TOXICOLOGICAL REVIEW

of

METHYL METHACRYLATE

(CAS No. 80-62-6)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

January 1998

U.S. Environmental Protection Agency
Washington, DC

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DISCLAIMER

Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

FOREWORD

The purpose of this review is to provide scientific support and rationale for hazard identification and dose-response assessments for both cancer and noncancer effects (the oral reference dose and the inhalation reference concentration) from chronic exposure to methyl methacrylate. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of methyl methacrylate.

In Section 6, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose-response (U.S. EPA, 1995a). Matters considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to make apparent the limitations of the individual assessments and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to the Integrated Risk Information System (IRIS), the reader is referred to EPA's Risk Information Hotline at 513-569-7254.

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This document and summary information on IRIS have received peer review both by EPA scientists and by independent scientists external to EPA (U.S. EPA, 1994a). Subsequent to external review and incorporation of comments, this assessment has undergone an Agencywide review process whereby the IRIS Program Director has achieved a consensus approval with EPA's Program Offices (the Offices for Air and Radiation; Planning and Evaluation; Prevention, Pesticides, and Toxic Substances; Research and Development; Solid Waste and Emergency Response; and Water) and Regional Offices.

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Summaries of the external peer reviewers' comments and the disposition of their recommendations are in Appendix B.

1. INTRODUCTION

This document presents the derivation of the noncancer dose-response assessments for oral exposure (the oral reference dose or RfD) and for inhalation exposure (the inhalation reference concentration or RfC) and the cancer hazard and dose-response assessments for methyl methacrylate (MMA).

The RfD and RfC are meant to provide information on long-term toxic effects other than carcinogenicity. The RfD is based on the assumption that thresholds exist for certain toxic effects, such as cellular necrosis, but may not exist for other toxic effects, such as some carcinogenic responses. The RfD is expressed in units of mg/kg/day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The inhalation RfC is analogous to the oral RfD. The inhalation RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). It is expressed in units of mg/m^3.

The carcinogenicity assessment is meant to provide information on three aspects of the carcinogenic risk assessment for the agent in question: the U.S. Environmental Protection Agency (EPA) classification, quantitative estimates of risk from oral exposure, and inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are presented in three ways. The *slope factor* is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The *unit risk* is the quantitative estimate in terms of either risk per µg/L of drinking water or risk per $µg/m^3$ of air breathed. The third form in which risk is presented is drinking water or air concentration, providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

Development of these hazard identifications and dose-response assessments for MMA has followed the general guidelines for risk assessments as set forth by the National Research Council (1983). Other EPA guidelines that were used in the development of this assessment include Risk Assessment Guidelines of 1986 (U.S. EPA, 1987a), 1996 (proposed) Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991b), (proposed) Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity (U.S. EPA, 1994b), (proposed) Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1995b), Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994c), Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996b) Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988a), and Use of the Benchmark Dose Approach in Health Risk Assessment (U.S. EPA, 1995c).

Literature search strategies employed for this compound were based on the Chemical Abstracts Service Registry Number (CASRN) and at least one common name. As a minimum, the following databases were searched: RTECS, HSDB, TSCATS, CCRIS, GENETOX, EMIC,

EMICBACK, DART, ETICBACK, TOXLINE, CANCERLINE, and MEDLINE and MEDLINE backfiles.. Information in previous reviews (U.S.EPA, 1988b, 1991c; ECETOC, 1995) and any pertinent information submitted by the public to the Integrated Risk Information System (IRIS) submission desk was also considered in the development of this document.

2. CHEMICAL AND PHYSICAL INFORMATION RELEVANT TO ASSESSMENTS

The structural formula of MMA is shown here:

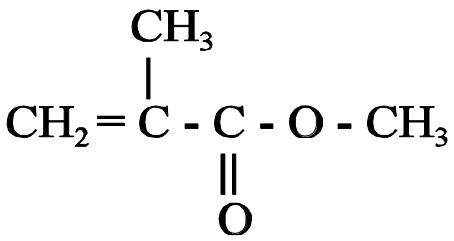

Figure 1. Structure of methyl methacrylate.

The empirical formula for MMA is $C_5H_8O_2$, and the CAS registry number is 80-62-6. The synonyms for MMA listed in MEDLARS (1986), are as follows: metakrylan metylu; methacrylate de methyle; methacrylic acid methyl ester (8CI); methacrylsaeuremethyl ester; methyl alpha-methacrylate; methyl methacrylate; methyl methacrylate monomer, inhibited; methyl methacrylate monomer, uninhibited; methyl methylacrylate; methyl 2-methyl-2-propenoate; methyl 2-methylpropenoate; methyl-methacrylat; methylmethacrylaat; metil metacrilato; MME; NA 1247; NCI-C50680; Pegalan; RCRA waste number U162; UN 1247; 2-propenoic acid, 2-methyl-methyl ester.

Some physical and chemical properties of MMA are shown in Table 1. MMA undergoes reactions that are typical of its constituent functional groups. The sites of chemical reactivity are the terminal vinylic carbon, the double bond, the allylic methyl group, the ester moiety, and the functional group in the nonmethacrylate moiety (Nemec and Kirch, 1978). MMA takes part in Diels-Alder reactions. When combined with 1,3-butadiene, a cyclic co-oligomerization occurs, catalyzed by nickel complexes in the presence of phosphites and triethylaluminum (Nemec and Kirch, 1978). The addition of MMA to nitric acid containing various concentrations of dinitrogen trioxide results in the substitution of an allylic hydrogen with nitro or nitroso groups (Nemec and Kirch, 1978).

MMA is a colorless flammable liquid with a strong acrid odor. It readily polymerizes on exposure to light, heat, oxygen, ionizing radiation, or catalysts (EPA, 1991b; IARC, 1979; NTP, 1986). It is used primarily to make a variety of resins and plastics, and is most often polymerized to polymethyl methacrylate, which is used to make acrylic sheets, acrylic moldings, and extrusion powders. MMA is also copolymerized with other acrylates and used to make surface coating resins, lacquers, and emulsion polymers. The chemical is used in medicine and dentistry to make

prosthetic devices and as a ceramic filler or cement (EPA, 1991b; IARC, 1979; NTP, 1986). Because MMA is relatively volatile (vapor pressure of 40 mmHg at 25°C) and widely used, significant occupational exposure to the chemical can be expected to occur. The potentially exposed population includes manufacturers of MMA and its polymers, as well as doctors, nurses, dentists, and dental technicians.

Table 1. Physical and chemical properties of methyl methacrylate

Parameter	Data	Reference
Molecular wt.	100.11	Nemec and Kirch, 1978
Melting pt. (°C)	-48	Nemec and Kirch, 1978; Weast et al., 1988
Boiling pt. (°C)	100-101	Nemec and Kirch, 1978; Weast et al., 1988
Specific gravity at 20°C	0.945	Weiss, 1980
Heat of polymerization (cal/g)	-138	Weiss, 1980
Vapor pressure (mmHg at 25°C)	40	Sandmeyer and Kirwin, 1981
Refractive index (nD^2)	1.4142	IARC, 1994; Weast et al., 1988
Autoignition temperature (°C)	421	Hawley, 1981
Solubility	Slightly soluble in water	Hawley, 1981
	Soluble in alcohol, ether, acetone, methyl ethyl ketone, tetrahydrofuran, hydrofuran, esters, aromatic and chlorinated hydrocarbons	Windholz et al., 1983; Weast et al., 1988

3. TOXICOKINETICS/TOXICODYNAMICS RELEVANT TO ASSESSMENTS

3.1. Absorption

MMA is readily absorbed into the blood via the lungs, gastrointestinal tract, and skin. Absorption through the respiratory tract is indicated by the lethal effects seen in several animal inhalation studies (Section 4.2.1). MMA was found in the blood of Sprague-Dawley rats following inhalation exposure to 96.7 ppm (395.9 mg/m^3) for 1, 2, 3, or 4 h (Raje et al., 1985). The concentration of MMA in blood did not vary significantly with exposure duration. The mean concentration in the blood for the four exposure periods was 11.14 mg/100 mL blood. Although

some parent compound is initially present in the blood, MMA is metabolized rapidly and completely within 10 days (see Table 2).

Morris and Frederick (1995) measured uptake of MMA in the surgically isolated upper respiratory tract of male F344 rats under various flow conditions. Under cyclic flow conditions, 18%, 20%, and 16% was deposited at inspired MMA concentrations of 25, 100, and 500 ppm, respectively. Under unidirectional flow conditions, deposition of MMA was 3% less on the average.

The experiments of Bratt and Hathway (1977) show that MMA is rapidly absorbed from the gastrointestinal tract of rats. Adult male Wistar rats were treated with 5.7 mg/kg ^{14}C-MMA by gavage. Up to 65% of the dose was expired from the lungs in 2 h, which shows the rapidity of the absorption. Recovery of radiolabel in the urine and feces accounted for only 7.4% of the administered dose, thereby indicating nearly complete absorption from the gastrointestinal tract (see Table 2). In addition, significant levels of methacrylic acid ($>$ 0.5mM), a product of MMA degradation, were found in rat serum 5 min after a single dose of 8 mmol MMA/kg body weight (Bereznowski, 1995).

MMA can be absorbed through the skin, causing death of the animals (Autian, 1975; see also Table 10). Verkkala et al. (1983) showed that MMA is absorbed through the skin. In their study, male Wistar rats exposed to MMA liquid on 12 cm^2 of tail skin absorbed 0.78 ± 0.20 g MMA during a 3-h occlusive exposure.

3.2. Distribution

The only studies that provide definitive information regarding the distribution of MMA in a mammalian system following inhalation, oral, or intravenous exposures are those of Raje et al. (1985), Bratt and Hathway (1977), and Wenzel et al. (1973). Once absorbed, MMA is largely metabolized to methacrylic acid and eventually to CO_2 via the TCA cycle. Very little is retained in the body as unchanged MMA after 10 days (Bratt and Hathway, 1977). That which is not metabolized to CO_2 and exhaled or excreted in the urine or feces is primarily retained in the liver and adipose tissue, though Raje et al. (1985) report finding small amounts of MMA in the brain and lungs immediately following 1-, 2-, 3-, and 4-h exposures.

Table 2. Excretion and retention of radioactivity in rats after administration of methyl[^{14}C]methacrylate[a]

		Recovery of ^{14}C (% of Dose)[b]					
			Exhaled gases				
Route of administration	Dose (mg/kg)	Urine	Feces	$^{14}CO_2$	Unchanged methyl[^{14}C] methacrylate	Carcass plus skin	Total
By stomach tube	5.7	4.7	2.7	88.0	0.1	4.1	99.6
Intravenous	5.7	6.6	1.7	84.0	0.7	6.6	99.6

[a]Form of labeled compound was methyl[1,3- ^{14}C]-propylene-2-carboxylate.
[b]10 days after administration.

Source: Bratt and Hathway (1977).

Raje et al. (1985) exposed Sprague-Dawley rats to 96.7 ppm (395.9 mg/m^3) MMA vapor for 1, 2, 3, or 4 h and the blood, brain, and lungs from each rat were analyzed for MMA content. The MMA content of each tissue type did not vary significantly with exposure duration, so the results were averaged to calculate the mean concentration in each tissue for the four exposure periods. Blood showed the highest concentration of MMA of the three tissues (11.4 mg/100 mL blood), followed by brain (25.24 µg/g) and lung (20.6 µg/g). This experiment indicates that saturation of the tissues with MMA occurs, but the data were not sufficient to establish the time to saturation for the exposure concentration tested.

In the experiments of Bratt and Hathway (1977) mentioned above, it was found that 10 days after oral or i.v. dosing of rats with ^{14}C-MMA, only 4.1%-6.6% remained in the carcass, most of which was found only in the liver and adipose tissue. Approximately 3.3% of an intraperitoneally administered dose of MMA was retained in the carcass of female Wistar rats (Crout et al., 1982).

Wenzel et al. (1973) administered radiolabeled MMA intravenously to Wistar rats. Autoradiographic analyses showed that high activities occurred in the blood and kidneys; low activities were detected in the liver and bone marrow at 5 min after injection. No activity was detected in the brain or spinal cord at this time point. At 2 h post injection, the total activity had decreased and detected activity had shifted to compact bone. From 4 to 8 h after administration, the activity was found only in bones, liver, intestine, and salivary glands.

3.3. Metabolism

Labeled methylmalonic acid, methacrylic acid, succinic acid, methylmalonic semialdehyde, and β-hydroxyisobutyric acid have been identified in the urine of male Wistar rats administered

^{14}C-MMA by either gavage or intravenous injection (Bratt and Hathaway, 1977; Crout et al., 1982) and methylmalonic acid was also detected in the urine of a human volunteer following ingestion of the chemical (Crout et al., 1982). The authors propose that administered MMA is metabolized in the same way as the small amounts of methacrylate that are formed in the course of valine metabolism. According to the proposed pathway, MMA ([1] in Figure 2) is enzymatically converted to methacrylic acid (2) and is esterified to its CoA ester (4), which is a normal catabolite of valine (3). The CoA derivative is then hydroxylated to β-hydroxyisobutyric acid, oxidized and esterified by CoA to methylmalonyl 0CoA (5), and enters the citric acid cycle as succinyl CoA (6).

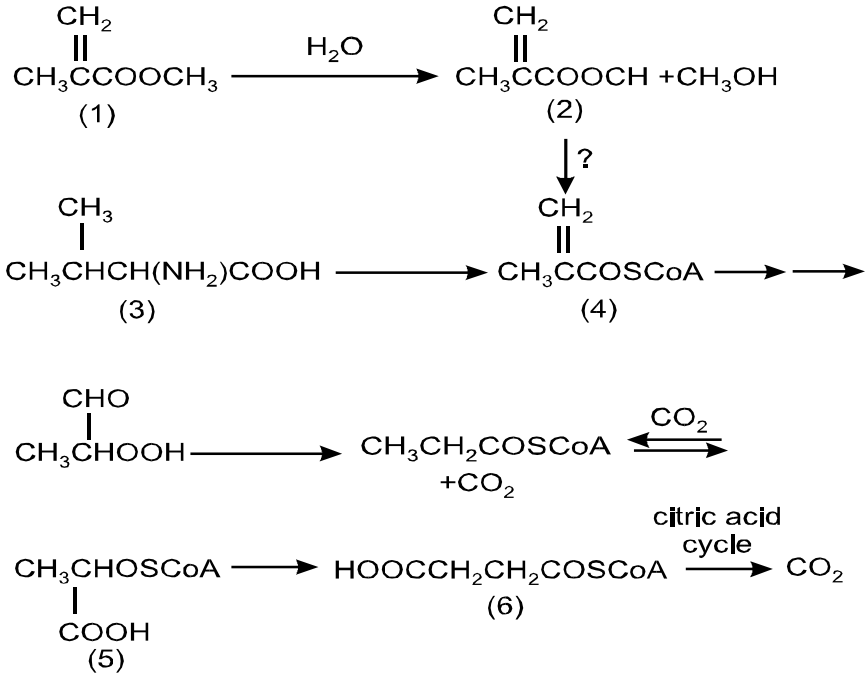

Figure 2. Proposed pathway for MMA metabolism.

Source: Crout et al. (1992).

Further evidence in support of this pathway for MMA metabolism comes from in vitro studies with rat and human blood. It has been shown that MMA is hydrolyzed by both human and rat serum enzymes to methacrylic acid and presumably to methanol in vitro (Bereznowski, 1995; Corkill et al., 1976) and in vivo (Morris and Frederick, 1995; Bereznowski, 1995; Crout et al., 1979). Bereznowski (1995) reported that the rate of methacrylic acid production in vitro by rat blood serum was approximately threefold higher than the rate in human blood serum. Both Bereznowski (1995) and Corkill et al. (1976) found that the rate of disappearance of MMA from blood showed a first-order dependence on MMA concentration and suggested that a simple enzymatic reaction is involved. The half-life at 37°C was 20–40 min (Corkill et al., 1976). Miller et al. (1981) suggested that the rapid disappearance of MMA from the blood could be due to the

binding of this compound with nonprotein sulfhydryl compounds in red blood cells rather than hydrolysis. However, in a series of in vitro experiments, Bereznowski (1995) showed that the accumulation of methacrylic acid in rat and human blood serum exposed to MMA results in a typical enzymatic substrate-saturation curve, which is reduced by inhibitors of nonspecific carboxylesterase and negated when the serum was boiled (to denature the serum proteins). Thus, the most likely explanation for MMA's rate of disappearance in blood is serum esterase-catalyzed hydrolysis to methacrylic acid and methanol. The kinetics of conversion when methacrylic acid was isolated from human serum incubated with MMA (Corkill et al., 1976; Bereznowski, 1995) indicate that this pathway was the major, and possibly the only, initial step in the metabolism of MMA in blood.

Morris and Frederick (1995) showed that MMA is also metabolized to methacrylic acid by enzymes in the upper respiratory tract of rats following inhalation exposure. They measured uptake of MMA and ethyl acrylate (EA) in the surgically isolated upper respiratory tract of male F344 rats under various vapor flow conditions and over a wide range of inspired concentrations. To examine the potential influences of carboxylesterase metabolism, uptake was measured in non-pretreated rats and in rats pretreated with the carboxylesterase inhibitor bis-nitrophenylphosphate (BNPP). BNPP pretreatment reduced upper respiratory tract (URT) uptake for both EA and MMA by approximately one-third, indicating that a large fraction of these vapors is metabolized by carboxylesterase in the nose. In addition, MMA exposure at 566 ppm and absolute deposition rates of 35-42 µg/min (unidirectional flow) resulted in 20% lowering of nasal nonprotein sulfhydryl content (NPSH). EA only required an 88 ppm exposure at a 7-15 g/min (unidirectional flow) absolute deposition rate to cause the same drop in NPSH levels, suggesting that EA is 3-5 times more reactive with nasal SH groups than is MMA. These results are consistent with in vitro reaction rates of these vapors with glutathione (Tanii and Hashimoto, 1982). In contrast to their parent esters, acrylic or methacrylic acid exposures were not found to deplete nasal NPSH even at delivered dose rates greater than those for the parent esters. While the reported metabolism of MMA to methacrylic acid in the nose, and evidence for similar olfactory damage caused by the acid versus the ester (Miller et al., 1981; 1985) strongly suggest an acid metabolite-dependent mechanism for olfactory toxicity, it is important to note that the esters are directly reactive. The depletion of NPSH or covalent binding to macromolecules may play an important role in initiating olfactory toxicity as well (Frederick et al., 1994).

Studies using both ∝-naphthyl butyrate (Bogdanffy et al., 1987) and MMA (Greene, 1996) as substrates for determining carboxyesterase activity consistently demonstrate a higher level of activity for this enzyme in olfactory tissue of humans and rodents than in other nasal tissue. The hydrolysis of MMA to methacrylic acid is strongly inhibited by the addition of low concentrations of ∝-naphthyl butyrate in rat and human nasal tissue (Greene, 1996), suggesting that MMA and ∝-naphthyl butyrate are metabolized by the same carboxyesterase enzyme. In rats and mice, olfactory homogenates of p-nitrophenyl butyrate (Bogdanffy et al., 1987) and dibasic esters (Bogdanffy et al., 1991) metabolize these esters 7-10 times more efficiently than respiratory tissue homogenates. Greene (1996) showed that olfactory tissue metabolized MMA at rates threefold higher than respiratory tissue in rats and humans, and 12-fold higher than respiratory tissue in hamsters.

Other studies have shown that the rate of carboxyesterase activity in olfactory tissue is significantly lower in humans than in F344 rats (Mattes and Mattes, 1992; Greene, 1996) and Syrian hamsters (Greene, 1996). Greene (1996) has reported that maximum rates (V_{max}) of MMA metabolism in rat and hamster olfactory tissue were comparable, and human olfactory tissue rates were at least 13-fold lower. Mattes and Mattes (1992) examined carboxylesterase activity in total F344 rat nasal epithelium and human nasal polyps using the substrate ∝-naphthyl butyrate. They found substantially higher enzyme activity in the rat nasal extracts than in human nasal polyps (see summary of K_{max} and V_{max} values from these studies in Table 3). The Michaelis constant (K_m) was approximately the same in rat and human nasal extract and was significantly less than that reported for rat nasal carboxylesterase activity using dibasic esters as a substrate. Using MMA as a substrate, Greene (1996) found that carboxyesterase activity in human liver tissue was 500-fold higher than in human olfactory tissue.

Intraperitonal injection of MMA into female Wistar rats caused no significant difference in urinary excretion of thioethers (mercapturic acids) compared with controls unless the animals were pretreated with the carboxylesterase inhibitor, tri-*o*-tolyl phosphate (Delbressine et al., 1981). The authors suggest that MMA can be detoxified by addition of glutathione to the ethylene group, as well as by hydrolysis by carboxylesterase.

