Methyl methacrylate; CASRN 80-62-6 (03/02/98)

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Methyl methacrylate

File First On-Line 03/02/98

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	03/02/1988*
Inhalation RfC (I.B.)	yes	03/02/1998*
Carcinogenicity Assessment (II.)	yes	03/02/1988*

*A comprehensive review of toxicological studies was completed (June 5, 2006) - please see section I.A.6., I.B.6., II.D.2. for more information.

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Methyl methacrylate
CASRN — 80-62-6
Last Revised — 03/02/1998

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It 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. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses	UF	MF	RfD
None **Rat drinking water study** **Borzelleca et al. (1964)**	NOAEL:136 mg/kg/day	100	1	1.4 mg/kg/day

I.A.2. Principal and Supporting Studies (Oral RfD)

Borzelleca, JF; Larson, PS; Hennigar, GR, Jr; Huf, EG; Crawford, EM; Smith, RB, Jr., (1964) Studies on the chronic oral toxicity of monomeric ethyl acrylate and methyl methacrylate. Toxicol. Appl. Pharmacol. 6:29-36.

Borzelleca et al. (1964) exposed groups of 25 male and 25 female Wistar rats to MMA in drinking water continuously 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; this 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. No abnormalities or lesions related to MMA were identified from histopathological examination of the tissues of exposed rats. The only effect observed was an increased kidney/body-weight ratio in female rats exposed to 2,000 ppm MMA, but the

increase was only marginally significant and was not associated with any histopathological findings. Thus, 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.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — 100.

The following uncertainty factors are applied to this effect level: 10 for consideration of intraspecies variation (UF_H; human variability), a partial 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). The total UF = 10 × 3 × 3 = 100.

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, 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 three-fold 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.

MF — 1.

I.A.4. Additional Studies/Comments (Oral RfD)

There are three repeat exposure studies that were of long enough 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 Borzolleca 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) were 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 for female rats, but it was only marginally significant and was not associated with any histopathological 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).

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.

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 histopathological alterations of the liver, ulcerations of the stomach, and biochemical alterations (elevated serum enzyme activity), but no further details were described.

The LD_{50} for MMA was estimated to be 8.41-10 mL/kg (7.87-9.36 g/kg) in rats, 6.3 mL/kg (5.9 g/kg) in guinea pigs, and 5 (4.68 g/kg) in dogs (Deichmann, 1941; Spealman et al., 1945). The lowest lethal concentration in rabbits administered MMA by gavage was 6.55 g/kg body weight. Toxic symptoms in both species included increased respiratory rate and motor weakness. These were followed by decreased respiration at 15 to 40 minutes post-administration, shallow and irregular respiration, increased urination and defecation, hemoglobinuria, loss of reflex activity, coma, and death. Adverse intestinal changes were observed in orally exposed animals.

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 to controls.

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 (1979) 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). 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.

MMA is readily absorbed through the lungs, gastrointestinal tract, and skin. 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. 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).

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. In the experiments of Bratt and Hathway (1977), it was found that 10 days after oral or i.v. dosing of rats with ^{14}C-MMA, only 4.1%-6.6% ^{14}C-MMA remained in the carcass. 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 following acute exposures.

Metabolism of MMA has been studied in vitro (Corkill et al., 1976; Bereznowski, 1995) and oral in vivo (Bratt and Hathway, 1977; Crout et al., 1982) in both rodents and humans. Several studies have confirmed the initial hydrolysis of MMA to methacrylic acid and methanol, and one in vitro study (Bereznowski, 1995) indicates that the rate of hydrolysis is slower in human than in rat blood. Available evidence suggests that MMA is enzymatically converted to methacrylic acid and is esterified to CoA, which is hydroxylated to -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 (Bratt and Hathway, 1977; Crout et al., 1982), and methyl malonic acid has been shown to be a urinary metabolite of humans (Crout et al., 1982).

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, 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 $^{14}CO_2$. An estimated 0.19%-1.4% of the administered dose was excreted by the lungs as unmetabolized MMA. The percent excreted as CO_2 decreased and the percent exhaled as unchanged MMA increased with increasing dose regardless of route (Bratt and Hathway, 1977). Urinary excretion accounted for about 4.7%-14.5% of the administered radioactivity (Bratt and Hathway, 1977; Crout et al., 1982), with about 0.22% of the radioactivity in the methylmalonic acid fraction (Crout et al., 1982). Other metabolites detected in the urine following oral or intravenous dosing with radiolabeled MMA include methacrylic acid, succinic acid, methylmalonic semialdehyde, -hydroxyisobutyric acid, and an unidentified ^{14}C-labeled acid. An estimated 1.7%-3% was excreted in feces following intragastric or intravenous administration (Bratt and Hathway, 1977). Methylmalonic acid was also detected in the urine of a human volunteer administered an ^{2}H-labeled dose of the sodium salt of MMA. ^{2}H-labeled methylmalonic acid was detected in the urine in an amount equal to about 1% of the administered dose (Crout et al., 1982).

