemiatycki, 1991).

Identified studies on the potential genotoxicity of methyl methacrylate in occupationally exposed populations contribute limited information. There was no increase in the number of sister chromatid exchanges in the peripheral lymphocytes of 31 male workers occupationally exposed to methyl methacrylate (mean value per 8 hours ranged from 0.70 to 21.6 ppm [2.9–88.6 mg/m<sup>3</sup>]) in four factories compared with that of 31 unexposed male workers of similar mean age and smoking habits (Marez et al., 1991). The distribution frequency of sister chromatid exchange, however, was significantly higher in the group exposed to methyl methacrylate at peak concentrations ranging from 114 to 400 ppm (467–1640 mg/m<sup>3</sup>), although the number of individuals in this exposure subgroup was small ( $n = 6$ ). Similarly, no increase in the frequency of chromosomal aberrations was observed in the peripheral lymphocytes of 38 male workers who were engaged in organic glass production (polymethyl methacrylate plates) and exposed to 8-hour, time-weighted-average concentrations of methyl methacrylate of 0.9–71.9 ppm (3.7–295 mg/m<sup>3</sup>) (Seiji et al., 1994). The frequency of sister chromatid exchange was higher in the exposed group than in controls; however, this was considered to be due to a higher age distribution in the exposed workers.

## 10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

### 10.1 Aquatic environment

Bailey et al. (1985) studied the toxicity of methyl methacrylate in juvenile bluegill sunfish at 22°C under static and flow-through conditions of various durations (1–96 hours). The 96-hour LC<sub>50</sub> under flow-through conditions was 191 mg/litre, whereas LC<sub>50</sub> values for durations of 1–24 hours ranged from 420 to 356 mg/litre, respectively. The 96-hour LC<sub>50</sub> for rainbow trout under flow-through conditions was >79 mg/litre, the highest concentration tested. Sublethal/behavioural responses were noted among the fish in the 40 and 79 mg/litre concentration groups (Bowman, 1990).

The 24-hour EC<sub>50</sub> for immobilization of *Daphnia magna* was 720 mg/litre, with extrapolated EC<sub>0</sub> and EC<sub>100</sub> values of 502 and 1042 mg/litre, respectively (Bringmann & Kuhn, 1982). The 24-hour LC<sub>50</sub> was 1760 mg/litre, with extrapolated values for the LC<sub>0</sub> and LC<sub>100</sub> of 875 and 2500

mg/litre, respectively (Bringmann & Kuhn, 1977). The threshold for onset of inhibition of cell multiplication was 447 mg/litre for the flagellate protozoan *Entosiphon sulcatum* after 72 hours of exposure (Bringmann, 1978). These studies were done in static, open systems, with only nominal concentrations reported.

Thresholds for onset of inhibition of cell multiplication following 8 days of exposure to methyl methacrylate were 120 mg/litre for the blue-green alga *Microcystis aeruginosa* and 37 mg/litre for the green alga *Scenedesmus quadricauda* at pH 7 (Bringmann & Kuhn, 1976, 1978a,b). The 96-hour LC<sub>50</sub> for *Selenastrum capricornutum* was 170 mg/litre, with a NOEL of 100 mg/litre (Forbis, 1990). No studies were identified on the effects of methyl methacrylate on higher aquatic plants.

## 10.2 Terrestrial environment

Data on the toxicity of methyl methacrylate to terrestrial animals are limited to a single study on soil microflora in which no effects of biological significance were observed (Hossack & Thomas, 1992).

# 11. EFFECTS EVALUATION

## 11.1 Evaluation of health effects

### 11.1.1 Hazard identification and dose–response assessment

Data on effects of methyl methacrylate in humans are informative primarily with respect to irritation and sensitization (for exposure both dermally and by inhalation) and carcinogenicity. Although there are some quantitative data on exposure to methyl methacrylate in available cross-sectional investigations of other end-points (NIOSH, 1976; Jedrychowski, 1982; Marez et al., 1993), they are considered inadequate as the principal basis for hazard identification and dose–response assessment owing to limitations of design and the potential role of confounding factors. Data on hazard identification and dose–response assessment for effects other than irritation/sensitization and carcinogenicity are derived primarily, therefore, from investigations in experimental animals.

The acute toxicity of methyl methacrylate is low. Irritation of the skin, eye, and nasal cavity has been observed in rodents and rabbits exposed to relatively high concentrations of methyl methacrylate. This

substance is a mild skin sensitizer in animals. Methyl methacrylate is a mild skin irritant in humans and has the potential to induce skin sensitization in susceptible individuals. Although occupational asthma associated with methyl methacrylate has also been reported, there is no conclusive evidence that methyl methacrylate is a respiratory sensitizer.

The effect observed most frequently at lowest concentration after repeated inhalation exposure of experimental animals to methyl methacrylate is irritation of the nasal cavity. Effects on the kidney and liver at higher concentrations have also been reported.

Limited available data indicate that methyl methacrylate is unlikely to induce fetotoxic effects in the absence of maternal toxicity. There has been no evidence of reproductive toxicity, based on limited available data (a dominant lethal assay in mice and examination of the gonads in repeated-dose toxicity studies). Based on limited available data, neurological effects have been observed following ingestion of doses greater than those that induce minimal renal effects.

As a whole, the available epidemiological studies do not provide strong or consistent evidence of a carcinogenic effect of methyl methacrylate on any target organ in humans, nor can it be inferred with any degree of confidence that the possibility of an excess risk has been disproved. Methyl methacrylate has not been carcinogenic in an extensive, well documented 2-year bioassay in rats and mice exposed by inhalation and in additional chronic inhalation studies in rats and hamsters. Although not mutagenic *in vitro* in bacterial systems, methyl methacrylate has been mutagenic and clastogenic in mammalian cells *in vitro*. In *in vivo* studies (primarily by the inhalation route) in which there has been clear evidence of toxicity within the target tissue, there has been limited evidence of genotoxicity of methyl methacrylate. On the basis of these observations, methyl methacrylate is considered unclassifiable with respect to carcinogenicity in humans.