In short, metabolism of MMA has been studied in vitro and in vivo in both rodents and humans. Several studies have confirmed the initial hydrolysis of MMA to methacrylic acid and methanol, one study indicates that the rate of hydrolysis is slower in human than in rat blood, and studies suggest that the rate of metabolism by carboxylesterase is substantially higher in rat nasal tissue than in human nasal tissue, including olfactory tissue. Available evidence suggests that MMA is enzymatically converted to methacrylic acid and is esterified to CoA, which is hydroxylated to β-hydroxyisobutyric acid, oxidized and esterified by CoA to methylmalonyl CoA, and enters the citric acid cycle as succinyl CoA. Methacrylic acid, methyl malonic acid, ethyl malonic acid, b-hydroxyisobutyric acid, and mercapturic acid have been identified as urinary metabolites of the rat, and methyl malonic acid has been shown to be a urinary metabolite of humans.

3.4 Excretion

Most of an orally or parenterally administered dose of ^{14}C-labeled MMA is excreted as CO_2 (Bratt and Hathway, 1977; Crout et al., 1982). Wistar rats given MMA orally,

Table 3. Kinetic constants for carboxyesterase activity in human, rat, and hamster nasal tissue

Species	Tissue	K_m [a]	V_{max} [b]	n[c]	Source
Human	Nasal (polyps)	60.8 ± 7.90	145.5 ± 11.3	17	Mattes and Mattes, 1992
Human	Nasal (olfactory)		0.48 ± 0.42[d,e]	NR	Greene, 1996
Human	Nasal (respiratory)		2.7[d]	NR	Greene, 1996
			0.15 ± 0.13[d,e]	NR	Greene, 1996
Human	Liver		494.0	NR	Greene, 1996
Rat	Nasal (total)	50.0 ± 2.9	5007 ± 377	19	Mattes and Mattes, 1992
Rat	Nasal (olfactory)	140	12[d,e]	NR	Greene, 1996
Rat	Nasal (respiratory)	150	18.0[d]	NR	Greene, 1996
			3.5[d,e]	NR	Greene, 1996
Rat	Liver	100	137.0	NR	Greene, 1996
Hamster	Nasal (olfactory)	280	46	NR	Greene, 1996
Hamster	Nasal (respiratory)	400	137.0	NR	Greene, 1996
Hamster	Liver	200	3.6	NR	Greene, 1996

[a]μM ± SE.
[b]nmol/min/mg protein ± SE.
[c]Number of experiments.
[d]Quantity of human tissue precluded obtaining true V_{max} on individual samples; samples were assayed using a concentration of MMA that would give maximal rate based on animal studies.
[e]S9 fractions were used for comparison purposes because of limited amount of human sample tissue.

intraperitoneally, or intravenously exhaled 65%–86% of the administered radiolabel as CO_2 within 10 h of dosing. After 10 days, 88% and 84% of 5.7 mg/kg doses given orally and intravenously, respectively, were excreted as $^{14}CO_2$ (Bratt and Hathway, 1977; Table 1). Just 0.19%–1.4% of

the administered dose was excreted by the lungs as unmetabolized MMA. Urinary excretion accounted for about 4.7%–14.5% of the administered radioactivity (Bratt and Hathway, 1977; Crout et al., 1982). Metabolites detected in the urine following oral or intravenous dosing with radiolabeled MMA included methacrylic acid, succinic acid, methylmalonic acid, methylmalonic semialdehyde, β-hydroxyisobutyric acid, and an unidentified ^{14}C-labeled acid. No parent compound was detected in the urine. These results indicate that the small amount of inhaled MMA that initially reaches the blood as reported by Raje et al. (1985) would be almost completely metabolized within a few days.

Wistar rats administered MMA by intraperitoneal injection excreted increased amounts of thioethers in their urine when carboxylesterase activity was inhibited by pretreatment with tri-*o*-tolyl phosphate (Delbressine et al., 1981). *N*-acetyl-*S*-(2-carboxypropyl)cysteine was identified in the urine of pretreated rats (Delbressine et al., 1981).

By examining workers following occupational inhalation exposures, Mizunuma et al. (1993) determined that about 1.5% of inhaled MMA is excreted in the urine as methanol. Even though urine detection of methanol shows some promise for biologic monitoring of MMA exposure, the lowest MMA exposure concentration at which exposed subjects could be distinguished from nonexposed subjects was reported to be about 20 ppm MMA.

4. Hazard Identification

4.1 Studies in Humans

This section is a review of human studies relevant to the derivation of health benchmarks. An overall synthesis of this information and its relation to the potential for MMA to cause cancer and noncancer effects are presented in Sections 4.5 and 4.6, respectively.

4.1.1. Human Noncancer Studies

There have been several reported cases of reactions in individuals exposed to MMA for short periods during mixing of the monomer and polymer. Typical nervous system symptoms included headache, lethargy, lightheadedness, and a sensation of heaviness in the arms and legs (Lozewicz et al., 1985; Donaghy et al., 1991; Scolnick and Collins, 1986). No measured exposure concentrations were reported for these cases. In one case, the exposure concentration was estimated to be about 0.4 to 1.5 ppm (1.6 to 6.1 mg/m^3) (Scolnick and Collins, 1986).

Respiratory symptoms reported in humans include chest tightness, dyspnea, coughing, and wheezing (Lozewicz et al., 1985; Pickering et al., 1986; Savonius et al., 1993), and reduced peak expiratory flow (Savonius et al., 1993). Exposure measurements were not taken, but Pickering et al. (1986) estimated environmental concentrations of MMA ranged from 0 to 374 ppm (0 to 1,531.3 mg/m^3) during the poly-MMA mixing procedures employed. Cases of contact dermatitis have also been reported (Scolnick and Collins, 1986; Guill and Odom, 1978). These cases may represent individuals who are sensitive to the neurologic, dermal, and respiratory effects of exposure to MMA. However, in some cases high exposures (not quantified) persisted for several years.

A decrease in olfactory function was not detected among 175 MMA-exposed workers relative to 88 nonexposed controls in a cross-sectional study at an acrylic sheet production facility in Germany (Muttray et al., 1997). Time-weighted average MMA exposures were characterized as being up to 50 ppm over the past 6 years and up to 100 ppm prior to that. Duration of exposures as determined from work histories ranged from 1 to 33 years with a mean exposure duration of 9.6 (±7.1) years. The authors indicated that workers were not exposed to other confounding substances. Only one out of 175 exposed workers (0.6%) had an olfactory disorder as determined by the Rhino-Test,® which was described as being sufficiently sensitive to detect "clinically relevant hyposmia." Five out of 88 controls (5.7%) exhibited a diminished sense of smell. All five cases of smell disorder were attributed to either trauma or nasal septoplasty surgery. The authors stated that "low-level hyposmia" could not be ruled out with this test.

Olfactory function was investigated in 731 workers from a facility involved in the manufacture of acrylates and methacrylates (Schwartz et al., 1989; University of Pennsylvania, 1988). Participants were administered the University of Pennsylvania Smell Identification Test (UPSIT) and a questionnaire to collect background information on age, gender, health status, smoking history, work information, and other necessary data. The study was conducted in a manner that examined the effects of both current exposure (cross-sectional study) and cumulative exposure (nested case-control study) to acrylates and methacrylates on olfactory function. For the cross-sectional study, workers were classified into four exposure groups: those having no significant chemical exposures; those exposed to chemicals other than acrylic acid, methacrylic acid, acrylates, or methacrylates; those having low exposure to these chemicals only (low-acrylate/methacrylate group); and those having high exposure to these chemicals only (high-acrylate/methacrylate group). In the case-control study, classification into one of the two acrylate/methacrylate exposure categories, duration of employment at the plant, and cumulative exposure to acrylate/methacrylate were considered individually for their possible association with olfactory function. There were no significant differences in scores on the UPSIT among the four exposure categories in the cross-sectional study. However, the case-control study revealed significantly ($p < 0.05$) elevated crude exposure odds ratios for olfactory function loss for all workers and for workers who never smoked (2.0 and 6.0 for these two groups, respectively). After controlling for multiple confounding factors (chemical exposure, smoking status, ethnic group, medications, age, history of smell dysfunction, history of medical problems, level of education, gender, and work shift tested), the odds ratios were 2.8 and 13.5 for all workers and never-smokers, respectively. There was also evidence of a concentration-dependent relationship between olfactory dysfunction and cumulative exposure scores. While an exposure-related effect is suggested in this study, actual exposure concentrations were not reported, MMA exposure was not examined separately from exposure to other acrylates/methacrylates, and it is not possible to make a specific assessment of the effects of exposure to MMA on olfactory function. The reason effects were reported in this study and not the Muttray et al. (1997) study could be due to a higher coexposure to other acrylates, the use of a more sensitive diagnosis method, or a combination of both explanations.

A study was conducted in December 1992 to identify the prevalence of occupational asthma attributable to MMA exposure in ICI's acrylic factories in Darwen, Lancashire, UK (Pickering et al., 1993). Approximately 400 (90%) of the exposed workforce were administered lung function tests to determine forced expiratory volume in 1 sec (FEV_1) and forced vital

capacity, as well as a questionnaire. Each individual's level of exposure was estimated to be none, low, medium, or high based on knowledge of their current work area, previous work areas, length of time in the industry, and their self-reported exposure to short-term but high levels of MMA. Work-related respiratory symptoms were reported by 5/125 (4%), 16/198 (8%), and 6/61 (10%), and work-related nasal symptoms were reported by 6/125 (5%), 14/198 (7%), and 4/61 (7%) for workers classified in the low, medium, and high exposure groups, respectively. Although these data are suggestive of a dose-response, the trends did not reach statistical significance at the 5% level according to three-way and paired chi-squared tests. Number of packets of cigarettes smoked times number of years was the only parameter associated with loss of lung function. Exposure classification had no statistically significant effect on lung function once smoking habits were accounted for. Workers reported eye irritation and nasal irritation following 51% and 37%, respectively, of the incidences of transient high exposures.

Two studies in the literature have addressed the issue of whether occupational exposure to MMA has the potential to cause chromosome aberrations and sister chromatid exchange (SCE). Marez et al. (1991) scored SCE in lymphocytes from 31 workers occupationally exposed to MMA (mean exposures 1 to 22 ppm) and a control of 31 men whose mean age and smoking habits were similar. The number of SCE in exposed workers (7.85 ± 2.66) was similar to the control group (7.49 ± 2.33). However, the rate of SCE was significantly higher (10.0 ± 1.65) for a group that had been exposed to MMA at peak concentrations ranging from 114 to 400 ppm. Seiji et al. (1994) evaluated chromosome aberration rates and SEC frequencies in peripheral lymphocytes of 38 male workers exposed to MMA vapors at concentrations of 0.9 to 71.9 ppm. Consistent with the results of Marez et al. (1991), comparison of the exposed group with a concurrent nonexposed group revealed no evidence of mutagenicity at these relatively low exposure levels.

Marez et al. (1992) reported an increased incidence of cardiac arrhythmias and paroxysmal unspecific repolarization changes (large T waves in the ECG) among 22 workers exposed to MMA concentrations (8-h average) of either 18.5 or 21.6 ppm over 18 controls. The effects among exposed workers were found to be equally distributed over the day, did not correlate with exposure, and were few in number relative to known data concerning the normal heart. However, the authors could not exclude a role of MMA in the significant increases in these effects over controls. The relevance of this effect and its relation to MMA exposure are unclear.

Marez et al. (1993) investigated the pulmonary effects of MMA in a group of 40 occupationally exposed workers compared with a group of 45 controls. The exposed groups worked in two French factories with reported air concentrations (8-h averages) of 18.5 and 21.6 ppm MMA. Peak exposures were not reported, but the ranges were 9 to 32 ppm and 11.9 to 38.5 ppm, respectively. Eight of the 40 workers had between 5 and 10 years exposure to MMA and 32 workers had been exposed for more than 10 years. The study made use of a questionnaire and spirometry measurements of FVC, FEV_1, and maximum expiratory flow volume (MEFV) and expiratory flow volume when 50% of the forced vital capacity remained to be exhaled ($MEFV_{50}$). $MEFV_{50}$ (p=0.04) and $MEFV_{50}$/MEFV (p=0.01) showed significant reductions in the exposed group as compared with the controls following an 8-h work shift, indicating possible mild airway obstruction. An increased incidence of chronic cough was also reported for the exposed group over controls. No data were given regarding the exposure concentrations on the day pulmonary

function tests were performed, and these effects, including the reduced average $MEFV_{50}$, may have been due to acute airway irritation caused by peak exposures.

Workers (n=441) with potential exposure to MMA during 1976–1983 were given a health examination to assess possible toxic effects of the chemical (Lang et al., 1986). Duration of employment ranged from 3 months to about 30 years. Exposure concentrations ranged from 11.3 to 203.2 mg/m^3 depending on the location and year of sampling. Workers were divided into control, low-, and high-exposure groups, but the cutoff for these divisions was not given. Certain effects were increased in the high-exposure group during some years but not others (e.g., increased laryngitis, pulse rate, palpitations, dyspnea, fever, neurasthenia). Quantitative use of this study in a dose-response assessment is not possible because of concomitant exposure to other chemicals and the general lack of consideration of other possible confounding factors.

A retrospective study was conducted on 134 workers at 5 plants manufacturing polymethyl methacrylate sheets (Cromer and Kronoveter, 1976). Of these workers, 91 were exposed to MMA and 43 had no known exposure to the chemical. Effects of both acute (pre- vs. post-shift) and chronic (of unspecified duration) exposure to MMA were investigated. The authors did not report duration of exposure or employment history for any of the workers. The evaluation for chronic effects included questions administered via an extensive questionnaire (including questions on smoking habits, occupational and medical history, and respiratory, renal, hepatic, gastrointestinal, dermatologic, and neurologic symptomatology), as well as pulse and blood pressure measurements, pulmonary function tests, hematology, urinalyses, and blood chemistry. TWA concentrations were measured over an 8-h work shift for each exposed worker by personal samplers. Two samples were taken per worker per work shift and averaged. Air samples were also taken during work shifts (approximately 3 h per sample) in the buildings in which the controls worked. The exposed population was divided into three exposure groups according to average exposure: 25–50 ppm, 5–25 ppm, and less than 5 ppm per day. Concentrations of MMA in control areas were less than 0.3 ppm for all samples except one (this one was 0.8 ppm).

There were no significant differences in symptomatology, pulse rate, or blood pressure between the exposed and unexposed workers during the course of a normal workday (i.e., without peak accidental exposures). For chronically exposed workers, the only significant differences in symptomatology were for cough in the under 5 ppm group (p=0.029) and for expectoration in the 5–25 ppm group (p=0.006). However, the percentages of smokers in the under 5 ppm (62%) and 5 to 25 ppm (70%) were markedly higher than for the control group (39%). A greater number of workers in the 25–50 ppm and 5–25 ppm groups reported skin and allergy problems and nervous system symptomatology than the control group, but the difference was not statistically significant. No differences in pulmonary function parameters were observed. No significant differences in urinalysis results were found. There were no control values for this effect, however, only a “not currently exposed” group. There were several significant differences in various blood chemistry parameters between various groups and the control group, but none of these could be clearly related to exposure. The authors suggested that variations in triglycerides in all exposure categories, calcium, phosphorus, and serum glucose in the “not currently exposed” group, and serum glucose in the 25–50 ppm group warranted further investigation. The results of this study are not considered useful for a quantitative assessment because of the lack of

adjustment for smoking and the lack of information regarding worker employment history and duration of exposure.

Four hundred and fifty-four male workers, who were exposed to styrene and MMA in their work environment, were compared with a control population of workers with no known exposure to these compounds (Jedrychowdki, 1982). The control population was known to be exposed to several other chemicals, including methanol, phenol, and/or carbon monoxide. The mean concentration of MMA in workplace air was 11.06 mg/m^3 (range of 0.2–382.2 mg/m^3). Surveyed workers of both populations were also divided into subgroups of nonsmokers (consisting of ex-smokers and those who never smoked) and smokers. Chronic bronchitis and/or asthmatic symptoms were slightly lower in the exposed group than in the control group, even when smoking and nonsmoking subgroups were analyzed separately, but this difference was not significant. There was a significant difference ($p < 0.05$) in the frequency of lung obstruction between the groups, with the exposed group having an occurrence rate of more than twice the control group (45.4% vs. 18%). Smokers in the control group had a higher incidence of lung obstruction than nonsmokers (20.9% vs. 13.6%), but there was very little difference between smokers and nonsmokers in the exposed group (46.5% vs. 42.7%). There was also a significant difference in lung function, as determined by the ratio of the observed forced expiratory volume at 1 min to the expected volume ($FEV_{1(obs)}/FEV_{1(exp)}$), between exposed and control group workers and between smokers and nonsmokers. Exposed workers and smokers had lower $FEV_{1(obs)}/FEV_{1(exp)}$ values than controls and nonsmokers. Calculations of the relative risk of developing obstructive lung syndrome (using unexposed nonsmokers as the unit risk) showed the risk was highest for the group of exposed current smokers (5.5 compared with 4.7 for exposed nonsmokers and 1.7 for nonexposed smokers). Problems with this study are that concomitant exposure to other chemicals, particularly styrene, occurred in both the exposed and control groups, and there was no attempt to correlate exposure levels of MMA with observed effects. The observed lung obstruction could be due to styrene, which has been linked in other studies to throat irritation (Harkonen, 1978) and lung obstruction (Chmielewski and Renke, 1975; Lorimer et al., 1976).

Thirty-five workers from three different laboratories manufacturing dental prostheses using MMA responded to questionnaires administered by mail (Money et al., 1987). Skin exposure occurs as the dough used to make the prostheses is worked with bare hands. In addition, concentrations of MMA in the air and personal exposure concentrations in the laboratories were monitored. Of the 35 workers, 19 reported skin rashes (or similar problems), 17 reported tingling in hands, 15 suffered eye irritation during use, 12 had regular headaches, and 12 had whitening of fingers in cold. Other conditions reported (incidences not reported) were irritation to the lining of the nose, increased tingling in fingers on immersion in hot water, and dry fingertips after contact with MMA. Air concentrations in the three labs measured ranged from 0.2 to 6 ppm in one lab with good ventilation and hygiene conditions, and from 24 to 102 ppm in a lab set up in a garage that had no ventilation and poor hygiene conditions. No attempt was made to correlate measured concentrations with reported symptoms and no control group was monitored.

In a survey of the respiratory health of 780 workers exposed to MMA, information was collected on the individuals via a questionnaire, forced expiratory volume was measured, and a

posteroanterior chest x-ray was done on each participant (Monroe et al., 1981). Sex, smoking, work history, and length of service at the plant were considered in the data analyses. When confounding factors were controlled for, the only factor associated with MMA exposure was a decrease in FEV_1 in never-smokers who worked with the chemical ($p < 0.005$). The authors state that this could be an artifact of the small sample size in this category (n=17).

A cohort of 2,671 men from two American Cyanamid plants was observed from 1951 to 1983 to determine any differences in mortality between those exposed to MMA (1,561 workers) and those having no exposure (1,110 workers) (Collins et al., 1989). Cumulative exposure (calculated as the product of the number of days in the job and estimated average exposure in ppm divided by 365) to MMA was estimated for each person based on information on plant operation, and smoking status was considered in the analyses. Estimated mean cumulative exposure levels ranged from 0.13 to 1.00 ppm over the study period. Results from standard mortality ratios (SRMs) calculated for the cohort showed no increase in mortality from all causes, or from any specific cause, between the exposed and unexposed plant workers, or between exposed workers and the U.S. population.

4.1.2. Human Cancer Studies

Several cancer mortality studies have been conducted on workers exposed to MMA (and other acrylates). Walker et al. (1991) have summarized a series of studies performed by Rohm and Haas Company at their Bristol and Knoxville acrylic manufacturing sites. These studies involved a total cohort of 13,863 workers, including 3,934 white males employed at the Bristol plant between 1933 and 1945 (the so-called Early Bristol cohort; 2,904 were hired between 1941 and 1945), 6,548 white males hired at the Bristol plant between 1946 and 1986 (Later Bristol cohort), and 3,381 white males employed at the Knoxville plant between 1943 and 1982. Exposure to ethyl acrylate and/or MMA was based on job history and a job-specific exposure scale. Ethyl acrylate exposure was not determined separate from MMA exposure at any of the plants. An excess of colon cancer in workers exposed to ethyl acrylate and/or MMA when compared to local rates was reported in the Early Bristol cohort, reported by Walker et al. (1991) as shown in Table 4.

Table 4. Deaths from colon cancer in Early Bristol cohort

Achieved dose[a]	Observed deaths	Expected deaths	Fitted rate ratio[b]
None (not exposed)	12	9.66	1.24
0-4 units	13	9.39	1.39
5-9 units	6	5.17	1.16
10-14 units	1	2.24	0.45
≥ 15 units	11	4.58	2.4

[a]Doses of ethyl acrylate/MMA at least 20 years since first achieving dose; employment > 10 months.
[b]Fitted mortality ratio of cohort mortality rate and the combined Bucks County and Burlington County white male mortality rate for the same age and calendar period.

Source: Walker et al. (1991).