For more detail on other Hazard Identification Issues, exit to the toxicological review, Section 4.7 (PDF)

I.A.5. Confidence in the Oral RfD

Study — Low to medium
Database — Low to medium
RfD — Low to medium

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. Relevant, quantitative human subchronic or chronic studies are not available. Although repeat exposure inhalation studies, including developmental, reproductive, and chronic studies, bolster the weak and dated oral database somewhat, no developmental or reproductive studies are available by the oral route, 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.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is presented in the Toxicological Review of Methyl Methacrylate. (CAS No. 80-62-6). (EPA, 1998)

U. S. Environmental Protection Agency. (1985) Health and environmental effects profile for methyl methacrylate. Cincinnati, OH: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/X-85/364. Available from: NTIS, Springfield, VA; PB88-17885/XAB.

U.S. Environmental Protection Agency. (1988) Health and environmental effects profile for methyl methacrylate. NTIS/PB88-178785.

U.S. Environmental Protection Agency. (1991) Summary review of health effects associated with methyl methacrylate: health issue assessment. Environmental Criteria and Assessment Office, Research Triangle Park, NC; ECAO-R-092A.

Other EPA Documentation — U.S. EPA, 1987

Date of Agency Consensus — 11/25/97

To review the Summary of and Response to External Peer Review Comments, exit to the toxicological review, Appendix B (PDF).

A comprehensive review of toxicological studies published through June 2006 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing RfD for Methyl methacrylate and a change in the RfD is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Methyl methacrylate
CASRN — 80-62-6
Last Revised — 03/02/1998

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Degeneration/atrophy of olfactory epithelium (male rats) **Rat chronic inhalation study** **Hazelton Laboratories 1979a; Lomax, 1992; Lomax et al., 1997**	BMC_{10}: 35 ppm BMC_{10}(ADJ): 25.6 mg/m^3 BMC_{10}(HEC): 7.2 mg/m^3	10	1	7E-1 mg/m^3

*Conversion Factors and Assumptions — The concentration associated with a 10% increased incidence (or extra risk) in the critical effect was determined using two dose-response functions. The 95% confidence limit on the concentration causing this benchmark response (BMC_{10}) was estimated to be 35 ppm (polynomial regression model). Assuming 25 ^{o}C and 760 mmHg and a molecular weight of 100.11, BMC_{10} (mg/m^3) = 35 ppm × 100.11/24.45 = 143 mg/m^3. BMC_{10}(ADJ) = 143 mg/m^3 × 6 h/24 h/day × 5 days/7 days = 25.6 mg/m^3. The BMC_{10}(HEC) was calculated for a gas:respiratory effect in the extrathoracic region. MVa = 0.25 L/min, MVh = 13.8 L/min, Sa(ET) = 11.6 cm^2, Sh(ET) = 177 cm^2. RGDR = (MVa/Sa)/(MVh/Sh) = 0.28. BMC(HEC) = 25.6 × RGDR = 7.2 mg/m^3.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Hazelton Laboratories America, Inc. (1979a). A two-year vapor inhalation safety evaluation study in rats: methyl methacrylate, final report. Vienna, VA: Hazleton Laboratories America, Inc.; project no. 417-354.

Lomax, LG. (1992) Histopathologic evaluation of the nasal cavities from Fisher 344 rats exposed to methyl methacrylate vapor for two years. Spring House, PA: Rohm and Haas Company.

Lomax, LG; Krivanek, N; Frame, SR. (1997) Chronic inhalation toxicity and oncogenicity of methyl methacrylate in rats and hamsters. Food Chem Toxicol 35:393-407.

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, 1,621.7 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). 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 with 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 squamous metaplasia, 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., 1995). 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. This reanalysis confirmed that chronic exposure to MMA does not appear to effect 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 hypoplasia, 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 polypoid mass attached to the lateral wall of one side of the anterior nasal cavity. These masses were morphologically similar, consisting of differentiated pseudoglandular 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.

