

PRIORITY SUBSTANCES LIST  
ASSESSMENT REPORT

METHYL METHACRYLATE

Government of Canada  
Environment Canada  
Health and Welfare Canada

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*Liste des substances d'intérêt prioritaire*  
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## Synopsis

Methyl methacrylate (MMA) is not produced in Canada, but is imported for use in manufacturing cast acrylic sheet, acrylic emulsions, and molding and extrusion resins. Although data on concentrations of methyl methacrylate in the environment are not available, concentrations of MMA in various media to which humans and other organisms may be exposed have been predicted on the basis of modelling.

Exposure of aquatic organisms was estimated from the predicted concentration of methyl methacrylate in surface water. This exposure is considerably less (by about 1 000 000 times) than levels estimated to cause effects in algae and fish. Based on predicted concentrations of methyl methacrylate in air, water, and fish, the total average daily intake for wild mink was estimated. This estimate is also considerably less (by about 100 000 000 times) than the levels causing effects in chronic inhalation studies on mammals.

Because of the short persistence of methyl methacrylate in the troposphere (a few hours to a few days) and its predicted low concentrations, it is not considered to be associated with depletion of stratospheric ozone or with global warming.

Based on predicted concentrations of methyl methacrylate in ambient air, water, soil, and fish, the total average daily intakes of MMA have been estimated for various age groups in the general population. These estimates are considerably less (by approximately 200 000 times) than the intake to which it is believed that a person can be exposed over a lifetime without deleterious effects, i.e., the Tolerable Daily Intake derived on the basis of data from bioassays in animal species.

**Based on these considerations, the Minister of the Environment and the Minister of National Health and Welfare have concluded that the predicted concentrations of methyl methacrylate in the Canadian environment do not constitute a danger to the environment, or to the environment on which human life depends, or to human life or health. Therefore, methyl methacrylate is not considered to be "toxic" as defined under Section 11 of the *Canadian Environmental Protection Act*.**

## 1.0 Introduction

The *Canadian Environmental Protection Act* (CEPA) requires the Minister of the Environment and the Minister of National Health and Welfare to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents, and wastes that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances to determine whether they are "toxic" as defined under Section 11 of the Act which states:

"...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions:

- (a) having or that may have an immediate or long-term harmful effect on the environment;
- (b) constituting or that may constitute a danger to the environment on which human life depends; or
- (c) constituting or that may constitute a danger in Canada to human life or health."

Substances that are assessed as "toxic" according to Section 11 may be placed on Schedule I of the Act. Consideration can then be given to developing regulations, guidelines, or codes of practice to control any aspect of these substances' life cycle, from the research and development stage through manufacture, use, storage, transport, and ultimate disposal.

The assessment of whether methyl methacrylate (MMA) is "toxic", as defined under CEPA, was based on the determination of whether it **enters** or is likely to enter the Canadian environment in a concentration or quantities or under conditions that could lead to **exposure** of humans or other biota at levels that could cause adverse **effects**.

To identify the toxicological and environmental data relevant to the preparation of the Supporting Document, literature searches were conducted on the following computerized databases: Hazardous Substances Data Bank (HSDB), Registry of Toxic Effects of Chemical Substances (RTECS), Chemical Carcinogenesis Research Information System (CCRIS) (1991), Toxline (1981 to 1991), Toxlit (1989 to 1991, only), Chemistry Abstracts (1967 to 1991), Biological Abstracts (1969 to 1991), National Technical Information Service (NTIS) (1964 to 1989), Pollution and Toxicology Database (POLTOX) (1987 to 1992), Pollution Abstracts (1978 to 1989), and International Register of Potentially Toxic Chemicals (IRPTC), DIALOG, and Environmental Bibliography (to 1989). Other sources of information were identified through FATERATE (1989) and Chemical Evaluation Search and Retrieval System (CESARS) (1988). For toxicological data, searches were also conducted of the three most recent monthly editions of CURRENT CONTENTS.

To identify data relevant to the estimation of exposure of the general population to methyl methacrylate, the following databases were searched: Environment Canada Departmental Library Catalogue (Elias) (1991), AQUAREF (1970 to 1991), Canadian Research Index (MICROLOG) (1979 to 1991), Cooperative Documents Project (CODOC) (1991).

For assessment of data other than those considered to be critical for determination of whether MMA is "toxic" to the environment or human health under the Act, existing evaluations, such as those of the United States Environmental Protection Agency (U.S. EPA, 1985) and the International Agency for Research on Cancer (IARC, 1979), have been consulted where considered appropriate. The Methacrylate Producers Association also provided a report entitled "Methyl Methacrylate: A Toxicology Review" (MPA, 1991) for consideration in the preparation of the Supporting Document. Unvalidated studies of Industrial Biotest (IBT) Laboratories have been cited but not used directly in the assessment of "toxic" under CEPA.

Information was also sought from the following agencies:

- World Health Organization, Geneva, Switzerland;
- Dutch Expert Committee for Occupational Standards, Netherlands;
- Department of Toxic Substances, Ministry of Social Affairs and Employment, Netherlands;
- International Agency for Research on Cancer, Lyon, France;
- European Chemicals Industry Ecology and Toxicology Centre, Brussels, Belgium;
- Norwegian State Pollution Control Authority, Oslo, Norway; and
- United States Environmental Protection Agency (U.S. EPA).

Data relevant to the assessment of whether MMA is "toxic" to human health obtained after the completion of human health-related sections of this report (i.e., September 1992) were not considered for inclusion. Similarly, data relevant to the assessment of whether MMA is "toxic" to the environment obtained after the completion of these sections of the report (i.e., March 1992) were not considered for inclusion.

