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Provisional Peer-Reviewed Toxicity Values for

Methyl Acrylate
(CASRN 96-33-3)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

J. Phillip Kaiser, PhD
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

ICF International
9300 Lee Highway
Fairfax, VA 22031

PRIMARY INTERNAL REVIEWERS

Anuradha Mudipalli, MSc, PhD
National Center for Environmental Assessment, Research Triangle Park, NC

Q. Jay Zhao, PhD, MPH, DABT
National Center for Environmental Assessment, Cincinnati, OH

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Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR METHYL ACRYLATE (CASRN 96-33-3)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Methyl acrylate (CAS No. 96-33-3), also known as 2-propenoic acid, methyl ester, is a clear, colorless, volatile liquid with a persistent acrid odor (see Figure 1). It is used primarily as a comonomer with acrylonitrile in the production of acrylic and modacrylic fibers used in the clothing and home furnishing industries. Methyl acrylate is also used in the preparation of thermoplastic coatings, adhesives, sealants, and amphoteric surfactants for shampoos. It is used to produce medical and dental prostheses, contact lenses, and other specialty plastics. It also can serve as a resin in the purification of industrial effluents, and to aid in the timed release and disintegration of pesticides.

Methyl acrylate is unlikely to persist in the environment, and is not expected to bind to soil or sediment. When released to air, methyl acrylate undergoes degradation by photochemically produced hydroxyl radicals within days. Methyl acrylate is not expected to accumulate in the food chain (bioconcentration potential is low), and its simulated biodegradation rate in laboratory testing is high. Table 1 presents selected physicochemical properties of methyl acrylate.

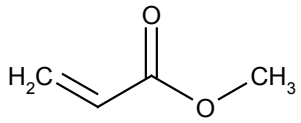

Figure 1. Methyl Acrylate Structure

Table 1. Physicochemical Properties of Methyl Acrylate (CASRN 96-33-3)[a]

Property (unit)	Value
Boiling point (ºC)	80.6
Melting point (ºC)	−76.5
Density (g/cm^3)	0.936
Vapor pressure (kPa at 20ºC)	9.3
pH (unitless)	ND
Solubility in water (g/100 mL at 20ºC)	6
Relative vapor density (air = 1)	3.0
Molecular weight (g/mol)	86.1

[a]ACGIH (1991).

ND = no data.

No Reference Dose (RfD) or Reference Concentration (RfC) for methyl acrylate is included in IRIS (U.S. EPA, 2011a) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). IRIS assigned methyl acrylate a human carcinogenicity weight-of-evidence (WOE) classification of D (not classifiable as to human carcinogenicity). The HEAST (U.S. EPA, 2011b) reports an oral chronic and subchronic RfD of 3×10^{-2} mg/kg-day based on a long-term inhalation study; an RfC is not reported. The Chemical Assessments and Related Activities (CARA) list does not include a Health and Environmental Effects Profile (HEEP) for methyl acrylate. The toxicity of methyl acrylate has not been reviewed by ATSDR (2011) or the World Health Organization (WHO, 2011). CalEPA (2008, 2009) has not derived toxicity values for exposure to methyl acrylate. Occupational exposure limits for methyl acrylate have not been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2011), the National Institute of Occupational Safety and Health (NIOSH, 2010), and the Occupational Safety and Health Administration (OSHA, 2010). OSHA standards include a Permissible Exposure Limit (8-hour time-weighted average [TWA]) of 10 ppm (35 mg/m^3); skin designation. The ACGIH Threshold Limit Value (8-hour TWA) is 2 ppm based on skin sensitization. Worker exposure levels may exceed 3 times the TLV-TWA for no more than a total of 30 minutes during a work day, and, under no circumstances, should they exceed 5 times the TLV-TWA. The ACGIH categorizes methyl acrylate as A4 (not classifiable as a human carcinogen). The NIOSH Recommended Exposure Limit (10-hour TWA) is 10 ppm (35 mg/m^3); skin designation. The Immediately Dangerous to Life or Health level is 250 ppm.

The HEAST (U.S. EPA, 2011b) does not report a cancer WOE classification or an oral slope factor for methyl acrylate. The International Agency for Research on Cancer (IARC, 2011) has reviewed the evidence for the carcinogenicity of methyl acrylate and places it in Group 3 (not classifiable as to its carcinogenicity to humans). Methyl acrylate is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2008) has not derived a quantitative estimate of carcinogenic potential for methyl acrylate.

Literature searches were conducted on sources published from 1900 through September 2011 for studies relevant to the derivation of provisional toxicity values for methyl acrylate (CASRN 96-33-3). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); WHO; and Worldwide Science. The following databases outside of HERO were searched for health-related values: ACGIH, ATSDR, CalEPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the potentially relevant studies comprising the database for methyl acrylate and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. The phrase, "statistical significance," used throughout the document, indicates a *p*-value of <0.05.

HUMAN STUDIES

No studies were identified.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to methyl acrylate have been evaluated in one subchronic-duration study by Wade et al. (1981).

Subchronic Studies

Wade et al. (1981) as summarized in ACGIH (1991)

The original document was not obtainable; limited information was cited in an ACGIH book chapter on methyl acrylate (ACGIH, 1991). It is unknown if this study was performed according to GLP guidelines. In a subchronic-duration study, Wade et al. (1981) administered methyl acrylate in drinking water to Fischer 344 rats (number/sex unknown) at dose levels of 0, 1, 5, or 20 mg/kg-day, 7 days/week, for 13 weeks. No additional information concerning the methods was provided. The report stated that the following effects were observed at 20 mg/kg-day: decreased water consumption, reduced body-weight gain, increased relative kidney weights, and increased incidence of renal disease. Tabular results were not presented. The study authors defined a NOEL of 5 mg/kg-day. Based on the limited data, the NOAEL is considered to be 5 mg/kg-day, and the LOAEL is 20 mg/kg-day. The report is not a published study, and there is no evidence that it was peer reviewed. Due to the overall lack of information and rigor, this study is not adequate for the derivation of a subchronic oral provisional RfD.

Chronic Studies

No studies were identified.

Developmental Studies

No studies were identified.

Reproductive Studies

No studies were identified.

Carcinogenicity Studies

No studies were identified.

Table 2. Summary of Potentially Relevant Data for Methyl Acrylate (CASRN 96-33-3)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Human								
1. Oral (mg/kg-d)[a]								
Acute[b]	ND							
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
2. Inhalation (mg/m^3)[a]								
Acute[b]	ND							
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
Animal								
1. Oral (mg/kg-d)[a]								
Subchronic	Number/sex not reported, Fischer 344 rats, drinking water, 7 d/wk, 13 wk	0, 1, 5, or 20	Decreased water consumption and body-weight gain; increased relative kidney weights and renal disease	5	NDr	20	Wade et al. (1981); as summarized in ACGIH (1991)	NPR
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							

Table 2. Summary of Potentially Relevant Data for Methyl Acrylate (CASRN 96-33-3)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
2. Inhalation (mg/m^3)[a]								
Subchronic	12 male, Sprague-Dawley (S-D) rats, whole body inhalation, 4 h/d, 5 d/wk, 32 d	0 or 46	No adverse effects	46	NDr	NDr	Oberly and Tansy (1985)	PR
Chronic	**86/86, S-D rats, whole body vapor inhalation, 6 h/d, 5 d/wk for 12 mo (10/sex), 18 mo (15/sex), or 24 mo (remaining survivors)**	**0, 9.8, 29, or 88 for cornea lesions in males and females; 0, 3.1, 9.2, or 28 for nasal lesions in males; 0, 2.2, 6.4, or 19 for nasal lesions in females**	**Olfactory epithelium atrophy; cornea parenchymal degeneration and neovascularization**	**2.2**	**3.1 for nasal lesions in male rats**	**6.4**	**Rohm and Haas Company (1992a)[g]**	**PR, PS**
Developmental	21−25 females, S-D rat, inhalation, 6 h/d Gestation Days 6−20	0, 22, 44, or 88	Decreased maternal body weight (when gravid uterus was excluded); reduced fetal body weight; decreased maternal food consumption	Maternal: 22 Offspring: 22	29 for decreased maternal food consumption	Maternal: 44 Offspring: 44	Saillenfait et al. (1999)	PR
Reproductive	ND							