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 cytotoxicity in the olfactory region. Though it has been suggested that MMA metabolism is a detoxifying mechanism following oral exposure (Bereznowski, 1995), the metabolite, methacrylic acid, appears to be the toxic moiety in the olfactory tissues (Morris and Frederick, 1995; Lomax et al., 1995). In support of this assumption, the localization and activity of the metabolic enzyme, carboxylesterase, correlates quite well with the localization and severity of nasal lesions in rodents following MMA exposure (i.e., both occur predominantly in the olfactory epithelium and not respiratory epithelium) (Dahl et al., 1987; Bogdanffy et al., 1987; Bogdanffy, 1990; Frederick et al., 1994). Further, similar toxicity from compounds that metabolize to acids 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), and exposures to acrylic and acetic acids directly have also caused similar olfactory- specific lesions (Miller et al., 1981; Stott and McKenna, 1985).

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. (1995) by the maximum likelihood method. These models were developed for use with dichotomous (incidence) data, and can either calculate a response threshold (for circumstances in which it is appropriate to presume the existence of an exposure level below which there is no response) or assign a threshold of zero (for circumstances in which it is appropriate to presume that all exposure levels emit a response). Because the mechanism for MMA olfactory toxicity is not well understood, the conservative model assumption of no threshold was employed. These models also provide the option of assuming a zero or nonzero background response. The only effect noted in control animals was minimal basal cell hyperplasia (5/39 control animals). 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, the two models were applied to incidence data reported by Lomax (1992) and Lomax et al. (1995) for observed olfactory lesions in male and female rats.

Data for degeneration/atrophy of olfactory epithelium in males (0/39, 0/47, 35/48, and 38/38) were chosen for 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 (p values = 0.616 and 0.768, respectively), and the resultant BMC values were lower than the BMCs for replacement by ciliated epithelium, the only other endpoint for which good model fit could be reached. An EPA review of benchmark analysis performed for several upper respiratory toxicants indicates that both the BMC values for 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 benchmark response (BMR) chosen for use in the RfC derivation was 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 (143 mg/m^3) 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. Details of the BMC_{10}

derivation for this data set (model used, input assumptions, etc.) are provided in the IRIS support document for this compound.

When the BMC_{10}(mg/ m^3) is derived from a study in which laboratory animals are exposed intermittently (e.g., 6 h/day, 5 days/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, 1994) recognize that, depending on the mechanism of action, such duration adjustment may not always be appropriate. In the case of 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 (Green, 1996), combined with the presence of lesions in rats following chronic (2-year) 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 to a BMC_{10}(ADJ) of 25.6 mg/m^3(143 mg/m^3 × 6 h/24 h/day × 5 days/7 days = 25.6 mg/m^3). A human equivalent BMC_{10}, BMC_{10}(HEC), of 7.2 mg/m^3. is then calculated using default procedures for a gas:respiratory effect in the extrathoracic region [MVa = 0.25 L/min, MVh = 13.8 L/min, Sa(ET) = 11.6 cm^2, Sh(ET) = 177 cm^2. RGDR = (MVa/Sa)/(MVh/Sh) = 0.28. BMC(HEC) = 25.6 × RGDR = 7.2 mg/m^3], appropriate when peer-reviewed PBPK models are not available (US EPA, 1994).

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — 10.

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). This UF is reduced from 10 because of 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.

Two studies have 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, no uncertainty factor is applied to the RfC for database deficiencies.

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 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, 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 morphologic interspecies 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 human 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.

MF — 1.

I.B.4. Additional Studies/Comments (Inhalation RfC)

A. SUPPORTING STUDIES

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).

The EPA Toxicological Review for MMA summarizes key subchronic and chronic laboratory animals and human studies of MMA. Subchronic and chronic exposure of rats and mice to MMA by oral and inhalation routes (as well as dermal) 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, as they are generally nonspecific and workers were exposed to several other toxic compounds. In general, MMA has not resulted in 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.

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 (1979) 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). However, 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, 1976). 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 has been considered in the determination of uncertainty factors.

For more detail on other Hazard Identification Issues, exit to the toxicological review, Section 4.7 (PDF)

I.B.5. Confidence in the Inhalation RfC

Study — High
Database — Medium to high
RfC — Medium to high

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 (Lomax, 1992; Lomax et al., 1995), 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 subsequent reanalyses (Lomax, 1992; Lomax et al., 1995) 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 only observed in offspring at levels more than 10-fold higher than the LOAEL for the chosen critical (olfactory) effect. Multigenerational reproductive studies are not available for MMA. However, protection against the portal-of-entry effects observed at low exposure levels across both the oral and inhalation routes of exposure is deemed likely to also protect against any

possible multigenerational reproductive effects. Given these considerations the inhalation database and the RfC are given medium to high confidence.

EPA recognizes that PBPK models are under development for MMA (Andersen et al., 1996) and other acrylates (Morris and Frederick, 1995; Bogdanffy and Taylor, 1993). The results of these ongoing investigations are under review by the Agency and are expected to help increase confidence in the estimation of a human equivalent concentration and clarify the different species sensitivities.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is presented in the Toxicological Review of Methyl Methacrylate (CAS No. 80-62-6). (EPA, 1998).