Owing to the limitations of the available studies in humans on effects associated with longer-term exposure to methyl methacrylate, it is necessary to rely primarily on information obtained from the studies in animals for determination of critical effect levels. The lowest reported effect level for inhalation was 100 ppm (410 mg/m<sup>3</sup>) in rats exposed to methyl methacrylate for 2 years (based upon inflammatory degeneration of the nasal epithelium); the NOEL in this investigation was 25 ppm (102.5 mg/m<sup>3</sup>) (Rohm & Haas, 1979a; Lomax, 1992; Lomax et al., 1997).

### 11.1.2 Criteria for setting guidance values for methyl methacrylate

The following quantitative guidance is provided as an example of a possible basis for derivation of limits of exposure and judgement of the quality of environmental media by relevant authorities. As methyl methacrylate is considered to be “unclassifiable with respect to carcinogenicity in humans,” guidance values are derived on the basis of a lowest-observed-(adverse)-effect level [LO(A)EL] or a no-observed-(adverse)-effect level [NO(A)EL] for non-neoplastic effects. For methyl methacrylate, the route of exposure most relevant to the general population is likely inhalation.

The value considered most appropriate as a basis for development of a tolerable concentration in air is the NOEL of 25 ppm (102.5 mg/m<sup>3</sup>) in rats exposed to methyl methacrylate for 2 years (Rohm & Haas, 1979a; Lomax, 1992; Lomax et al., 1997). Effects at the next higher concentration were degenerative changes in the olfactory epithelium.

There is some debate currently about extrapolation of data on nasal irritation of the olfactory epithelium observed in rodents in risk assessment for humans. There are significant morphological differences between species in the structure of the nasal cavity, which result in differences in concentrations of inhaled materials at the nasal tissue. These are reflected in differences in surface area normalized to minute ventilation, being fivefold greater in rodents than in humans (DeSesso, 1993). A much greater percentage of the nasal cavity is lined by olfactory epithelium in rats than in humans. In addition, rodents are obligate nose breathers, whereas humans can also breathe through their mouths, which is expected to reduce exposure of the nasal epithelium for much of the population. There are also differing nasal flow patterns, with the greater airflow across the human olfactory epithelium during the expiratory phase when the vapour concentration would be considerably reduced as a result of absorption in the lower respiratory tract.

The pattern of the critical effects of inhalation of methyl methacrylate in animal studies (i.e. the olfactory epithelium being affected at lowest concentration) is consistent with toxicity resulting from metabolism of the inhaled material in the olfactory tissue by carboxylic esterases to methacrylic acid. Data on species differences in olfactory tissue carboxylesterase activity have not been identified; however, based on limited data from human tissue samples that may not have been morphologically normal taken at polyp biopsy, the activity of alpha-naphthylbutyrate carboxylesterase in human nasal respiratory tissue is less than that in the rat (Mattes & Mattes, 1992).

Although it is possible that humans may be less sensitive than rodents to lesions of the nasal epithelium caused by methyl methacrylate, currently available data are inadequate to account quantitatively for potential interspecies variation in sensitivity. However, studies that are currently under way may shed some additional light on this aspect (T. Green, personal communication, 1997; P.J. Pinto, personal communication, 1997). Therefore, on the basis of the available data, a tolerable concentration (TC) has been derived on the basis of a commonly adopted default value of 10-fold for interspecies variation as follows:

$$\begin{aligned} \text{TC} &= (102.5 \text{ mg/m}^3/100) \times (6/24) \times (5/7) \\ &= 0.2 \text{ mg/m}^3 \text{ (rounded to one significant figure)} \end{aligned}$$

where:

- € 102.5 mg/m<sup>3</sup> (25 ppm) is the lowest NOEL reported in inhalation bioassays of adequate quality in animal species (rats) conducted to date (exposure-related and concentration-dependent microscopic changes [degeneration/atrophy of the olfactory epithelium and underlying Bowman’s glands, hyperplasia of basal (reserve) cells, replacement of olfactory epithelium by ciliated (respiratory-like) epithelium, and inflammation of the mucosa and/or submucosa] were observed in anterior portions of the nasal cavity in rats exposed to the next higher concentration) (Rohm & Haas, 1979a; Lomax, 1992; Lomax et al., 1997);
- € 6/24 and 5/7 are the conversion of intermittent exposure of rats (i.e. 6 hours/day, 5 days/week) to continuous exposure of humans; this is appropriate in view of data that suggest that continuous exposure to methyl methacrylate could result in effects at concentrations below the NOAEL for intermittent exposure (Lomax et al., 1994); no scaling factor for inhalation volume to body weight was used, as effects at the next higher dose level are limited to the site of entry; and
- € 100 is the uncertainty factor (×10 for intraspecies variation; ×10 for interspecies variation).

Based on the results of limited available cross-sectional studies on respiratory effects in human populations, this value is likely to be protective.

A TDI can be derived for the oral route of exposure based on a 2-year drinking-water study in rats in which the NOAEL in females was considered to be 146 mg/kg body weight per day; the NOEL in males was 121 mg/kg body weight per day, the highest dose level tested (Borzelleca et al., 1964). Incorporating an uncertainty factor of 100 (×10 for intraspecies variation; ×10 for

interspecies variation), the TDI would be 1.2 mg/kg body weight per day.

### 11.1.3 Sample risk characterization

The extremely limited nature of the available data as a basis for estimation of exposure should be borne in mind in interpreting the comparisons presented here for predicted indirect population exposure in the general environment and estimated exposure from the use of consumer products containing methyl methacrylate. Moreover, the sample exposure estimates presented in section 6.2 will vary considerably as a function of production and use patterns and control measures in various countries.