Table 2. Summary of Potentially Relevant Data for Methyl Acrylate (CASRN 96-33-3)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Carcinogenicity	86/86, S-D rat, whole body vapor inhalation, 6 h/d, 5 d/wk for 12 mo (10/sex), 18 mo (15/sex), or 24 mo (remaining survivors)	0, 9.8, 29, or 88	No adverse effects	NA	NA	NA	Rohm and Haas Company (1992b)	PR

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer and carcinogenic effects. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure.
[b]Acute = Exposure for 24 hours or less (U.S. EPA, 2002).
[c]Notes: IRIS = Utilized by IRIS, date of last update; PS = principal study; PR = peer reviewed; NPR = not peer reviewed.
[d]Short-term = Repeated exposure for >24 h ≤30 d (U.S. EPA, 2002).
[e]Long-term = Repeated exposure for >30 d ≤10% lifespan (based on 70 years typical lifespan) (U.S. EPA, 2002).
[f]Chronic = Repeated exposure for ≥10% lifespan (U.S. EPA, 2002).
[g]This study was also the subject of the following citations: BASF Aktiengesellschaft (1992), Reininghaus et al. (1991) (peer reviewed), and Union Carbide Corporation (1989).

DU = data unsuitable, NA = not applicable, NV = not available, ND = No data, NDr = Not determinable, NI = not identified, NP = not provided, NR = Not reported, NR/Dr = Not reported but determined from data, NS = not selected.

HED = avg. mg test article ÷ avg. kg body weight ÷ Number daily dosed.

HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood:gas partition coefficient.

Inhalation Exposures

The effects of inhalation exposure of animals to methyl acrylate have been evaluated in one subchronic study in rats (i.e., Oberly and Tansy, 1985), one developmental study in rats (i.e., Saillenfait et al., 1999), and in one combined chronic toxicity/carcinogenicity study (i.e., Rohm and Haas Company, 1992a,b).

Subchronic Studies

Oberly and Tansy (1985)

In a peer-reviewed study, Oberly and Tansy (1985) administered methyl acrylate (98−98.5% pure) as a vapor by whole-body inhalation to groups of 12 male Sprague-Dawley (S-D) rats at mean measured concentrations of 0 or 110 ppm (HEC = 46 mg/m^3) for 4 hours per day, 5 days per week, for 32 days. It is unclear if this study was performed according to GLP guidelines. A subset of six animals per group was designated for special metabolic performance studies. The animals were exposed in stainless steel chambers. At the end of the exposure day, the metabolic performance subset rats were placed overnight in metabolism cages. Metabolic performance measurements were made for 20 hour periods on 5 consecutive days. At least 24 hours after the end of the last exposure, the animals were terminated. The following organ weights were measured: brain, heart, lung, liver, kidneys, spleen, adrenals, and testes. Blood serum analyses included measurements of the following parameters: total protein, albumin, albumin:globulin ratio, calcium, inorganic phosphorus, cholesterol, blood urea nitrogen, uric acid, total bilirubin, alkaline phosphatase, lactate dehydrogenase, serum glutamic-pyruvic transaminase, serum glutamic-oxaloacetic transaminase, and glucose. Additional parameters that were evaluated included mortality, gross pathology, clinical signs, body weight, food consumption, water consumption, urination, and defecation. Additionally, intercontractile-interval measurements obtained from small bowel segments were measured. The study authors reported no adverse effects on any of the evaluated parameters. Behavior during exposure consisted of exploration, self-grooming, and huddling. The study authors did not define a NOAEL or LOAEL. As no effects were observed at 46 mg/m^3, this concentration is considered to be a NOAEL. A LOAEL is not observed under the conditions of this study.

Chronic Studies

Rohm and Haas Company (1992a). Also see BASF Aktiengesellschaft (1992), Reininghaus et al. (1991), and Union Carbide Corporation (1989)

Four references for combined chronic toxicity/carcinogenicity studies were located. Based on the company, authors, sponsors, similarity of methods and results, and the similarity of the presentation of the results, it is concluded that the following citations all refer to the same study: Reininghaus et al. (1991), BASF Aktiengesellschaft (1992), Union Carbide Corporation (1989), and Rohm and Haas Company (1992a). The most complete reporting of this study was provided in Rohm and Haas Company (1992a); this study was also published in a peer-reviewed journal (Reininghaus et al., 1991). It is not known if this study was conducted under GLP standards. For clarity, information from these four reports is cited in this document as Rohm and Haas Company (1992a,b).

The combined chronic toxicity/carcinogenicity study in the rat (i.e., Rohm and Haas Company, 1992a) is selected as the principal study for derivation of the subchronic and chronic p-RfC. In this study, the authors administered methyl acrylate (>99.8% pure) to groups of S-D rats (86 rats/sex/dose) as a vapor by whole body inhalation at nominal concentrations of

0, 15, 45, or 135 ppm (analytical concentrations of 0, 15.6, 46.3, or 140.3 ppm; equivalent to 55, 163, and 496 mg/m^3) for 6 hours/day, 5 days per week, for up to 24 months. It is not known if this study was performed under GLP standards. Interim euthanasia or necropsy were performed after 12 months (10 rats/sex/dose) and 18 months (15 rats/sex/dose). The animals were obtained from WIGA (Sulzfeld, Germany). Environmental conditions included 10−15 air changes per hour, 22 ± 2°C mean room temperature, 55 ± 10% relative humidity, and 12-hour light cycle. Animals were housed individually, but male and female rats in the same treatment group were exposed together in an inhalation chamber. All rats were checked for their general condition and for signs of toxicity before and after each daily exposure, and once daily during the postexposure observation period. Body weight, food consumption, reflexes, and any abnormal tissue masses were recorded weekly. Rats found dead were necropsied on the same day. Moribund rats were euthanized and necropsied. Prior to euthanasia, rats were anesthetized with diethyl ether and blood was collected from the orbital sinus of all rats for the determination of erythrocyte and leukocyte counts. In addition, blood from rats in the control and 135-ppm groups were examined with respect to reticulocyte, normoblast, and differential leukocyte counts, as well as the number of erythrocytes with Heinz bodies, packed cell volume, erythrocyte volume, hemoglobin content, and hemoglobin concentration. Bone marrow smears were prepared from the rats of these groups and also from all moribund rats. Urine was collected from all rats scheduled for necropsy and was examined for volume, color, transparency, pH, protein, glucose, bilirubin, urobilinogen, ketone bodies, occult blood, and sediments.

Shortly before the rats were necropsied, the eyes were examined for external changes, pupillary reflex, changes in the anterior part of the bulbus, and changes of the fundus. The rats were euthanized by exsanguination under diethyl ether anesthesia (not fasted) and necropsied. Terminal body weights and the absolute and relative weights (to body weight and brain weight) of all major organs were determined for each rat. All tissues with gross lesions and representative sections of organs and tissues (according to the OECD requirements for combined chronic toxicity/carcinogenicity studies, with the exception of the accessory genital organs) were preserved in a 4% neutral formaldehyde solution. The testes were preserved in Bouin's fixative and the lumbar vertebrae in Schaffer's fixative. Tissue sections were routinely processed and stained with hematoxylin and eosin. The nasal cavity, liver, and kidney sections were additionally stained with periodic acid-Schiff stain. Frozen sections of the liver and the kidney were stained with Sudan III. The nasal cavity, larynx, trachea, lungs, and liver of all rats, as well as all tissues having gross lesions, were examined. The heart, kidneys, urinary bladder, ovaries, pituitary gland, thyroid, adrenals, brain, spleen, lumbar vertebrae, and lymph nodes from all rats in the control and 135-ppm groups were also examined. In addition, at each necropsy 11 tissue samples from each of at least 10 randomly selected male and female rats from the control and 135-ppm groups were histologically examined. Furthermore, an extensive histological examination was performed on all rats found dead or moribund (98 rats). All changes were graded according to severity. All neoplastic changes were classified according to tissue of origin, type, and biological behavior if possible. Mortality was analyzed using the Armitage life-table method, after accounting for nonspontaneous deaths. Moribund rats, rats found dead, and rats with apparently outlying values were excluded from routine statistics; findings in those rats were interpreted separately.