U. S. Environmental Protection Agency. (1985) Health and environmental effects profile for methyl methacrylate. Cincinnati, OH: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/X-85/364. Available from: NTIS, Springfield, VA; PB88-178785/XAB.

U.S. Environmental Protection Agency. (1988) Health and environmental effects profile for methyl methacrylate. NTIS/PB88-178785.

U.S. Environmental Protection Agency. (1991) Summary review of health effects associated with methyl methacrylate: health issue assessment. Environmental Criteria and Assessment Office, Research Triangle Park, NC;-092A.

Agency Consensus Review Date -- 11/25/97

To review the Summary of and Response to External Peer Review Comments, exit to the toxicological review, Appendix B (PDF)

A comprehensive review of toxicological studies published through June 2006 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing RfC for Methyl methacrylate and a change in the RfC is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Methyl methacrylate
CASRN — 80-62-6
Last Revised — 03/02/1998

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The 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 estimated in terms of either risk per ug/L drinking water or risk per ug/m^3 air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in the Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under EPA's 1986 Guidelines for Carcinogen Risk Assessment, MMA would be classified as *evidence of non-carcinogenicity for humans* or a Group E chemical. Under the Proposed Guidelines for Carcinogenic Risk Assessment (U.S. EPA, 1996), MMA is considered *not likely to be carcinogenic to humans* by any route of exposure because it has been evaluated in four well-conducted chronic inhalation studies in three appropriate animal species without demonstrating carcinogenic effects.

Basis — The results of the 2-year inhalation studies conducted for NTP showed no evidence of carcinogenicity of MMA for male F344/N rats exposed at 500 or 1,000 ppm, for female F344/N rats exposed at 250 or 500 ppm, or for female B6C3F1 mice exposed at 500 or 1,000 ppm. In addition, no increase was seen in the number or type of tumors in either rats or hamsters from the chronic inhalation study performed by Hazelton Laboratories (1979a,b). No carcinogenic activity was reported in a chronic oral study (Borzelleca et al., 1964). Fewer animals were used and the experimental protocal and results of this oral study were not as well documented as for the inhalation study. However, acute oral exposure studies and structure-activity relationship comparisons with other acrylates suggest that the introduction of a methyl group to the acrylate moiety (e.g., EA to MMA) negates carcinogenic activity. Epidemiology studies show no clear excess of 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 structure-activity relationship 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.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on other Hazard Identification Issues, exit to the toxicological review, Section 4.7 (PDF)

II.A.2. Human Carcinogenicity Data

Inadequate. 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 or not 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, and in subsequent evaluations of the same site (Walker et al., 1991; ECETOC, 1995; Collin et al, 1989). Collins et al. (1989) have noted that during the 1970's, the county in which the plant was located had a high colorectal cancer rate, at the 75^{th} 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).

Some instances of possible association of human neoplasms with MMA have been reported, but most have been clearly associated with polymethyl methacrylate. Wines (1973) reported on a patient who developed bladder carcinoma adjacent to intrapelvic cement (polymethyl methacrylate) following a Charnley total hip replacement; Thompson and Entin (1969) reported on the occurrence of a chondrosarcoma intimately associated with the fibrous capsule surrounding lucite (polymethacrylate) spheres used as plombage for compressing a tuberculous cavity; Routledge (1973) described a case of granuloma of the upper lobe of the left lung in a worker in a hospital department making polymethacrylate contact lenses.

II.A.3. Animal Carcinogenicity Data

No Evidence. Carcinogenic tests have been performed which 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 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. In the experiments of Oppenheimer et al. (1955), no tumors were induced when monomeric MMA was applied dermally to the back of the neck of rats. While suggestive with respect to whether mode of application has bearing on the results of such experiments, the Oppenheimer study should not be considered sufficient for evaluating the carcinogenic potential of MMA, as the exposure period 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 (Lomax, 1992) is not likely to be associated with MMA exposure, and these benign neoplasms have been reported in control rats as well. Similarly, a 2-year NTP inhalation bioassay in rats and mice gave negative results for carcinogenicity, although the animals may not have been tested at the maximum tolerated dose (National Toxicology Program, 1986; Chan et al., 1988).

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 five weeks, to 1,400 ppm at seven weeks, and to 1,500 ppm at nine 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. 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.

II.A.4. Supporting Data for Carcinogenicity

When tested at cytotoxic concentrations, MMA does not appear to be mutagenic to bacteria (National Toxicology Program, 1986; ECETOC, 1995; Waegemaekers and Bensink, 1984). MMA has been shown to be an in vitro clastogen in mammalian cell gene mutation and chromosomal aberration assays (National Toxicology Program, 1986; ECETOC, 1995). 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 reports of chromosomal damage from in vivo human data (Marez et al., 1991; Seji et al., 1994) are equivocal.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

No data available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

No data available.