Based upon the sample predicted concentration (based on fugacity modelling) of methyl methacrylate in air of  $2.44 \times 10^{-4}$  : g/m<sup>3</sup>, presented in section 6.1, levels of methyl methacrylate in ambient air are many orders of magnitude less than the calculated tolerable concentration of 200 : g/m<sup>3</sup>. Estimated intakes associated with inhalation exposure (predicted by computer modelling) during the use of consumer products containing methyl methacrylate, such as dispersion paints (estimated to be in the 10–100 : g/kg body weight per day range) and oil-based paints (predicted exposure in the 100–1000 : g/kg body weight per day range) (see section 6.2), may be up to an order of magnitude higher than the tolerable intake associated with exposure at the level of the tolerable concentration. Although it has been reported that in some countries these products are not supplied to the general public, information on use patterns of these products in other countries was not available.

With respect to occupational exposure, mean levels of methyl methacrylate in the air of production and manufacturing facilities and dental facilities range up to several hundred mg/m<sup>3</sup>, whereas levels in beauty salons are generally less than 100 mg/m<sup>3</sup> (IARC, 1994). Elevated levels (greater than 1500 mg/m<sup>3</sup>) during floor coating with methyl methacrylate-containing resins have been reported, although time-weighted-average concentrations would be less.

## 11.2 Evaluation of environmental effects

Because of its release principally in emissions from industrial sources and its relatively high volatility, the atmosphere is the predominant environmental sink for methyl methacrylate. It is highly reactive with hydroxyl radicals; thus, its lifetime in the atmosphere is short. Substances whose atmospheric half-lives do not exceed 1 year are not considered to contribute to global warming; therefore, methyl methacrylate is not considered to be a greenhouse gas, nor would it contribute directly to depletion of the ozone layer. Methyl methacrylate is not expected to bioconcentrate in the environment.

Terrestrial organisms will have the greatest potential for exposure to methyl methacrylate in ambient air. However, as no field or laboratory studies on birds, terrestrial invertebrates, or terrestrial plants were identified, the toxicity of methyl methacrylate to these organisms could not be assessed. Chronic studies on laboratory mammals are available, however, as well as data on levels of exposure of aquatic-based mammals to methyl methacrylate, thus permitting the comparison between effects and environmental exposure for these organisms. The mink was chosen as the model species, with aquatic organisms comprising up to 100% of its diet. Based on the concentrations of methyl methacrylate in air, water, and fish predicted by fugacity modelling and assuming daily consumption rates for mink of 0.55 m<sup>3</sup> of air, 0.1 litre of water, and 158 g of fish, the estimated total daily intake of methyl methacrylate by mink in southern Ontario, Canada, is 0.17 ng/kg body weight per day, with approximately 80% of the exposure being attributable to inhalation (Government of Canada, 1993). The lowest NOEL observed in chronic inhalation studies in laboratory animals is 102.5 mg/m<sup>3</sup>, based on exposure-related and concentration-dependent microscopic changes in anterior portions of the nasal cavity (degeneration/atrophy of the olfactory epithelium and underlying Bowman's glands, hyperplasia of basal cells, replacement of olfactory epithelium by respiratory epithelium, and inflammation of the mucosa and/or submucosa) (Rohm & Haas, 1979a; Lomax, 1992; Lomax et al., 1997). Using a factor of 10 to account for interspecies variability in sensitivity, the NOEL is 10<sup>8</sup> times higher than levels predicted to occur in the environment in Canada (i.e. 0.24 ng/m<sup>3</sup>).

No chronic studies on aquatic organisms were identified; however, acute tests have been conducted on fish, *Daphnia magna*, and algae. The most sensitive effect was the onset of inhibition of cell multiplication by the green alga *Scenedesmus quadricauda* at 37 mg/litre following 8 days of exposure. This is similar to the concentration (i.e. 40 mg/litre) at which sublethal/

behavioural responses were noted in rainbow trout following 96 hours of exposure. Using a factor of 20 to convert from an acute to a chronic end-point and another factor of 10 to account for interspecies variability in sensitivity, the estimated effects threshold is approximately  $10^6$ -fold higher than the concentration predicted to occur in surface water in Canada (i.e. 0.13 ng/litre).

Therefore, although available data on the environmental effects of methyl methacrylate are limited and predicted concentrations in various media are highly uncertain, a wide margin exists between observed effect levels and uncertain predicted environmental concentrations of methyl methacrylate. As such, the concentrations of methyl methacrylate predicted to be in the environment are unlikely to pose a risk to aquatic or terrestrial organisms.

## **12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES**

The International Agency for Research on Cancer (IARC, 1994) has classified methyl methacrylate in Group 3 (not classifiable as to its carcinogenicity to humans) based on inadequate evidence for carcinogenicity in humans and evidence suggesting a lack of carcinogenicity in experimental animals.

Information on international hazard classification and labelling is included in the International Chemical Safety Card reproduced in this document.

## **13. HUMAN HEALTH PROTECTION AND EMERGENCY ACTION**

Human health hazards together with preventative and protective measures and first aid recommendations are presented in the International Chemical Safety Card (ICSC 0300) reproduced in this document.

### **13.1 Human health hazards**

Methyl methacrylate is highly flammable. After long-term or repeated exposure, it may cause skin sensitization and asthma and may have effects on the nervous system.

### **13.2 Advice to physicians**

In the event of poisoning, the treatment is supportive. Owing to reports of systemic vasodilation and transient hypotension in patients following use of methyl methacrylate as a bone cement in total hip replacement procedures, monitoring for hypotension and respiratory depression is recommended. Because a stabilizer or inhibitor is always a part of the formulation, toxicological properties may be different.

### **13.3 Health surveillance advice**

Periodic medical examination of the area of the skin exposed to methyl methacrylate, tests to determine any disturbances of the nervous system, and surveillance of the respiratory system should be included in the health surveillance programme.