The chronic toxicity results are discussed in this section; the carcinogenicity results from the study (Rohm and Haas Company, 1992a) are presented in the appropriate section. With

regards to chronic toxicity, the study authors reported no adverse, treatment-related effects on mortality, clinical signs, body weights, food consumption, hematology, urinalysis, organ weights, or gross pathology. Two treatment-related effects, identified as irritant effects in the eyes and nose, are presented in Tables B.1 and B.2, respectively. Increased incidences of cornea parenchymal changes (degeneration or vascularization) were noted as follows compared to 0−2% incidence in the respective controls: (i) at 12 months: 8−50% in all treated male groups and 8−17% in the 45- and 135-ppm females; (ii) at 18 months: 7−67% in all treated male groups and 13−60% in all treated female groups; (iii) at 24 months: 12−60% in all treated male groups and 8−59% in all treated female groups; and (iv) considering all animals in the study: 10−59% in all treated male groups and 8−53% in all treated female groups with all treated groups being statistically significantly different than the controls (see Table B.1). The study authors stated that the resulting changes in the corneal parenchyma are attributed to the irritating properties of the test substance. Increased incidences of reserve cell hyperplasia with loss of olfactory and ciliated cells were noted as follows compared to 0−1% in the respective controls: (i) at 12, 18, and 24 months and when considering all animals in the study: 90−100% in the males and 60−100% in the females at 45 and 135 ppm ($p \leq 0.001$ considering all animals, each sex); (ii) at 24 months: 8% in the 15-ppm males; and (iii) considering all animals in the study: 5% in the 15-ppm males. Changes occurred in a narrowly defined region of the nasal mucosa at the level of the dorsal lamella of the second endoturbinate. Changes in the olfactory epithelium consistent with stratified reserve cell hyperplasia with loss of the functional epithelial component were determined in rats in the 45- and 135-ppm groups of both sexes, and were statistically significant only in these groups. Some of the 15-ppm males exhibited very mild atrophy or very mild to mild reserve cell hyperplasia of the olfactory epithelium at the same location. The respiratory epithelium in the area of transition to olfactory epithelium also exhibited reserve cell hyperplasia to a much lesser extent, in part with loss of the portion of functional epithelium. The altered epithelium exhibited no atypical cells or infiltrative growth. A NOAEL of 15 ppm (55 mg/m^3) with a corresponding LOAEL 45 ppm (163 mg/m^3) for increased incidence of nasal lesions in female rats are identified from this study.

Developmental Studies

Saillenfait et al. (1999)

In this peer-reviewed study, Saillenfait et al. (1999) administered methyl acrylate (99+% pure) to groups of 21−25 pregnant female S-D rats as a vapor by whole-body exposure at nominal concentrations of 0, 25, 50, or 100 ppm (analytical concentrations of 0, 25.1, 49.7, or 100.4 ppm; equivalent to 88, 175, and 353 mg/m^3) for 6 hours/day on Gestation Days (GDs) 6−20. It is not known if this study was performed under GLP standards. Nulliparous S-D rats, obtained from IFFA CREDO Breeding Laboratories (Saint-Germain-sur-l'Arbresle, France), were housed overnight with adult males (one male:two or three females) from the same strain and supplier. The day that vaginal smears were found to be sperm positive was considered GD 0. Mated females were randomly assigned to treatment groups using a randomization system stratified by body weight on GD 0. Mated females were singly housed in clear polycarbonate cages with stainless-steel wire lids and hardwood shavings as bedding in rooms maintained at 21 ± 2°C, a relative humidity of 50 ± 5%, and a 12-hour light/dark photocycle. For exposures, the females were transferred to stainless-steel wire mesh exposure cages, and the cages were moved into the chambers. After each exposure, the animals were returned to their original cages. Food pellets (UAR Alimentation Villemoisson, France) and filtered tap water were available ad libitum, except during exposures. No differences in particle counts were noted

between the clean filtered air (control) and the vapor-laden air in the exposure chambers. Food consumption was measured for the intervals GDs 6−13 and 13−21. Maternal body weights were recorded on GDs 0, 6, 13, and 21. On GD 21, the females were euthanized, and the uteri were removed and weighed. The number of implantation sites, resorptions, and dead and live fetuses were recorded. Uteri that had no visible implantation sites were stained with 10% ammonium sulfide to detect very early resorptions. Live fetuses were weighed, sexed, and examined for external anomalies including those of the oral cavity. Half of the live fetuses from each litter were preserved in Bouin's solution and examined for internal soft tissue changes. The other half were fixed in 70% ethanol, eviscerated, and then processed for skeletal staining with alizarin red S for skeletal examination. The number of implantation sites and live fetuses and the various body weights were analyzed by one-way analysis of variance, followed by Dunnett's test if differences were found. The percentages of nonlive implants and resorptions and the proportions of fetuses with alterations in each litter were evaluated by using the Kruskal-Wallis test, followed by the Dixon-Massey test where appropriate. Rates of pregnancy, fetal sex ratio, and percentages of litters with malformations or external, visceral, or skeletal variations were analyzed by using Fisher's test. When applicable, least-squares analysis was carried out.

Saillenfait et al. (1999) reported no maternal death at methyl acrylate exposures up to 100 ppm. However, statistical significant decreases in maternal weight gain (absolute) and in food consumption were observed at 50 and 100 ppm during the entire exposure period (see Table B.3). Exposure to 50 or 100 ppm was associated with maternal weight loss when gravid uterus weights were subtracted from the body-weight gains. No significant effects on the implantation sites, live fetuses, incidence of nonlive implants and resorptions, or on fetal sex ratio were observed in any of the groups exposed to methyl acrylate. Methyl acrylate induced a concentration-related decrease in fetal body weights that achieved biological significance at 50 ppm (6.7% lower than control; see Table B.3). A single 100-ppm fetus was observed with multiple malformations, including craniorachischisis, protruding tongue, and multiple skull and vertebral alterations including fused thoracic vertebral arches, thoracic hemicentrae, bilobed thoracic and lumbar vertebral centrae, and fused vertebral centrea and arches in the caudal and sacral regions. There were no statistically significant increases in the incidences of external, visceral, or skeletal variations in any treatment group relative to controls. Therefore, this single finding is considered incidental to treatment. The study authors reported a maternal LOAEL of 50 ppm (175 mg/m^3), based on decreases in maternal body-weight gain and food consumption, and a maternal NOAEL of 25 ppm (88 mg/m^3). An offspring LOAEL of 50 ppm (175 mg/m^3) based on a biologically significant (≥5% change) decrease in fetal body weights with a corresponding offspring NOAEL of 25 ppm (88 mg/m^3) is also identified from this study.

Reproductive Studies

No studies were identified.

Carcinogenicity Studies

Rohm and Haas Company (1992b). Also see Basf Aktiengesellschaft (1992), Reininghaus et al. (1991), and Union Carbide Corporation (1989).