Although review articles were consulted where considered appropriate, all original studies relevant to the assessment of whether MMA is "toxic" under Section 11 of CEPA have been critically evaluated by the following Health and Welfare staff (human exposure and effects on human health) and Environment Canada staff (entry, and environmental exposure and effects):

Environment Canada

K.M. Lloyd

Health and Welfare

P.K.L. Chan

M.E. Meek

F. Wandelmaier

The human health-related sections of the Supporting Document and/or Assessment Report were reviewed externally by Dr. J. Siemiatycki, University of Quebec; Dr. N.D. Krivanek, E.I. du Pont de Nemours, Delaware (Supporting Document only), and British Industrial Biological Research Association (BIBRA) Toxicology International. These sections were then approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health and Welfare Canada. As part of the review and approvals process established by Environment Canada, the environmental portions of the Assessment Report and Supporting Document were reviewed by Dr. N. Bunce, University of Guelph and Dr. N.D. Krivanek, E.I. du Pont de Nemours. The final Assessment Report was reviewed and approved by the Environment Canada/Health and Welfare Canada CEPA Management Committee.

In this report, a Synopsis is presented which will appear in the Canada Gazette. An extended summary of technical information that is critical to the assessment is presented in Section 2.0. This information is presented in greater detail in a Supporting Document which is available upon request. The assessment of whether MMA is "toxic" under CEPA is presented in Section 3.0.

Copies of this Assessment Report and the unpublished Supporting Document are available upon request from:

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Hull, Quebec  
K1A 0H3

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## 2.0 Summary of Information Critical to Assessment of "Toxic"

### 2.1 Identity, Properties, Production, and Uses

Methyl methacrylate ( $C_5H_8O_2$ ) is a colourless, volatile liquid with an acrid, fruity odour. It has a relatively high vapour pressure (4000 Pa at 20°C), moderate water solubility (15 800 mg/L), and a low log octanol:water partition coefficient ( $K_{ow}$ ) (1.38) (ACGIH, 1986; Dean, 1985; Tanii and Hashimoto, 1982). Methyl methacrylate is manufactured commercially using the acetone cyanohydrin process. Common analytical methods used to quantify and qualify acrylic compounds include gas chromatography (GC) (Shen and Woo, 1988); mass spectrometry (MS) (Gjos *et al.*, 1983); GC/MS (Horna *et al.*, 1986); nuclear magnetic resonance (NMR) (Shen and Woo, 1988); and infrared spectroscopy (O'Neill and Christensen, 1975).

Methyl methacrylate is not known to occur naturally and is not produced in Canada. Methyl methacrylate used in Canada is imported primarily from the United States. In 1988, Canada imported 20.11 kilotonnes from the United States and minor amounts from the United Kingdom (0.14 kilotonnes) and West Germany (0.04 kilotonnes). The amount of MMA forecast to be imported in 1993 is 24 kilotonnes (CPI, 1989).

Methyl methacrylate polymerizes easily, especially when heated or in the presence of hydrochloric acid. The polymer forms clear, ceramic-like resins and plastics, commonly known as Plexiglas and Lucite. In Canada, MMA is used captively in the production of cast acrylic sheet, acrylic emulsions, and molding and extrusion resins. Demand for these products increased sharply in the early 1980s but has moderated recently. Its use is expected to increase by 3 to 4% by 1993 (CPI, 1989).

### 2.2 Entry into the Environment

Methyl methacrylate can enter the environment during transport, bulk storage, and use. Data on emissions of MMA in Canada have not been identified. Estimates from the United States Toxic Chemical Release Inventory on the emissions to air, water, and soil from plants in the United States correspond to about 0.46% of production (TRI, 1989). Most emissions, i.e., 98%, were estimated to be to air, with very small amounts to water and soil. Assuming the same level of emissions in Canada and Canadian imports of 22 kilotonnes, it is estimated that 100 000 kg/yr or 11.4 kg/h are emitted into the Canadian environment. The major importers of MMA in Canada are located in Morrisburg and Niagara Falls, Ontario; therefore, releases from its use in manufacturing cast acrylic sheet, and molding and extrusion resins are expected to occur in southern Ontario.

## 2.3 Exposure-related Information

### 2.3.1 Fate

The environmental fate of MMA is determined by the rates of photolysis, hydrolysis, volatilization, and biotic degradation, as well as adsorption to sediment and soil, and bioconcentration by aquatic organisms. The significance of each of these factors is discussed in this subsection.

No data were available on the photolysis rates of MMA; however, because the ultraviolet/visible absorption maximum is 231 nm, MMA should not absorb radiation >290 nm (the radiation reaching the earth's surface) and photolyze. Free radicals formed in natural waters by the action of light might react with MMA; however, environmentally pertinent data are limited in this area. Because MMA is highly reactive with hydroxyl radicals, its lifetime in the atmosphere is short. The estimated half-life of MMA in the troposphere at a latitude such as that of Toronto will vary from <5 hours in summer to a few days in winter (Bunce, 1992). The reported photo-oxidation half-life of MMA is 1.1 to 9.7 hours (Howard *et al.*, 1991). Methyl methacrylate is readily polymerized by light and heat (Hawley, 1981).

Hydrolysis, which is base-catalyzed, is not significant at neutral and acidic pH. Based on the measured second order hydrolysis rate constant of  $200/(M \cdot h)$  at 25°C and pH 11 (Ellington *et al.*, 1987), the hydrolysis half-life of MMA is estimated to be 3.9 years at pH 7 and 14.4 days at pH 9 (Howard, 1989).

No field or laboratory data were identified on the rate of volatilization. Based on the Henry's Law constant, the half-life for evaporation from a river 1-metre deep with a 1 m/s current and 3 m/s wind is calculated to be 6.3 hours. Because of the high vapour pressure of MMA and its weak adsorption to soil, evaporation from soil is expected to be rapid (Howard, 1989).

Several studies have shown that MMA can be biodegraded. The aqueous aerobic degradation half-life is estimated to be 1 to 4 weeks and the anaerobic degradation half-life to be 4 to 16 weeks (Howard *et al.*, 1991).