II.C.1. Summary of Risk Estimates

II.C.1.1. Unit Risk

No data available.

II.C.1.2. Extrapolation Method

No data available.

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

No data available.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

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.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Although some cases of sarcomas have been reported following implants of poly-MMA, it is likely that these are the result of mechanical processes involving topographic interaction of the solid surface with normal cells and are not due to leaching of monomeric MMA from poly-MMA surgical implants. The results of the 2-yr inhalation studies conducted for NTP showed no evidence of carcinogenicity of MMA for male F344/N rats exposed at 500 or 1,000 ppm, for female F344/N rats exposed at 250 or 500 ppm, or for female B6C3F1 mice exposed at 500 or 1,000 ppm. In addition, no increase was seen in the number or type of tumors in either rats or hamsters from the chronic inhalation study performed by Hazelton Laboratories (1979a,b). Appearance of a polypoid adenoma in the nasal cavity of two MMA exposed male rats (Lomax, 1992) is not likely to be associated with MMA exposure, and these benign neoplasms have been reported in control rats as well.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — This assessment is presented in the Toxicological Review of Methyl Methacrylate (CAS No. 80-62-6). (EPA, 1998).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to Toxicological Review of Methyl Methacrylate (MMA) in support of summary information on Integrated Risk Information System (IRIS). ***To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF)***

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 11/25/97

A comprehensive review of toxicological studies published through June 2006 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing carcinogenicity assessment for Methyl methacrylate and a change in the assessment is

not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS in general at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (Internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Methyl methacrylate
CASRN — 80-62-6

VI.A. Oral RfD References

Bereznowski, Z. (1995) In vivo assessment of methyl methacrylate metabolism and toxicity. Int. J Biochem 27:1311-1316.

Borzelleca, JF; Larson, PS; Hennigar, GR, Jr.; Huf, EG; Crawford, EM; Smith, RB, Jr. (1964) Studies on the chronic oral toxicity of monomeric ethyl acrylate and methyl methacrylate. Toxicol Appl Pharmacol 6:29-36.

Bratt, H; Hathway, DE. (1977) Fate of methyl methacrylate in rats. Br J Cancer 36:114-119.

Corkill, JA; Lloyd, EJ; Hoyle, P; Crout, DHG; Ling, RSM; James, ML; Piper, RJ. (1976) Toxicology of methyl methacrylate: the rate of disappearance of methyl methacrylate in human blood in vitro. Clin Chim Acta 68:141-146.

Crout, DHG; Lloyd, EJ; Singh, J. (1982) Metabolism of methyl methacrylate: evidence for metabolism by the valine pathway of catabolism in rat and in man. Xenobiotica 12:821-829.

Deichmann, W. (1941) Toxicity of methyl, ethyl and n-butyl methacrylate. J Ind Hyg Toxicol 23:343-351.

Ghanayem, BI; Bour, PJ; Ahmed, AE. (1985) Acrylonitrile-induced gastric mucosal necrosis: role of gastric glutathione. J Pharmacol Exp Ther 232:570-577.

Ghanayem, BI; Maronpot, RR; Matthews, HB. (1986) Association of chemically induced forestomach cell proliferation and carcinogenesis. Cancer Lett 32:271-278.

Husain R; Khan, S; Husain, I; Seth, PK; Pandya, KP. (1989) Effect of methyl methacrylate on selected lipids in rat brain and sciatic nerve. Ind Health 27(3):121-124.

Husain, R; Srivastava, SP; Seth, PK. (1985) Methyl methacrylate induced behavioural and neurochemical changes in rats. Arch Toxicol 58:33-36.

ICI (1977) Methylmethacrylate monomer: teratogenicity studies in the rat. Hodge, MCE and Palmer, S., eds. Report CTL/P/316. ICI, Macclesfield, Cheshire.

Luo, SQ, et al. (1986) Study on embryotoxicity and fetotoxicity in rats by maternal inhalation of low level methyl methacrylate. Toxicol Lett 31:80.

McLaughlin, RE; Reger, SI; Barkalow, JA; Allen, MS; Difazio, CA. (1978) Methylmethacrylate: a study of teratogenicity and fetal toxicity of the vapor in the mouse. J Bone Jt Surg Am 60-A:355-358.