### **13.4 Explosion and fire hazards**

#### **13.4.1 Explosion hazards**

Methyl methacrylate is explosive in the form of vapour when exposed to heat, sparks, or flame. Vapours may travel to a source of ignition and flash back. Methyl methacrylate may undergo spontaneous, explosive polymerization. It reacts in air to form a heat-sensitive explosive product. Containers of methyl methacrylate may explode in the heat of a fire. Runoff to sewers may create a fire or explosion hazard.

#### **13.4.2 Fire hazards**

Methyl methacrylate is highly flammable material. When heated to decomposition, methyl methacrylate emits acrid smoke and irritating fumes.

#### **13.4.3 Fire-extinguishing agents**

Water may not be effective, except to absorb heat, keep containers cool, and protect exposed materials.

### **13.5 Storage**

Store in a cool, dry, well ventilated area, out of direct sunlight. Store away from heat and ignition sources and incompatible materials, such as flammable/combustible materials, materials that support combustion (oxidizing materials), and corrosive materials (strong acids or bases). If storing small quantities under refrigeration, use an approved, explosion-proof refrigerator. Methyl methacrylate monomer should not be stored for longer than 1 year.

### **13.6 Transport**

Methyl methacrylate cannot be carried on passenger or cargo aircraft.

### **13.7 Spillage**

Methyl methacrylate is highly flammable. In the event of spillage, eliminate all sources of ignition in the vicinity. Because the chemical is absorbed through the skin, do not touch or walk through the spilled material without proper equipment. To avoid the flammability hazard, remove clothing immediately if wet or contaminated, and use non-sparking tools to clean up. Do not let the chemical enter drains or watercourses.

## **14. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS**

Information on national regulations, guidelines, and standards is available from the International Register of Potentially Toxic Chemicals (IRPTC) legal file.

The reader should be aware that regulatory decisions about chemicals taken in a certain country can be fully understood only in the framework of the legislation of that country. The regulations and guidelines of all countries are subject to change and should always be verified with appropriate regulatory authorities before application.

**METHYL METHACRYLATE MONOMER, INHIBITED****0300**

March 1995

**CAS No: 80-62-6**  
 RTECS No: OZ5075000  
 UN No: 1247  
 EC No: 607-035-00-6

Methacrylic acid methyl ester  
 Methyl 2-methylpropenoate  
 $\text{CH}_2\text{C}(\text{CH}_3)\text{COOCH}_3$   
 Molecular mass: 100.1

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
<b>FIRE</b>	Highly flammable.	NO open flames, NO sparks, and NO smoking.	Foam, powder, carbon dioxide.
<b>EXPLOSION</b>	Vapour/air mixtures are explosive.	Closed system, ventilation, explosion-proof electrical equipment and lighting. Do NOT use compressed air for filling, discharging, or handling.	In case of fire: keep drums, etc., cool by spraying with water.

EXPOSURE		PREVENT GENERATION OF MISTS!	
<b>Inhalation</b>	Cough. Drowsiness. Headache. Shortness of breath. Sore throat. Unconsciousness.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
<b>Skin</b>	Redness.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse and then wash skin with water and soap.
<b>Eyes</b>	Redness. Pain.	Safety goggles 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.
<b>Ingestion</b>	Nausea. Vomiting.	Do not eat, drink, or smoke during work.	Rinse mouth. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent and remove to safe place. Do NOT wash away into sewer.	F Symbol Xi Symbol R: 11-36/37/38-43 S: (2-)9-16-29-33 Note: D UN Hazard Class: 3 UN Pack Group: II

EMERGENCY RESPONSE	STORAGE
Transport Emergency Card: TEC (R)-196 NFPA Code: H2; F3; R2;	Fireproof. Separated from strong oxidants, strong bases, strong acids. Cool. Keep in the dark. Keep in a well-ventilated room. Store only if stabilized.

## IMPORTANT DATA

**Physical State; Appearance**

COLOURLESS LIQUID, WITH CHARACTERISTIC ODOUR.

**Physical Dangers**

The vapour is heavier than air and may travel along the ground; distant ignition possible. The vapour mixes well with air, explosive mixtures are easily formed. Vapours are not inhibited, they may polymerize and block the vents.

**Chemical Dangers**

The substance may polymerize due to warming or due to heating under the influence of light, polymerization catalysts and strong oxidants with fire or explosion hazard. Reacts with strong acids, strong bases and oxidants.

**Occupational Exposure Limits**

TLV: 100 ppm; 410 mg/m<sup>3</sup> (as TWA) (ACGIH 1994-1995).  
MAK: 50 ppm; 210 mg/m<sup>3</sup>; I, A II (1993).

**Routes of Exposure**

The substance can be absorbed into the body by inhalation, through the skin and by ingestion.

**Inhalation Risk**

A harmful contamination of the air can be reached rather quickly on evaporation of this substance at 20°C.

**Effects of Short-term Exposure**

The substance irritates the eyes, the skin and the respiratory tract.

**Effects of Long-term or Repeated Exposure**

Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation exposure may cause asthma. The substance may have effects on the central nervous system and the peripheral nervous system.

## PHYSICAL PROPERTIES

Boiling point: 100-101°C  
Melting point: -48°C  
Relative density (water = 1): 0.94  
Solubility in water, g/100 ml at 20°C: 1.6  
Vapour pressure, kPa at 20°C: 3.9  
Relative vapour density (air = 1): 4.16

Relative density of the vapour/air-mixture at 20°C (air = 1): 1.1  
Flash point: 10°C o.c.  
Auto-ignition temperature: 421°C  
Explosive limits, vol% in air: 1.7-12.5  
Octanol/water partition coefficient as log Pow: 1.38

## ENVIRONMENTAL DATA

This substance may be hazardous to the environment; special attention should be given to water.