No data were identified on the adsorption of MMA to soil or sediment. From the log  $K_{ow}$ , the log  $K_{oc}$  is calculated to range from 1.17 to 2.13 (depending on the relationship to log  $K_{ow}$  chosen) which indicates that little adsorption to soil or sediment should occur. Although no studies have been conducted to measure the bioconcentration factor (BCF) for MMA, based on the equation by Veith *et al.* (1979) (which estimates BCF from the log  $K_{ow}$ ), the BCF is about 3. Methyl methacrylate is therefore not expected to bioconcentrate or biomagnify in food chains.

### 2.3.2 Concentrations

No information was found in the literature on MMA levels in any environmental medium in Canada. In a study conducted in Atlantic Canada to detect organic and

inorganic contaminants in edible shellfish, MMA was not detected [detection limit (D.L.) = 0.01 µg/g wet weight (w.w.)] in any of the 30 assayed samples from various locations (Environment Canada, 1989).

In a database containing 5700 entries on the frequency of organic compounds identified in water in the United States, MMA was listed four times, once in river water and three times in drinking water (Shackelford and Keith, 1976). One of the drinking water listings was a result of analyses of 204 water samples collected from 14 heavily industrialized river basins in the United States (Ewing and Chian, 1977). Methyl methacrylate was detected (D.L. = 1 µg/L) only once in the survey (10 µg/L in final tap water after chlorination in Chicago). It is not known how valid this number is as no additional information was provided.

Due to the lack of identified data, the environmental fate and concentrations of MMA were predicted using a Level III Fugacity Model (Mackay and Paterson, 1991; 1981; 1982; and Mackay *et al.*, 1985) based on the physical and chemical properties of the substance, its transformation half-lives, and emission rates (Mackay *et al.*, 1992). The following assumptions were included:

- MMA is used and emitted only in southern Ontario, in an area of approximately 170 000 km<sup>2</sup>;
- 95%, 4.5%, and 0.5% of emissions were to air, water, and soil, respectively; and
- total emissions were 100 000 kg/yr or 11.4 kg/h (see Subsection 2.2).

The following environmental concentrations were predicted:

- $2.44 \times 10^{-4}$  µg/m<sup>3</sup> in air;
- 0.13 ng/L in surface water;
- $1.2 \times 10^{-6}$  µg/g in soil;
- $8.7 \times 10^{-8}$  µg/g in sediment; and
- $1.5 \times 10^{-7}$  µg/g in fish.

The environmental persistence was estimated to be about one day.

The MMA monomer may be present in food as a result of migration from food wrap made from polymethyl methacrylate. However, quantitative data on concentrations of MMA in food have not been identified. Migration of MMA from bone cement into prepared tissue media has also been reported in a limited study (IARC, 1979).

## 2.4 Effects-related Information

### 2.4.1 Experimental Animals and In Vitro

In all species studied, the acute toxicity of MMA was low, though in some cases, effects have been observed at the site of entry (i.e., the lungs after inhalation) after short periods of exposure to relatively low concentrations. [Indeed, intra-alveolar congestion/hemorrhage, pulmonary vasodilation, and edema were observed in rats exposed to concentrations as low as 100 ppm of MMA for 2, 3, or 4 hours (Raje *et al.*, 1985)]. Inhalation of high concentrations of MMA for brief periods resulted in significant changes in pulmonary function, edema, hemorrhage, and congestion in the lung, irritation of the eye and mucous membranes, prostration and narcosis with death in 24 hours (Deichmann, 1941; Spealman *et al.*, 1945; McLaughlin *et al.*, 1973; Mir *et al.*, 1974; Tansy *et al.*, 1980a; Raje *et al.*, 1985; U.S. EPA, 1985). The 4-hour LC<sub>50</sub>s for MMA in rats ranged from 3750 to 7093 ppm (15 375 to 29 080 mg/m<sup>3</sup>) (Kennedy and Graepel, 1991; Tansy *et al.*, 1980a) and the 8-hour LC<sub>50</sub>s were 4634 ppm (19 000 mg/m<sup>3</sup>) in rats, rabbits, and guinea pigs (U.S. EPA, 1985). The oral LD<sub>50</sub>s ranged from 5.0 mL/kg (4.7 g/kg) in dogs to 10.0 mL/kg (9.44 g/kg) in rats (Spealman *et al.*, 1945). The signs of toxicity following oral administration included decreased respiration, loss of reflexes, coma, corrosion of the stomach walls, and liver and kidney degeneration (Deichmann, 1941; Spealman *et al.*, 1945).

In short-term, repeated-dose studies, death, decreases in body weight, cardiovascular effects, changes in respiration rate, increases in level of blood urea nitrogen, and pulmonary damage were observed after exposure to high concentrations of MMA. Mice were found to be more susceptible than rats; effects on the respiratory tract of mice were observed at the lowest tested concentration of 500 ppm (2050 mg/m<sup>3</sup>) for 10 days [IBT for NTP (1986)]. Histopathological effects were limited to those at the site of entry (i.e., the lung in inhalation studies). Renal effects were also reported in rats which were administered MMA by subcutaneous injection for 34 days, though available data in the published account of this study were inadequate for evaluation (Miller *et al.*, 1982).