This study is a combined chronic toxicity/carcinogenicity study; the methodology has been discussed previously in this document. With regards to carcinogenicity, the study authors reported that the numbers of animals with soft tissue sarcoma (n = 86) were 1, 4, 1, and 7 for the 0-, 15-, 45-, and 135-ppm male rats, respectively (Rohm and Haas Company, 1992b). The

concentration-dependency of this effect is unclear, and there was no other tumor incidence that could be considered possibly concentration dependent. Compared with the controls, there was no increase in soft tissue sarcomas in the females. The time-related occurrence of grossly visible or palpable tumors was not affected by treatment, nor was the frequency distribution of all rats with benign and malignant tumors. For these reasons, there is no clear, treatment-related increase in neoplastic incidence. The conclusion of U.S. EPA IRIS (1990) concerning these data is that no differences in incidences of preneoplastic or neoplastic lesions were observed between control and exposed groups.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Other studies that are not appropriate for selection of a POD for methyl acrylate and the determination of p-RfD, p-RfC, p-OSF, or p-IUR values provide supportive data supplementing a WOE approach to dose-response assessment. These studies may include genotoxicity (see Table 3A), as well as immunotoxicity, neurobehavioral toxicity, metabolism, and mechanistic studies (see Table 3B).

Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity

A total of eight reports were located evaluating the mutagenicity of methyl acrylate. Four studies demonstrated no mutagenicity in the prokaryotic test systems utilized (i.e., McMahon et al., 1979; Ishidate et al., 1981; Waegemaekers and Bensink, 1984; Florin et al., 1980). Mutagenicity of methyl acrylate in Drosophila was evaluated by Zimmering et al. (1989). Other studies indicated that methyl acrylate was clastogenic (i.e., Moore et al., 1989), can cause chromosome aberrations (i.e., Ishidate et al., 1981; Moore et al., 1988), and induce micronucleus formation (i.e., Przybojewska et al., 1984).

McMahon et al. (1979) evaluated 855 test chemicals in 10 tester strains over a 10,000-fold concentration gradient (0.1−1000 μg/mL) with and without metabolic activation using a modification of the Ames assay. Agar plates were prepared with a concentration gradient of the test compound. *Salmonella typhimurium* tester strains included G46, TA1535, TA100, C3076, TA1537, D3052, TA1538, and TA98. *E. coli* tester strains included WP2 and WP2 *uvrA*-. Sometimes *S. typhimurium* TA92 and TA94 and *E. coli* CM881 and CM891 were also used. The S9 was prepared from the livers of adult male Fischer rats treated once with Aroclor 1254. Measures were taken to minimize the loss of volatile test compounds. Methyl acrylate was not mutagenic in any of these assays.

Ishidate et al. (1981) reported a review of the screening data on about 500 different compounds tested over a 5-year period for their mutagenic activity on *Salmonella typhimurium* TA98, TA100, and TA1537 in the Ames Assay with preincubation of test chemical, bacteria, and S9/buffer. Protocols were detailed for tests with and without S9 metabolic activation; however, the results tables did not make it clear when metabolic activation was used. The S9 was prepared from the livers of Wistar rats pretreated with polychlorinated biphenyl (KC-400). Methyl acrylate was reported as not mutagenic in the Ames Assay.

Table 3A. Summary of Methyl Acrylate Genotoxicity Studies

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	A modification of the Ames assay evaluated the test compound (and 854 other chemicals) in 10 tester strains over a 10,000-fold concentration gradient with and without metabolic activation.	0.1−1000 µg/mL	−	−	No mutagenicity was observed in any strain or dose, in the presence or absence of S9.	McMahon et al. (1979)
Reverse mutation	Ames assay was conducted with and without activation using *Salmonella typhimurium* TA98, TA100, and TA1537.	NR	−	−	No mutagenicity was observed in any strain or dose, in the presence or absence of S9.	Ishidate et al. (1981)
Reverse mutation	Ames assay was performed with and without activation using *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and TA1538. The Ames assay with preincubation (suspension test) was conducted with and without activation using TA100.	0 or 40−2500 µg/plate in plate assay and 0, 30, 300, or 3000 µg/mL in suspension test	−	−	No mutagenicity was observed in any strain or dose, in the presence or absence of S9.	Waegemaekers and Bensink (1984)
Reverse mutation	Ames assay was conducted with and without metabolic activation using *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537.	0 or 3 µmol/plate	−	−	No mutagenicity was observed in any strain, in the presence or absence of S9.	Florin et al. (1980)
SOS repair induction	ND					
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	The sex-linked recessive lethal mutation assay was conducted after administration of methyl acrylate to *Drosophila melanogaster* larvae.	0, 500 ppm	−	NA	Mutagenicity was not observed.	Zimmering et al. (1989)
Recombination induction	ND					

Table 3A. Summary of Methyl Acrylate Genotoxicity Studies

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Chromosomal aberration	ND					
Chromosomal malsegregation	ND					
Mitotic arrest	ND					
Genotoxicity studies in mammalian cells—in vitro						
Mutation	A mouse lymphoma assay and a suspension-adapted CHO assay were conducted to quantify thymidine kinase and hypoxanthine-guanine phosphoribosyltransferase mutants.	0, 16, 22, or 24 µg/mL in the mouse lymphoma assay and 0, 14, 16, or 18 µg/mL in the CHO assay.	+ in mouse lymphoma assay ± in CHO assay	NA	Little or no evidence of genotoxicity when evaluated using selection for HGPRT-deficient mutants, but clearly clastogenic.	Moore et al. (1989)
Chromosomal aberrations	A Chinese hamster cell line of lung fibroblast origin was used in a chromosome aberration test.	NR	NR	NR	Genotoxicity was detected.	Ishidate et al. (1981)
Chromosomal aberrations	A mouse lymphoma assay in L5178Y cells was conducted without exogenous activation.	Cytotoxicity and mutagenicity tests: 0 and 10−24 µg/mL (multiple tests); chromosomal aberrations: 0, 16, 22, and 24 µg/mL.	+	ND	Concentration-dependent increases in mutation frequency and chromosome aberrations were noted.	Moore et al. (1988)
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					

Table 3A. Summary of Methyl Acrylate Genotoxicity Studies

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
DNA adducts	ND					
Genotoxicity studies in mammals—in vivo						
Chromosomal aberrations	A micronucleus test was conducted using the male Balb C mouse.	0, 37.5, 75, 150, or 300 mg/kg.	+	NA	Induction of chromosome damage and micronuclei formation was observed.	Przybojewska et al. (1984)
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adducts	ND					
Mouse biochemical or visible specific locus test	ND					
Dominant lethal	ND					
Genotoxicity studies in subcellular systems						
DNA binding	ND					

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive, ± = equivocal or weakly positive, − = negative, T = cytotoxicity, DU = data unsuitable, NA = not applicable, NV = not available, ND = no data, NDr = not determinable, NI = not identified, NP = not provided, NR = not reported, NR/Dr = not reported but determined from data, NS = not selected.