## NOTES

Usually contains hydroquinone, hydroquinone methyl ether and dimethyl t-butylphenol as inhibitors of polymerization. An added stabilizer or inhibitor can influence the toxicological properties of this substance, consult an expert.

## ADDITIONAL INFORMATION

## LEGAL NOTICE

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible for the use which might be made of this information

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## APPENDIX 1 — SOURCE DOCUMENTS

### Government of Canada (1993)

Copies of the *Canadian Environmental Protection Act* Priority Substances List Assessment Report (Government of Canada, 1993) and unpublished Supporting Documentation for methyl methacrylate may be obtained from the:

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

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

Initial drafts of the Assessment Report and unpublished Supporting Documentation for methyl methacrylate were prepared by staff of Health Canada and Environment Canada. The human health-related sections of this document were reviewed externally by Dr J. Siemiatycki (University of Quebec), Dr N. Krivanek (E.I. duPont de Nemours) (Supporting Documentation only), and the Information Department of BIBRA Toxicology International. These sections were approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health Canada. The environmental sections were reviewed externally by Dr N. Bunce (University of Waterloo) and Dr N. Krivanek (E.I. duPont de Nemours).

### IARC (1994)

Copies of *Some industrial chemicals* (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 60) (IARC, 1994) may be obtained from the:

International Agency for Research on Cancer  
150 cours Albert Thomas  
69372 Lyon Cedex 08  
France

The members of the Working Group on the Evaluation of Carcinogenic Risks to Humans of Some Industrial Chemicals (including methyl methacrylate), which met in Lyon on 15–22 February 1994, were:

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M. Sorsa, Institute of Occupational Health, Topeliuksenkatu 41 a A, 00250 Helsinki, Finland (*Vice-Chairperson*)

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## APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on methyl methacrylate 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:

Bundesinstitut für Gesundheitlichen Verbraucherschutz und Veterinärmedizin, Berlin, Germany

CEFIC, Brussels, Belgium

Department of Health, London, United Kingdom

Department of Public Health, Albert Szent-Gyorgyi University Medical School, Szeged, Hungary

Dirección General de Salud Ambiental, Subsecretario de Regulación y Fomento Sanitario, San Luis Potosí, Mexico

ECETOC, Brussels, Belgium

Guy's & St. Thomas' Hospital Trust, Medical Toxicology Unit, London, United Kingdom

International Agency for Research on Cancer, Lyon, France

Ministry of Health, National Centre of Hygiene, Medical Ecology and Nutrition, Sofia, Bulgaria

Ministry of Health and Welfare, International Affairs Division, Government of Japan, Tokyo, Japan

National Institute for Working Life, Solna, Sweden

National Institute of Public Health, Oslo, Norway

Russian Register of Potentially Hazardous Chemical and Biological Substances, Moscow, Russia

United States Department of Health and Human Services (National Institute of Environmental Health Sciences)

United States Environmental Protection Agency (Office of Pollution Prevention and Toxics; National Center for Environmental Assessment, Office of Research and Development; Office of Drinking Water)

## APPENDIX 3 — CICAD FINAL REVIEW BOARD

**Brussels, Belgium, 18–20 November 1996**

### Members

Dr A. Aitio, Institute of Occupational Health, Helsinki, Finland

Dr K. Bentley, Director, Environment Policy Section, Commonwealth Department of Human Services and Health, Canberra, Australia

Mr R. Cary, Toxicology and Existing Substances Regulation Unit, Health and Safety Executive, Merseyside, United Kingdom

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

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

Mr J.R. Hickman, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

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Professor S. Tarkowski, Department of Environmental Health Hazards, The Nofer Institute of Occupational Medicine, Lodz, Poland

Dr M. Wallen, National Chemicals Inspectorate (KEMI), Solna, Sweden

### **Observers**

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<sup>1</sup> Invited but unable to attend.

## RÉSUMÉ D'ORIENTATION

La Direction de l'Hygiène du Milieu de Santé Canada a rédigé ce CICAD (document international succinct sur l'évaluation des risques chimiques) relatif au méthacrylate de méthyle en s'inspirant principalement d'une étude menée par le Gouvernement du Canada (1993) pour évaluer les effets potentiels d'une exposition indirecte au méthacrylate de méthyle dans l'environnement général et les effets de cette substance sur l'environnement, ainsi que d'une étude du Centre international de Recherche sur le Cancer (CIRC, 1994), visant principalement à déterminer les risques de cancérogénicité. L'étude du Gouvernement du Canada (1993) a pris en compte les données qui étaient disponibles en mars 1992; ces données ont été mises à jour ultérieurement à la suite d'une recherche bibliographique approfondie menée en septembre 1995 dans des bases de données en ligne et dans le Registre international des substances chimiques potentiellement toxiques. Des informations concernant la nature de l'évaluation par les pairs et la disponibilité des études du Gouvernement du Canada (1993) et du CIRC (1994) figurent à l'appendice 1. Au cours de la phase d'évaluation par les pairs du présent CICAD, d'autres travaux ont été pris en compte, à savoir des projets d'études du United Kingdom Health Safety Executive (Cary et al., 1995) et de l'Union européenne (Draft Assessment on Methyl Methacrylate), ainsi que des études publiées par l'ECETOC (1995) et le Bureau consultatif finlandais des substances chimiques (1992), principalement en vue de rechercher des informations supplémentaires pertinentes. Des informations supplémentaires identifiées lors des examens pratiqués par les correspondants et par le Comité d'évaluation finale ont également été incorporées. L'appendice 2 contient des informations sur le processus d'évaluation par les pairs du présent CICAD. Ce CICAD a été approuvé pour publication à une réunion du Comité d'évaluation finale qui s'est tenue à Bruxelles (Belgique) du 18 au 20 novembre 1996. La liste des participants à cette réunion figure à l'appendice 3. La fiche d'information sur la sécurité chimique du méthacrylate de méthyle (ICSC 0300), préparée par le Programme international sur la Sécurité chimique (IPCS, 1993), est également reproduite dans le présent document.