Gross or microscopic pathological effects reported in long-term, repeated-dose studies in rats, mice, and dogs are limited. In most studies conducted to date, animals have been exposed to MMA by inhalation; the effects most commonly observed in these investigations were decreases in body weight gain and irritation of the skin, nasal cavity, and eye at high concentrations [generally greater than or equal to 500 ppm (2050 mg/m<sup>3</sup>)] [IBT for Rohm and Haas (1977a); IBT and Batelle Northwest for NTP (1986)]. Other effects on the kidney, such as renal cortical necrosis and tubular degeneration, and liver necrosis have also been reported (Tansy *et al.*, 1980b; NTP, 1986; Deichmann-Gruebler and Read, 1989). On the basis of decreases in final mean body weight and squamous metaplasia at the site of entry (i.e., the lung), the lowest reported "no-observed-effect-levels"(NOELs) and "lowest-observed-effect-levels" (LOELs) in a subchronic inhalation bioassay in which several dose levels were administered were 250 and 500 ppm (1025 and 2050 mg/m<sup>3</sup>) in mice, respectively

[IBT for Rohm and Haas (1977a); IBT and Batelle Northwest for NTP (1986)]. With the exception of effects at the site of entry, histopathological effects have not been observed in the two most extensive bioassays in rats at concentrations less than or equal to 1000 ppm (4100 mg/m<sup>3</sup>) [IBT for Rohm and Haas (1977a); IBT and Batelle Northwest for NTP (1986)]. In less extensive and well documented studies conducted by Tansy *et al.* (1976; 1980b; 1980c), effects on the trachea and some indications of liver damage in mice were recorded at the lowest concentration of 116 ppm, administered for 7 hours/day for 6 months (though 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 groups of 20 male mice administered "intermittent daily exposures" of 100 ppm for a total of 160 hours (Tansy *et al.*, 1980c). Initial reports of reduced fat deposits after exposure for 3 months were not confirmed in repeat studies (Tansy *et al.*, 1980b; 1980c).

In the few studies identified in which the chronic toxicity and carcinogenicity of MMA were investigated, the observed effects were generally similar to those reported in short- and long-term studies, including 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 conducted at Batelle Northwest Laboratories and reported by the NTP (1986) and Chan *et al.* (1988), it was concluded that there was no evidence of carcinogenicity of MMA for male F344/N rats and male and female B6C3F<sub>1</sub> mice exposed to 500 or 1000 ppm (2050 or 4100 mg/m<sup>3</sup>) and female rats exposed to 250 or 500 ppm (1025 or 2050 mg/m<sup>3</sup>). From observations of inflammation and degeneration of the olfactory epithelium and minimal increases in the numbers of alveolar macrophages in the nasal cavity in rats at all dose levels, the LOEL for 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 mice and localized histopathological effects at the site of entry (including inflammation and degeneration of the olfactory epithelium).

In earlier studies conducted by Hazelton Laboratories for Rohm and Haas (1977b; 1979), no treatment-related increases in tumour incidence occurred in either golden hamsters or albino rats (strain not reported) exposed to 0, 25, 100, or 400 ppm (0, 102.5, 410, or 1640 mg/m<sup>3</sup>) MMA 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 increased slightly in the nasal mucosa in rats. The NOELs and LOELs were considered to be 100 ppm and 400 ppm (410 and 1640 mg/m<sup>3</sup>), respectively, in both species based on the observed effects on body weights (both species) and respiratory tract (rats) in the group exposed to the highest concentration.

In an early study (Borzelleca *et al.*, 1964), the ratio of kidney weight to body weight was increased in a small group of female rats exposed to 2000 ppm of MMA in drinking water for 2 years. The LOEL was, therefore, considered to be 2000 ppm [about 146 mg/(kg b.w. • day) for females]; the NOEL was 60 ppm [about 5 mg/(kg b.w. • day)]

for females], though it should be noted that the administered doses varied considerably in this study. In another study of extremely small groups of beagle dogs (n=2) exposed to doses of up to 1500 ppm MMA [about 38 mg/(kg b.w. · day)] in their feed for 2 years, there were no treatment-related effects upon gross or histopathological examination, urinalysis, or hematology (Borzelleca *et al.*, 1964).

Based on the limited available information, MMA has not been mutagenic in a number of standard *in vitro* studies in *Salmonella typhimurium* (Lijinsky and Andrews, 1980; Waegemaekers and Bensink, 1984). However, MMA has been mutagenic and clastogenic in mammalian cells in culture (Moore *et al.*, 1988; Doerr *et al.*, 1989; Ishidate *et al.*, 1981; Galloway *et al.*, 1985; NTP, 1986). At high atmospheric concentrations (1000 ppm), MMA induced chromosome damage in mice after a single, but not after multiple, exposures (Anderson and Richardson, 1976; U.S. EPA, 1985). Results of a dominant lethal study in male mice administered similarly high concentrations, however, were negative (Anderson and Hodge, 1976). The results of a bone marrow micronucleus test were also negative (Hachitani *et al.*, 1981).

Based on the available studies on the developmental effects of MMA in different species, no significant differences were found in the number of dead or live fetuses, and litter size after inhalation or intraperitoneal (i.p.) exposure. Gross abnormalities in rats were observed only following intraperitoneal injection or inhalation during pregnancy of doses only slightly less than acute lethal doses [(125 mg/kg b.w.) by i.p. injection (Singh *et al.*, 1972); 110 mg/L (110 000 mg/m<sup>3</sup>) by inhalation (Nicholas *et al.*, 1979)]. In the former study, in which group sizes were small, Singh *et al.* (1972) reported a dose-dependent increase in hemangiomas; effects observed in the mothers were not addressed. Nicholas *et al.* (1979) reported decreases in maternal body weight gain associated with decreases in food consumption. Ossification was delayed, and there were early deaths, hematomas, and a decrease in fetal weight in the offspring of rats exposed to doses at which decreases in body weight gain in the mothers were observed (probably associated with decreases in food consumption).