Table 3B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism/ toxicokinetic	Methyl acrylate was administered intraperitoneally or orally as methyl [2,3-^{14}C]-acrylate to groups of 6 adult male Wistar Albino rats in a single dose at 100 mg/kg (3.7 MBq/kg) in soya-bean oil. Excreta, expired air, blood, and selected organs/tissues were collected, and radioactive residues were quantified in subsets of the animals (six/group). The amount of radioactivity excreted, the rate of excretion into expired air, the elimination of radioactivity from the blood, and the distribution of radioactivity in tissues were reported.	Total recovery within 72 h was 91−96% of the administered dose (AD). Methyl acrylate was excreted primarily in the air (39−54% AD) and urine (40−51% AD) with relatively little excreted in the feces (2% AD). Excretion was rapid and most of the radioactivity found in the expired air occurred within the first 2 h, and the majority isolated in the urine occurred within 24 h. Peak blood levels were noted at 1 h postdose; biphasic elimination provided half-lives of 5 and 34 h for the fast and slow compartments. The highest initial specific radioactivity was isolated in the liver, kidneys, and lungs; levels in liver and lungs remained higher than in erythrocytes at 48 h post dose. Only 1% AD remained in the examined tissues 48 h after dosing.	Absorption and excretion are rapid. The dose was essentially cleared from the tissues within 48 h.	Sapota (1988)
Metabolism/ toxicokinetic	Male Fischer 344 rats and B6C3F$_1$ mice were treated with methyl acrylate. All experiments were performed in vitro, and blood and tissues from the animals were used in these experiments. Hydrolysis of methyl acrylate was measured in rat whole blood. Hydrolysis of acrylic acid and methyl acrylate were measured in rat tissue homogenates and rat blood.	The hydrolysis rate of methyl acrylate was approximately 20 times higher in liver homogenates than in kidney or lung homogenates. Methyl acrylate disappeared rapidly when added to blood in vitro. However, the disappearance in blood was not associated with the appearance of acrylic acid.	The disappearance of methyl acrylate in blood in vitro could be due at least in part to binding with nonprotein sulfhydryls in red blood cells rather than to hydrolysis.	Miller et al. (1981)

Table 3B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism/ toxicokinetic	Urinary mercapturic acids formed following the administration of methyl acrylate to adult female Wistar rats were isolated and identified. Methyl acrylate in arachis oil was administered intraperitoneally 5 d per week for 3 wk at 0.14 mmol/kg-d. Urine samples were collected daily. Carboxylesterase inhibition studies were also performed where animals were injected with tri-*o*-tolyl phosphate at 0.34 mmol/kg in arachis oil 18 h before injection with the acrylic esters. Reference standards were synthesized and then characterized by mass and NMR spectra. Urine metabolites were isolated through extraction and column chromatography, prior to characterization by comparison of the retention factor on thin layer chromatography plates to reference standards.	After administration of methyl acrylate, the excretion of thioethers amounted to 6.6% of the administered dose; this excretion increased to 40.6% after carboxylesterase inhibition. The ratio of the excreted dicarboxylic acid and monomethyl ester was 20:1; following pretreatment with tri-*o*-tolyl phosphate, this ratio was 1:2.	Carboxylesterase activity is an important factor in detoxification of methyl acrylate.	Delbressine et al. (1981)
Mode of action/ mechanistic	Methyl acrylate was administered to six adult male Wistar rats in vapor at 0, 500, 1000, or 2000 mg/m^3 for 6 h (whole body exposure). Urine was collected during exposure, and thioether excretion was measured. Blood, liver, lungs, and brain were collected from animals after exposure. Blood glucose was measured. Methyl acrylate (10 mM) was incubated with 10 mM glutathione in vitro. Reaction rate of acrylates with GSH was estimated by measuring the decrease of sulfhydryl group in the mixture over time.	Blood glucose was increased ($p < 0.05$) at all concentrations. The half-life of glutathione disappearance was determined to be 18.4 min after methyl acrylate administration.	The authors suggested that glutathione depletion may participate in acute lethal and biochemical toxic effects of acrylic acid esters.	Vodicka et al. (1990)

DU = data unsuitable; NA = not applicable, NV = not available; ND = No data, NDr = not determinable, NR = not reported, NR/Dr = not reported by the study author, but determined from data, NS = not selected.

Waegemaekers and Bensink (1984) evaluated 27 acrylate esters in the standard Ames assay with TA1535, TA1537, TA1538, TA98, and TA100, both with and without Aroclor 1254-induced rat liver S9 or phenobarbital-induced male Wistar rat liver S9. The Ames assay with preincubation (suspension test) was also performed with methyl acrylate and 3 other compounds. The concentrations tested for methyl acrylate were 0 or 40−2500 µg/plate in the Ames Assay or 0, 30, 300, or 3000 µg/mL incubation volume in the suspension test. To minimize the loss of the volatile test substance, the petri dishes were transferred quickly after plating into airtight glass jars. The tubes used in the suspension test were tightly closed during the incubation. No mutagenic potential was detected with or without metabolic activation.

Florin et al. (1980) evaluated 239 compounds found in tobacco smoke for mutagenicity in the Ames assay using *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537 with and without metabolic activation using Aroclor 1254- or methylcholanthrene-induced male S-D rat liver S9. Methyl acrylate was not mutagenic in any test at 3 µmol/plate.

Zimmering et al. (1989) evaluated 22 chemicals for mutagenicity in the sex-linked recessive lethal mutation assay after being fed to *Drosophila melanogaster* larvae. Methyl acrylate at 500 ppm did not induce mutations.

Moore et al. (1989) conducted a mouse lymphoma assay to determine thymidine kinase mutants and a suspension adapted CHO assay to determine hypoxanthine-guanine phosphoribosyltransferase mutants resulting from incubations with methyl acrylate. Incubations were performed at methyl acrylate concentrations of 0, 16, 22, or 24 µg/mL in the mouse lymphoma assay and 0, 14, 16, or 18 µg/mL in the CHO assay. Methyl acrylate induced almost exclusively small-colony TK mutants and very few if any HGPRT mutants. Aberration analysis revealed that both the mouse lymphoma and CHO cells responded to the clastogenicity of the compound. Incubations resulted in little or no evidence of genotoxicity when evaluated using selection for HGPRT-deficient mutants, but methyl acrylate was clearly clastogenic. Total number of abnormalities and cells with abnormalities were increased at all doses compared to the controls in the mouse lymphoma test.

Ishidate et al. (1981) reported a review of the screening data on about 500 different compounds tested over a 5-year period for their potential to induce chromosomal aberrations in Chinese hamster cells of lung fibroblast origin with preincubation of test chemical, cells, and S9/buffer. Protocols were detailed for tests with and without S9 metabolic activation; however, the results tables did not make it clear when metabolic activation was used. The S9 was prepared from the livers of Wistar rats pretreated with polychlorinated biphenyl (KC-400). Methyl acrylate was genotoxic in the chromosome test. The D_{20} (the calculated dose at which aberrations would be detected in 20% of metaphase cells) was 0.0065 mg/mL; the TR-value (the incidence of cells with exchange-type aberrations per unit dose, mg/mL) was 533.

Moore et al. (1988) conducted a mouse lymphoma assay in L5178Y cells without exogenous activation evaluating five compounds. Methyl acrylate was tested for cytotoxicity and mutagenicity at 0 and 10−24 µg/mL (multiple tests) and for chromosomal aberrations at 0, 16, 22, and 24 µg/mL. Concentration-dependent increases in mutation frequency were noted. Small-colony, trifluorothymidine-resistant mutants were primarily induced, suggesting a

clastogenic MOA. Clastogenicity was confirmed; an induction of gross chromosome aberrations was noted.

Przybojewska et al. (1984) performed a micronucleus test by administering methyl acrylate to male Balb C mice by i.p. injection in two doses, separated by 24 hours. The total dose administered was 0, 37.5, 75, 150, or 300 mg/kg. Increased micronuclei in bone marrow polychromatic erythrocytes were noted at all doses compared to controls, and decreased ratio of polychromatic to normochromatic erythrocytes was observed at 75 mg/kg and above.