Cancer of the rectum was also elevated in the Early Bristol cohort (10 deaths observed; 5.23 expected) but these data are considered less significant and robust than the colon cancer data (Walker, 1991; ECETOC, 1995). In the Later Bristol cohort, a deficit of colorectal cancer, based on U.S. mortality rates, was observed (SMR for colon cancer of 0.91; SMR for rectal cancer of zero). The Knoxville cohort also showed a deficit of colorectal cancer, with SMRs for colon and rectal cancer in the whole cohort (including those not exposed) of 0.96 (20 observed versus 20.74 expected) and 0.16 (1 observed versus 6.34 expected), respectively. At 20 years after exposure, the SMR for colon cancer in the Knoxville cohort was 1.52 for all exposure categories. However, there were deficits at the higher exposure levels and an excess at the lowest level.

In the Early Bristol cohort, mortality from all causes, all malignant neoplasms, and cancer and noncancer respiratory diseases were all lower than expected. Similarly, all but mortality from all malignant neoplasms (SMR=1.02) and mortality from cancer of the respiratory system (SMR=1.05) were reduced in the Later Bristol cohort. The Knoxville cohort showed marginal increases in mortality from all causes (SMR=1.06), all malignant neoplasms (SMR=1.13), and cancer (SMR=1.44) and noncancer (SMR=1.10) respiratory disease.

As described above in Section 4.1.1, Collins et al. (1989) observed no increase in mortality from all causes, or from any specific cause, between the exposed and unexposed American Cyanamid plant workers, or between exposed workers and the U.S. population. Mortality from malignant neoplasms was similar to the U.S. population (SMR=1.04) and unexposed men in the same plant (SMR=1.01). Cancers of both digestive organs and peritoneum (SMR=0.74) and large intestine (SMR=0.39) were less than expected, with 1 colon cancer death compared to 2.6 expected (SMR=0.39), and no rectal cancer deaths. In the exposed population there was a small excess of both cancer (15 observed deaths vs. 12.5 expected; SMR=1.20) and noncancer (4 observed deaths vs. 1.9 expected; SMR=2.16) respiratory disease.

4.2. Prechronic, Chronic, and Cancer Bioassays in Animals

This section is a review of laboratory animal studies relevant to the derivation of health benchmarks for MMA. An overall synthesis of this information and its relation to the potential for MMA to cause noncancer and cancer effects is presented in Sections 4.5 and 4.6, respectively. Certain studies that were considered inadequately documented for the purposes of this assessment or that used irrelevant dosing regimens may not have been discussed in this section. A more complete listing/discussion of all types of repeat or single-exposure studies can be found in other, more detailed reviews (ECETOC, 1995; U.S. EPA, 1991).

4.2.1. Acute Inhalation Studies

Lomax et al. (1994) performed a short-term exposure study using acrylic acid, which has bearing on the relevance of the RfC derivation practice of adjusting from intermittent to continuous dosing regimens for MMA (see Section 5.1.3). Conversion of MMA to methacrylic acid is believed to be an important factor in the appearance of olfactory changes in the nasal passages of rodents exposed to MMA (Lomax et al., 1997; U.S. EPA, 1991b). Similar

observations have been made for the corresponding metabolite of ethyl acrylate, acrylic acid (AA) (Miller et al., 1985). While there are some differences between methyl-substituted and un-substituted acrylics at low exposure levels, such as the rate of glutathione binding for methacrylic acid versus acrylic acid (Stott and McKenna, 1985; Delbrissine et al., 1981; Frederick et al., 1994), the toxicologic endpoint for both compounds is the same, and the Lomax et al. (1994) acrylic acid study is deemed relevant to the derivation of the MMA RfC. Lomax et al. (1994) exposed groups of 15 B6C3F1 female mice to 0, 5, or 25 ppm AA in a whole-body inhalation apparatus for 14 consecutive days (two weeks) for 4.4, 6, or 22 h/day. Upon termination of exposure, the nasal cavity was collected from 10 animals per exposure group. The remaining 5 animals per group were maintained under standard animal husbandry conditions without exposure for 6 weeks prior to histopathologic analysis. They found that the three dose groups having similar concentration x time products (5 ppm × 22 h; 25 ppm × 4.4 h; 25 ppm × 6 h) all had very similar incidence and severity of lesions in the nasal cavity following 14 days of exposure. They also note that while nasal cavity effects induced by AA are fully reversible for these exposure groups, effects from exposure to 25 ppm AA for 22 h/day were both more severe than would be expected from a linear C × T relationship and induced lasting respiratory metaplasia.

Another inhalation study with bearing on the issue of whether to apply a duration adjustment factor to MMA intermittent exposure levels is a recent study by Pinto (1997) in which groups of 45 female F344 rats (five animals per time point) were exposed whole body for 6 h/day to 0, 110, or 400 ppm MMA for 1, 2, 5, 10, or 28 consecutive days. Minimal degeneration/ necrosis was noted at the 110-ppm exposure level following 1 and 2 days of exposure. "Regenerative changes" at the 110-ppm exposure level were noted following 5 and 10 days of exposure. These regenerative changes were characterized as disorganized epithelium of varying height "with loss of regular arrangement of cells, focal loss of apical cytoplasm and pseudoglands within the epithelium." Also noted at this exposure concentration and duration was a "depletion/loss of PAS staining affinity in the Bowman's glands, minimal hypertrophy of the Bowman's glands/ducts, and exudate within the nasal passages." No lesions were noted in rats exposed to 110 ppm for 28 days, nor in rats exposed to 110 ppm for 28 days followed by 28- day and 13-week recovery periods. The reported regeneration at the 5th and 10th days of 110-ppm exposure and lack of lesions at subsequent time points may be somewhat misleading. Other studies have shown that some functional loss occurs in rats despite apparent complete regeneration of olfactory epithelium (Wong et al., 1997; Youngentob, 1997). In addition, there is question as to whether humans have this ability to regenerate olfactory epithelium and recover even partial olfaction (Yamagishi and Nakano, 1992). Finally, Lomax et al. (1997) have reported degenerative changes in olfactory epithelium following chronic exposure to 100 ppm MMA. As noted by Pinto (1997), the apparent lack of olfactory lesions following 28 days of exposure to 110 ppm MMA suggests that degenerative olfactory epithelial changes, attributable to a direct irritant effect of MMA, develop over an extended period of time. It could also mean that degenerative changes were present in this study at 28 days in an as yet undetectable form. In any case, the extent to which rats and humans tend to recover with continuous exposure to MMA is still under investigation, and duration of exposure cannot be ruled out as a contributing factor toward the development/progression of adverse olfactory effects of MMA.

Repetitive exposures of F344/N rats and $B6C3F_1$ mice (5 of each sex and species) for 6 h/day, 5 days/week to air containing MMA at concentrations of 0, 75, 125, 250, 500, 1,000,

2,000, 3,000, or 5,000 ppm (0, 307, 512, 1,024, 2,047, 4,094, 8,189, 12,283, or 20,472 mg/m^3) for 10 or 11 days resulted in the death of all animals at the highest concentration (NTP, 1986). Two of 5 female rats exposed to 3,000 ppm died. In the groups of male mice, 2/5, 1/5, 3/5, and 4/5 exposed to concentrations of 500, 1,000, 2,000, and 3,000 ppm, respectively, died before the end of the study. Mean body weights for rats exposed to 2,000 or 3,000 ppm were 10%–19% lower than those of controls. Ruffled fur was the only clinical sign observed in rats that appeared to be related to exposure. In mice, dyspnea as well as redness and swelling of the nasal region were attributed to exposure. Short-term exposure of rats and mice to concentrations of MMA ranging from 1,191 to 16,000 ppm (4,876.5 to 65,512 mg/m^3) for 4 h produced central nervous system and respiratory effects at all exposure levels and death at the highest exposure levels. Hypoactivity, dyspnea, and anesthesia were observed in exposed animals.

Female ICR white mice were exposed to an average concentration of 1,520 ppm (6,224 mg/m^3) for 4 h/day, (two 2-h exposure periods/day, separated by 1 h of no exposure), 5 days/week, for 2 weeks (McLaughlin et al. 1979). Weight loss was greater in treated animals versus controls. No treatment-related pathological changes were observed in the tissues examined.

Exposure of 10 male Sprague-Dawley rats to 1,000 ppm (4,094 mg/m^3) for 56 h over a 7-day period produced statistically significant variations in blood chemistry and lung damage (Tansy et al., 1980b). Albumin, glucose, blood urea nitrogen, serum glutamate-oxaloacetate transaminase, serum glutamate-pyruvate transaminase, and albumin/glucose ratio were significantly lower ($p \leq 0.05$) in exposed animals than in controls. Frank lung damage consisted of adherence of visceral pleura to parietal pleura, fibrosis, lung edema, and parenchyma changes suggestive of emphysema, and was greater in exposed rats than in the sham-treated controls (quantitative data not presented). The same experimenters exposed groups of male Swiss Webster mice intermittently to 0, 100, or 400 ppm (0, 409, or 1,638 mg/m^3) MMA vapor for a total of 160 h for each group. Sleeping times, as determined by time to return of righting reflex following intraperitoneal injection of sodium pentobarbital, were significantly decreased with increasing dose in the high-exposure group ($p < 0.05$). This decrease in sleeping time could represent an induction of enzymes capable of metabolizing pentobarbital. However, at approximately 100-fold higher exposure concentrations, acute (14 min) exposures to MMA can cause an increase in pentobarbitol sleep time (Lawrence and Autian, 1972), indicating that metabolic rates and processes can vary considerably with different dosing regimens.

Male Sprague-Dawley rats were exposed to 400 ppm (1,638 mg/m^3) MMA for periods of 60 min interspersed with 30-min periods of no exposure (Innes and Tansy, 1981). Decreases in the neuronal firing rate from cells located in the lateral hypothalamus and the ventral hippocampus were observed in exposed but not control animals. No statistical analyses were done and the relevance of this observation to MMA toxicity in humans is not known.

The brains and lungs of male Sprague-Dawley rats (4 per group) were examined microscopically following exposure to 96.7 ppm (395.9 mg/m^3) MMA for 1, 2, 3, or 4 h (Raje et al., 1985). No lesions were observed in the brains of the rats. Examination of the lungs of animals exposed for 2 h or longer revealed interalveolar congestion and hemorrhage, pulmonary

vasodilation, and edema. This may be indicative of the irritating effect of MMA on pulmonary and alveolar capillaries; however, no controls were used and the group size was small.

Several studies of the acute effects of high MMA exposures, including LC_{50} studies, have been performed (Tansy et al., 1980, as reported in Oberly and Tansy, 1985; Spealman et al., 1945; Deichmann, 1941). LC_{50} estimates range from 7,093 ppm for 4-h exposures to rats to 13,200 ppm for 3-h exposures to mice. Other effects from acute (approximately 1,000 to 10,000 ppm) exposures to rats, mice, guinea pigs, and dogs included irritation of the eyes, nose, and respiratory tract, including labored breathing, hemoglobinuria, loss of reflex activity, coma, liver degeneration, and tubular degeneration in the kidney (dogs only).

4.2.2. Subchronic and Chronic Inhalation Studies

This section is a review of subchronic and chronic inhalation laboratory animal studies relevant to the derivation of health benchmarks for MMA. An overall synthesis of this information and its relation to the potential for MMA to cause noncancer and cancer effects is presented in Sections 4.5 and 4.6, respectively. Sections 4.5 and 4.6 also contain summary tables of key subchronic and chronic laboratory animal studies (Table 8) and carcinogen bioassays (Table 10).

Eighteen male beagle dogs were exposed to 0, 100, or 400 ppm (0, 409, or 1,638 mg/m^3) MMA in air for 6 h/day, 5 days/week (duration adjusted to 0, 73, or 292.5 mg/m^3), for 3 mo (Drees et al., 1979). Response of 36 variables (including systolic and diastolic blood pressure, EKG, heart and respiratory rates, hematology, pathology, clinical chemistry, and urinalyses) to exposure were monitored. No significant differences were found between exposed and unexposed animals for any of the parameters monitored.

Male Sprague-Dawley rats (50 per group) were exposed to 0 or 116 ppm (0 or 475 mg/m^3) MMA vapor for 8 h/day, 5 days/week (duration adjusted to 0 or 113 mg/m^3), for either 3 or 6 mo (Tansy et al., 1976). The authors noted that the experimental animals looked shaggy and did not groom themselves during exposure periods, and that the sham-treated controls generally had a better appearance than experimental animals. Animals exposed for 3 mo were observed to have an absence of visceral and subcutaneous fat deposits. Animals exposed for 6 mo were deficient in subcutaneous fat compared with control animals. Whole-body weight was decreased ($p < 0.05$) following both 3 and 6 mo of exposure, but the decrease was less than 10% relative to that of control animals. Lung weight and spleen weight were significantly decreased ($p < 0.05$) following 3 mo of exposure, but not following 6 mo of exposure. The weights of the epididymal fat pads and the left popliteal fat pad were decreased after 6 months exposure, but the decrease was significant only for the popliteal fat pad ($p < 0.05$). Mean serum alkaline phosphatase was significantly increased ($p < 0.05$) in both the 3-mo and 6-mo exposure groups. In the 6-mo exposure group, inorganic phosphate was significantly higher ($p < 0.05$), and total serum protein, cholesterol, blood urea nitrogen, serum glutamate-oxaloacetate transaminase, and calcium/phosphate ratio were significantly lower ($p < 0.05$) than those of the control group. The intestinal transit time was significantly lower ($p < 0.05$), and the length of the small intestine was significantly greater ($p < 0.05$) than control animals.

Sprague-Dawley rats (23 per group) were exposed to 0 or 116 ppm (0 or 475 mg/m^3) for 7 h/day, 5 days/week, for 3 mo (duration adjusted to 99 mg/m^3) (Tansy et al., 1980a). A subset of 9 animals from each group underwent special metabolic performance studies that determined food and water consumption, total fluid output, and fecal number and weight. Blood analyses, measurements of terminal body weight and organ weights, and routine histological examination of selected tissues (heart, lungs, kidneys, small bowel, and liver) were performed at the end of the 3-mo exposure period. There were no significant differences between the body weights or weights of the adrenals, epididymal fat pads, or left popliteal fat pad between exposed and control groups. Total bilirubin was significantly lower ($p < 0.05$) and cholesterol was significantly higher ($p < 0.05$) in experimental animals. Metabolic performance data were divided into two categories, 5-day mean values covering the exposure days (when only data could be collected only during the 17-h periods of no exposure) and 48-h weekend values. The only significant difference ($p < 0.05$) between exposed and control groups was an increase in average weekday fecal excretion during weeks 7, 10, and 11.

Adult male Sprague-Dawley rats were exposed by inhalation to 116 ppm (475 mg/m^3) MMA for periods of either 3 or 6 mo (Tansy, 1979a; Tansy et al., 1980b). Histologic examination of the tracheas of rats exposed for both time periods revealed epithilia denuded of cilia and reduction of the cellular covering of microvilli. The data in these papers were so poorly presented that they cannot be used to draw any meaningful conclusions regarding the effects of MMA.

Groups of F344/N rats and B6C3F$_1$ mice (10 of each sex and species per group) were exposed by inhalation to concentrations of 0, 500, 1,000, 2,000, 3,000, or 5,000 ppm (0, 2,047, 4,094, 8,189, 12,283, or 20,472 mg/m^3) for 6 h/day, 5 days/week (duration adjusted to 0, 365.5, 731, 1,462, 2,193, or 3,656 mg/m^3) for 14 weeks (NTP 1986). Animals were monitored daily, body weights were taken weekly, and necropsy and/or histologic examinations were performed on all animals. Histologic exams were done on animals in the 1,000, 3,000, and 5,000 ppm groups and on all animals dying before the end of the study. Controls were also examined histologically.

All rats in the 5,000 ppm group died. Nine of 10 and 3 of 10 females died at 3,000 and 2,000 ppm, respectively. One of 10 male rats died from each group exposed to 2,000 and 3,000 ppm. Final mean body weights were 20% and 25% less for surviving males and females, respectively, in the 3,000 ppm exposure group. At 2,000 ppm, these numbers were 7% and 11% for males and females, respectively. Initial compound-related clinical signs included listlessness, serous ocular discharge, nasal discharge, and prostration. Significant inflammation of the nasal cavity associated with necrosis and loss of olfactory epithelium was observed at 3,000 ppm and above in male rats and at 2,000 ppm and above in female rats (increased in incidence and severity with dose). Other compound-related pathologic changes included follicular atrophy of the spleen (4/10 males) and bone marrow atrophy (8/10 males in the high-dose group). Malacia and gliosis of the brain in surviving females that increased in incidence and severity with dose, and cerebellar congestion and hemorrhage of the cerebellar peduncles in early-death females at the two highest doses were observed. No NOAEL was identified for rats in this subchronic study.

In male mice, 2/10, 4/10, and 8/10 died at 2,000, 3,000, and 5,000 ppm, respectively. In female mice, 1/10 and 8/10 died at 2,000 and 5,000 ppm, respectively. Final mean body weight in

males was 13%–27% lower in exposed groups compared with controls, and final mean body weight in females was 6%–18% less than that of controls. In both sexes, final mean body weight and body weight gain decreased with increasing concentration at levels of 500 ppm and greater. Nasal epithelium metaplasia was observed in mice exposed to 500 ppm or greater. Kidney lesions (cortical necrosis, cortical tubular degeneration, and/or focal mineralization) were observed in 1/10, 3/10, and 5/10 males at concentrations of 2,000, 3,000, and 5,000 ppm, respectively. Nasal turbinate inflammation with necrosis and loss of olfactory epithelium was observed in 4/10, 5/10, and 8/10 males and 5/10, 4/10, and 8/10 females at concentrations of 2,000, 3,000, and 5,000 ppm, respectively. Three of 10 male mice had extensive necrosis of the liver at 5,000 ppm. No NOAEL was identified for mice in this subchronic study.

Male F344/N rats (50 per group) and B6C3F$_1$ mice (50 of each sex per group) were exposed to concentrations of 0, 499, or 984 ppm (0, 2,043, or 4,029 mg/m^3) for 6 h/day, 5 days/week (duration adjusted to 0, 365, or 719 mg/m^3), for 102 weeks (Chan et al., 1988; NTP, 1986). Female rats (50 per group) were exposed to concentrations of 0, 249, or 499 ppm (0, 1,020, or 2,043 mg/m^3; duration adjusted to 0, 182, or 365 mg/m^3) following the same exposure regimen as for mice and male rats. All animals were observed twice daily and clinical examinations were conducted once per week. Body weights were taken once per week for the first 13 weeks and once per month for the remainder of the study. Necropsy and histologic exams were performed on all animals. Tissues examined included gross lesions and tissue masses, regional lymph nodes, mandibular lymph node, sternebrae including marrow, thyroid gland, parathyroids, small intestine, rectum, colon, liver, mammary gland, prostate/testes/epididymis or ovaries/uterus, lungs and mainstem bronchi, nasal cavity and turbinates, skin, heart, esophagus, stomach, salivary gland, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, preputial or clitorial gland, and tracheobronchial lymph nodes. There was no significant difference in survival of rats or mice at the concentrations tested.

Mean body weights were 5%–10% lower than those of controls in male rats in the highest exposure group after week 81, and 6%–11% lower in female rats in the highest exposure group after week 73. Mean body weights in male and female mice were lower than in controls throughout most of the study period (7%–19% lower after week 21 in the low-exposure group, 5%–18% lower after week 13 in the high-exposure group for males; 5%–16% lower in the low-dose group after week 34, 4%–17% lower after week 34 in the high-dose group for females).

Inflammation of the nasal cavity was observed in both male and female rats at both exposure concentrations, at a frequency that was significantly ($p < 0.05$) greater than that observed in the control group. Both serous (37/50 low-dose males, 44/50 high-dose males, 17/50 low-dose females, 32/50 high-dose females) and suppurative (21/50 low-dose males, 30/50 high-dose males, 12/50 low-dose and high-dose females) inflammation occurred (the incidence of suppurative inflammation in females was not statistically significant). Incidences of olfactory epithelium degeneration (atrophy and metaplasia) were also significantly ($p < 0.01$) elevated in all groups (39/50 low-dose males, 42/50 high-dose males, 39/50 low-dose females, 44/50 high-dose females). LOAELs of 249 and 499 ppm for extrathoracic effects were identified for female and male rats, respectively. Alveolar macrophages were increased significantly ($p < 0.05$) in male rats (20/49 and 16/50 in the low- and high-exposure groups, respectively) and focal or multifocal fibrosis of the lung was significantly ($p < 0.05$) higher in high-exposure females (7/50). A

LOAEL of 499 ppm was identified for pulmonary effects in male rats, and a NOAEL of 249 ppm was identified for pulmonary effects in female rats. Other observed effects included a moderate increase in mononuclear cell leukemia in exposed female rats and dose-related decreases in tumors of the pituitary gland and neoplasms of the preputial gland in exposed male rats.