Slight decreases in maternal weight gain and increased incidence of early resorptions were reported in rats exposed during pregnancy to 1000 ppm MMA (4100 mg/m<sup>3</sup>) (Hodge and Palmer, 1977). In a well documented study in rats, there was no embryo- or feto- toxicity and no increase in the incidence of malformations or variations following exposure during pregnancy to concentrations that ranged from 99 to 2028 ppm (406 to 8315 mg/m<sup>3</sup>; NOEL = 8315 mg/m<sup>3</sup>), though there was transient overt maternal toxicity (Solomon *et al.*, 1991). Slight fetotoxicity manifested as a decrease in fetal weight in offspring of pregnant mice administered a single dose level of 116 ppm (476 mg/m<sup>3</sup>) (Tansy, 1975) or delayed ossification in rats at higher concentrations in the absence of maternal toxicity, has been reported (Hodge and Palmer, 1977; Luo *et al.*, 1986). No effects were observed on reproductive performance in males in the only reproductive study identified (Anderson and Hodge, 1976).

Very few studies of the neurotoxicity of MMA have been identified. In an inhalation study by Innes and Tansy (1981) in which chloralose-urethanized mature male

rats were exposed to 400 ppm (1640 mg/m<sup>3</sup>) of MMA for 60 minutes, depression of multiple-unit electrical activity in the lateral hypothalamus and ventral hippocampus was observed. Methyl methacrylate markedly impaired locomotor activity and learning, while significantly increasing aggressive behaviour in male rats orally administered 500 mg/kg b.w. for 21 days (Husain *et al.*, 1985). In a separate study under the same experimental conditions (Husain *et al.*, 1989), a significant increase in cholesterol (26%) and triglycerides (65%) and a slight decrease in the total phospholipid content of the sciatic nerve were noted.

#### 2.4.2 Humans

Available clinical studies on human volunteers are restricted to investigations of effects on the skin following patch testing (Spealman *et al.*, 1945; van Joost *et al.*, 1988; Kaaber *et al.*, 1979). In cross-sectional studies of populations exposed occupationally to MMA, effects on the skin (Rajaniemi and Tola, 1985), lungs (Jedrychowski, 1982; Andrews *et al.*, 1979), nervous system (Seppalainen and Rajaniemi, 1984; Schwartz *et al.*, 1989) and blood (NIOSH, 1976; Lang *et al.*, 1986) have been examined. There are few quantitative data on exposure of these workers to MMA, however, and interpretation of several of these studies is complicated by concomitant exposure of the examined populations to other compounds.

Several historical cohort studies have been conducted to examine the mortality rate from cancer of the colon or rectum among male workers at two of the Rohm and Haas Company's plastics manufacturing plants, in Bristol, Pennsylvania and Knoxville, Tennessee (DeFonso and Maher, 1981; 1986; Maher and DeFonso, 1987a; 1987b; Walker *et al.*, 1991). Earlier investigations are subsumed, however, by the most recent study by Walker *et al.*, (1991), in which data were re-analyzed by the period of employment of the workers. In this investigation, the two cohorts were comprised of 6548 white men hired from January 1, 1946 to December 31, 1982 in the Bristol plant and 3381 white men hired between January 1, 1943 and December 31, 1982 in the Knoxville plant, followed either to death or to December 31, 1986. 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 a late cohort (1946 to 1982, inclusive).

In the two cohorts with workers first hired at later dates (Knoxville and the late cohort at Bristol), there was no excess mortality due to cancer of the colon or rectum. In the early cohort, there was an apparent excess of deaths due to colon cancer. This cohort worked in conditions that likely involved high exposures to the vapour phase of ethyl acetate (EA) and MMA monomer, as well as to a variety of volatile by-products of the EA/MMA polymerization process. While the risk was highest in the subgroup of workers having the greatest 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 (SMR = 1.44) in the Knoxville cohort, with no excess in either of the Bristol cohorts. In view of the large number of statistical estimates in this study, and the absence of clear dose-response

trends, the evidence of an association of MMA with respiratory cancer is far from convincing. The apparent excess may have been due to statistical fluctuation or to confounding by other occupational exposures in the environment at the time (e.g., lead, ethylene dichloride, methylene chloride, and acrylonitrile). If the apparent excess reflects a true risk, it is noteworthy that the cause of the risk appears to have disappeared for workers hired after 1946, and this excess risk has not been confirmed in other studies of MMA-exposed workers.

In a limited study of a much smaller cohort of workers exposed for considerably shorter periods to MMA at two American Cyanamid Company plants between 1951 and 1983, there was no excess mortality for any type of cancer examined (Collins *et al.*, 1989). However, it should be noted that workers were not exposed during the early period in which the excess mortality due to colon cancer was observed by Walker *et al.*, (1991). Though there was a very weak indication of an excess of rectal cancer, and weak-to-moderate indication of an excess risk of lung cancer in a population-based (as opposed to cohort-based), case-control study of workers in Montreal exposed to MMA, these results are inconclusive due to the small numbers of subjects involved, i.e., 21 (Siemiatycki, 1991).

There was no increase in the number of sister chromatid exchange (SCE) in the peripheral lymphocytes in 31 male workers occupationally exposed to MMA [mean value/8 h ranged from 0.70 to 21.6 ppm (3.0 to 90 mg/m<sup>3</sup>)] in four factories as compared with the control group ( $7.85 \pm 2.66$  vs.  $7.49 \pm 2.33$ ) (Marez *et al.*, 1991). The distribution of SCE, however, was significantly higher in the group exposed to MMA at peak concentrations ranging from 114 to 400 ppm (467 to 1640 mg/m<sup>3</sup>), although the number of individuals in this exposure subgroup was small ( $n = 6$ ). The control group consisted of 31 healthy male workers with similar mean age and smoking habits.

#### 2.4.3 Ecotoxicology

The only information on aquatic toxicity of MMA includes acute toxicity tests on fish, water flea (*Daphnia magna*), and algae. Because MMA is a volatile compound, it requires aquatic testing procedures that eliminate potential losses through volatilization, i.e., maintenance of closed systems, with measured concentrations (not nominal) throughout the test period. As few of the aquatic toxicity studies met these criteria, actual concentrations may have been less than nominal, and the values presented may have been questionable.