Le méthacrylate de méthyle (CAS N/ 80-62-6) est un produit chimique de synthèse volatil, utilisé principalement dans la production de feuilles acryliques moulées, d'émulsions acryliques et de résines pour moulage et extrusion. Des polymères et copolymères de méthacrylate de méthyle entrent dans la composition de nombreux produits: revêtements de surfaces, adhésifs, produits d'étanchéité, enduits pour cuirs et papiers, encres, encaustiques, apprêts pour textiles, prothèses

dentaires, ciments pour chirurgie osseuse, écrans anti-radiations au plomb, ongles artificiels, semelles orthopédiques, etc. Selon les calculs, la plus grande partie du méthacrylate de méthyle devrait être émise dans l'atmosphère, les quantités émises dans l'eau et le sol étant minimales. Le méthacrylate de méthyle ne persiste pas longtemps dans l'atmosphère et il est admis qu'il ne contribue pas directement à la destruction de la couche d'ozone. Il ne devrait pas subir de bioconcentration dans l'environnement et l'inhalation est probablement la principale voie d'exposition pour l'homme.

Le méthacrylate de méthyle est rapidement absorbé et distribué dans l'organisme après inhalation ou administration par voie orale aux animaux d'expérience. Les données concernant l'absorption après exposition cutanée sont limitées. Le méthacrylate de méthyle est rapidement métabolisé en acide méthacrylique, aussi bien chez l'animal que chez l'homme. Chez le rat, 16 à 20 % du produit inhalé se dépose dans les voies respiratoires supérieures, où il est surtout métabolisé par les estérases tissulaires locales.

La toxicité aiguë du méthacrylate de méthyle est faible. On a observé une irritation de la peau, des yeux et des fosses nasales chez des rongeurs et des lapins exposés à des concentrations relativement élevées. Il se révèle légèrement sensibilisant pour la peau des animaux. L'effet le plus souvent observé après inhalation répétée de faibles doses est une irritation des fosses nasales. Des effets ont également été signalés sur les reins et le foie à des concentrations plus élevées. La plus faible concentration suivie d'effet (dégénérescence inflammatoire de l'épithélium nasal) a été de 410 mg/m<sup>3</sup> chez des rats exposés pendant 2 ans; dans cette étude, la dose sans effet observé (NOEL) a été évaluée à 100 mg/m<sup>3</sup> environ.

Une étude de qualité menée sur des rats n'a révélé aucun effet sur le développement, malgré une diminution du poids des mères après inhalation de concentrations allant jusqu'à 8315 mg/m<sup>3</sup>. Les seules autres données disponibles en ce qui concerne les effets sur le développement sont les résultats d'études limitées, anciennes ou peu documentées, faisant état d'une fœtotoxicité à des concentrations qui, lorsqu'elles étaient mentionnées, étaient toxiques pour la mère. Les données relatives aux effets du méthacrylate de méthyle sur la reproduction sont limitées. Il n'y a pas eu de baisse de la fécondité dans un test de létalité dominante chez des souris exposées à des concentrations atteignant 36 900 mg/m<sup>3</sup> et aucun effet indésirable n'a été observé sur les organes de la reproduction dans les études menées jusqu'ici avec des doses répétées. Les données disponibles sur la neurotoxicité du méthacrylate de méthyle sont également limitées; on a observé une dégradation de l'activité locomotrice, de la capacité

d'apprentissage et du comportement, ainsi que des effets biochimiques sur le cerveau de rats exposés par voie orale à une dose de 500 mg/kg de poids corporel par jour pendant 21 jours.

Le méthacrylate de méthyle ne s'est pas révélé cancérigène dans une étude approfondie et bien documentée de 2 ans au cours de laquelle des rats et des souris ont été exposés par inhalation, ni dans une autre étude d'inhalation chronique menée sur des rats et des hamsters. *In vitro*, le méthacrylate de méthyle n'est pas mutagène dans les systèmes bactériens, mais il s'est révélé mutagène et clastogène dans des cellules mammaliennes. Dans les études *in vivo* (principalement les études d'inhalation) qui ont clairement démontré la toxicité du méthacrylate de méthyle pour les tissus cibles, on trouve également quelques indices de génotoxicité.

Le méthacrylate de méthyle est légèrement irritant pour la peau de l'homme et il peut induire une sensibilisation cutanée chez des individus prédisposés. Bien que l'on ait également signalé des cas d'asthme professionnel liés au méthacrylate de méthyle, il n'est pas prouvé de façon concluante que cette substance soit un sensibilisant des voies respiratoires. Dans l'ensemble, les études épidémiologiques disponibles n'apportent pas de preuve convaincante d'un effet cancérigène chez l'homme, mais on ne peut pas en déduire non plus avec quelque certitude que l'exposition au méthacrylate de méthyle n'entraîne aucun risque supplémentaire.

Le méthacrylate de méthyle est peu toxique pour les organismes aquatiques. Aucune étude de toxicité chronique portant sur ce type d'organismes n'a été retrouvée, mais des épreuves de toxicité aiguë ont été effectuées sur des poissons, sur *Daphnia magna* et sur des algues. L'effet le plus sensible a été l'inhibition de la multiplication cellulaire chez l'algue verte *Scenedesmus quadricauda* après 8 jours d'exposition à la concentration de 37 mg/litre. La valeur la plus faible de CE<sub>50</sub> à 24 heures pour l'immobilisation des *Daphnia* est de 720 mg/litre. La CL<sub>50</sub> à 96 heures pour le poisson *Lepomis macrochirus*, en conditions de renouvellement continu, était de 191 mg/litre, tandis que les CL<sub>50</sub> pour des durées de 1 à 24 heures allaient de 420 à 356 mg/litre. La CL<sub>50</sub> à 96 heures pour la truite arc-en-ciel (*Oncorhynchus mykiss*) en conditions de renouvellement continu était supérieure à la plus forte concentration testée, soit 79 mg/litre. Des réactions sublétales/comportementales ont été notées chez des poissons à 40 mg/litre.