Mice exposed to MMA also had an increase of nasal lesions relative to control animals. These included significant ($p < 0.01$) increases in the incidences of acute and chronic inflammation (37/50 low-dose males, 42/50 high-dose males, 42/49 low-dose females, 45/50 high-dose females), epithelial hyperplasia (44/50 low-dose males, 46/50 high-dose males, 43/49 low-dose females, 47/50 high-dose females), cytoplasmic inclusions in the nasal mucosa (46/50 low-dose and high-dose males, 44/49 low-dose females, 46/50 high-dose females), and degeneration of the olfactory sensory epithelium (48/50 low-dose and high-dose males, 44/49 low-dose females, 47/50 high-dose females). A LOAEL of 500 ppm for both male and female mice was identified. Lung interstitial inflammation was significantly ($p < 0.05$) more frequent in male mice in the highest exposure group (8/50 compared to 1/50 and 0/50 in the control and low-exposure groups, respectively). This corresponds to a NOAEL of 499 ppm. Concentration-related decreases in the incidences of hepatocellular tumors in mice of both sexes, in the frequency of alveolar/bronchial tumors in male mice, and in the frequency of pituitary gland neoplasms in female mice were also observed.

F344 rats (70 of each sex per group) were exposed to mean concentrations of 0, 25, 99.79, or 396.07 ppm (0, 102.4, 408.6, 1621.7 mg/m^3) for 6 h/day, 5 days/week (duration adjusted to 0, 18.3, 73, 289.6 mg/m^3) for 2 years (Hazelton Laboratories, 1979a). Parameters monitored included mortality and other clinical signs of toxic effects, body weights, organ weights (brain, kidneys, lungs, spleen, thyroids, adrenals, and testes/ovaries), ophthamology, hematology, clinical chemistry, urinalysis, and gross and histopathology (only on animals from the control and high-exposure groups at weeks 13 and 52). Interim studies were conducted on selected animals from each group at weeks 13, 52, and 104, and from the control and high-level group at weeks 26 and 78. There were no significant differences in mortality between the exposed and nonexposed groups. Body weights in the females exposed to the highest concentration were generally significantly lower than controls after week 52, and the authors considered this to be related to exposure. There was some evidence of decreased weight gain in animals exposed to the two higher doses, but this was not analyzed in the study (the mean body weights for the control groups were about 15 to 25 grams lower at the start of the experiment than those of the high-exposure group). No differences in hematological parameters between control and exposed groups could be clearly correlated with exposure. There were significant ($p < 0.05$) increases in relative lung, liver, kidney, and ovary weights in females sacrificed at week 13, and significant ($p < 0.05$) decreases in relative thyroid and adrenal weights of rats of both sexes sacrificed at week 52. There were no adverse pathological findings that could be clearly associated with exposure to MMA vapor. No consistent trend with exposure was revealed, but microscopic examination of nasal tissues revealed minimal to slight focal rhinitis in 4/10 females exposed to 396.07 ppm (compared to 1 male and 1 female in the control group), and an inflammatory exudate was observed in 3 of the 4 exposed females. At 52 weeks, livers of 9/10 males and 6/10 females exposed to 396.07 ppm showed minimal nonsuppurative pericholangitis (compared with 5/10 control males and 2/10 control females). An increased incidence in lesions of mild rhinitis was observed in the nasal turbinates of exposed animals at week 104. These consisted of serous and

purulent exudates, pleocellular infiltrates, distended submucosal glands, focal squamousmetaplasia, and inflammatory polyps. Because the increased incidence was found in all exposure groups and did not appear to be concentration dependent, these lesions may not have been treatment related.

At the request of EPA, the U.S. Methacrylate Producers Association (MPA) commissioned a reexamination of the nasal tissue block and a rereview of the histopathology of the rat nasal tissues from the Hazelton (1979a) study (Lomax, 1992; Lomax et al., 1997). This reevaluation was requested because the initial study did not involve examination of the nasal tissues of the low- and mid-exposure groups. In addition, because of MMA's propensity to cause effects in the olfactory epithelium as demonstrated in other studies (NTP, 1986), this reanalysis included examination of nasal tissue blocks in accordance with contemporary techniques with prescribed levels of sectioning (Young, 1980). Tables 5 and 6 show the effects of MMA on both olfactory and respiratory epithelium and the various exposure levels. Chronic exposure to MMA did not appear to affect squamous epithelium at any exposure level. Effects in the respiratory epithelium were observed primarily at the 400 ppm exposure level and were described as hyperplasia of submucosal glands and/or goblet cells in the anterior regions of the nasal cavity, especially around the dorsal meati and along the nasal septa. Inflammation of the mucosa and/or submucosa was also observed. Changes to respiratory epithelium were bilateral and slight to moderate in severity. Rats exposed to 100 or 400 ppm MMA had concentration-dependent histopathological changes to the olfactory portion of the dorsal meatus in the anterior portions of the nasal cavity. Microscopic changes were primarily observed in the olfactory region lining the dorsal meatus in the anterior region of the nasal cavity. These changes were characterized by degeneration and atrophy of the neurogenic epithelium and submucosal glands lining the dorsal meatus, basal cell hyperplasia, replacement of olfactory epithelium with ciliate (respiratory-like) epithelium, and inflammation of mucosa and submucosa. These changes were generally bilateral in distribution and the severity of the lesions varied from minimal to slight at 100 ppm to slight to moderate at 400 ppm. One male rat from the 400 ppm exposure group showed severe olfactory degenerative effects (Lomax, 1992). One male rat from each of the 100 and 400 ppm exposure groups had a small solitary polyploid mass attached to the lateral wall of one side of the anterior nasal cavity. These masses were morphologically similar, consisting of differentiated

Table 5. Summary of histopathology of rats exposed to MMA for 2 years

		Males affected[a]				Females affected[a]		
	Concentration (ppm):	**0**	**25**	**100**	**400**	**0**	**25**	**100**
	No./group:	**40**	**49**	**49**	**47**	**45**	**48**	**48**
Olfactory epithelium	No. examined:	39	47	48	38	44	45	41
Degeneration/atrophy, dorsal meatus, bilateral		0	0	39	36	0	0	23
Degeneration/atrophy, dorsal meatus, unilateral		0	0	3	2	0	0	1
Basal cell hyperplasia, unilateral		4	3	1	0	0	1	1
Basal cell hyperplasia, bilateral		1	0	32	33	0	0	17
Replaced by ciliated epithelium, bilateral		0	0	0	9	0	0	7
Replaced by ciliated epithelium, unilateral		0	0	1	6	0	0	0
Inflammation chronic/active, mucosa/submucosa bilateral		0	0	16	25	0	0	1
Inflammation chronic/active, mucosa/submucosa unilateral		0	0	1	4	0	0	4
Exudate, lumen, dorsal meatus, unilateral		1	0	0	1	1	0	0
Mononuclear cell infiltrate		0	1	0	0	0	1	0
Thrombosis, blood vessels, submucosa		0	0	0	0	0	0	1
Respiratory epithelium	No. examined:	44	47	48	42	45	45	41
Inflammation chronic/active, mucosa/submucosa bilateral		0	0	1	26	1	0	0
Inflammation chronic/active, mucosa/submucosa unilateral		4	0	1	0	1	0	0
Hyperplasia, submucosal gland/goblet cell, bilateral		0	0	1	25	0	0	0
Hyperplasia, submucosal gland/goblet cell, unilateral		1	0	0	0	0	0	1
Hyperplasia, unilateral		0	0	0	2	0	0	0
Mononuclear cell infiltrate		0	1	0	0	0	1	0
Foreign body, inflammation, ventral meatus, unilateral		3	0	1	0	4	1	3
Thrombosis, blood vessels, submucosa		0	0	0	0	1	0	1
B-adenoma		0	0	1	1	0	0	0
Squamous metaplasia, unilateral		1	0	0	1	0	0	0
Squamous metaplasia, bilateral		0	0	0	1	0	0	0

[a]Death status - all animals; controls from group(s): 1.

Sources: Lomax (1992); Lomax et al. (1997).

Table 6. Severity grade of selected nasal cavity microscopic tissue changes from rats exposed to MMA for 2 years

		Males				Females			
		Concentration (ppm)							
	Severity grade	**0**	**25**	**100**	**400**	**0**	**25**	**100**	**400**
Olfactory epithelium									
Degeneration/atrophy, dorsal meatus, unilateral or bilateral	Minimal	0	0	7	0	0	0	0	0
	Slight	0	0	33	11	0	0	24	10
	Moderate	0	0	2	26	0	0	0	29
	Severe	0	0	0	1	0	0	0	0
Basal cell hyperplasia, unilateral or bilateral	Minimal	5	3	5	0	0	1	0	0
	Slight	0	0	27	14	0	0	18	23
	Moderate	0	0	1	19	0	0	0	8
Replaced by ciliated epithelium, unilateral or bilateral	Slight	0	0	2	12	0	0	7	16
	Moderate	0	0	0	3	0	0	0	5
Inflammation, mucosa/submucosa, unilateral or bilateral	Slight	0	0	16	21	0	0	5	17
	Moderate	0	0	1	7	0	0	0	8
	Severe	0	0	0	1	0	0	0	0
Respiratory epithelium									
Hyperplasia, submucosal gland/goblet cell, unilateral or bilateral	Slight	0	0	1	13	0	0	0	6
	Moderate	1	0	0	12	0	0	1	3
Inflammation, mucosa/submucosa, unilateral or bilateral	Slight	3	0	2	20	2	0	0	8
	Moderate	1	0	0	6	0	0	0	1

Sources: Lomax (1992); Lomax et al. (1997).

seudoglandular structures arising from the respiratory epithelium, and were diagnosed as polypoid adenomas. The male rat from the 100 ppm group with the adenoma had concurrent moderate chronic inflammation of the nearby respiratory epithelium. Two male rats exposed to 400 ppm MMA had squamous metaplasia of the respiratory epithelium in the anterior region of the nasal cavity.

Lakeview Golden hamsters (56 per sex per group) were exposed to 0, 24.77, 100.06, or 398.68 ppm (0, 101, 410, or 1,632 mg/m^3) MMA vapor for 6 h/day, 5 days/week, for 78 weeks (duration adjusted to 0, 18, 73, or 291 mg/m^3) (Hazelton Laboratories, 1979b). Clinical signs, body weight, hematology, and gross and histopathology were monitored in the animals. Microscopic examination was done only on tissues from control and high-exposure animals. At week 78, mortality in the male hamsters exposed to 400 ppm was about twice that of controls. Mortality in females in the high-level group was more than twice that of controls from weeks 0–52, but was about the same as controls at week 78. No treatment-related differences in body weight, clinical signs, hematological parameters, or gross pathology were observed. There was an increased incidence of blood in the nasal turbinates of high-exposure males which the authors attributed to the necropsy procedure. No other significant differences were found on microscopic examination of the hamsters.

4.2.3. Acute Oral Studies

Central nervous system effects were observed in Wistar rats given 500 mg/kg body weight/day MMA in olive oil by gavage for 21 days (Husain et al., 1985; Husain et al., 1989). Treated rats were observed to be lethargic and had gait defects and hind limb weakness for about 10 min after each treatment. Locomotor activity and learning ability were significantly decreased and aggressive behavior was significantly increased in exposed rats compared with controls. There were several significant alterations in biogenic amines in exposed animals. Significant increases in cholesterol and triglycerides and a significant decrease in total phospholipids were observed in the sciatic nerve of treated rats compared with controls.

Ghanayem et al. (1986) administered MMA in corn oil (0, 100, and 200 mg/kg/day, 5 days/7 days/week) for 2 weeks to male F344 rats. No significant increase of mucosal cell proliferation or hyperkeratosis was observed following histopathologic examination of the forestomach (only organ examined).

Microscopic examination of the livers of Swiss strain white mice (Swiss strain) administered 1% to 20% MMA in olive oil by direct esophageal instillation showed a dose-dependent increase in the frequency and severity of mild to moderate liver injury at doses of 6% and greater (Mallory et al., 1973). Abnormalities consisted of swollen cells with nuclei altered in size and shape and congested sinusoids at concentrations of 6% to 10%. At concentrations of 11%, there was evidence of central and mid-zonal fatty changes with central lobular alteration, and at concentrations above 11% there was massive fatty infiltration with alteration and disruption of the liver nuclei.

The LD_{50}s for MMA have been estimated to be 7.9–9.4 g/kg, 5.9 g/kg, and 4.7 g/kg in rats, guinea pigs, and dogs, respectively (Deichmann, 1941; Spealman et al., 1945). The lowest

lethal dose in rabbits administered MMA by gavage was 6.5 g/kg (Deichmann, 1941). Toxic symptoms included increased respiratory rate and motor weakness. These were followed by decreased respiration at 15 to 40 min post-administration, shallow and irregular respiration, increased urination and defecation, hemoglobinuria, loss of reflex activity, coma, and death.

4.2.4. Subchronic and Chronic Oral Studies

This section is a review of subchronic and chronic oral laboratory animal studies relevant to the derivation of health benchmarks for MMA. An overall synthesis of this information and its relation to the potential for MMA to cause noncancer and cancer effects is presented in Sections 4.5 and 4.6, respectively. These sections also contain summary tables of key subchronic and chronic laboratory animal studies (Table 8) and carcinogen bioassays (Table 10).

Borzelleca et al. (1964) found no significant toxic effects in male and female dogs (2 males and 2 females per treatment group) receiving MMA via gelatin capsule in the diet at 10, 100, or 1,473 ppm daily for 1 year. The high exposure concentration represented a time-weighted average based on the 1,000 ppm value increasing to 1,200 ppm at 5 weeks, to 1,400 ppm at 7 weeks, and to 1,500 ppm at 9 weeks.

Borzelleca et al. (1964) also exposed groups of 25 male and 25 female Wistar rats to MMA in drinking water for 104 weeks. The initial exposure concentrations were 6, 60, and 2,000 ppm MMA. The low and medium exposures were increased to 7 and 70 ppm, respectively, at the start of the fifth month, resulting in TWA exposure concentrations of 6.85 and 68.46 ppm MMA. Survival of exposed rats was not significantly different from controls. An initial reduction in body weight gain was observed in both males and females exposed to 2,000 ppm MMA, which reverted to control levels by week 3 (females) and week 6 (males). This is likely the result of reported reduced food intake during the first month, which was not observed in the second month and beyond. No other effects on body weight gain were reported, but drinking water consumption was significantly lower than controls in males and particularly females of the high-exposure groups. Hematological parameters were normal throughout the study in all groups, and no compound-related effects were observed on urinary protein or reducing substances. Tissues examined included heart, lung, liver, kidney, urinary bladder, spleen, gastroenteric, skeletal, muscle, skin, brain, thyroid, adrenal, pancreas, pituitary, and gonads. The only effect observed was an increased kidney/body-weight ratio in female rats exposed to 2,000 ppm MMA. No abnormalities or lesions related to MMA were identified from histopathological examination of the tissues of exposed rats. In addition to testing with MMA, these authors also exposed Wistar rats to ethyl acrylate (EA) under the same exposure regimen. The EA-exposed rats closely paralleled the MMA-exposed rats with respect to all results except female body weight. EA caused a significant reduction in the body weights of the females in the high-dose group.

Motoc et al. (1971) orally administered methyl methacrylate to albino rats for 3 (20 exposures), 5 (41 exposures), or 8 (63 exposures) months. Total doses were reported as 2,750, 5,500 and 8,125 mg/kg, respectively, for these exposure periods. The authors reported duration-related increases in histopathologic alterations of the liver, ulcerations of the stomach, and biochemical alterations (elevated serum enzyme activity), but no further details were described.

4.3. Reproductive and Developmental Studies

This section is a review of reproductive and developmental studies relevant to the derivation of health benchmarks for MMA. An overall synthesis and summary table (Table 9) of this information and its relation to the potential for MMA to cause reproductive or developmental effects is presented in Section 4.5. Certain studies that were considered to be inadequately documented for the purposes of this assessment or used irrelevant dosing regimens may not have been discussed in this section. A more complete listing/discussion of all types of repeat or single-exposure studies can be found in other, more detailed reviews (ECETOC, 1995; U.S. EPA, 1991).

Pregnant Sprague-Dawley rats were exposed to ≈110 mg/L (110,000 mg/m^3) MMA for either 17.2 or 54.2 min/day (approximately 1/4 and 3/4 of the $LT_{50,}$ time required to kill 50% of the exposed group, for this concentration) on days 6 through 15 of gestation (Nicholas et al., 1979). Clinical signs, body weight, and food consumption were monitored in the dams. On the 20th day of gestation, the dams were necropsied and reproductive parameters were examined (number of corpora lutea, number and position of living fetuses, and number and position of resorptions and early fetal deaths). The crown-rump length, sex, and weight of each fetus was determined and each was examined for gross and skeletal abnormalities. Maternal body weight in the long-exposure group was significantly different from sham-treated and untreated controls on days 11, 15, and 20. Maternal body weight in the short-exposure group was significantly decreased compared to untreated controls on day 15 and from both control groups on day 20. Initial deviation from control values for both groups was obvious from day 7, with untreated controls having the highest weights, followed by sham-treated, short-exposure, and long-exposure, in order of decreasing body weights. Normalized food consumption values were lower throughout the exposure days (6–15) for exposed groups than for controls. Early fetal deaths were significantly higher for the exposed animals. Fetal body weight and crown-rump length were significantly lower ($p < 0.05$) for both the short- and long-exposure groups and appeared to decrease with increasing exposure time. A dose-related increase in hematomas occurred, with the difference from controls significant ($p < 0.05$) for the long-exposure group. An increase in short crooked tails also occurred in the long-exposure group, but the difference was not significant. There were increases in the incidence of fetal skeletal anomalies (delayed ossification of the vertebrae and other vertebral anomalies, delayed ossification of the sternebrae, rudimentary 14th ribs, and fused and stunted ribs) in the exposed group, but only the increases in the delayed ossification of vertebrae in the long-exposure group and the delayed ossification of sternebrae in the short- and long-exposure groups were significantly different ($p < 0.05$) from controls. The LOAEL (and $LOAEL_{HEC}$) for developmental effects in these animals is 110,000 mg/m^3.

Eighteen pregnant ICR white mice were exposed to the vapors of the liquid monomer of the acrylic cement Simplex P (97.4% MMA, 2.6% N,N-dimethyl-p-toluidine, and 75 ppm hydroquinone) (McLaughlin et al., 1978). Animals were exposed to 1,330 ppm (5,446 mg/m^3) for 2 h/day, twice daily from day 6 through day 15 of gestation. The two exposure periods were separated by a 1-h period of no exposure. Fourteen pregnant mice of the same strain served as unexposed controls. The majority of the fetuses from both groups of mice were normal (94.9% in the control group and 96.2% in the treated group). There was no significant difference in the

number of fetal resorptions, abnormal or dead fetuses, or litter size between the treated and control animals. However, the average fetal weight of the exposed animals was significantly greater ($p < 0.001$) than that of controls (0.84 g and 0.90 g for the control and treated groups, respectively). The significance of this is unknown.

CD-BR rats (27 rats per group) were exposed to concentrations of 0, 99, 304, 1,178, or 2,028 ppm (0, 405, 1,245, 4,823, or 8,304 mg/m^3) MMA for 6 h/day on days 6 to 15 of gestation (Solomon et al., 1991, 1993). Clinical signs, body weight, food consumption, and morbidity and mortality were monitored in the dams. Dams were sacrificed and necropsied on day 20 of gestation, and reproductive developmental parameters were examined (uterus weight, number of corpora lutea, implantation sites, resorptions, number of fetuses per litter and their location, fetus weight and sex, and external, visceral, and skeletal alterations). Treatment-related decreases in maternal body weight gain during the experimental period were observed in all exposure groups, but were transient at the two lowest exposure concentrations. Food consumption was decreased in all exposed groups during the exposure period. No gross pathological changes were observed in the dams at necropsy. Unlike the study described above by Nicholas et al. (1979), in which dams were exposed during gestation to much higher concentrations but shorter daily exposure durations, no treatment-related effects on reproductive or developmental parameters were observed. A NOAEL of 2,028 for developmental effects in rats is identified from the results of this study.

Pregnant CD1 mice were exposed to 0 (38 mice), 116 (32 mice), or 400 (18 mice) ppm (0, 475, or 1,638 mg/m^3) for two 3-h periods per day, interrupted by a 1-h nonexposure period, on days 4 to 13 of gestation (Tansy, 1979b). Condition and body weight of the mothers was monitored. Mice were sacrificed on day 18 of gestation and offspring were examined for viability, gross abnormalities, or skeletal and visceral abnormalities. No adverse effects of exposure were observed in the dams. The mean weight of living fetuses was significantly lower ($p \leq 0.05$) in both exposed groups than in the sham-treated controls, but there was no concentration-related trend. No other adverse effects appeared to be related to treatment. The high concentration is considered a NOAEL for reproductive and developmental effects (NOAEL of 400 ppm).