Motoc, F; Constantinescu, S; Filipescu, G; Dobre, M; Bichir, E; Pambuccian, G. (1971) Noxious effects of certain substances used in the plastics industry (acetone cyanohydrin, methyl methacrylate, azobis-isobutylronitrile and anthracene oil). Relation between the agressor agent and its effects. Arch Mal Prof Med Trav Secur Soc 32:653-658.

Nicholas, CA; Lawrence, WH; Autian, J. (1979) Embryotoxicity and fetotoxicity from maternal inhalation of methyl methacrylate monomer in rats. Toxicol Appl Pharmacol 50:451-458.

Raje, RR; Ahmad, S; Weisbroth, SH. (1985) Methylmethacrylate: tissue distribution and pulmonary damage in rats following acute inhalation. Res Commun Chem Pathol Pharmacol 50:151-154.

Solomon, HM; McLaughlin, JE; Swenson, RE; Hagan, JV; Wanner, FJ; O'Hara, GP; Krivanek, ND. (1993) Methyl methacrylate: inhalation developmental toxicity study in rats. Teratology 48:115-125.

Spealman, CR; Main, RJ; Haag, HB; Larson, PS. (1945) Monomeric methyl methacrylate: studies on toxicity. Ind Med 14:292-298.

Tansy MF. (1979) Final report of teratology studies of mice exposed to methyl methacrylate vapor. Rohm and Haas Company, Spring House, PA; Report No. 78RC-1021.

U.S. Environmental Protection Agency (U.S. EPA). (1985) Health and environmental effects profile for methyl methacrylate. Cincinnati, OH: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/X-85/364. Available from: NTIS, Springfield, VA; PB88-178785/XAB.

U.S. Environmental Protection Agency (U.S. EPA). (1986) The Risk Assessment Guidelines of 1986. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-87/045.

U.S. Environmental Protection Agency (U.S. EPA). (1988) Health and environmental effects profile for methyl methacrylate. NTIS/PB88-178785.

U.S. Environmental Protection Agency (U.S. EPA). (1991) Summary review of health effects associated with methyl methacrylate: health issue assessment. Environmental Criteria and Assessment Office, Research Triangle Park, NC; ECAO-R-092A.

U.S. Environmental Protection Agency (U.S. EPA). (1998). Toxicological review of Methyl Methacrylate (CAS No. 80-62-6). in Support of Summary Information on Integrated Risk Information System (IRIS). Available online at http://www.epa.gov/iris.

Wenzel, H; Garbe, A; Nowak, H. (1973) Untersuchungen zur pharmakokinetik von monomethylmethacrylat. 1st Int. Kongr. Prothesentecknok funkt. Rehabil. Wien. (Cited in Borchard, 1982)

VI.B. Inhalation RfC References

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. Report prepared by ICF Kaiser Engineers, Inc. for the Methacrylate Producers Association, Inc.

Bereznowski, Z. (1995) In vivo assessment of methyl methacrylate metabolism and toxicity. Int J Biochem 27:1311-1316.

Chan, PC; Eustis, SL; Huff, JE; Haseman, JK; Ragan, H. (1988) Two-year inhalation carcinogenesis studies of methyl methacrylate in rats and mice: inflammation and degeneration of nasal epithelium. Toxicology 52:237-252.

Dahl, AR; Miller, SC; Petridou-Fischer, J. (1987) Carboxylesterases in the respiratory tracts of rabbits, rats and Syrian hamsters. Toxicol Lett 36:129-136.

Frederick, CB; Udinsky, JR; Finch, L. (1994) The regional hydrolysis of ethyl acrylate to acrylic acid in the rat nasal cavity. Toxicol Lett 70:49-56.

Gift, JS. (1996) Deriving reference concentrations when adverse effects are reported in all exposure groups. 1996 Society for Risk Analysis Meeting. New Orleans, LA, December, 1996.

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.

Hazleton Laboratories America, Inc. (1979a) 18-month vapor inhalation safety evaluation study in hamsters: methyl methacrylate vapor, final report. Vienna, VA: Hazleton Laboratories America, Inc.; project no. 417-354.

ICF Kaiser, Inc., (1990a) THC: A computer program to compute a reference dose from continuous animal toxicity data using the benchmark dose method. K.S. Crump Division, Ruston, LA.

ICF Kaiser, Inc., (1990b) THWC: A computer program to compute a reference dose from continuous animal toxicity data using the benchmark dose method. K.S. Crump Division, Ruston, LA.

ICI. (1976) Methylmethacrylate monomer: dominant lethal study in the mouse. Anderson, D. and Hodge, MCE, eds. Report CTL/P/295. ICI, Macclesfield, Cheshire.

ICI. (1977) Methylmethacrylate monomer: teratogenicity studies in the rat. Hodge, MCE and Palmer, S, eds. Report CTL/P/316. ICI, Macclesfield, Cheshire.