Other Studies

Sapota (1988) administered methyl [2,3-^{14}C]-acrylate intraperitoneally or orally to 10 groups of 6 adult male Wistar Albino rats in a single dose of 100 mg/kg (3.7 MBq/kg) in soybean oil. The animals were placed individually in glass metabolism cages for the separate collection of urine, feces, and expired air. Excreta, blood, liver, kidneys, spleen, lungs, brain, sciatic nerve, and fat were collected from specified groups, and radioactive residues were quantified. The study author reported the amount of radioactivity excreted (percent of administered dose [AD]), the rate of excretion into expired air, the elimination of radioactivity from the blood, and the distribution of radioactivity in tissues (kBq/g). Total recovery of the administered dose within 72 hours was 91−96% AD. The excretion of radioactivity was rapid, and the radioactive dose was excreted primarily in the air (39−54% AD) and urine (40−51% AD) with relatively little excreted in the feces (2% AD). The majority of the radioactivity recovered in expired air was detected within the first 2 hours, while the majority of the radioactivity found in the urine was excreted within 24 hours. Peak levels of radioactivity in blood were noted at 1 hour postdose; biphasic elimination provided half-lives of 5 and 34 hours for the fast and slow compartments, respectively. The highest initial specific radioactivity was isolated in the liver, kidneys, and lungs; levels in liver and lungs remained slightly higher than in erythrocytes at 48 hours post dose. Only 1% of the AD remained in the examined tissues 48 hours after dosing. This study was republished (matching results data) in 1993.

Miller et al. (1981) evaluated the rate of disappearance of methyl acrylate in blood in vitro and the extent to which methyl acrylate is converted to acrylic acid in tissue. Male Fischer 344 rats and B6C3F$_1$ mice were treated with methyl acrylate (>99% pure). All experiments were performed in vitro, and blood and tissues from the animals were used in these experiments. Methyl acrylate was measured in rat whole blood using a custom-built cycloidal mass spectrometer. Acrylic acid and methyl acrylate were measured in rat tissue homogenates and rat blood using gas chromatography. The conversion of methyl acrylate to acrylic acid was determined by adding 1 μmole/mL of the test chemical to the tissue homogenates, and then measuring the amount of the ester and acrylic acid in the homogenates after 5, 10, 15, and 20 minutes. Methyl acrylate is hydrolyzed to acrylic acid in tissues in vitro; however, the disappearance of methyl acrylate in blood was not associated with the appearance of acrylic acid. The hydrolysis rate of methyl acrylate was approximately 14-fold higher in liver homogenates than in lung homogenates and 28-fold higher than in kidney homogenates. Based on experimental results using ethyl acrylate, the study authors suggested that disappearance of acrylate esters, such as methyl acrylate, in blood in vitro could be due at least in part to binding with nonprotein sulfhydryls in red blood cells rather than to hydrolysis.

Delbressine et al. (1981) isolated and identified urinary mercapturic acids formed following the administration of methyl acrylate (>99% pure) to adult female Wistar rats. Methyl acrylate in arachis oil was administered intraperitoneally 5 days per week for 3 weeks at 0.14 mmol/kg-day. Carboxylesterase inhibition studies were also performed where animals were injected with tri-*o*-tolyl phosphate at 0.34 mmol/kg in arachis oil 18 hours before injection with methyl acrylate. Urine samples were collected daily for 3 days. Reference standards were synthesized and then characterized by mass and NMR spectra. Urine metabolites were isolated through extraction and column chromatography, and then characterized by comparison of the retention factor on thin layer chromatography plates to reference standards. The molar ratio of mercapturic acid from methyl acrylate was determined. After administration of methyl acrylate, the excretion of thioethers amounted to 6.6% AD; this excretion increased to 40.6% AD after carboxylesterase inhibition. The ratio of the excreted dicarboxylic acid and monomethyl ester was 20:1; following pretreatment with tri-*o*-tolyl phosphate, this ratio was 1:2. The study authors concluded that carboxylesterase activity is a very important factor in detoxification of methyl acrylate.

Vodicka et al. (1990) administered methyl acrylate (99% pure) to adult male Wistar rats in vapor at 0, 500, 1000, or 2000 mg/m^3 for 6 hours (whole body exposure). Urine was collected for 24 hours, beginning during exposure, and urinary thioether was measured. Blood, liver, lungs, and brain were collected from animals after exposure, and blood glucose was measured. Methyl acrylate was incubated in vitro with glutathione (both at 10 mM) in 0.1 M phosphate buffer (pH 7.3) at 37°C in the presence of 0.15 mM KCN. The reaction rate of methyl acrylate with glutathione was estimated by measuring the decrease of sulfhydryl group in the mixture over time. Blood glucose was increased ($p < 0.05$) by approximately 30−70% at all concentrations. The half-life of glutathione disappearance was determined to be 18.4 minutes after methyl acrylate administration.

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present a summary of noncancer and cancer values, respectively. IRIS data are indicated in the table, if available.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic and Chronic Provisional RfD (p-RfD)

Neither a subchronic nor a chronic p-RfD can be derived because no published studies investigating the effects of subchronic or chronic oral toxicity of methyl acrylate in humans or animals were obtained that are acceptable for use in dose-response assessment. One subchronic-duration study was identified, but the source document could not be obtained, and the summary of the study (contained in ACGIH, 1991) provided inadequate details of the methodology and results, which prevented independent verification of conclusions. No other toxicity or carcinogenicity studies were identified where methyl acrylate was administered orally.

Table 4. Summary of Reference Values for Methyl Acrylate (CASRN 96-33-3)							
Toxicity Type (units)	**Species/Sex**	**Critical Effect**	**Provisional Reference Value**	**POD Method**	**POD**	**UF_C**	**Principal Study**
Subchronic p-RfD (mg/kg-d)	ND						
Chronic p-RfD (mg/kg-d)	ND						
Subchronic p-RfC (mg/m^3)	Rat/F	Nasal lesions	2×10^{-2}	$NOAEL_{HEC}$	2.2	100	Rohm and Haas Company (1992a)
Chronic p-RfC (mg/m^3)	Rat/F	Nasal lesions	2×10^{-2}	$NOAEL_{HEC}$	2.2	100	Rohm and Haas Company (1992a)

DU = data unsuitable, NA = not applicable, NV = not available, ND = no data, NDr = not determinable, NI = not identified, NP = not provided, NR = not reported, NR/Dr = not reported but determined from data, NS = not selected.

Table 5. Summary of Cancer Values for Methyl Acrylate (CASRN 96-33-3)				
Toxicity Type	**Species/Sex**	**Tumor Type**	**Cancer Value**	**Principal Study**
p-OSF	ND			
p-IUR	ND			

DU = data unsuitable, NA = not applicable, NV = not available, ND = No data, NDr = Not determinable, NI = not identified, NP = not provided, NR = Not reported, NR/Dr = Not reported but determined from data, NS = not selected.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

Two studies were located which provided data concerning the subchronic inhalation toxicity in rats. A developmental toxicity study (Saillenfait et al., 1999) was performed in rats and a chronic inhalation study also in rats was performed by Rohm and Hass Company (1992a). The possible PODs identified from these studies for derivation of the subchronic and chronic p-RfC are listed in Table 6 (see below for a discussion of the toxicological effects observed in these studies and the potential of these effects to be used for derivation of a subchronic p-RfC).

Table 6. Possible PODs for Methyl Acrylate.