Pregnant rats were exposed by inhalation to 0, 0.52, or 4.48 mg/L (0, 520, or 4,480 mg/m^3) MMA vapors for 2 h/day, every 3 days from days 6 to 18 of gestation (Luo et al., 1986). There were no obvious toxic effects on the dams. There was a statistically significant ($p < 0.01$) increase in resorptions in the high-level group compared to both the low-level and control groups. Delayed ossification was observed in both groups, but the incidences and statistical significance were not reported. The high concentration is considered a LOAEL for embryotoxicity. This reference was an abstract and had no data tables or figures.

In a dominant lethal assay performed by ICI (1976a), CD-1 male mice were exposed to 100, 1,000 or 9,000 ppm MMA, 6 h/day, for 5 days. Each male was mated with 2 different unexposed female mice weekly over a period of 8 weeks. There were no significant differences in the fertility of the exposed males or in the survival rate, total implants, and early or late post-implantation loss in the offspring of exposed males compared with controls.

ICI (1977) also exposed groups of 30 female Alderley Park SPF rats to 0, 100 and 1,000 ppm MMA, 5 h/day, from days 6 to 15 of gestation. The experiment was performed a second time using the same exposure levels plus 25 ppm. In the first experiment, the 1,000 ppm exposure level, which was slightly maternally toxic, produced an increase in the numbers of early resorptions and possibly affected the total numbers of late resorptions. Delayed ossification was also noted at this exposure level.

Smirnova and Blagodatin (1977, as reported in U.S. EPA, 1985) reported that rats inhaling 54 mg/m^3 MMA continuously for 1 to 4 months showed increased estrogen secretion by the ovaries, and this apparently increased the follicle-stimulating activity of the pituitary. The relevance of these data to a human hazard assessment is questionable.

Groups of 5 female Sprague-Dawley rats were administered i.p. doses of 0, 0.1328, 0.2656, and 0.4427 mL MMA/kg/bw (1/10, 1/5, and 1/3 of the acute LD_{50} value) on days 5, 10, and 15 of gestation (Singh et al., 1972). No skeletal malformations were seen, but a dose-dependent increase of gross abnormalities (haemangiomas) was found in fetuses. Maternal toxicity to the dams was not examined. In addition, the extent to which the fetus is exposed following maternal i.p. injection and the relevance of this route of administration to other exposure routes remains unclear.

4.4. Other Studies Related to Noncancer or Cancer Effects From Chronic Exposure to Methyl Methacrylate

This section is a review of other studies relevant to the derivation of health benchmarks for MMA. An overall synthesis of this information and its relation to the potential for MMA to cause noncancer and cancer effects is presented in Sections 4.5 and 4.6, respectively. Certain studies that were considered to be inadequately documented for the purposes of this assessment or used irrelevant dosing regimens may not have been discussed in this section. A more complete listing/discussion of all types of studies can be found in other, more detailed reviews (ECETOC, 1995; U.S. EPA, 1991b).

4.4.1. Genotoxicity

Table 7 gives a summary of the genotoxicity data for MMA. MMA has demonstrated positive and negative results in tests for genotoxicity. An increased incidence of chromosome aberrations and sister-chromatid exchange (SCE) was noted in lymphocytes of workers occupationally exposed to 114 to 400 ppm MMA (Marez et al., 1991). The study did not exclude for several factors (e.g., vaccinations, virus infections, white blood counts, alcohol consumption,

Table 7. Genotoxicity of methyl methacrylate

Test	Indicator organism	Metabolic activation[a]	Dose[b]	Response	Reference
In vitro bacterial gene mutation assays	*Salmonella typhimurium* strains TA 100, TA 1535, TA 1537, TA 1538, TA 98	+ and -	100 to 10,000 µg/plate	-	Waegemaekers and Bensink, 1984; National Toxicology Program, 1986; Anderson et al., 1979; also Dupont, 1975; ICI, 1980; Zeiger, 1987; Hachiya et al., 1981; and Jensen et al., 1991; as referenced in ECETOC, 1995
	Salmonella typhimurium strain TM677 (forward mutation to 8-azaguanine resistance)	+	0, 10, 50, 100 mM × 2 h	+	Poss et al., 1979
	Salmonella typhimurium strain TM677 (forward mutation to 8-azaguanine resistance)	-	0, 10, 50, 100 mM × 2 h	-	Poss et al., 1979
In vitro mammalian cell gene mutation assays	L5178Y/TK$^{+/-}$ mouse lymphoma cells	+ and -	500 to 3,100 µg/mL	+	Moore et al., 1988; and Dearfield et al., 1991, as referenced in ECETOC, 1995
	L5178Y/TK$^{+/-}$ mouse lymphoma cells	+ and -	0.125 to 1.5 µL/mL	+	National Toxicology Program, 1986; also Cifone, 1981; and Myhr et al., 1990, as referenced in ECETOC, 1995
In vitro chromosome damage assays	Chinese hamster ovary cells	+	160, 500, 1,600, 5,000 µg/mL	Increase at 5,000 µg/mL only	National Toxicology Program, 1986
	Chinese hamster ovary cells	-	750, 1,000, 1,600, 3,000 µg/mL	Slight dose-related increase	National Toxicology Program, 1986
In vitro sister chromatid exchange assays	Chinese hamster ovary cells	+ and -	Up to 3,000 µg/mL	Dose-related increase	National Toxicology Program, 1986
	Human lymphocyte cultures	NG	Up to cytotoxic levels	-	Cannas et al., 1987

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Table 7. Genotoxicity of methyl methacrylate (continued)

Test	Indicator organism	Metabolic activation[a]	Dose[b]	Response	Reference
Dominant lethal assay	CD-1 male mice	NA	100 to 9,000 ppm 6 h/day, 5 days	-	ICI, 1976a
In vivo chromosome damage laboratory animal assays	Rat bone marrow	NA	100 to 9,000 ppm 6 h/day, 5 days	-	ICI, 1979
	Rat bone marrow cells	NA	NG	Non-dose-related chromosome damage	Anderson et al. (1979)
	Rat bone marrow cells	NA	0, 100, 1,000, 9,000 ppm, or 100, 400, 700, 1,000 ppm, single 2-h exposures or multiple exposure of 5 h/day for 5 days	Weak increase in chromosone damage	Smith, 1980
In vivo chromosome damage human occupational studies	Cells from peripheral lymphocytes of human volunteers occupationally exposed to MMA	NA	1 to 72 ppm in air	-	Marez et al., 1991 Seiji et al., 1994
	Cells from peripheral lymphocytes of human volunteers occupationally exposed to MMA	NA	114 to 400 ppm	+	Marez et al., 1991

[a]NA = not applicable.
[b]NG = not given.

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and smoking) that can affect SCE. In addition, the SCE increase was slight and in a small subgroup of workers. The significance of SCE assay results for this and other studies has been questioned (Tucker et al., 1993; ECETOC, 1995).

Positive results were obtained in a gene mutation assay with mouse lymphoma cells with and without activation (National Toxicology Program, 1986), in a sister-chromatid exchange assay using Chinese hamster cells (CHO cells) with and without activation; in a chromosome aberration test using CHO cells with and without activation (no dose response, however, with activation); in a chromosome damage assay using rat bone marrow cells (no dose response); and in the induction of forward mutation to 8-azaguanine resistance in *S. typhimurium* strain TM677, with activation (only at doses resulting in 80% cell mortality, according to National Toxicology Program, 1986). The results of the mouse lymphoma cell assay, in which the response with activation was proportional to concentration and was observed at lower concentrations than in tests without activation, and positive results seen in the *S. typhimurium* strain TM677 test suggest that a metabolite of MMA may be contributing to the observed genotoxicity.

Negative results were seen in the Ames assay using the standard tester strains and in a bone marrow micronucleus test (Hachiya et al., 1982), and workers exposed occupationally to no more than 72 ppm did not show signs of sister chromatid exchange or chromosome aberrations (Marez et al., 1991; Seiji et al., 1994). In addition, several short-term tests on the carcinogenic effects of MMA conducted at Imperial Chemical Industries' (ICI) Central Toxicology Laboratories (CTL) were negative (Smith, 1980). In the BHK21 mammalian cell transformation assay (so-called Styles test) MMA was found to be a nontransforming agent. Four other tests—the sebaceous gland suppression test, the subcutaneous gland implant test, the tetrazolium reduction test, and Rabin's degranulation of RER test—were also negative.

4.4.2. Allergies/Sensitization

Sensitization has not been tested in experimental animals following either oral or inhalation exposure to MMA. There is currently no recognized and validated animal model available for the prediction of respiratory sensitization hazard (ECETOC, 1995). However, MMA has been extensively tested in more than 40 skin sensitization assays in guinea pigs or mice. A detailed review of the numerous studies in this area is beyond the scope of this document. A complete review was performed by the ECETOC Joint Assessment of Commodity Chemicals (ECETOC, 1995). In summary, positive reactions were obtained in skin tests of laboratory animals, particularly when high concentrations were used and evaporation of the substance from the skin was avoided by using a highly viscous solvent or occluded application. Cross reactions with other methacrylic acid esters and stabilizers such as hydroquinone may contribute to the observed sensitization reactions of MMA.

Repeated exposure of human volunteers to undiluted MMA has also led to skin sensitization (Cavelier et al., 1981; Spealman et al., 1945). However, the data with respect to MMA's potential to be a respiratory sensitizer are less clear (ECETOC, 1995). A case report (Pickering et al., 1986) reported a delayed asthmatic response following challenge with MMA. However, there is no evidence of a respiratory sensitization effect in several recent occupational studies of workers exposed to MMA (ECETOC, 1995).

4.4.3. Dermal and Ocular Effects

MMA has been determined in laboratory animal and human studies to be mildly irritating to the skin and eyes, and to the mucosa of the respiratory tract (ECETOC, 1995). Single doses of 10 mL/kg MMA applied to the clipped abdomen of rabbits produced temporary local irritation, but the animals recovered within an hour (Deichmann, 1941). Castellino and Colicchio (1969) observed slight reaction in rabbit skin following the topical application of MMA for 15 days to the shaved skin. Acute local necrotic toxicity was noted by Linder (1976) when MMA was injected subperichondrially on the outer surface of the ears of rabbits.

Castellino and Colicchio (1969), Cavelier et al. (1981), and others (see ECETOC, 1995) have observed reddening of the conjunctiva in rabbits after repeated instillations of MMA in the eyes. Holyk and Eifrig (1979) studied the effects of MMA on rabbit eyes by injecting 500, 5,000, and 50,000 ppm into the anterior chamber. At these high exposure concentrations, MMA was highly toxic to the tissues of the anterior segment of the rabbit eye, causing limbal hyperemia, corneal edema, corneal neovascularization, iris engorgement, anterior chamber inflammation, iris atrophy, and cataract.

4.5. Synthesis and Evaluation of Major Noncancer Effects and Mode of Action

The absorption and hydrolysis of MMA to methacrylic acid and subsequent metabolism via physiological pathways results in a low systemic toxicity by any route of exposure. However, 10% to 20% of inhaled MMA is deposited in the upper respiratory tract of rats, and the hydrolysis of MMA by local nasal tissue esterases to methacrylic acid in this region has been cited as the primary reason for MMA's selective olfactory toxicity (Lomax, 1992; Lomax et al., 1997).

Table 8 summarizes key subchronic and chronic laboratory animal studies of MMA. Subchronic and chronic exposure of rats and mice to MMA by oral and inhalation (and dermal) routes results in effects consistent with its irritant properties. In inhalation studies, dose-related lesions have been observed in the upper respiratory tract, including rhinitis, inflammation associated with necrosis, degeneration/loss of olfactory epithelium in the nasal turbinates, and lung congestion. Exposures to very high levels of MMA (> 1,000 ppm) can result in neurochemical and behavioral changes, reduced body weight gain, and degenerative and necrotic changes in the liver, kidney, brain, spleen, and bone marrow. Relatively low concentrations can cause changes in liver enzyme activities. The data concerning MMA's ability to cause cardiovascular effects are inconsistent. Several publications in the literature suggest that MMA may have cardiovascular and/or neurotoxic effects in occupationally exposed human beings. These effects may not represent neurotoxicity because they are generally nonspecific, and workers were exposed to several other toxic compounds. In general, MMA has not resulted in

Table 8. Key subchronic and chronic laboratory animal studies of methyl methacrylate

Animal	Route	Number of animals	Dose/concentration	Critical effects/NOAEL/LOAEL	Reference
Rat	ihl	Not given	116 ppm for 3 or 6 mo (542 h or 1,105 h)	Damage to tracheal mucosa: small areas of focal hemorrhage in 6-mo group. Epithelium denuded of cilia, reduction in cellular covering of microvilli in 3-mo group. LOAELs at 116 ppm (both durations) based on extrathoracic respiratory effects.	Tansy et al., 1980b
Rat	ihl	70 M, 70 F	0, 25, 100, 400 ppm × 6 h/d, 5 d/wk × 2 yr	Histopathological changes to the olfactory portion of the dorsal meatus in the anterior portions of the nasal cavity at 100 or 400 ppm. NOAEL at 25 ppm; LOAEL at 100 ppm.	Hazelton Laboratories America, 1979b; Smith, 1980; Lomax, 1992; Lomax et al., 1997
Hamster	ihl	Not given	0, 25, 100, 400 ppm × 6 h/day, 5 day/week × 18 mo	Cumulative mortality of males in 400-ppm group higher than controls at week 78. NOAEL at 100 ppm; LOAEL at 400 ppm.	Hazelton Laboratories America, 1979a; Smith, 1980
Rat	ihl	50 M, 50 F	Male - 0, 500, 1,000 ppm Female - 0, 250, 500 ppm × 6 h/day, 5 day/week × 102 wk	Inflammation of nasal cavity and degeneration of olfactory sensory epithelium. LOAELs at 500 and 250 ppm (males and females, respectively) based on extrathoracic (olfactory) effects.	National Toxicology Program, 1986
Rat	ihl	10 M, 10 F	0, 500, 1,000, 2,000, 3,000, 5,000 ppm 6 h/day, 5 day/week over 14 week	All died at 5,000 ppm dose, 1 male and 9 females died at 3,000 ppm dose. Necrosis and loss of olfactory epithelium in nasal turbinates at 3,000 and 5,000 ppm in males and at >2,000 ppm in females. Malacia and gliosis in 5/9 females at 2,000 ppm. LOAEL at 500 ppm based on nasal effects.	National Toxicology Program, 1986
Mouse	ihl	50 M, 50 F	0, 500, 1,000 ppm × 6 h/day, 5 d/week × 102 week	Inflammation and epithelial hyperplasia of the nasal cavity, degeneration of olfactory sensory epithelium. LOAEL of 500 ppm (males and females) based on olfactory effect.	National Toxicology Program, 1986
Mouse	ihl	10 M, 10 F	0, 500, 1,000, 2,000 3,000, 5,000 ppm × 6 h/day, 5 d/week over 14 week	8 males and 8 females died at 5,000, 3,000, 5,000 ppm 6 h/day, ppm. Inflammation of nasal turbinates, nasal epithelium metaplasia. Renal cortical necrosis, renal tubular degeneration, liver necrosis in males. LOAEL of 500 ppm based on olfactory effects.	National Toxicology Program, 1986
Rat	orl	25 M, 25 F	up to 2,000 ppm × 2 yr	NOAEL of 2,000 ppm based on lack of exposure-related effects.	Borzelleca et al., 1964
Dog	orl	2 M, 2 F	up to 1,500 ppm × 2 yr	No significant toxic effects. NOAEL of 1,500 ppm.	Borzelleca et al., 1964

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Table 9. Developmental and reproductive effects of methyl methacrylate

Route	Species	Dose	Fetal effects	Reference
Inhalation	Male CD-1 mice	100, 1,000 or 9,000 ppm, 6 h/day, for 5 days	No effect on fertility of males, nor on survival rate, total implants, and early or late post-implantation death in offspring of exposed males.	ICI, 1976
Inhalation	Female Aderley Park SPF rats	0, 25, 100, and 1,000 ppm, 5 h/day from days 6 to 15 of gestation	The 1,000 ppm exposure level was slightly maternally toxic, and produced an increase in numbers of early resorptions and possibly impacted total numbers of late resorptions. Delayed ossification was also noted at this exposure level.	ICI, 1977
Inhalation	Rats (strain not stated)	2 h/day, every 3 days from days 6 to 18 of gestation	Statistically significant ($p < 0.01$) increase in resorptions in high-level group compared with both the low-level and control groups. Delayed ossification both groups, but the incidences and statistical significance were not reported.	Luo et al., 1986
Inhalation	Female ICR mice	1,330 ppm for 2 hrS, 2x/day during day 6 through day 15 of pregnancy	Slight increase in average weight of fetuses.	McLaughlin et al., 1978
Inhalation	Female Sprague-Dawley rats	110 mg/L (26,646 ppm) for 17.2 or 54.2 min (approx. 1/4 and 3/4 or the LT_{50}) daily on days 6 through 15 of gestation	Longer exposure group had significant deaths, decrease in fetal weight and crown-rump length, increase of fetuses with hematomas, increase in occurrence of delayed ossification, skeletal anomalies such as missing vertebral center and stunted ribs. Neither group had significant alteration of implantations, resorptions, number of living fetuses per litter. Both groups had delayed skeletal ossification.	Nicholas et al., 1979
Inhalation	Female Crl:CDRBR rats	0, 99, 304, 1,178, and 2,028 ppm, 6 h/day from days 6 to 15 of gestation	Treatment-related decreases in maternal body weight gain in all exposure groups (transient at the two lowest exposure concentrations). Decreased food consumption in all exposed groups. No gross pathological changes in the dams at necropsy. No treatment-related effects on reproductive or developmental parameters.	Solomon et al., 1991, 1993
Inhalation	Female CD-1 mice	0, 116, and 400 ppm, 6 h/day from days 4 to 13 of gestation	Decreased mean weight of living fetuses ($p \leq 0.05$) in both exposed groups, but no concentration-related trend. No other adverse effects appeared to be related to treatment.	Tansy, 1979b
Injection	Chickens (White Leghorn), three-day-old embryos	2.3, 4.5, 9, 18, 36 mol/per egg	67% of all embryos were affected in the 36 µmol/egg group and in the 4.5, 9, and 18 µmol/egg groups, respectively (i.e, a low-dose range). 71% of corneal and lid defects occurred ED^{50} µmol/egg.	Korhonen et al., 1983
Intraperitoneal injection	Sprague-Dawley rats	0.4427, 0.2656, 0.1328 mL/kg on days 5, 10, and 15 of gestation	5.9% resorptions, 16.7% gross abnormalities (hemangiomas) in 0.4427 mL/kg group. No skeletal malformations.	Singh et al., 1972

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serious adverse effects to humans. In certain individuals it has been shown to induce allergic dermatitis from skin contact. Mild eye irritation and respiratory tract irritation have been reported, but the evidence available does not allow for a determination regarding respiratory sensitization.

Table 9 summarizes developmental and reproductive studies of MMA. No oral studies have investigated the developmental or reproductive toxicity of MMA. Evidence for developmental effects from inhalation exposure is mixed and generally occurred at maternally toxic exposure levels. Solomon et al. (1993) found no developmental effects in rats exposed 6 h/day during days 6-15 of gestation to atmospheric concentrations of up to 2,028 ppm (8,304 mg/m^3). Tansy (1979b) and McLaughlin et al. (1978) found no developmental effects in mice exposed 6 h/day to up to 400 ppm and 2 h/day to 1,330 ppm, respectively, during days 6-15 of gestation. However, Nicholas et al. (1979) found evidence of developmental effects (early fetal deaths, delayed ossification, decreased fetal body weight and crown-rump length, hematomas) in Sprague-Dawley rats exposed for approximately 1 h/day during days 6-15 of gestation to levels more than an order of magnitude higher (110,000 mg/m^3). But nearly 20% of the exposed pregnant rats died at this exposure level. In addition, ICI (1977) and Luo et al. (1986) describe both delayed ossification and increased resorptions in rats exposed during days 6-15 of gestation to 1,000 ppm MMA (5 h/day and 2 h/3 days, respectively). No adequate one- or two-generation reproductive studies were available by any route of exposure. MMA did not reveal an effect on male fertility in mice inhaling up to 9,000 ppm MMA for 6 h/day over a period of 5 days (ICI, 1976a). These data suggest that at high, maternally toxic doses, MMA can cause developmental effects. However, there is no reason to believe that developmental toxicity should represent a critical or co-critical effect in the RfC or RfD derivation. The lack of adequate reproductive studies is not a major concern given the limited evidence for systemic or genotoxic effects from MMA exposure, but will be considered in the determination of uncertainty factors (Sections 5 and 6).

4.6. Weight-of-Evidence Evaluation and Cancer Characterization

4.6.1. Genotoxicity and Animal Evidence

Table 7 gives a summary of the genotoxicity assay results. When tested at cytotoxic concentrations, MMA does not appear to be mutagenic to bacteria. MMA has been shown to be an in vitro clastogen in mammalian cell gene mutation and chromosomal aberration assays. However, MMA has not been shown to result in clastogenic effects or dominant lethal mutations following laboratory animal in vivo, inhalation (ICI, 1976a), or oral exposures (Hachiya et al., 1981), and human data (Marez et al., 1991; Seji et al., 1994) are equivocal.