Keenan, CM; Kelly, DP; Bogdanffy, MS. (1990) Degeneration and recovery of rat olfactory epithelium following inhalation of dibasic esters. Fundam Appl Toxicol 15:381-393.

Klimisch, HJ. (1984) Carcinogenicity of acrylates: long-term inhalation studies on methyl acrylate (MA) and n-butyl acrylate (BA) in rats. Toxicologist 4:53.

Lomax, LG. (1992) Histopathologic evaluation of the nasal cavities from Fisher 344 rats exposed to methyl methacrylate vapor for two years. Spring House, PA: Rohm and Haas Company.

Lomax, LG, Krivanek, ND; Frame, SR. (1997) Chronic inhalation toxicity and oncogenicity of methyl methacrylate in rats and hamsters. Food Chemi Toxicol 35:393-407.

Lomax, LG; Brown, DW; Frederick, CB. (1994) Regional histopathology of the mouse nasal cavity following two weeks of exposure to acrylic acid for either 6 or 22 hours per day. Spring House, PA: Rohm and Haas Company.

Luo, SQ, et al. (1986) Study on embryotoxicity and fetotoxicity in rats by maternal inhalation of low level methyl methacrylate. Toxicol Lett 31:80.

Mattes, PM; Mattes, WB. (1992) Alpha-naphthyl butyrate carboxylesterase in human and rat nasal tissue. Toxicol Appl Pharmacol 114:71-76.

McLaughlin, RE; Reger, SI; Barkalow, JA; Allen, MS; Difazio, CA. (1978) Methylmethacrylate: a study of teratogenicity and fetal toxicity of the vapor in the mouse. J Bone Jt Surg Am Vol. 60-A:355-358.

Miller, RR; Ayres, JA; Jersey, GC; McKenna, MJ. (1981) Inhalation toxicity of acrylic acid. Fundam Appl Toxicol 1:271-277.

Miller, RR; Hermann, EA; Young, JT; Calhoun, LL; Kastl, PE. (1984) Propylene glycol monomethyl ether actetate (PGMEA) metabolism, disposition, and short-term vapor inhalation toxicity studies. Toxicol Appl Pharmacol 75:521-530.

Miller, RR; Young, JT; Kociba, RJ; Keyes, DG; Bodner, KM; Calhoun, LL; Ayres, JA. (1985) Chronic toxicity and oncogenicity bioassay of inhaled ethyl acrylate in Fischer 344 rats and B6C3F1 mice. Drug Chem Toxicol 8:1-42.

Morris, JB.; Frederick, CB. (1995) Upper respiratory tract uptake of acrylate ester and acid vapors. Inhal Toxicol 7:557-574.

National Toxicology Program (NTP). (1986) Toxicology and carcinogenesis studies of methyl methacrylate (CAS no. 80-62-6) in F344/N rats and B6C3F_1 mice (inhalation studies). Research Triangle Park, NC: U. S. Department of Health and Human Services, National Institutes of Health; report nos. NTP-TR-314 and NIH/PUB-87-2570. Available from: NTIS, Springfield, VA; PB87-146742/XAB.

Nicholas, CA; Lawrence, WH; Autian, J. (1979) Embryotoxicity and fetotoxicity from maternal inhalation of methyl methacrylate monomer in rats. Toxicol Appl Pharmacol 50:451-458.

Pickering, CAC; Bainbridge, D; Birtwistle, IH; Griffiths, DL. (1986) Occupational asthma due to methyl methacrylate in an orthopedic theater sister. Br Med J 192:1362-1363.

Solomon, HM; McLaughlin, JE; Swenson, RE; Hagan, JV; Wanner, FJ; O'Hara, GP; Krivanek, ND. (1993) Methyl methacrylate: inhalation developmental toxicity study in rats. Teratology 48:115-125.

Stott, WT; McKenna, MJ. (1985) Hydrolysis of several glycol ether acetates and acrylate esters by nasal mucosal carboxylesterase in vitro. Fundam Appl Toxicol 5:399-404.

Tansy MF. (1979) Final report of teratology studies of mice exposed to methyl methacrylate vapor. Rohm and Haas Company, Spring House, PA; Report No. 78RC-1021.

U.S. Environmental Protection Agency (U.S. EPA). (1985) Health and environmental effects profile for methyl methacrylate. Cincinnati, OH: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/X-85/364. Available from: NTIS, Springfield, VA; PB88-178785/XAB.

U.S. Environmental Protection Agency (U.S. EPA). (1986) The Risk Assessment Guidelines of 1986. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-87/045.

U.S. Environmental Protection Agency (U.S. EPA). (1988) Health and environmental effects profile for methyl methacrylate. NTIS/PB88-178785.