Bailey *et al.* (1985) studied the toxicity of MMA to juvenile bluegill sunfish (*Lepomis macrochirus*) at 22°C under static and flow-through conditions of various durations (1 to 96 hours). The lowest value was achieved in the 96-hour flow-through assay, the LC<sub>50</sub> being 191 mg/L. In shorter exposure flow-through assays, the LC<sub>50</sub>s were: 420, 373, 367, 360, 360, and 356 mg/L for 1, 2, 4, 8, 16, and 24 hours exposure, respectively. The 96-hour LC<sub>50</sub> for rainbow trout (*Oncorhynchus mykiss*) under flow-through conditions was > 79 mg/L, the highest concentration to which fish were

exposed. Sublethal/behavioural responses were noted among the fish in the 40 and 79 mg/L dose groups (Bowman, 1990).

The 24-hour  $EC_{50}$  for immobilization of *Daphnia magna* was 720 mg/L, with the extrapolated  $EC_0$  and  $EC_{100}$  being 502 and 1042 mg/L, respectively (Bringmann and Kuhn, 1982). The 24-hour  $LC_{50}$  for *Daphnia magna* was 1760 mg/L and for the  $LC_0$  and  $LC_{100}$ , 875 and 2500 mg/L, respectively (Bringmann and Kuhn, 1977). In a similar study, the toxicity threshold for onset of inhibition of cell multiplication was 447 mg/L for the flagellate protozoan *Entosiphon sulcatum* after 72 hours of exposure (Bringmann, 1978). These studies were done in static, open systems and only the nominal concentrations were reported.

Toxicity thresholds for onset of inhibition of cell multiplication following 8 days of exposure to MMA were 120 mg/L for the blue green alga *Microcystis aeruginosa* and 37 mg/L for the green alga *Scenedesmus quadricauda*, at pH 7 (Bringmann and Kuhn, 1976; 1978a; 1978b). The 96-hour  $LC_{50}$  for the green alga *Selenastrum capricornutum* was 170 mg/L with a NOEL of 100 mg/L (Forbis, 1990). No studies on effects on aquatic vascular plants were identified.

Data on the acute or chronic effects of MMA on terrestrial organisms are sparse; field or laboratory studies on birds, terrestrial invertebrates, or terrestrial plants have not been identified. Although there were no field data on the effects on wild mammals, toxicity studies have been conducted on laboratory mammals and can be used for extrapolation to effects on wild mammals (see Subsection 2.4.1).

### 3.0 Assessment of "Toxic" Under CEPA

#### 3.1 CEPA 11(a) Environment

It is difficult to estimate average exposure of organisms to methyl methacrylate in the Canadian environment due to the lack of data on concentrations in any environmental medium. Based on estimates from the United States that 0.46% of the total amount of MMA used per year is emitted into the environment, the predicted environmental concentrations in southern Ontario using the Fugacity Level III model are:

$2.44 \times 10^{-4} \mu\text{g}/\text{m}^3$  in air; 0.13 ng/L in surface water;  $1.2 \times 10^{-6} \mu\text{g}/\text{g}$  in soil;  $8.7 \times 10^{-8} \mu\text{g}/\text{g}$  in sediment; and  $1.5 \times 10^{-7} \mu\text{g}/\text{g}$  in fish. The overall persistence is approximately 1 day.

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 in the green alga *Scenedesmus quadricauda* at 37 mg/L following 8 days of exposure (Bringham and Kuhn, 1976; 1978a; 1978b). This is similar to the concentration (i.e., 40 mg/L) at which sublethal/behavioural responses were noted in rainbow trout following 96 hours of exposure (Bowman, 1990). Using a factor of 20 to convert from an acute to a chronic endpoint and another factor of 10 to account for interspecies variability in sensitivity, the estimated effects threshold is approximately  $10^6$  times higher than the concentration predicted to occur in surface water (i.e., 0.13 ng/L).

Studies of the effects on terrestrial organisms are lacking. As no field or laboratory studies on birds, terrestrial invertebrates, or terrestrial plants were identified, the toxicity of MMA to these organisms could not be assessed. Chronic studies on laboratory mammals are available, however, as well as data on levels of exposure to aquatic-based mammals, thus permitting the comparison between effects and environmental exposure for these organisms. Mink (*Mustela vison*) was chosen as the model species as it is an opportunistic carnivore with aquatic organisms comprising up to 100% of its diet, depending on the season. Based on the data presented in Table 1, total daily intake of MMA by mink in southern Ontario is estimated to be 0.17 ng/(kg b.w. · day), with approximately 80% of the exposure being attributable to inhalation. Based on chronic laboratory studies using the inhalation route of exposure, there was a significant decrease in body weight in golden hamsters and albino rats exposed to 1640 mg/m<sup>3</sup> for 6 hours per day, 5 days per week for 18 months, with the NOEL being 410 mg/m<sup>3</sup> [Hazelton Laboratories for Rohm and Haas (1977b; 1979)]. Using a factor of 10 to account for interspecies variability in sensitivity, the NOEL is  $10^8$  times higher than levels predicted to occur in the environment (i.e., 0.24 ng/m<sup>3</sup>).

Although data to evaluate the toxicity to aquatic and terrestrial ecosystems are sparse, given that the levels causing effects are many orders of magnitude greater than the exposures predicted to occur in the Canadian environment using the Fugacity model, effects in the field are not anticipated.