Table 10 gives a summary of carcinogenicity tests in experimental animals. One interest in the testing for carcinogenicity is to determine whether prostheses and other medical applications of MMA are carcinogenic in humans. Carcinogenic tests have been performed that suggest that tumors can form when laboratory animals are subjected to subcutaneous implants of poly-MMA (Laskin et al., 1954; Ferguson, 1977). While some researchers (Homsy et al., 1972; Bright et al., 1972) have shown some leaching of monomeric MMA from poly-MMA surgical

Table 10. Key carcinogenicity findings in laboratory animal studies of methyl methacrylate

Route of administration	Species/strain	Dose	Duration of exposure	Findings	Reference
Subcutaneous implants in flank	A/BiF/F50+ mice	2.4 × 13 mm discs of poly-MMA. Some with cellulose filters bonded by Millipore MF cement	83 weeks	Discs alone produced sarcomas in 12% of mice at 64 weeks. Discs covered by 0.45 µm filters produced no sarcomas up to 83 week (p<0.001). Discs covered by 0.025 to 0.1 µm filters produced sarcomas in 60% of mice in 64 weeks (p<0.001)	Ferguson, 1977
Implanted subcutaneously in lateral abdominal wall	50 Harlan strain albino Swiss mice, 6 weeks old	1 × 1 on MMA film (combined monomer and polymer compressed into film and polymerized)	First tumor observed at 257 days. Others at 405, 438, 454, and 469 days	25% incidence of fibrosarcomas (5 of 20 surviving mice)	Laskin et al., 1954
Subcutaneous injection in back, painting on back, or subcutaneous implantation in abdominal wall	Sprague-Dawley and Donryu rats (8 groups of 20 animals)	Implants in form of perforated bowl, unperforated square film or resin tooth (combined monomer and polymer compressed and polymerized. Injection or painting with 0.1 to 0.2 mL of monomer, 2× week for 3 mo	3 mo, observed until natural death or appearance of tumors	38.8% tumors (fibrosarcomas) in rats with square film implants, 26.3% tumors in rats with square film implants + painting, 30.8% tumors in rats with resin tooth implant. No tumors in rats with perforated bowl implants, or in those injected or painted.	Okada, 1966
Dermal (on back of neck)	10 rats	Painting 3× per week (concentration not given)	4 mo	No tumors induced	Oppenehimer et al., 1955

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Table 10. Key carcinogenicity findings in laboratory animal studies of methyl methacrylate (continued)

Route of administration	Species/strain	Dose	Duration of exposure	Findings	Reference
Drinking water	Wistar rats (25/sex/group)	0, 6, 60, 2,000 ppm in drinking water. At 5th mo 6, 60 ppm levels were raised to 7, 70 ppm and continued for 2 years	2 years	Hispathology performed on heart, lung, liver, kidney, bladder, spleen, gastroenteric, skeletal muscle, bone marrow, skin, brain, thyroid, adrenal, pancreas, pituitary, gonads. No abnormalities or lesions.	Borzelleca et al., 1964
Inhalation	F334/N rats (50/sex/group)	Males: 0, 500, 1,000 ppm Females: 0, 250, 500 ppm 6 h/day, 5 days/week	102 weeks	Increased incidence of mononuclear cell leukemia in females in 500-ppm group compared with controls (control, 11/50; 250 ppm, 13/50; 500 ppm, 20/50); not significantly by life table tests. Significant dose-related decrease in incidence of pituitary gland and preputial gland tumors in males. Body weights of male and female rats within 10% of controls.	National Toxicology Program, 1986
Inhalation	B6C3F_1 mice (50/sex/group)	0, 500, 1,000 ppm 6 h/day, 5 days/week	102 weeks	No neoplastic lesions were found. Significant dose-related decrease in incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in males, hepatocellular adenomas in males and females, pituitary gland adenomas or adenocarcinomas (combined) and uterine adeno-carcinomas in females.	National Toxicology Program, 1986
Inhalation	Golden hamsters (56/sex/group)	0, 25, 100, 400 ppm 6 h/day, 5 days/week	78 weeks	Histophathological examination showed no treatment-related tissue alterations. Cumulative mortality of high-level males higher than controls at week 78.	Hazelton, 1979a
Inhalation	F-344 rats (70/sex/group)	0, 25, 100, 400 ppm 6 h/day, 5 days/week	104 weeks	Histophathological examination showed no increased incidence of neoplasma in treated animals compared with controls	Hazelton, 1979b

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implants, Ferguson (1977) suggests that sarcomas that arise following subcutaneous implants of poly-MMA can be attributed to mechanical processes involving topographic interaction of the solid surface with normal cells, especially macrophages. Consistent with this explanation are the experiments of Oppenheimer et al. (1955), in which no tumors were induced when monomeric MMA was applied dermally to the back of the neck of rats. However, the exposure period in the Oppenheimer study was just 4 mo and only 10 animals were tested.

In the studies by Hazelton Laboratories (1979a,b), Fischer 344 rats and Charles River Lakeview Golden Hamsters were exposed to MMA vapors at 0, 25, 100, and 400 ppm for 6 h/day for 5 days/week for 2 years and 18 mo, respectively. No increase was seen in the number or type of tumors in either rats or hamsters, indicating that MMA was not carcinogenic in these two species under those conditions. Appearance of a polypoid adenoma in the nasal cavity of two MMA-exposed male rats (one each from the 100 and 400 ppm groups) (Lomax, 1992; Lomax et al., 1997) is not likely to be associated with MMA-exposure as these benign neoplasms have been reported in control rats as well (Miller et al., 1985). Similarly, a 2-year NTP inhalation bioassay of rats and mice exposed to up to 1,000 ppm gave negative results for carcinogenicity, although the animals may not have been tested at the maximum tolerated dose (NTP, 1986; Chan et al., 1988).

Borzelleca et al. (1964) reported the absence of carcinogenic effects in groups of 25 male and 25 female Wistar rats given drinking water containing 0, 6, 60, or 2,000 ppm MMA for 2 years. Taken together, the genotoxicity, chronic inhalation, and chronic oral studies available suggest that MMA is not carcinogenic in laboratory animals.

4.6.2. Human Evidence

Limited epidemiological data are available to determine whether the incidence of various malignancies is higher in groups occupationally exposed to MMA versus those not exposed, and no studies have been reported on whether smoking is a related factor in the occurrence of malignancies in MMA-exposed workers. One retrospective epidemiological study that relates to malignancies was conducted at the Bristol Plant, PA, which manufactures plastics, leather chemicals, etc. (Monroe, 1984; Walker et al., 1991). In this study of Bristol Plant employees hired prior to 1946 (Early Bristol cohort), an excess of cancer of the large intestine and rectum was noted. However, an increase in these types of cancers was not observed in similar populations at separate sites, or in subsequent evaluations of the same site (Walker et al., 1991; ECETOC, 1995; Collins et al, 1989). Collins et al. (1989) have noted that during the 1970s, the county in which the plant was located had a high colorectal cancer rate, at the 75th percentile for the United States.

Some evidence of an increased death rate from cancer and noncancer respiratory disease is provided by the American Cyanamid (Collins et al., 1989) and Knoxville (Walker et al., 1991) cohorts. However, in both of these cohorts, exposure to MMA was considerably lower than in the Early Bristol cohort, which showed no such excess. Others have suggested that these increases were lifestyle related (ECETOC, 1995).

4.6.3. Structure-Activity Relationships

Acrylic acid, four monofunctional acrylates, eight polyfunctional (di- or tri-) acrylates, a dimethacrylate, and a trimethacrylate have been tested in skin painting cancer bioassays. Acrylic acid, 2-ethylhexyl acrylate, and three diacrylates caused skin tumors. Methyl acrylate (MA), ethyl acrylate (EA), n-butyl acrylate (BA), and methyl methacrylate have been tested in chronic inhalation bioassays and found to be negative with respect to carcinogenicity (Woo et al., 1988). While the Borzelleca et al. (1964) drinking water studies did not report carcinogenicity for either EA or MMA exposure, EA was found to cause forestomach tumors following gavage exposure (NTP, 1983). However, the fact the EA has been found to cause forestomach tumors at high gavage doses (NTP, 1983) does not necessarily implicate MMA. This is suggested by structure-activity relationship studies that demonstrate that the addition of a methyl group to the acrylate moiety tends to abolish carcinogenic activity (Woo et al., 1988) and gavage dosing of analogues of EA demonstrating that the forestomach toxicity required the intact molecule (an ester moiety, the double bond, and no substitution at carbon number 2) (Ghanayem et al., 1985). In another paper, Ghanayem et al. (1986) reported that cell proliferation of the rat forestomach (believed to be a precursor effect to tumors caused by this compound) was apparent in all rats (12/12) following 2-week gavage administration of EA at both 100 and 200 mg/kg, but was not apparent in any rats exposed to 100 mg/kg MMA (0/8) and in just 1/8 rats exposed to 200 mg/kg MMA. This latter increase was not statistically significant and the effect was much less severe than the effects caused by EA at either dose. Thus, structure-activity relationship analysis does not suggest that MMA would be carcinogenic by any route.

4.6.4. Summary

Cases of sarcomas reported following implants of polyMMA are attributed to mechanical processes, not MMA. Carcinogenic activity was not detected in four well-conducted chronic inhalation bioassays in three different species: rats, mice, and hamsters (NTP, 1986; Hazelton, 1979a,b). Results of a 2-year drinking water study of Wistar rats (25/sex) (Borzelleca et al., 1964), though not as well documented as the inhalation studies, also showed no carcinogenicity. Mutagenicity data are mixed and human epidemiologic evidence is inadequate for basing a carcinogenicity determination. Under the Proposed Guidelines for Carcinogenic Risk Assessment (U.S. EPA, 1996a), MMA is considered *not likely to be carcinogenic to humans* because it has been evaluated in two well-conducted studies in two appropriate animal species without demonstrating carcinogenic effects.

4.7. Other Hazard Identification Issues

4.7.1. Possible Childhood Susceptibility

A number of factors may differentially affect children's responses to toxicants. The only toxicity information on MMA of possible relevance to this issue is that several studies showed that developmental effects are observed only at exposure levels that are maternally toxic, even lethal. There is too little information to make any further statements about how children may be differentially affected by methyl methacrylate, as there are no data regarding methyl methacrylate

exposure prior to mating, from conception through implantation, or during late gestation, parturition, or lactation.

4.7.2. Possible Gender Differences

No gender-related differences were observed in the current data on methyl methacrylate. Male and female laboratory animals appear to respond similarly in all respects. It should be noted, however, that all human epidemiology studies to date have involved solely male cohorts. No epidemiologic data exist for females at this time.

5. Dose-Response Assessments

5.1. Oral Reference Dose (RfD)

5.1.1. Choice of Principal Study and Critical Effects

Relevant, quantitative human subchronic or chronic studies of MMA are not available. No oral developmental or reproductive studies are available. There are three repeat exposure studies that were of long enough exposure duration to be considered for use in the derivation of an oral RfD, the Motoc et al. (1971) rat study, the Borzelleca et al. (1964) rat study, and the Borzelleca et al. (1964) dog study. Of the three, only the Borzelleca et al. (1964) drinking water study in rats was of chronic duration (2 years). Motoc et al. (1971) was a subchronic gavage study, and the assessment of dogs by Borzelleca et al. (1964) involved the administration of MMA in gelatin capsules. The Motoc et al. (1971) gavage study showed that large bolus doses can overwhelm detoxification mechanisms and cause stomach ulcerations in rats. Thus, the less than chronic gavage studies of Motoc et al. (1971) and Borzelleca et al. (1964) are considered less desirable for use in the derivation of an RfD than the chronic drinking water study in rats of Borzelleca et al. (1964). Borzelleca et al. (1964) reported an increase in kidney-to-body ratios reported for female rats, but it was only marginally significant and was not associated with any histopathologic findings. The fact that MMA was not reported to cause gastric toxicity in this study is not in and of itself a reason to doubt the results of the study. Substitution on the number 2 carbon of acrylic acid has been shown in gavage studies to abolish gastric toxicity (Ghanayem et al., 1985) and cell proliferation (Ghanayem et al., 1986). Thus, the Borzelleca study is deemed adequate for RfD derivation and the highest exposure level, 136 mg/kg/day (2,000 mg/L × 0.0313 L/rat/day divided by the default body weight for Wistar rats of 0.462 kg), is considered a NOAEL for this study.

5.1.2. Method of Analysis

The NOAEL discussed above will serve as the basis for the RfD. A benchmark dose analysis could not be attempted from this study as no adverse effect was identified.

5.1.3. Chronic RfD Derivation

The following uncertainty factors are applied to this effect level: 10 for consideration of intraspecies variation (UF_H; human variability), an uncertainty factor of 3 for extrapolation for interspecies differences (UF_A; animal to human), and an uncertainty factor of 3 to account for a deficient database (UF_D), including the lack of a chronic study in a second species and the lack of

other supporting studies (e.g., neurologic, developmental, and reproductive). The UF_D is not higher because the lack of oral studies is partially compensated for by a more complete inhalation exposure database, though reproductive studies are lacking from the inhalation database as well. The total UF = $10 \times 10^{1/2} \times 10^{1/2} \approx 100$. No MF is applied.

RfD = 136 mg/kg/day ÷ 100 = 1.4 mg/kg/day

5.2. Inhalation Reference Concentration

5.2.1. Choice of Principal Study and Critical Effect

No epidemiologic or occupational studies of MMA are available that adequately describe inhalation exposure concentrations and effects. Most of the available human studies did not account for one or more confounding exposures. Of the chronic laboratory studies available, only Hazelton Laboratories America (1979a,b) tested exposure levels (to rats and hamsters) below 250 ppm. The original study found only mild rhinitis as the principal effect in all exposure groups, with no mention of the olfactory effects so evident in all exposure groups (250 to 5,000 ppm) of rats and mice studied by NTP (1986). As a result of EPA discussions with the Methacrylate Producers Association (MPA), MPA commissioned a review (Lomax, 1992; Lomax et al., 1997) of the histopathology of the nasal tissues in the Hazelton (1979a) study. Because of MMA's propensity to cause effects in the olfactory epithelium as demonstrated in other studies (NTP, 1986), this reanalysis included a more thorough examination of the nasal cavity tissue blocks than was done in the original study. The Hazelton (1979a) study and the Lomax (1992) reanalysis were selected for use in the RfC derivation over the NTP (1986) because the combined analysis was well conducted, involved an adequate number of test animals, and identified a NOAEL at an exposure concentration 10-fold lower than the lowest exposure concentration in the NTP (1986) study.

Tables 5 and 6 show the effects of MMA on both olfactory and respiratory epithelium and the various exposure levels. The hydrolysis of MMA by carboxylesterase enzymes and subsequent release of methacrylic acid in the olfactory tissue (Morris and Frederick, 1995) is likely the cause of the greater effect in this region. Localization and severity of the lesion in the olfactory epithelium is consistent with the greater esterase activity reported in the olfactory epithelium as compared to respiratory epithelium in rodents (Dahl et al., 1987; Bogdanffy et al., 1987; Bogdanffy, 1990; Frederick et al., 1994). Similar toxicity from acids produced via the same metabolic route has been seen with ethyl acrylate (Miller et al., 1985), methyl and butyl acrylate (Klimisch, 1984), dibasic esters (Keenan et al., 1990) and glycol ether acetates (Miller et al., 1984). However, direct exposures to acrylic and acetic acids have also caused similar olfactory specific lesions (Miller et al., 1981; Stott and McKenna, 1985), suggesting that greater esterase activity in olfactory tissue is not the only factor leading to this specificity. Differing sensitivities among nasal tissues to the acid metabolite or further metabolism of the acid may contribute as well.

5.2.2. Method of Analysis

A polynomial mean response regression model (THRESH, I.C.F. Kaiser, 1990a) and a Weibull power mean response regression model (THRESHW, I.C.F. Kaiser, 1990b) were used to fit data from Lomax (1992) and Lomax et al. (1997) by the maximum likelihood method. These models were developed for use with dichotomous (incidence) data and provide the option of assuming a zero or nonzero background response. The only olfactory effect noted in control animals was minimal basal cell hyperplasia (5/39 control animals) (Table 6). For the purpose of calculating a BMC, it appears reasonable to assume a zero background for slight, moderate, and severe olfactory lesions. Minimal lesions were excluded from the BMC analysis and a zero background was assumed. Using these criteria, BMC_{15}, BMC_{10}, BMC_5, and BMC_1 analyses were performed for all four olfactory lesions (male and female) listed in Table 6. Table 11 provides a summary of these model runs.

From these data sets, data for degeneration/atrophy in males (0/39, 0/47, 35/48, and 38/38) were chosen for use in the derivation of the RfC because the concentration-response curves generated by both THRESH and THRESHW models were similar and of reasonable goodness of fit. In addition, the resultant BMC values were lower than the BMCs for replacement by ciliated epithelium, the only other endpoint for which a good model fit could be reached. An EPA review of benchmark analysis performed for several upper respiratory toxicants indicates that the BMC values for both the 5% and the 10% benchmark response (BMR) levels for a given endpoint generally fall between the NOAEL and the LOAEL for that endpoint (Gift, 1996). The BMR chosen for use in the MMA RfC derivation is a 10% increase in the incidence of a slight, moderate, or severe lesion. The 10% response level was chosen because of its closer proximity to the actual experimental data and because of the overall mild severity of the effect. The RfC is based on the BMC_{10}, which is the lower 95% confidence bound on the maximum likelihood estimate (MLE) of the concentration that causes a 10% increased incidence of this lesion. The two model predictions for the BMC_{10} from degeneration/atrophy of male rat olfactory epithelium were virtually identical, 39 (Weibull) and 35 (polynomial) ppm. The 35 ppm value was chosen for use in the RfC calculation because it results in a slightly more environmentally protective RfC. This value is slightly above the 25 ppm NOAEL and well below the 100 ppm LOAEL for degeneration/atrophy and inflammation. More details of the BMC_{10} derivation for this data set (model used, input assumptions, etc.) are provided in Appendix A. Appendix A also discusses the limitations of this data set and the limitations of the analysis. The following summarizes the results and describes how the BMC_{10} was used to derive the BMC_{10}(HEC), which serves as the basis for the RfC. Assuming 25 ºC and 760 mmHg and a molecular weight of 100.11,

$$BMC_{10}\ (mg/m^3) = 35\ ppm \times 100.11/24.45 = 143\ mg/m^3.$$

When the $BMC_{10}(mg/m^3)$ is derived from a study in which laboratory animals are exposed intermittently (e.g., 6 h per day, 5 days per week), an adjustment is usually applied to account for the fact that the RfC is to protect against the worst-case scenario, continuous exposures. However, the EPA guidelines (EPA, 1994c) recognize that, depending on the mechanism of action, such duration adjustment may not always be appropriate. In the case of

Table 11. Summary of benchmark analysis model runs on olfactory effects

Effect	Model	BMC 15 (ppm)	BMC10 (ppm)	BMC05 (ppm)	BMC01 (ppm)	Chi-square goodness of fit	Degrees of freedom	P value
Males								
Degeneration/atrophy	Weibull	46.2	39.4	30.2	16.6	0.087	1	0.768
Degeneration/atrophy	Polynomial	42.3	35.11	25.55	7.75	0.968	2	0.616
Basal cell hyperplasia	Weibull	21.2	13.1	5.8	0.92	12.7	1	0.00037
Basal cell hyperplasia	Polynomial	22.7	14.7	7.2	1.4	11.9	2	0.026
Replaced by ciliated	Weibull	156.3	112.5	63.4	16.5	0.167	1	0.683
Replaced by ciliated	Polynomial	167.4	118.7	62.8	12.5	0.256	2	0.613
Inflammation	Weibull					5.3	1	0.02
Inflammation	Polynomial	36.8	23.9	11.6	2.3	5.4	2	0.02
Females								
Degeneration/atrophy	Weibull	25.8	17.4	9.0	2.0	8.9	1	0.003
Degeneration/atrophy	Polynomial	20.7	13.4	6.5	1.3	10.1	2	0.0015
Basal cell hyperplasia	Weibull	28.9	17.3	7.3	1.0	8.07	1	0.045
Basal cell hyperplasia	Polynomial	33.8	21.9	10.7	2.1	7.5	2	0.023
Replaced by ciliated	Weibull	118.1	83.7	47.3	12.9	1.9	1	0.16
Replaced by ciliated	Polynomial	73.3	47.5	23.1	4.5	2.13	2	0.144
Inflammation	Weibull	89.2	62.0	33.5	8.1	0.77	1	0.38
Inflammation	Polynomial	89.6	59.8	29.4	5.8	1.16	2	0.28

acrylic acid, a compound that causes similar olfactory damage, there is information to suggest that a limited C × T relationship of exposure to toxic effects is operative over the course of at least the first 2 weeks of exposure at concentrations that cause minimal to moderate, reversible (if exposure is discontinued) olfactory effects (Lomax et al., 1994). The lack of lesions in rats after 28 days of exposure to 100 ppm MMA (Greene, 1996), combined with the presence of lesions in rats following chronic exposure to 100 ppm MMA (Lomax et al., 1997), suggests that these effects can progress with increased exposure duration. Thus, it is reasonable to suggest that continuous exposure to MMA could result in effects at concentrations below the NOAEL of an intermittent exposure study, and that the application of an adjustment factor to account for this is appropriate. Thus, the BMC_{10} of 143 mg/m^3 is adjusted as follows:

$$BMC_{10}(adj) = 143 \times 6 \text{ h}/24 \text{ h/day} \times 5 \text{ days}/7 \text{ days/week} = 25.6 \text{ mg/m}^3.$$

The human equivalent BMC10, BMC_{10}(HEC), is calculated using default procedures appropriate when peer-reviewed PBPK models are not available. For a category 1 gas, gas:respiratory effect in the extrathoracic region is as follows:

Minute volume for the laboratory animal (Mva) = 0.25 L/min[1]
Minute volume for humans (Mvh) = 13.8 L/min
Extrathoracic surface area for the laboratory animal [Sa(ET)] = 11.6 cm^2
Extrathoracic surface area for humans [Sh(ET)] = 177 cm^2
Regional gas deposition ratio (RGDR) = (MVa/Sa)/(MVh/Sh) = 0.28

$$BMC_{10}(HEC) = 25.6\ mg/m^3 \times RGDR = 7.2\ mg/m^3.$$

5.2.3. Chronic RfC Derivation

The BMC_{10}(HEC) for degeneration/atrophy of olfactory epithelium described by Lomax (1992) and Lomax et al. (1997) is estimated at 7.2 mg/m^3. A partial threefold uncertainty factor (UF) is applied to this effect level in consideration of possible intraspecies variation (UF_H, to protect sensitive human subpopulations), and a partial threefold interspecies uncertainty factor (UF_A) is applied because of possible toxicodynamic differences between rats and humans. The total UF = $10^{1/2} \times 10^{1/2} \approx 10$. No modifying factor (MF) is applied.

$$RfC = 7.2\ mg/m^3 \div 10 \approx 0.7\ mg/m^3 = 7\ E\text{-}1\ mg/m^3.$$

5.3. Cancer Assessment

As discussed in Section 4.6, MMA is considered *not likely to be carcinogenic to humans* because it has been evaluated in two well-conducted studies in two appropriate animal species without demonstrating carcinogenic effects. No data exist to support a quantitative cancer assessment for this compound.