U.S. Environmental Protection Agency (U.S. EPA). (1991) Summary review of health effects associated with methyl methacrylate: health issue assessment. Environmental Criteria and Assessment Office, Research Triangle Park, NC; ECAO-R-092A.

U.S. Environmental Protection Agency (U.S. EPA). (1998) Toxicological Review of Methyl Methacrylate (CAS No. 80-62-6) in Support of Summary Information on Integrated Risk Information System (IRIS). Available online at http://www.epa.gov/iris.

VI.C. Carcinogenicity Assessment References

Bright, DS; Clark, HG; McCollum, DE. (1972) Serum analysis and toxic effects of methylmethacrylate. Surg Forum 23:455-457.

Chan, PC; Eustis, SL; Huff, JE; Haseman, JK; Ragan, H. (1988) Two-year inhalation carcinogenesis studies of methyl methacrylate in rats and mice: inflammation and degeneration of nasal epithelium. Toxicology 52:237-252.

Collins, JJ; Page, LC; Caporossi, JC; Utidjian, HM; Saipher, JN. (1989) Mortality patterns among men exposed to methyl methacrylate. JOM J Occup Med 31:41-46.

Ferguson, DJ. (1977) Cellular attachment to implanted foreign bodies in relation to tumorigenesis. Cancer Res 37:4367-4371.

Hazleton Laboratories America, Inc. (1979b) A two-year inhalation safety evaluation study in rats: methyl methacrylate, final report. Vienna, VA: Hazleton Laboratories America, Inc.; project no. 417-354.

Homsy, CA; Tullos, HS; Anderson, MS; Diferrante, NM; King, JW. (1972) Some physiological aspects of prosthesis stabilization with acrylic polymer. Clin Orthop Relat Res 83:317-328.

Laskin, DM; Robinson, IB; Weinmann, JP. (1954) Experimental production of sarcomas by methyl methacrylate implants. Proc Soc Exp Biol Med 87:329-332.

Lomax, LG. (1992) Histopathologic evaluation of the nasal cavities from Fisher 344 rats exposed to methyl methacrylate vapor for two years. Spring House, PA: Rohm and Haas Company.

Marez, T; Shirali, P; Hildebrand, HF; Haguenoer, JM. (1991) Increased frequency of sister chromatid exchange in workers exposed to high doses of methylmethacrylate. Mutagenesis 6:127-129.

Monroe, CB. (1984) Interim communication on the results of a mortality study of Bristol plant employees hired prior to 1946. Philadelphia, PA: Rohm and Haas Co.; FYI-OTS-0384-0300.

National Toxicology Program. (1986) Toxicology and carcinogenesis studies of methyl methacrylate (CAS no. 80-62-6) in F344/N rats and B6C3F_1 mice (inhalation studies). Research Triangle Park, NC: U. S. Department of Health and Human Services, National Institutes of Health; report nos. NTP-TR-314 and NIH/PUB-87-2570. Available from: NTIS, Springfield, VA; PB87-146742/XAB.

Oppenheimer, BS; Oppenheimer, ET; Danishefsky, I; Stout, AP; Eirich, FR. (1955) Further studies of polymers as carcinogenic agents in animals. Cancer Res 15:333-340.

Routledge, R. (1973) Possible hazard of contact lens manufacture. Br Med J 1:487-488.

Thompson, JR; Entin, SD. (1969) Primary extraskeletal chondrosarcoma: report of a case arising in conjunction with extrapleural lucite ball plombage. Cancer 23:936-939.

U.S. Environmental Protection Agency (U.S. EPA). (1986) The risk assessment guidelines of 1986. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-87/045.

U. S. Environmental Protection Agency. (U.S. EPA). (1996, April 23) Proposed guidelines for carcinogen risk assessment Federal Register 61 (79):17960-18011.

U.S. Environmental Protection Agency (US EPA). (1998) Toxicological review of Methyl Methacrylate (CAS No. 80-62-6)in Support of Summary Information on Integrated Risk Information System (IRIS). Available online at http://www.epa.gov/iris.

Wines, RD. (1973) Possible hazard of polymethyl methacrylate. Br Med J 3:409.

VII. Revision History

Substance Name — Methyl methacrylate
CASRN — 80-62-6

Date	Section	Description
03/02/1998	I.A., I.B., II., VI.	New RfD, RfC, and cancer assessments
12/03/2002	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.
07/05/2006	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

VIII. Synonyms

Substance Name — Methyl methacrylate
CASRN — 80-62-6
Last Revised — 03/02/98

- Methacrylic acid, methyl ester
- Methacrylate monomer
- Methyl a-methylacrylate
- Methyl 2-methyl-2-propenoate