**Table 1 Estimated Total Daily Intake of Methyl Methacrylate for 1 kg Adult Mink**

Medium	Concentration*	Rate of Consumption** /(kg b.w. • d)	Daily Intake [ng/(kg b.w. • d)]
Air	0.24 ng/m <sup>3</sup>	0.55 m <sup>3</sup>	0.132
Water	0.13 ng/L	0.1 L	0.013
Fish	1.5 × 10 <sup>-4</sup> ng/g	158 g	0.024
Total	—	—	0.169

\* predicted using the Fugacity Model Level III

\*\* rate of consumption data for air from Stahl (1967), for water from Calder and Braun (1983) and for fish from Nagy (1987), assuming that fish comprise 75% of the mink diet

Although available data on the environmental effects of MMA are limited, a wide margin exists between observed effect levels and predicted environmental concentrations of MMA. As such, the concentrations of MMA predicted to be in the Canadian environment are unlikely to have an immediate or long-term harmful effect on the environment.

**Therefore, on the basis of available data, MMA is not considered to be “toxic” as defined under Paragraph 11(a) of the *Canadian Environmental Protection Act*.**

### 3.2 CEPA 11(b) Environment on Which Human Life Depends

Substances whose atmospheric half-life do not exceed 1 year are not considered to contribute to global warming. As such, MMA is not considered to be a greenhouse gas nor would it contribute directly to the depletion of the ozone layer.

**Therefore, on the basis of available data, MMA is not considered to be “toxic” as defined under Paragraph 11(b) of the *Canadian Environmental Protection Act*.**

### 3.3 CEPA 11(c) Human Life or Health

#### 3.3.1 Population Exposure

Available data on concentrations of MMA in environmental media to which humans are exposed are inadequate to serve as a basis for quantitative estimation of

exposure of the general population in Canada. Therefore, levels have been predicted by fugacity modelling (estimated concentrations of  $2.44 \times 10^{-4} \mu\text{g}/\text{m}^3$  in air,  $0.13 \text{ ng}/\text{L}$  in water,  $1.2 \times 10^{-6} \mu\text{g}/\text{g}$  in soil, and  $1.5 \times 10^{-7} \mu\text{g}/\text{g}$  in fish). On the basis of these predicted concentrations, it is estimated that inhalation would be the principal route of exposure to MMA in the general environment.

Based on the predicted concentrations in fish and soil, estimated intake from food and soil are expected to be negligible compared to that inhaled, though it should be noted that migration from food wrap into foodstuffs may contribute to total daily intake of MMA. For 5- to 11-year-olds, the age group with greatest predicted exposure on a body weight basis, the estimated intake is  $11.3 \times 10^{-5} \mu\text{g}/(\text{kg b.w.} \cdot \text{day})$ , assuming an average body weight of 27 kg, daily inhalation volume of  $12 \text{ m}^3$  of air, ingestion of 0.9 L of water daily, ingestion of 35 mg/day of soil per day, and consumption of 4.8 g of fish daily (Health and Welfare, 1992).

### 3.3.2 Effects

Potentially the most sensitive endpoint for assessment of whether MMA is "toxic" under Paragraph 11(c) of CEPA is genotoxic carcinogenicity (an effect for which it is generally believed there is no threshold). Initially, therefore, the weight of evidence for carcinogenicity has been considered as a basis for classification of MMA in a category of the scheme developed for the assessment of "toxic" under Paragraph 11(c) of CEPA (Health and Welfare, 1992).

As a whole, the available epidemiologic studies do not provide strong or consistent evidence of a carcinogenic effect of MMA on any human target organ. Nor is there enough data to infer with any degree of confidence that the possibility of an excess risk has been disproven. In particular, it remains plausible that the conditions of exposure in one plant in the pre-1946 era led to some excess risk of colon cancer among workers heavily exposed to MMA and other compounds (Walker *et al.*, 1991). There is some evidence that MMA is clastogenic *in vitro* and *in vivo* (in both experimental animals and humans). However, inhaled MMA has not been carcinogenic in an extensive, well documented two-year bioassay in rats and mice (NTP, 1986; Chan *et al.*, 1988), additional chronic inhalation studies in rats and hamsters [Hazelton Laboratories for Rohm and Haas (1977b; 1979)], or in an early study in which small groups of Wistar rats ingested drinking water containing MMA for two years (Borzelleca *et al.*, 1964).

Based on these considerations, MMA has been classified in Group VI ("Unclassifiable with respect to Carcinogenicity in Humans") of the classification scheme for carcinogenicity developed for the assessment of "toxic" under Paragraph 11(c) of CEPA (Health and Welfare, 1992). For compounds classified in Group VI, a Tolerable Daily Intake (TDI) is derived on the basis of either a no-observed-adverse-effect-level (NOAEL) or a lowest-observed-adverse-effect-level (LOAEL) in humans or animal species divided by an uncertainty factor (Health and Welfare, 1992). For MMA, a TDI for the route of exposure most relevant to the general population (i.e., inhalation) can be derived only on the basis of the results of studies in animals. Though there are

some quantitative data on exposure to MMA in available cross-sectional studies (Jedrychowski, 1982; NIOSH, 1976), workers were exposed to other compounds (Jedrychowski, 1982) or observed effects may have been attributable to confounders (NIOSH, 1976).

In long-term repeated dose inhalation studies in rats and mice, effects observed most commonly at high concentrations were decreases in body weight gain and irritation of the skin, nasal cavity, and eye [generally following exposure to greater than or equal to 500 ppm (2050 mg/m<sup>3</sup>)] (NTP, 1986). The lowest reported NOEL in a subchronic inhalation bioassay in which several dose levels were administered was 250 ppm (1025 mg/m<sup>3</sup>) in mice [IBT for Rohm and Haas (1977a)]. With the exception of effects at the site of entry, histopathological effects have not been observed in the most extensive bioassays in rats at concentrations less than or equal to 1000 ppm (4100 mg/m<sup>3</sup>) (NTP, 1986). In less extensive and well documented studies conducted by Tansy (1976) and Tansy *et al.*, (1980a; 1980b), effects on the trachea (the statistical significance of which was not reported) and possibly on the liver following subchronic exposure to 116 ppm have also been reported. Effects at the site of entry (intra-alveolar congestion/hemorrhage, pulmonary vasodilation, and edema) were also observed in rats exposed to 100 ppm MMA for periods as short as 2, 3, or 4 hours (Raje *et al.*, 1985).