6. Major Conclusions in Characterization of Hazard and Dose-Response

6.l. Hazard Identification

MMA is a colorless flammable liquid with a strong acrid odor. It is primarily used to make a variety of resins and plastics, and is most often polymerized to polymethyl methacrylate, which is used to make acrylic sheets, acrylic moldings, and extrusion powders. Because MMA is relatively volatile (vapor pressure of 40 mmHg at 25°C) and widely used, significant occupational exposure to the chemical can be expected to occur. Potential for significant exposure exists for employees of manufacturers of MMA and its polymers, as well as doctors, nurses, dentists, and dental technicians.

[1]Calculated using Equation 4-4 of EPA (1994c) for male rats with a body weight of 380 g; confirmed by actual measurements taken by Mauderly (1986) and Phalen (1984).

MMA is rapidly absorbed and distributed in laboratory animals following oral and inhalation exposure. It is similarly metabolized in animals and humans. From a toxicologic standpoint, the key metabolic step is MMA hydrolysis to methacrylic acid, considered to be the toxic moiety responsible for the irritant properties of MMA. The rate of this metabolic step has been shown to proceed slower in human blood and nasal tissues than in the corresponding rat tissues, but at a faster rate in human liver tissue. Subchronic and chronic exposures to various laboratory animal species by dermal, oral, and inhalation routes produced effects consistent with the irritant properties of MMA and methacrylic acid. In inhalation studies, exposure-related lesions were observed in the respiratory tract at exposure levels at and above 100 ppm. The most frequent, sensitive, and severe lesions generally occurred in the olfactory tissue and consisted of olfactory epithelial loss and degeneration. Developmental, CNS, and other systemic effects were sporadically reported, but generally at concentrations exceeding 1,000 ppm. No carcinogenic potential was shown for MMA in four chronic inhalation bioassays (rats, mice, and guinea pigs) and one chronic oral bioassay (rats).

Limited human epidemiologic information exists for MMA. Several occupational studies are available, but none reported MMA-specific exposure information useful for the derivation of a health benchmark. Many of the human studies were poorly reported and lacked details regarding confounding exposures and the health status of exposed individuals. Nevertheless, the extensive occupational literature does suggest that MMA would not be expected to cause death or serious adverse health effects as a result of acute exposures. The distinct odor and low odor threshold of MMA tend to assist workers in avoiding significant exposures. However, laboratory animal studies and one human study (Schwartz et al., 1989) suggest that MMA may erode olfactory function. This ability is considered to be MMA's most sensitive effect and perhaps its most serious potential human hazard following inhalation exposure. Although other effects have been noted (e.g., cardiovascular and neurologic effects), they are generally nonspecific, occur at higher exposures, and are often not clearly attributable to MMA exposure. Sensitization from MMA inhalation exposure has been reported in a single case study (Pickering et al., 1986). While the potential for sensitization following either oral or inhalation MMA exposure can not be ruled out, it has not been observed in several occupational studies and has only been clearly demonstrated following dermal exposure to certain individuals. Epidemiology studies show no clear excess of respiratory disease or cancer. Though a report suggesting increased colon cancer among ethyl acrylate/MMA-exposed workers exists, a high background for this effect has been documented for the location and time of this study, the effects were not reproduced in other similar and more recent studies, a clear relationship between exposure and effect was not demonstrated, and the extent that ethyl acrylate concurrent exposure confounded results could not be determined. Given these considerations, the low potential for cancer from MMA exposure indicated in genotoxicity, laboratory animal, and epidemiology studies suggests that MMA does not represent a carcinogenic hazard to humans. Structure-activity relationship analysis relative to other acrylates also does not suggest that MMA would be carcinogenic by any route. Under the Proposed Guidelines for Carcinogenic Risk Assessment (U.S. EPA, 1996a), MMA is considered *not likely to be carcinogenic to humans* because it has been evaluated in two well-conducted studies in two appropriate animal species without demonstrating carcinogenic effects. Under EPA's (1987a) Guidelines for Carcinogen Risk Assessment, MMA would be classified as *evidence of non-carcinogenicity for humans*, or a Group E chemical.

6.2. Dose-Response Assessment

The quantitative estimates of human risk as a result of low-level chronic exposure to methyl methacrylate are based on laboratory animal experiments because adequate human data are not available.

The human dose that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime (the RfD) is 1.4 mg/kg/day. Because of the application of uncertainty factors, this amount is approximately 1/100 of the dose that resulted in no effects in a chronic rat drinking water study (Borzelleca et al., 1964).

The overall confidence in the RfD assessment is low to medium. The confidence in the principal study is low to medium. The Borzelleca (1964) study is well documented, but does not appear to be conducted in accordance with what would now be considered Good Laboratory Practice and did not identify a LOAEL. Confidence in the database is judged to be low to medium. Although repeat exposure inhalation studies, including developmental, reproductive, and chronic studies, bolster the weak and dated oral database somewhat, no developmental or reproductive studies by the oral route are available, and no multigenerational studies are available by any route of exposure. Gastrointestinal irritation has been identified in a rat subchronic gavage study (Motoc et al., 1971), but acute exposures to humans via the oral route are rare. Irritation is still considered the most likely effect of concern from oral exposure to humans, however, primarily because of extensive evidence from occupational studies and case reports that MMA is a respiratory irritant in humans.

A full uncertainty factor for intraspecies differences (UF_H) was used to account for potentially sensitive human subpopulations. This UF was not reduced because of the lack of human oral exposure information. A partial threefold uncertainty factor to account for laboratory animal to human interspecies differences (UF_A) was used. The slower blood metabolism of MMA in humans (Bereznowski, 1995), combined with the fact that humans do not have a forestomach (target organ in the Borzelleca et al., 1964 study) lowers the potential for a more pronounced portal-of-entry effect in humans. However, complete elimination of this UF is not justified, given the lack of human oral exposure information and remaining uncertainty regarding MMA's potential to cause other effects in humans following chronic oral exposure.

The major areas of uncertainty in this assessment are the lack of an identified critical effect to humans, the lack of a chronic study in a second species, and the lack of a neurologic study and the lack of a developmental or reproductive toxicity study via the oral route (given that developmental effects have been seen in laboratory animals following other routes of exposure). A partial threefold database uncertainty factor (UF_D) was employed, however, because a number of repeat exposure inhalation studies, including developmental, reproductive, and chronic studies, lend support to the oral database.

The daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime (the RfC) is 7 E-1 mg/m^3. This concentration is 1/10 of the estimated BMC_{10}(HEC) for degeneration/atrophy of olfactory epithelium described by Lomax (1992) and Lomax et al. (1997).

The overall confidence in this RfC assessment is medium to high. The RfC is based on a long-term rat inhalation study (Hazelton Laboratories, Inc., 1979a) performed with relatively large group sizes, in which, with additional investigations performed by Lomax et al. (1997), thorough histopathologic analyses were performed on all relevant tissues. What is considered to be the primary target organ, the nasal passage, was particularly well described, and the study was able to identify both a NOAEL and a LOAEL. The scientific quality of the combined Hazelton Laboratories (1979a) and Lomax et al. (1997) investigations is high.

The confidence in the inhalation database available for MMA is rated as medium to high. Acceptable developmental studies were carried out in two species, rats and mice, with effects observed only in offspring at levels more than 10-fold higher than the LOAEL for the chosen critical (olfactory) effect. Two studies noted increased resorptions in rats at 1,000 ppm exposures (Luo et al., 1986; ICI, 1977) and one did not (Solomon et al., 1993). However, the latter study was peer reviewed whereas Luo et al. (1986) was an abstract and ICI (1977) was an unpublished industry report. Multigenerational reproductive studies are not available for MMA; however, MMA is so reactive at the portal of entry that the potential for systemic effects is deemed remote. The observation of a portal-of-entry effect is consistent across both the oral and inhalation routes of exposure. Given these considerations, the inhalation database and the RfC are given medium to high confidence, and no uncertainty factor is applied to the RfC for database deficiencies.

A partial threefold intraspecies uncertainty factor is applied to the RfC for protection of sensitive subpopulations. This UF is reduced by extensive human occupational studies and case reports that consistently identify the irritant properties of MMA as the principal effect of concern from MMA inhalation exposures. Little intraspecies variance is observed with respect to the identified critical effect, olfactory degeneration in laboratory animals (ECETOC, 1995; Lomax et al., 1997), and there is no reason to expect a high degree of intrahuman variability from this type of effect. Although Pickering et al. (1986) reported delayed asthmatic response following challenge with MMA, which would suggest that MMA is a possible respiratory sensitizer, no occupational studies identified MMA as a respiratory sensitizer. A partial intraspecies uncertainty factor of 3 is deemed sufficiently protective.

A partial threefold uncertainty factor is used for interspecies extrapolation to account for potential toxicodynamic differences between rats and humans. This concern for potential toxicodynamic differences is warranted given the fact that humans may be less capable of recovering from olfactory damage than are rats. “Rapid potentially anatomically correct recovery after massive destruction” is observed in rats when underlying basal cells are not damaged (Youngentob, 1997) and small islands of intact olfactory epithelium are “sufficient to allow for olfactory function” (Wong et al., 1997). In humans, however, it has been reported that patients with relatively mild to moderate olfactory damage fail to recover olfaction and “...even when basal cells remain intact, differentiating cells developing from them do not mature into receptor cells but can develop into squamous cells....” (Yamagishi and Nakano, 1992). An attempt was made to account for toxicokinetic differences between the rat and human in the derivation of BMC_{10}(HEC). The HEC calculation attempts to account for the morphological differences in the species as reflected by the different ratio of normal minute volume to surface area in rats versus humans.

While there remain several differences between rats and humans that are not accounted for, most of these differences suggest that rat nasal passages are likely to be affected at lower MMA concentrations than those of humans. Most evidence suggests that the main metabolite of MMA, methacrylic acid, is the toxic moiety of concern (Lomax et al., 1997; Bereznowski, 1995; Morris and Frederick, 1995; ECETOC, 1995). Studies of carboxylesterase metabolic rates suggest that humans metabolize MMA in blood (Bereznowski, 1995) and in olfactory tissue (Mattes and Mattes, 1992; Greene, 1996) at a slower rate than rats, though at a slightly faster rate in the liver (Greene, 1996). In addition, rats are obligate nose breathers, whereas humans can breathe through the mouth during exertion and to avoid overpowering odors. EPA is aware of PBPK models for MMA (developed for the Methacrylate Producers Association by Andersen et al., 1996) and other acrylates (Morris and Frederick, 1995; Bogdanffy and Taylor, 1993) that should eventually help to reduce uncertainty in the quantification of these differences. The use of a PBPK model to update this assessment will be considered when EPA has completed its analysis of these various model approaches. In the meantime, a majority of the dosimetric/toxicokinetic evidence currently available suggests that humans would not be more sensitive than rats on this basis and that further reduction of the BMC_{10}(HEC) to account for interspecies dosimetric/toxicokinetic uncertainty is not necessary.

7. References

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8. APPENDICES

APPENDIX A: RFC BENCHMARK CONCENTRATION ANALYSES OF DATA FROM LOMAX (1995)

Degeneration/atrophy of olfactory epithelium in male rats

(1) Computational Models-Discontinuous (Quantal) Data

The polynomial mean response regression model (THRESH, I.C.F. Kaiser, 1990a) and the Weibull power mean response regression model (THRESHW, I.C.F. Kaiser, 1990b) were used to fit data by the maximum likelihood method. The following are the forms of the two equations used, excluding a background term (background = 0).

THRESH $P(d) = 1-\exp[-q_1 (d-d_0)_1 - \ldots - q_k (d-d_0)_k]$

THRESHW $P(d) = 1 - \exp[-\alpha(d-d_0)^{\beta}]$

where:

d	=	dose
d_0	=	threshold
$P(d)$	=	probability of a response (health effect) at dose d
$q_1 \ldots qk, \alpha, \beta, k$	=	estimated parameters

For data input to THRESH, the degree of the polynomial was set to the number of dose groups minus one, the response type was extra [P(d) - P(0)] / 1- P(0). For both models the threshold, d(0), was set to zero. For THRESHW, the lower limit of β was set at 1.0.

(2) Data Set

Group	Dose	#Responses/#animals
1	0	0/39
2	25	0/47
3	100	35/48
4	400	38/38

(3) Model Fit

Model fit was judged by the *p* values generated with the χ^2 goodness-of-fit generated by THRESH or THRESHW.

(4) Results

Table A-1. THRESHW model results

Model	BMC(10) (mg/m^3)	Estimated parameters	*p* Value	χ^2 goodness-of-fit	Degrees of freedom
THRESHW	39.4	α=4.38E-10 β=4.7362	0.768039	8.698995E-02	1
THRESH	35.1	q_1=0; q_2 =0 q_3 =1.27E-06	0.616323	0.967969	2

(5) Discussion

It is important to note that the *p* values and "goodness-of-fit" data given in the table above should not be interpreted as an indication of confidence in the results of this model run. They simply indicate that data were amenable to curve fitting, because there is only one data point in the set that is not at the limits of the scale. The incidence in control and low-dose groups was 0, and the incidence in the high-dose group was 100%. The incidence in the intermediate group was also high at 70%. Thus, confidence in the overall curve fitting exercise is actually quite low, given that there is no unique solution to fitting these points (a steeper or flatter curve could also be fit to these points). However, it is clear that the 10% response level must lie between 25 and 100 ppm. Given the nature of this effect and the gradual, not abrupt, increase in the severity of related effects such as basal cell hyperplasia and olfactory cell inflammation, it is reasonable to assume that a gradual increase in response begins at 25 ppm. This is also a conservative assumption because 25 ppm is a clear NOAEL and is not necessarily the point at which a response is initiated. The models reflect this gradual increase above 25 ppm, and the lower of the two model estimates for the BMC_{10}, 35 ppm, appears to be a reasonable and conservative estimate of the concentration required to elicit a 10% response. This value is consistent with the NOAEL from the study and other BMD_{10} values, and is chosen for further quantitation of the RfC.

APPENDIX B: SUMMARY OF AND RESPONSE TO EXTERNAL PEER REVIEW COMMENTS

The Toxicological Review for methyl methacrylate and all individual methyl methacrylate assessments have undergone both internal peer review performed by scientists within EPA or other Federal agencies and a more formal external peer review performed by scientists chosen by EPA in accordance with U.S. EPA (1994a). Comments made by the internal reviewers were addressed prior to submitting the documents for external peer review and are not part of this appendix. Public comments also were read and carefully considered. The external peer reviewers were tasked with providing written answers to general questions on the overall assessment and on chemical-specific questions in areas of scientific controversy or uncertainty. A summary of comments made by the external reviewers and EPA's response to these comments follows.

(1) General Comments

A. ***Comments:*** The reviewers suggested that EPA consider the following additional studies in the review:

1. ECETOC. 1995. Joint assessment of commodity chemicals no. 30: methyl methacrylate. JACC Report No. 30. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Brussels, Belgium.
2. Lomax, LG; Krivanek, ND; Frame, SR. 1997. Chronic inhalation toxicity and oncogenicity of methyl methacrylate in rats and hamsters. Food Chem Toxicol 35:393-407.
3. Muttray, A; Schmitt, B; Klimek, L. 1997. Effects of methyl methacrylate on the sense of smell. Cent Euro J Occup Environ Med, 3(1):58-66
4. Ghanayem, BI; Maronpot,RR; Mathews, HB. 1986. Association of chemically induced forestomach cell proliferation and carcinogensis. Cancer Lett 32:271-278.
5. Greene, T. 1997 (draft). Methyl methacrylate: the effect of carboxylesterase enzyme inhibition on the development of a nasal lesion in rats. Zeneca: Central Toxicology Laboratory Report No. CTL/R/1313, June 6, 1997. Sponsor: CEFIC.
6. Greene, T. 1996. The metabolism of methyl methacrylate in the nasal tissues of rat and human. Zeneca: Central Toxicology Laboratory Report No. CTL/R/1290, issued December 4, 1996. Sponsor: CEFIC.
7. Pinto, PJ. 1997. Methyl methacrylate: 28-da subchronic inhalation study in rats. Zeneca: Central Toxicology Laboratory Report No. CTL/P/5159, issued June 4, 1997. Sponsor: CEFIC.
8. Frederick, CB, Lomax, LG;. Black, KA; Finch, L;. Bush, ML; Ultman, JS; Kimbell, JS; Morgan, KT; Subramanian, RP; Morris, JB; Stott, WT; Young JT; Scherer, PW. 1997 (draft). Application of computational fluid dynamics and a physiologically-based inhalation model for interspecies extrapolation of the dosimetry of acidic vapors in the upper respiratory tract.
9. Bush, ML; Frederick, CB; Kimbell, JS; Ultman, JS. 1997 (draft). A computational fluid mechanics-physiologically based pharmacokinetic hybrid model for simulating gas and vapor uptake in the rat nose.

10. Andersen, ME;. Barton, HA; Covington. TR. 1996. Applying a physiologically based deposition model for methyl methacrylate in the olfactory regions of the rat and human nose to estimate dosimetric adjustment factors. Prepared for the Methacrylate Producers Association, September 27, 1996.
11. DeSesso, JM. 1993. The relevance to humans of animal models for inhalation studies of cancer in the nose and upper airways. Quality Assurance: Good Practice Regul Law 2(3):213-231.
12. Mauderly, JL. 1986. Respiration of F344 rats in nose-only inhalation exposure tubes. J Appl Toxicol 6(1):25-30.
13. Phalen, RF. 1984. Inhalation studies: foundations and techniques (Table 7). Boca Raton, FL: CRC Press, Inc., ISBN 0-8493-5469-2, p. 224.
14. Pickering, CAC; Niven, R; Simpson, J. 1993. A study of the prevalence of occupational asthma at the ICI acrylics site at Darwen, Lancashire. ICI Acrylics, Darwen, Lancashire U.K. (available through ICI or TSCA 8[d]).
15. Two reviewers submitted additional references on other routes of exposure, sensitization (primarily dermal exposure studies), epidemiology, genetic toxicology, and metabolism.