Les données disponibles chez l'homme sont jugées insuffisantes pour servir de base principale au calcul d'une valeur guide; on a donc établi une concentration tolérable sur la base de la dégénérescence inflam-

matoire de l'épithélium nasal observée chez des rats exposés pendant 2 ans à une concentration de 410 mg/m<sup>3</sup>. Dans cette étude, la NOEL était d'approximativement 100 mg/m<sup>3</sup>. Les données pouvant servir à évaluer l'exposition indirecte dans l'environnement général ou l'exposition des consommateurs sont extrêmement limitées. La concentration tolérable calculée (probablement avec une certaine marge de sécurité), qui est d'environ 0,2 mg/m<sup>3</sup>, est supérieure de plusieurs ordres de grandeur aux quelques prédictions qui ont été faites des concentrations atmosphériques de méthacrylate de méthyle dans l'environnement général. Le niveau d'exposition par inhalation auquel on peut s'attendre du fait de l'utilisation de peintures dispersables ou de peintures à l'huile contenant du méthacrylate de méthyle est peut-être supérieur d'un ordre de grandeur à la dose qu'entraînerait une exposition à la concentration tolérable, encore que dans certains pays ces produits ne soient pas destinés au grand public. Aucun renseignement n'a été trouvé sur leurs conditions d'utilisation dans d'autres pays. Une dose journalière tolérable (DJT) de 1,2 mg/kg de poids corporel par jour a été calculée sur la base d'une étude de toxicité chronique par voie orale.

Bien que les données disponibles au sujet des effets du méthacrylate de méthyle sur l'environnement soient limitées et que les concentrations prévues dans divers milieux soient très incertaines, il existe une marge considérable entre les concentrations suivies d'effets avérés et les concentrations prévues de façon approximative dans l'environnement.

## RESUMEN DE ORIENTACIÓN

Esta reseña de la evaluación química internacional del metacrilato de metilo fue preparada por la Dirección de Higiene del Medio de Health Canada y se basó principalmente en un examen realizado por el Gobierno del Canadá (1993) para evaluar los efectos potenciales sobre la salud humana de la exposición indirecta a dicha sustancia en el medio ambiente general, así como sus efectos ambientales, y en un examen del Centro Internacional de Investigaciones sobre el Cáncer (CIIC, 1994) centrado principalmente en la identificación de riesgos de carcinogenicidad. En el examen del Gobierno del Canadá (1993) se tuvieron presentes los datos obtenidos en marzo de 1992, actualizados posteriormente sobre la base de una amplia búsqueda bibliográfica realizada en septiembre de 1995 en las bases de datos en línea y el Registro Internacional de Productos Químicos Potencialmente Tóxicos. En el apéndice 1 se presenta información sobre la naturaleza de la revisión científica y sobre los exámenes del Gobierno del Canadá (1993) y del CIIC (1994). Durante la fase de revisión científica de esta reseña se tomaron en consideración otros exámenes provisionales de la Dirección de Salud y Seguridad del Reino Unido (Cary et al., 1995) y de la Unión Europea (Evaluación Provisional del Metacrilato de Metilo), así como exámenes ya publicados del ECETOC (1995) y de la Junta Consultiva Finlandesa de Sustancias Químicas (1992), con miras principalmente a obtener información adicional pertinente para la revisión. También se ha incorporado la información adicional identificada durante la revisión efectuada por los puntos de contacto y el examen realizado por el Comité de Revisión Final. La información relativa a la revisión científica de la presente reseña figura en el apéndice 2. La publicación de esta reseña fue aprobada en una reunión del Comité de Revisión Final celebrada en Bruselas (Bélgica) del 18 al 20 de noviembre de 1996. La lista de participantes en la reunión del Comité de Revisión Final figura en el apéndice 3. También se ha reproducido en este documento la ficha internacional de seguridad química para el metacrilato de metilo (ICSC 0300), emitida por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993).

El metacrilato de metilo (Nº CAS 80-62-6) es una sustancia química sintética y volátil que se utiliza principalmente en la producción de hojas acrílicas fraguadas, emulsiones acrílicas y resinas moldeadas y extruidas. Los polímeros y copolímeros de metacrilato de metilo también se utilizan en los revestimientos de exterior con base acuosa, con base disolvente y sin diluir, en adhesivos, selladores, revestimientos de cuero y de papel, tintas, ceras para suelos, aprestos textiles, prótesis dentales, cementos quirúrgicos fosfatados y pantallas acrílicas emplomadas contra la radiación, así

como en la preparación de uñas sintéticas y separadores ortóticos para zapatos. La mayor parte de las emisiones del metacrilato de metilo se producen en el aire, liberándose en muy pequeñas cantidades en el agua y en el suelo. Su persistencia en la atmósfera es corta y no se considera que contribuya directamente al agotamiento de la capa de ozono. No parece que se bioconcentre en el medio ambiente y su inhalación con el aire probablemente sea la principal vía de exposición humana.

El metacrilato de metilo tiene una absorción y distribución rápidas en animales de experimentación, tras su inhalación o administración por vía oral. Los datos de que se dispone sobre su absorción tras una exposición cutánea son limitados. Tanto en animales de experimentación como en seres humanos, el metacrilato de metilo se metaboliza rápidamente en ácido metacrílico. Tras su inhalación, el 16–20% de la sustancia química se deposita en las vías respiratorias altas de las ratas, donde principalmente es metabolizada por las esterasas del tejido local.