In the two-year NTP inhalation bioassay in F344/N rats and B6C3F<sub>1</sub> mice [Batelle Northwest for NTP (1986); Chan *et al.* (1988)], the lowest concentration at which effects were observed was 250 ppm (1025 mg/m<sup>3</sup>) which resulted in a marginal increase in alveolar macrophages and degeneration and inflammation of the olfactory epithelium of the nasal cavity in female rats. In addition to inflammation of the olfactory epithelium, decreases in the body weights of mice were also observed at the lowest administered concentration (500 ppm; 2050 mg/m<sup>3</sup>). The NOELs in hamsters and rats exposed to MMA for 18 months or two years, respectively, in studies conducted by Hazelton Laboratories (Rohm and Haas, 1977b; 1979) were considered to be 100 ppm (410 mg/m<sup>3</sup>) in both species. This was based on a decrease in body weight in both sexes of hamsters and increase in mortality in male hamsters and decrease in body weight in female rats and mild rhinitis in the mucosa lining the turbinates of both sexes of rats at the next highest concentration (400 ppm; 1640 mg/m<sup>3</sup>). In an earlier, less extensive study, an increase in the ratio of kidney weight to body weight in female rats only, was observed following ingestion of approximately 146 mg/kg b.w. of MMA in drinking water.

A small but significant decrease in mean fetal weights in the absence of maternal toxicity was observed in mice exposed during gestation to 116 ppm (476 mg/m<sup>3</sup>) (Tansy, 1975). Based on limited available data, MMA induced some neurological effects in experimental animals at a concentration of 400 ppm (1640 mg/m<sup>3</sup>); studies on immunotoxicity following exposure by routes of administration relevant to assessment of effects in the general environment have not been identified.

The effect level considered most appropriate, as a basis for development of a TDI is, therefore, the NOEL of 100 ppm (410 mg/m<sup>3</sup>) in hamsters and rats exposed to MMA

for 18 months and 2 years, respectively (Rohm and Haas, 1977b; 1979). On the basis of these data, a TDI is derived as follows:

$$\text{TDI} = \frac{(410 \text{ mg/m}^3) \times (6/24) \times (5/7) \times 0.11 \text{ m}^3/\text{day}}{1000 \times 0.35 \text{ kg}}$$

$$= 0.023 \text{ mg/ (kg b.w.} \cdot \text{ day) or } 23 \text{ } \mu\text{g/(kg b.w.} \cdot \text{ day)}$$

where:

- 410 mg/m<sup>3</sup> = the lowest NOEL reported in inhalation bioassays of adequate quality in animal species (both hamsters and rats) conducted to date [decrease in body weight in both sexes and increase in mortality in males (hamsters) and decrease in body weight in females and mild rhinitis in the mucosa lining the turbinates of both sexes (rats) observed at the next highest concentration];
- 6/24 and 5/7 = conversion of exposure for 6 hours/day, 5 days/week to continuous exposure;
- 0.11 m<sup>3</sup>/day = assumed inhaled air volume of an adult rat (Health and Welfare, 1992); rats were considered the appropriate species since the TDI developed on this basis is more conservative than that for hamsters;
- 0.35 kg = assumed body weight of adult rat (Health and Welfare, 1992); rats were considered the appropriate species since the TDI developed on this basis is more conservative than that for hamsters; and
- 1000 = uncertainty factor [ $\times 10$  for intraspecies variation;  $\times 10$  for interspecies variation;  $\times 10$  for some evidence of effects following inhalation of 100 ppm or slightly higher concentrations and following ingestion of approximately 146 mg/(kg b.w.  $\cdot$  day), though in much less extensive and well documented studies].

Available data on concentrations of MMA in environmental media to which humans are exposed are inadequate to serve as a basis for quantitative estimation of exposure of the general population in Canada. However, based on concentrations in air, water, soil, and fish predicted by fugacity modelling, for 5- to 11-year-olds (the age group with greatest predicted exposure on a body weight basis), the estimated intake is  $11.3 \times 10^{-5} \text{ } \mu\text{g/(kg b.w.} \cdot \text{ day)}$ . This estimated maximum average daily intake for various age groups in the population, although not based on actual data on concentrations in air, water, or food, is many orders of magnitude less (by approximately 200 000 times) than the tolerable daily intake previously derived.

**It is concluded, therefore, on the basis of currently available data, that concentrations of MMA predicted to be present in the environment do not constitute a danger in Canada to human life or health. Therefore, MMA is not considered to be “toxic”, as defined under Paragraph 11(c) of the *Canadian Environmental Protection Act*.**

### **3.4 Conclusion**

**Therefore, on the basis of available data, MMA is not considered to be “toxic” as defined under Paragraphs 11 (a), (b), and (c) of the *Canadian Environmental Protection Act*.**

#### 4.0 Recommendations for Research and Evaluation

1. Additional characterization is recommended of the exposure to ethyl acetate/methyl methacrylate (EA/MMA) and the volatile by-products of the EA/MMA polymerization process of the workers exposed in the early period of operation of the acrylic sheet manufacturing plant in Bristol, Pennsylvania examined in the study of Walker *et al.* (1991). This research is considered to be of high priority.
2. Due to the lack of information on levels in the Canadian environment and the determination of nontoxic to the Canadian environment on the assumption of very low levels, MMA should be measured in air, water, and sediment at sites adjacent to the plant using MMA. Similarly, monitoring of concentrations of MMA in environmental media (i.e., air, food, and water) to which the general population in Canada is exposed is desirable. This research is considered to be of medium priority.
3. Additional data on the neurotoxicity, immunotoxicity, and reproductive toxicity of MMA are also desirable. This research is considered to be of low priority.

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