Response: Citations that are either finalized industry reports (#6, #7, #13, #14), or published articles in the peer-reviewed literature (#2, #3, #4, #10, #11, #12) were considered for inclusion in the review. Of the 10 studies recommended that fall into either of these categories, all but two were summarized in appropriate sections, considered in the derivation of MMA benchmarks and weight-of-evidence, and added to the reference section of the MMA document. The two that were not incorporated into the MMA document at this time were the proposed PBPK model approach by Andersen et al. (1996; #10) and the paper by Desesso et al. (1993; #11). The proposed PBPK model approach of Andersen et al. (1996) is scheduled for review by an EPA-sponsored "Category 1" dosimetry workgroup in early 1998. Though the model will not be formally cited and used before the conclusions of this work group are known, preliminary analysis indicates that the model would result in a regional gas deposition ratio (RGDR), referred to as a dosimetric adjustment factor (DAF) in the Andersen et al. (1996) report, that is approximately twofold higher than that estimated in this MMA Toxicological Review document using the Agency's default dosimetric adjustment methods (0.64-0.67 vs. 0.28). It is believed that EPA's default approach provides a reasonable margin of safety in the interim. The paper by Desesso et al. (1993) was cited in support of a reviewer's position that the Agency should use a higher minute volume for the rat in doing the HEC calculation. This paper was a review and was not as relevant as other studies submitted by the reviewer, such as Mauderly (1986) and Phalen (1984). Draft industry reports (#5, #8, #9) will be considered, but cannot be included in the review and reference list until finalized. Secondary references are not necessarily cited, but because it is recent and complete, the ECETOC document (#1) has been cited as an alternative source of information. For the most part, the list of less directly related references submitted by two reviewers (#15) did not contain additional studies deemed necessary for the purposes of the MMA IRIS document. In order to clarify the scope of the MMA document, however, a paragraph similar to the following was inserted at the beginning of Sections 4.2, 4.3 and 4.4.

"This section is a review of laboratory animal studies relevant to the derivation of health benchmarks for MMA. An overall synthesis of this information and its relation to the potential for MMA to cause noncancer and cancer effects is presented in Sections 4.5 and 4.6, respectively. Certain studies that were considered to be inadequately documented for the purposes of this assessment or used irrelevant dosing regimens may not have been discussed in this section. A more complete listing/discussion of all types of repeat or single-exposure studies can be found in other, more detailed reviews (ECETOC, 1995; U.S. EPA, 1991)."

(2) Study Descriptions

A. ***Comment:*** One reviewer suggested that the document needs a NOAEL/LOAEL summary table.

Response: Summary tables already exist for key noncancer and reproductive/ developmental studies (Tables 4-5 and 4-6). Columns have been added for recording NOAELs and LOAELs from these studies.

B. ***Comment:*** One reviewer argued that too much emphasis is given in the allergies section of the document (Section 4.4.2) to Chung and Giles (1977) as an indicator of MMA sensitization potential, and that MMA is not a "very strong" sensitizer as suggested in this section.

Response: The reviewer correctly points out that there are other studies from which to draw to postulate a conclusion regarding the sensitization potential of MMA. However, none of the available sensitization studies tested the oral or inhalation routes of exposure. The dermal studies that are available are only qualitatively useful for the purposes of the IRIS document. A few other studies, but not all, have added to the Section 4.4.2 discussion, and the descriptive words "very strong" have been removed. The overall qualitative conclusion that MMA is a sensitizer has not changed.

C. ***Comment:*** One reviewer suggested that too much emphasis is placed on Linder (1976) and Holyk and Eifrig (1979) in the Dermal and Ocular Effects section (Section 4.4.3).

Response: Again, the entire large database of dermal and ocular acrylate studies does not need to be covered to serve the purpose of this section, as none of these short-term dermal or ocular studies are going to be useful in the establishment of an RfC, RfD, or cancer assessment. A few current studies have been added to this section to characterize the irritant nature of MMA. The reader is also referred to other, more detailed reviews in this area, such as the 1995 European Center for Ecotoxicology and Toxicology of Chemicals report (ECETOC, 1995)

D. ***Comment:*** One reviewer requested that the Marez (1991) publication should be qualified and given less credibility.

Response: The document was edited to reflect the fact that the reduced average $MEFV_{50}$ observed in workers by Marez et al. (1991) may have been due to acute airway irritation caused by peak MMA exposures.

E. ***Comment:*** One reviewer claimed that the Schwarz (1989) study is more equivocal than the MMA Toxicological Review document suggests.

Response: The document was edited to reflect the fact that Schwarz (1989) did not report actual exposure concentrations. Further, it is stated that, "The reason effects were reported in this study and not the Muttray et al. (1997) study could be due to a higher co-exposure to other acrylates, the use of a more sensitive diagnosis method, or a combination of both explanations."

(3) RfD/RfC Calculation

A. ***Comment:*** One reviewer suggested the use of a different weight for male rats to calculate the daily dose from the Borzelleca et al. (1964) study.

Response: The reviewer is correct in asserting that the 0.295 kg weight used is low. This weight was used in the risk assessment performed in the 1990 Health and Environmental Effects Document (HEED) for MMA, and was reported on page 9-10 of that document as being the "estimated weight at midpoint of study; based on author's data." According to EPA's 1988 "Recommendations for and Documentation of Biological Values for Use in Risk Assessment," the weight used for a chronic study should be the "time weighted average (TWA) body weights ... from weaning to 730 days post weaning (chronic)." The EPA default body weight for male Wistar rats is given in EPA (1988) as 0.462 kg for a chronic study. Data from the Borzelleca study confirm that this default value is close to the TWA body weight for male rats over the course of the study (approximated to be 0.506 kg). As requested by the reviewer, and to be consistent with prior assessments involving this strain, the default value of 0.462 kg is used in lieu of 0.295 kg.

B. ***Comment:*** One reviewer commented that the rat minute volume for use in the HEC derivation is incorrect and should be recalculated. The default body weight for F344 rats of 0.38 kg should be used instead of the terminal body weight of 0.41 kg.

Response: The reviewer is correct in his assertion that the 0.13 L/min value used for male rat minute volume in the RfC derivation is low relative to the data reported in the literature references he provided for the F344 rat (~0.24 L/min). The value of 0.13 L/min was calculated using Equation 4-4 and coefficients in Table 4-6 of the EPA RfC methods document (EPA, 1994). The 0.13 L/min value is low because the common logarithm was used, as suggested by the Equation 4-4 text "log," instead of the natural logarithm (LN), as stipulated in the text that follows the equation. The reviewer is also correct in suggesting that the use of the default body weight of 0.38 kg would be more consistent with past EPA practice. When the LN and the default body weight of

0.38 kg are used in the equation, the minute volume is calculated to be 0.25 L/min. This minute volume is in good agreement with the literature cited by the reviewer.

C. ***Comment:*** Two reviewers suggested that EPA should not duration-adjust the exposure concentration used to derive the RfC because C × T, the assumption that effect is proportional to concentration times duration exposed (time), does not hold true for the effect of concern.

Response: C × T was assumed and the duration adjustment was applied to derive the RfC primarily on the basis of a study that showed C × T to be operative for acrylic acid for short exposure durations (Lomax, 1994). In this study, three dose groups having similar C × T products (5 ppm × 22 h; 25 ppm × 4.4 h; 25 ppm × 6 h) all had very similar incidence and severity of lesions in the nasal cavity of rats following 14 days of exposure. One of the reviewers correctly points out that there are differences between substituted acrylates such as MMA and unsubstituted acrylates in the way they are metabolized. Changes have been made to the document to acknowledge this point. However, the acrylic acid study by Lomax (1994) cannot be discarded on this basis because, while it is apparently less potent than acyrlic acid, MMA does cause a similar, if not identical, toxicologic response in rats.

The reviewer also contended that a new 28-day study (Pinto, 1997) suggests that C × T does not apply for extrapolation from less than chronic to chronic duration exposures. The reviewer may be confusing the duration adjustment, which is applied to convert an intermittent exposure to an approximate continuous exposure equivalent, with the subchronic to chronic uncertainty factor adjustment. The subchronic to chronic uncertainty factor adjustment was not used in the MMA RfC derivation because the MMA RfC is already based on lesions from chronic exposure. Nevertheless, the reviewer's contention that 100 ppm exposure to MMA in the Pinto (1997) 28-day study resulted in lesions in F344 rats of the same severity as 100 ppm exposures in the chronic study (Lomax et al., 1997) is not accurate. Pinto did observe degeneration/necrosis at the 110 ppm exposure level following 1 and 2 days of exposure. However, "regenerative changes" were noted following 5 and 10 days of exposure, and no lesions were noted after 28 days of exposure to 100 ppm MMA. First of all, there is a great deal of uncertainty with respect to diagnosing the extent of olfactory damage following apparent regeneration. Other studies have shown that some functional loss occurs in rats despite apparent complete regeneration of olfactory epithelium (Wong et al., 1997; Youngentob, 1997). There is also a question as to whether humans have this ability to regenerate olfactory epithelium and recover even partial olfaction (Yamagishi et al., 1992). Second, as noted by the author of the 28-day study (Pinto, 1997), the lack of recognizable olfactory lesions following 28 days of exposure to 110 ppm MMA and the report of lesions following chronic exposure to 100 ppm (Lomax, 1997) suggest that degenerative olfactory epithelial changes do develop over an extended period of time. Thus, the extent to which rats and humans tend to recover with continuous exposure to MMA is still under investigation, and duration of exposure cannot be ruled out as a contributing factor toward the development/progression of the adverse olfactory effects of MMA.

D. ***Comment:*** One reviewer questioned whether the surface area adjustment should be done based on the entire extrathoracic region or target tissue (olfactory) area.

Response: The use of target tissue, as opposed to the entire extrathoracic region, for dosimetric extrapolations between rats and humans would be possible if the relative contributions of airflow patterns were well understood. This is part of what the EPA-sponsored "Category 1" dosimetry workgroup discussed previously (and below) should address in February of 1998. Until then, the margin of safety provided by the default method (RGDR = 0.28) is deemed adequate given preliminary model results (RGDR = 0.64-0.67).

E. ***Comment:*** Two reviewers urged that the PBPK model submitted by Andersen et al. (1996) be used in the derivation of the RfC.

Response: This model was submitted on September 20, 1996, and EPA has agreed to review it, along with other model approaches for acrylate olfactory toxicants (e.g., vinyl acetate and ethyl acrylate). The review process is under way and an EPA-sponsored work group meeting has been scheduled. Although the model will not be formally cited and used before the conclusions of this work group are known, preliminary analysis indicates that the model would result in a RGDR, referred to as a dosimetric adjustment factor (DAF) in the Andersen et al. (1996) report, that is approximately twofold higher than that which is estimated in the MMA document using the Agency's default dosimetric adjustment methods (0.64-0.67 vs. 0.28). Thus, use of the EPA default approach provides a reasonable margin of safety in the interim.

(4) Uncertainty Factors

A. ***Comment:*** Interspecies UF for RfD should be reduced.

Response: Two reviewers suggested that the interspecies UF be lowered from 10 for the purposes of the RfD derivation. The primary basis given for this position is that (1) large uncertainty with respect to animal-to-human extrapolation is not warranted for a local irritant such as MMA, and (2) metabolic/pharmacokinetic data suggest that rats convert MMA to the presumed irritant, methacrylic acid, at a faster rate. It is agreed that the slower blood metabolism of MMA in humans (Bereznowski, 1995), combined with the fact that humans do not have a forestomach (target organ in the Borzelleca et al., 1964 study) lowers the potential for a more pronounced portal-of-entry effect in humans. Since portal-of-entry irritation forms the basis of the MMA RfD, the interspecies UF has been lowered from 10 to 3. Complete elimination of this UF is not justified, however, given the lack of human oral exposure information and remaining uncertainty regarding MMA's potential to cause other effects in humans following chronic oral exposure.

B. ***Comment:*** Database UF for RfD should be eliminated.

Response: A threefold database UF was applied for the purposes of deriving the MMA RfD. The major areas of uncertainty in this assessment were identified as (1) the lack of an identified critical effect to humans, (2) the lack of a chronic study in a second species, (3) the lack of a neurologic study, and (4) the lack of a developmental or reproductive toxicity study via the oral route (given that developmental effects have been seen in laboratory animals following other routes of exposure). The number of repeat exposure inhalation studies, including developmental, reproductive, and chronic studies, were recognized as lending support to the oral database and obviating the need for a 10-fold database UF. Two reviewers suggested the elimination of the database UF, and one reviewer provided a copy of the original report (dated August 8, 1992), which included raw data, including individual animal records, used in the Borzelleca et al. (1964) study. The availability of this information increases confidence in the Borzelleca study and reduces the possibility of missed effects in rodents significantly. Largely because of this information, EPA is no longer considering the application of an additional modifying factor (see discussion below). However, database uncertainty remains because of the lack of human oral exposure information and the lack of any oral developmental or reproductive studies. Thus, the threefold partial database UF is retained.

C. ***Comment:*** Intraspecies UF for RfC should be reduced.

Response: One reviewer suggested that the intraspecies UF for the RfC should be reduced below 10, suggesting that a 10-fold UF is "enormously conservative when dealing with a point-of-contact irritant at *subthreshold* concentrations." New studies provided by the reviewer lend support to this position. The intraspecies UF was lowered to threefold and the following text was added to Section 6.2:

> "A partial threefold intraspecies uncertainty factor is applied to the RfC for protection of sensitive subpopulations. This UF is reduced by extensive human occupational studies and case reports that consistently identify the irritant properties of MMA as the principal effect of concern from MMA exposures. Little intraspecies variance is observed with respect to the identified critical effect, olfactory degeneration in laboratory animals (ECETOC, 1995; Lomax et al., 1997), and there is no reason to expect a high degree of intrahuman variability from this type of effect. Although Pickering et al. (1986) reported delayed asthmatic response following challenge with MMA, which would suggest that MMA is a possible respiratory sensitizer, no occupational studies identified MMA as a respiratory sensitizer. A partial intraspecies uncertainty factor of 3 is deemed sufficiently protective."

D. ***Comment:*** The interspecies UF for the RfC should be eliminated.

Response: One reviewer suggested that the interspecies UF for the RfC should be eliminated. The reasons given were (1) "...differences between animals and humans

are already factored into the calculation of the RGDR"; (2) "...differences in the response of rodent vs human tissues that would justify MORE protection/uncertainty, are unlikely"; (3) "...metabolic differences in carboxylesterase activity in the olfactory epithelium"; and (4) "...dosimetric/anatomical/airflow/tissue deposition considerations that make rodents' tissue 4 times more susceptible for chemical contact with nasal tissue than humans'." The reviewers' reasons 1, 3, and 4 were taken into account and were the primary reasons that the interspecies UF was lowered from 10 to 3. However, these reasons all deal with the potential for toxicokinetic differences. While the reviewer may be correct in asserting (reason 2 above) that significant toxicodynamic differences are not likely, some studies suggest that humans may be less capable of recovery from olfactory damage when it occurs. "Rapid potentially anatomically correct recovery after massive destruction" is observed in rats when underlying basal cells are not damaged (Youngentob, 1997) and small islands of intact olfactory epithelium are "sufficient to allow for olfactory function" (Wong et al., 1997). In humans, it has been reported that patients with relatively mild to moderate olfactory damage fail to recover olfaction and "...even when basal cells remain intact, differentiating cells developing from them do not mature into receptor cells but can develop into squamous cells..." (Yamagishi and Nakano, 1992). Thus, a partial 3-fold interspecies UF is retained.

(5) Weight-of-Evidence/Confidence Levels

A. ***Comment:*** There is not a clear "weight-of-evidence" assessment for each section.

Response: "Weight-of-evidence" and data synthesis is described in Sections 4.5 and 4.6. To some extent the data are also synthesized in earlier sections. However, in response to this comment, a paragraph similar to the following has been inserted at the beginning of Sections 4.2, 4.3 and 4.4.

> "This section is a review of laboratory animal studies relevant to the derivation of health benchmarks for MMA. An overall synthesis of this information and its relation to the potential for MMA to cause noncancer and cancer effects is presented in Sections 4.5 and 4.6, respectively. Certain studies that were considered to be inadequately documented for the purposes of this assessment or used irrelevant dosing regimens may not have been discussed in this section. A more complete listing/discussion of all types of repeat or single exposure studies can be found in other, more detailed reviews (ECETOC, 1995; U.S. EPA, 1991)."

B. ***Comment:*** Confidence in the RfD should be increased. Assignment of low confidence to RfD is "penalization" for MMA showing low oral irritation toxicity at concentrations limited by solubility in water and palatability in drinking water.

Response: Two reviewers suggested that confidence in the RfD database, particularly confidence in the Borzelleca et al. (1964) study, should be increased from "low." As discussed earlier, a copy of the original report (dated August 8, 1992), which included details and raw data from the Borzelleca et al. (1964) study, was submitted in support

of this contention. The availability of this information increases confidence in the Borzelleca study and in the overall database. However, database uncertainty remains because of the lack of human oral exposure information and the lack of any oral developmental or reproductive studies. Overall confidence in the RfD has therefore been changed from "low" to "low to medium."

(6) Comments on Chemical-Specific Questions

A. Question: MMA has been classified as *not likely to be carcinogenic to humans* under the Proposed Guidelines for Carcinogenic Risk Assessment (U.S. EPA, 1996). Is there sufficient evidence to support this classification? If so, has the evidence to support this classification been clearly presented?

Comments: All reviewers essentially responded "yes" to both questions. One suggested EPA consider the potential for MMA to be a tumor promoter. Another suggested greater emphasis be given to an ICI dominant lethal study (ICI, 1976a) in the mutagenicity section.

Response: The genotoxicity section of the document (Section 4.4.1) has been expanded to include discussions of additional relevant studies.

B. Question: As described in the Appendix to this report, there are limitiations to the benchmark analysis used to derive the RfC. Does the estimated BMC(10) serve as an appropriate basis for the RfC, or should the NOAEL of 25 ppm have been used?

Comments: One reviewer suggested NOAEL; all others suggested BMC(10) analysis.

Response: The majority of the reviewers suggested the use of the BMC(10) approach. The NOAEL approach would result in a slightly more conservative RfC, and the dose-response curve for use in the BMD analysis is difficult to model because of the high response level in the effected exposure group. However, one of the reviewers that suggested use of the BMC(10), a highly qualified pathologist, felt that the effect at the 100 ppm exposure level was slight and that the true NOAEL was likely closer to 100 ppm than to 25 ppm. Thus, an attempt at extrapolating, however difficult, was deemed justified and appropriate.

C. Question: The oral database for MMA is limited and a database uncertainty factor of 3 was employed in the derivation of the RfD. The study used in the derivation of the RfD was also questionable and an additional "modifying factor" (MF) has been suggested to account for this uncertainty surrounding the quality of the principal study itself. Ethyl acrylate (EA), a related compound, was found to severely irritate and cause cancer in the forestomach of gavaged rats (NTP, 1983), yet no effect was reported by Borzelleca et al. (1964) for either EA or MMA- exposed rats. This could be due to a lower dose and different dosing regimen, but could also mean that

Borzelleca and colleagues did not closely examine all aspects of the gastrointestinal tract. Although short-term strucure-activity relationship studies (discussed below) demonstrate that MMA may not cause the forestomach effects observed for EA, it is nevertheless curious that Borzelleca and colleagues did not report any such effects from EA chronic drinking water exposure. Is a modifying factor necessary to account for this uncertainty?

Comments: One reviewer suggested use of the Motoc (1971) study over Borzelleca et al. (1964). All others argued for use of the Borzelleca study. No reviewer suggested the need for a modifying factor. One reviewer argued strongly for increased confidence in the Borzelleca study.

Response: As discussed above, confidence in the Borzelleca study is increased with the submission by a reviewer of the original detailed report, raw data, and individual animal records. The Motoc (1971) study was a 32-week gavage study and is considered to be a less appropriate and potentially irrelevant exposure regimen when compared to the Borzelleca chronic drinking water study. One reviewer provided strong evidence in support of the EA toxic response being highly dependent on the exposure regimen, and that "changing the mode of oral administration to continuous small doses in drinking water allows effficient detoxification of EA and does not overwhelm glutathione-binding [detoxification] mechanisms." Studies submitted by this reviewer were used to improve the argument in Section 5.1.1 for use of the Borzelleca et al. (1964) study as the principal study.

D. Question: Olfactory tissue is considered the primary target organ with respect to inhalation exposure. Is there reason to suspect systemic toxicity from inhalation exposure? If so, would the calculated RfC be protective against such systemic toxicity?

Comments: All reviewers essentially said that the literature did not present a reason to expect systemic toxicity from MMA exposure.

Response: No change necessary.

E. Question: Is the information in the Toxicological Review sufficient to consider methyl methacrylate as having a low potential for causing reproductive effects?

Comments: For the most part the reviewers answered "yes" to this question. One reviewer commented that greater emphasis should be given in the Reproductive Toxicity section to the lack of effects on reproductive organs in lifetime exposure studies in several species and an ICI dominant lethal study, and that less emphasis should be given to the Singh intraperitoneal study.

Response: No significant changes were deemed necessary. Minor edits were made to Section 4.3, Reproductive and Developmental Studies, to reflect reviewer comments.