El metacrilato de metilo tiene una toxicidad aguda baja. En los roedores y conejos expuestos a concentraciones relativamente altas se han observado irritaciones cutáneas, oculares y de la cavidad nasal. Esta sustancia química es un sensibilizador cutáneo ligero en los animales. El efecto observado con mayor frecuencia tras una exposición repetida por inhalación en su concentración más baja es la irritación de la cavidad nasal. También se han señalado efectos en el riñón y el hígado con concentraciones más altas. El nivel mínimo de inhalación con efectos comunicados fue de 410 mg/m<sup>3</sup> en las ratas expuestas a metacrilato de metilo durante dos años (basado en la degeneración inflamatoria del epitelio nasal); el nivel sin efectos observados (NOEL) en esta investigación fue de aproximadamente 100 mg/m<sup>3</sup>.

En un estudio bien llevado sobre ratas no se observaron efectos en el desarrollo, aunque se produjeron disminuciones en el peso corporal materno tras la inhalación de concentraciones de hasta 8315 mg/m<sup>3</sup>. Los demás datos de que se dispone sobre la toxicidad para el desarrollo se limitan a los resultados de un número reducido de estudios precoces o mal documentados en los que se observaron efectos fetotóxicos con concentraciones (cuando se comunicaron) que resultaron tóxicas para las madres. Se dispone de pocos datos sobre los efectos del metacrilato de metilo en la reproducción. No hubo disminución de la fecundidad en una valoración de dominancia letal en ratones expuestos a concentraciones de hasta 36 900 mg/m<sup>3</sup> ni se observaron efectos negativos sobre los órganos reproductores en los estudios de administración repetida realizados hasta la fecha. Se dispone de pocos datos sobre la neurotoxicidad del metacrilato de metilo; se observaron una disminución de la actividad locomotora

y efectos a nivel de aprendizaje, de comportamiento y bioquímico en el cerebro, en ratas expuestas por vía oral a 500 mg/kg de peso corporal al día durante 21 días.

El metacrilato de metilo no resultó carcinógeno en una amplia biovaloración bien documentada de dos años realizada en ratas y ratones expuestos por inhalación, ni en otros estudios de inhalación crónica realizados en ratas y hámsters. Aunque no es mutagénico en los sistemas bacterianos *in vitro*, ha resultado mutagénico y clastogénico en las células de mamíferos *in vitro*. En los estudios *in vivo* (principalmente por inhalación) en los que ha habido pruebas claras de toxicidad en el tejido diana, ha habido pocos indicios de la genotoxicidad del metacrilato de metilo.

En los seres humanos, el metacrilato de metilo es un irritante cutáneo ligero y puede inducir sensibilización cutánea en las personas con predisposición. Aunque también se han señalado casos de asma profesional asociados a dicha sustancia, no existen pruebas concluyentes de que el metacrilato de metilo sea un sensibilizador respiratorio. En general, los estudios epidemiológicos disponibles no ofrecen indicios firmes ni sistemáticos de un efecto carcinogénico del metacrilato de metilo en ningún órgano diana en los seres humanos, pero tampoco se puede inferir con algún grado de confianza que se haya descartado la posibilidad de un exceso de riesgo.

El metacrilato de metilo tiene una toxicidad baja en organismos acuáticos. Aunque no se identificaron estudios de toxicidad crónica en organismos acuáticos, se han realizado pruebas de toxicidad aguda en *Daphnia magna* y en algas. El efecto más sensible fue el comienzo de la inhibición de la multiplicación celular en el alga verde *Scenedesmus quadricauda*, con niveles de 37 mg/litro tras ocho días de exposición. La CE<sub>50</sub> de inmovilización más baja notificada a las 24 horas para *Daphnia* es de 720 mg/litro. La CL<sub>50</sub> a las 96 horas en juveniles de *Lepomis macrochirus* en condiciones de flujo continuo fue de 191 mg/litro, mientras que los valores de la CL<sub>50</sub> para periodos de 1 a 24 horas oscilaron entre 420 y 356 mg/litro, respectivamente. La CL<sub>50</sub> a las 96 horas para la trucha arco iris (*Oncorhynchus mykiss*) en condiciones de flujo continuo fue >79 mg/litro, la concentración más alta probada. Se observaron respuestas subletales/comportamentales en los peces, con niveles de 40 mg/litro.

Los estudios de que se dispone en seres humanos se consideran inadecuados como base principal para establecer un valor orientativo; por consiguiente, a modo de orientación, se ha establecido una concentración tolerable sobre la base de la degeneración inflamatoria del epitelio nasal de las ratas expuestas a concentraciones de 410 mg/m<sup>3</sup> durante dos años. La

concentración sin efectos observados en esta investigación fue de aproximadamente 100 mg/m<sup>3</sup>. Los datos de que se dispone para establecer una base para la estimación de la exposición indirecta en el medio ambiente general y de la exposición en los usuarios son muy limitados. La concentración tolerable obtenida (probablemente moderada) de aproximadamente 0,2 mg/m<sup>3</sup> es muchos órdenes de magnitud más elevada que las concentraciones previstas de la muestra de metacrilato de metilo en el aire ambiente del medio ambiente general. La exposición por inhalación prevista por el uso de pinturas de dispersión y al aceite que contienen metacrilato de metilo puede ascender a un orden de magnitud superior a la ingesta tolerable asociada con la exposición al nivel de concentración tolerable, si bien se ha notificado que en algunos países esos productos no se suministran al público en general. No se obtuvo información sobre las modalidades de utilización de estos productos en otros países. Sobre la base de un estudio de toxicidad crónica realizado por vía oral, se ha determinado una ingesta diaria tolerable (IDT) de 1,2 mg/kg de peso corporal al día.

Si bien los datos de que se dispone sobre los efectos ambientales del metacrilato de metilo son limitados y los valores pronosticados en distintos medios son muy inciertos, existe un amplio margen entre los niveles con efectos observados y las concentraciones ambientales de pronóstico incierto.