Effect	Sex	NOAEL (mg/m^3)	LOAEL (mg/m^3)	$BMDL_{10}$ (mg/m^3)	Comment
Decreased Maternal Body Weight[a]	Females	22	44	Not Run	No Data Variability Available
Decreased Fetal Body Weight[a]	Both	22	44	No Fit	
Decreased Maternal Food Consumption[a]	Females	22	44	29	
Increased Incidence of Cornea Lesions[b]	Males	29	88	7.7	Data are from 12 mo timepoint
Increased Incidence of Cornea Lesions[b]	Females	88	Not Determinable	Not Run	Data are from 12 mo timepoint; No statistically significant increase over control was observed
Increased Incidence of Nasal Lesions[b]	Males	3.1	9.3	3.1	Data are from total nasal lesions observed through 24 mo
Increased Incidence of Nasal Lesions[b]	Females	2.2	6.4	Not Run	Data are from total nasal lesions observed through 24 mo; There is no information at the low dose range

[a]Saillenfait et al., 1999
[b]Rohm and Haas Company, 1992a

Exposure concentrations from the Saillenfait et al. study (1999) were adjusted to continous exposures and human equivalent concentrations (HECs) were determined prior to

modeling. The maternal and developmental $NOAEL_{HEC}$ of 22 mg/m^3 for decreased maternal body-weight gain and food consumption as well as decreased fetal body weight was calculated from the rat NOAEL of 25.1 ppm (analytical concentration) using EPA (1994b) methodology for an extra-respiratory effect as follows:

Exposure concentration adjustment for continuous exposure:

$$\begin{aligned} NOAEL_{ADJ} &= Conc_{Saillenfait\ et\ al.,\ 1999} \times (MW \div 24.45) \times (\text{hours exposed} \div 24\ \text{hours}) \times (\text{days exposed} \div \text{days of study}) \\ &= 25.1\ \text{ppm} \times (86 \div 24.45) \times (6\ \text{hours} \div 24\ \text{hours}) \times (15\ \text{days} \div 15\ \text{days}) \\ &= 25.1 \times 0.879 \\ &= 22\ \text{mg/m}^3 \end{aligned}$$

HEC conversion for extra-respiratory effects:

$$\begin{aligned} NOAEL_{HEC} &= NOAEL_{ADJ} \times (H_{b/g})_A \div (H_{b/g})_H \\ &= 22\ \text{mg/m}^3 \times 1 \\ &= 22\ \text{mg/m}^3 \end{aligned}$$

where:

$(H_{b/g})_A \div (H_{b/g})_H$ = the ratio of the blood:gas (air) partition coefficient of the chemical for the laboratory animal species to the human value. In the absence of data for methyl acrylate, the default value of 1 was used, as specified in EPA (1994b) guidance.

Rat dams were treated for 15 days during GDs 6 to 20. In this study at 44 mg/m^3, decreased maternal body-weight gain and food consumption were observed as well as decreased fetal body weight. Although decreased body maternal body weight may be due to a decrease in food consumption, it is most likely due to appetite suppression rather than decreased palatably because exposure was via inhalation instead of oral. Because it was possible to calculate estimated final absolute maternal body weight by taking the sum of body-weight gain on GD 6 and absolute weight gain throughout the treatment period, (see Table B.3), decreased body-weight gain was not considered further as a critical effect for derivation of a reference value. A 10% decrease in body weight, considered to be biologically significant for effects in adult animals, was calculated at a concentration of 44 mg/m^3. With respect to, decreased fetal body weight, the study authors reported a statistically significant change at a concentration of 88 mg/m^3. However, at a concentation of 44 mg/m^3, there is a 6.7% decrease in fetal body weight, which is considered to be biologically significant for developmental effects (≥5% change). A NOAEL of 22 mg/m^3 and a LOAEL of 44 mg/m^3 based on decreases in maternal food consumption and body weight, as well as decreased fetal body weight, are identified from this study (i.e., Saillenfait et al., 1999). A NOAEL of 46 mg/m^3 was reported in the subchronic-duration study (i.e., Oberly and Tansy, 1985). Details for these two studies are provided in the "Selection of Potentially Relevant Studies section."

The most sensitive endpoints observed in the Saillenfait et al. (1999) study were decreased maternal food consumption and decreased maternal and fetal body weight, and all of the common continuous models (i.e., Linear, Polynomial, Power, and Hill models) available in the EPA's Benchmark Dose Software (BMDS, version 2.1.2) were fit to the data if possible (see

Appendix C for modeling results). The data for decreased maternal body weight cannot be analyzed by BMDS because the endpoint lacks statistical information on variability. A potential POD for this effect would be its associated NOAEL of 22 mg/m^3.

In general, with regard to the potential critical endpoints, model fit was assessed by a χ^2 goodness-of-fit test (i.e., models with $p < 0.1$ failed to meet the goodness-of-fit criterion) and the Akaike Information Criterion (AIC) value (i.e., a measure of the deviance of the model fit that allows for comparison across models for a particular endpoint). For decreased maternal food consumption, only the Hill model (without constant variance) adequately fit the data providing a BMC_{1SD} and $BMCL_{1SD}$ of 41 and 29 mg/m^3, respectively. For decreased fetal body weight, data for males, females, and males and females combined were provided by the study authors; thus, data for all groups were modeled by BMDS. However, no adequate model fits were achieved with the decreased fetal body-weight data (see Appendix C), and the NOAEL of 22 mg/m^3 for decreased fetal body weight is considered as a POD. For the endpoint of decreased maternal food consumption, the lowest potential POD is a $BMCL_{1SD}$ of 29 mg/m^3. While the selection of the $BMCL_{1SD}$ from the maternal food consumption data set as the POD would protect against this effect, it may not confer protection against the possibly more sensitive endpoints of decreased maternal and fetal body weight. The most sensitive POD for systemic toxicity identified from this study is the NOAEL of 22 mg/m^3 based on decreased maternal and fetal body weight. However, as indicated in the U.S. EPA (1994b) *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*, "*the minimum laboratory animal toxicologic data base requirement for derivation of an RfC with low confidence is a well-conducted subchronic inhalation bioassay that evaluated a comprehensive array of endpoints, including an adequate evaluation of portal-of-entry (respiratory tract) effects."* Therefore, to fully analyze the subchronic toxicity of methyl acrylate, portal-of-entry effects should be evaluated because these types of effects could start to occur shortly after inhalation of a chemical begins. Although the available subchronic studies listed in Table 2 do not report portal-of-entry effects, there are chronic-duration studies that do report these effects that could possibly be used for derivation of a subchronic p-RfC.

The study prepared by the Rohm and Haas Company (1992) is selected as the principal study for the derivation of a subchronic p-RfC. The chronic carcinogenicity study by Rohm and Haas Company (1992a) observed statistically significant increased incidences of both nasal and cornea lesions in male and female rats, which are both portal-of-entry effects, throughout 24 months of exposure to methyl acrylate (see Tables B.1 and B.2). For incidence of cornea lesions in male and female rats, data at 12 months were considered as a potential POD choice because there were statistically significant differences between the 12-, 18-, and 24-month time points, suggesting that total cornea lesions (i.e., sum of cornea lesions observed at 12, 18, and 24 months) may not be representative of the 24-month exposure. For increased incidence of cornea lesions at 12 months, there was a statistically significant increase for this endpoint in male rats at 88 mg/m^3 (see Table B.1). These data for incidence of cornea lesions in male rats at 12 months of exposure were modeled by BMDS and provided a BMC_{10} and $BMCL_{10}$ of 20 and 7.7 mg/m^3, respectively. For incidence of cornea lesions in female rats, the data were not significant at any dose tested and therefore the data were not analyzed by BMDS. An alternate POD for cornea lesions in female rats would be the NOAEL of 88 mg/m^3. Unlike cornea lesions, the incidences of nasal lesions were not statistically significantly different between the different time points (see Table B.2). Therefore, the total nasal lesions observed throughout the

24-month exposure for male and female rats serve as a proper representative for nasal lesions observed at the various time points and thus were modeled by BMDS. For increased incidence of total nasal lesions in male rats observed throughout the 24 month exposure, BMDS provided a BMC_{10} and $BMCL_{10}$ of 3.5 and 3.1 mg/m^3, respectively (see Appendix C). For total nasal lesions in female rats, the data could not be modeled by BMDS because there is no dose-response information at the low dose range (see Table B.3) necessary for BMD modeling. The POD for total nasal lesions in female rats would be the NOAEL of 2.2 mg/m^3.

The most sensitive potential POD for derivation of the subchronic p-RfC is the NOAEL of 2.2 mg/m^3 for increased incidence of total nasal lesions in female rats observed in the chronic study by the Rohm and Haas Company (1992a). The selection of this NOAEL as the POD will protect against systemic effects (e.g., decreased fetal body weight, etc.) observed subchronically in the Saillenfait et al. (1999) study and will also protect against portal-of-entry effects (i.e., nasal and cornea lesions). Although nasal lesions occurred in a chronic-duration study, it is still suitable to use this endpoint as a critical effect for derivation of a subchronic p-RfC because portal-of-entry effects can occur shortly after onset of inhalation exposure to a chemical. Statistically significant increased incidence of nasal lesions occurred at the earliest time point tested (i.e., 12 months), but it is possible that these lesions could start to occur subchronically as well. In the absence of subchronic studies that specifically investigated the association between methyl acrylate exposure and nasal lesions, portal-of-entry considerations support the use of the chronic-duration study data. **Therefore, the NOAEL of 2.2 mg/m^3 based on increased incidence of total nasal lesions in female rats (Rohm and Haas Company, 1992a) is chosen as the POD to derive a subchronic p-RfC.**

The following dosimetric adjustments were made for inhalation treatment in adjusting inhalation concentrations for extrathoracic effects (i.e., nasal lesions) using the NOAEL analytical concentration of 15.6 ppm.

Exposure concentration adjustment for continuous exposure:

$$\begin{aligned} Conc_{ADJ} &= Conc_{\text{Rohm and Haas Company, 1992a}} \times (MW \div 24.45) \times (\text{hours exposed} \div 24 \text{ hours}) \\ &\quad \times (\text{days exposed} \div 7 \text{ days per week}) \\ &= 15.6 \text{ ppm} \times (86 \div 24.45) \times (6 \text{ hours} \div 24 \text{ hours}) \times (5 \text{ days} \div 7 \text{ days}) \\ &= 15.6 \times 0.628 \\ &= 9.8 \text{ mg/m3} \end{aligned}$$

HEC conversion for respiratory effects:

$$Conc_{HEC} = Conc_{ADJ} \times RGDR_{ET}$$

$$RGDR_{PU} = \frac{(V_E \div SA_{ET})_{rat}}{(V_E \div SA_{ET})_{human}}$$

V_{Erats} = rat minute volume (rat = 0.33157 m^3/day and 0.47376 m^3/day, based on a default body weight of 0.338 kg for S-D female rats and 0.523 kg for S-D male rats, respectively) (see U.S. EPA, 1994b)

V_{Ehuman} = 20 m^3/day

S_{Arats} = rat default surface area of the extrathoracic region (0.0015 m^2)

S_{Ahuman} = human default surface area of the extrathoracic region (0.02 m^2)

Female rats $RGDR_{ET}$ = (0.33157 ÷ 0.0015) ÷ (20 ÷ 0.02) = 0.221

Male rats $RGDR_{ET}$ = (0.47376 ÷ 0.0015) ÷ (20 ÷ 0.02) = 0.316

$Conc_{HEC, RESP}$ = $Conc_{ADJ} \times RGDR_{ET}$
= 9.8 mg/m^3 × 0.221
= 2.2 mg/m^3 for females and 3.1 mg/m^3 for males

The subchronic p-RfC for methyl acrylate, based on the NOAEL of 2.2 mg/m^3 for increased incidence of nasal lesions in female rats (Rohm and Haas Company, 1992a) is derived as follows:

Subchronic p-RfC = $NOAEL_{HEC, RESP}/UF_C$
= 2.2 ÷ 100
= **2×10^{-2} mg/m^3**

Table 7 summarizes the uncertainty factors for the subchronic p-RfC for methyl acrylate, and the confidence descriptors are provided in Table 8.

Table 7. Uncertainty Factors for Subchronic p-RfC of Methyl Acrylate

UF	Value	Justification
UF_A	3	A UF_A of 3 is applied for animal-to-human extrapolation to account for the toxicodynamic portion of the UF_A because the toxicokinetics portion ($10^{0.5}$) has been addressed in dosimetric conversions.
UF_D	3	A UF_D of 3 is selected because the database includes one acceptable developmental study in rats (Saillenfait et al., 1999), but no acceptable two-generation reproduction studies. Also, all available studies were performed in a single rat species, and there are no human toxicity data available.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied for using a POD based on a NOAEL.
UF_S	1	A UF_S of 1 is applied because a chronic study was utilized as the critical study.
UF_C	100	

Table 8. Confidence Descriptor for Subchronic p-RfC for Methyl Acrylate		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in Study	M	The study is given a medium confidence level because the study included most of the data expected to be reported for a chronic study.
Confidence in Database	M	The database is given a medium confidence level because acceptable toxicity and developmental toxicity studies were located in the absence of an acceptable two-generation reproductive toxicity study.
Confidence in Subchronic p-RfC[b]	M	The overall confidence in the subchronic p-RfC is designated as medium, because both the study and the database received designations of medium.

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than the lowest entry in table.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

The combined chronic toxicity/carcinogenicity study in the rat (Rohm and Haas Company, 1992a) is selected as the principal study for derivation of the chronic p-RfC. This study was also reported in a peer-reviewed journal (Reininghaus et al., 1991), but it is unknown if the study was performed according to GLP principles. The standards of study design and performance for a combined chronic toxicity/carcinogenicity study were generally met in regards to numbers of animals, examination of potential toxicity endpoints, and presentation of information. Details are provided in the "Selection of Potentially Relevant Data section." This is the only long-term study that could be located; however, this study was well-conducted and provides data that is sufficient to support derivation of a provisional toxicity value. The most sensitive endpoints were cornea and nasal lesions in male and female rats.

Because increased incidence of cornea and nasal lesions in male and female rats were the most sensitive endpoint, all of the common dichotomous models available in the U.S. EPA's Benchmark Dose Software (BMDS, version 2.1.2) were fit to the data. A detailed summary of BMD modeling results is provided in Appendix C. In general, model fit was assessed by a χ^2 goodness-of-fit test (i.e., models with $p < 0.1$ failed to meet the goodness-of-fit criterion) and the Akaike Information Criterion (AIC) value (i.e., a measure of the deviance of the model fit that allows for comparison across models for a particular endpoint). Table B.1 presents BMD input data for the cornea lesions data. At 12, 18, and 24 months, there were statistically significant changes in cornea lesions between the various time points. Therefore, total cornea lesions observed throughout the 24-month exposure may not be the most representative data of the entire study. To evaluate these data with BMDS, the cornea lesions observed at the 24–month time point were modeled for both male and female rats instead of total cornea lesions observed throughout the study. For increased incidence of cornea lesions at 24 months in male rats, BMD modeling provided a BMC_{10} and $BMCL_{10}$ of 12 mg/m^3 and 6.7 mg/m^3, respectively. For females, BMD modeling resulted in a BMC_{10} and $BMCL_{10}$ of 9.1 mg/m^3 and 7.3 mg/m^3, respectively. For increased incidence of total nasal lesions in male rats observed throughout the 24-month exposure, the BMD results were a BMC_{10} and $BMCL_{10}$ of 3.5 mg/m^3 and 3.1 mg/m^3. For female rats, the total nasal lesion data could not be modeled by BMDS because there is no

dose response information at the low dose range, which is necessary for BMD modeling. Thus for increased incidence of total nasal lesions in female rats, an alternate POD for this effect would be a NOAEL of 2.2 mg/m^3. The most sensitive POD from the endpoints reported by the Rohm and Haas Company (1992a) is the NOAEL of 2.2 mg/m^3 for increased incidence of nasal lesions in female rats. The selection of this value as the POD would protect against increased incidence of cornea lesions but also nasal lesions as well. **Therefore, the NOAEL of 2.2 mg/m^3 based on increased incidence of total nasal lesions in female rats (Rohm and Haas Company, 1992a) is chosen as the POD to derive a chronic p-RfC.**

The following dosimetric adjustments were made for inhalation treatment in adjusting inhalation concentrations for extra-respiratory effects (corneal damage).

Exposure concentration adjustment for continuous exposure:

$$\begin{aligned} Conc_{ADJ} &= Conc_{\text{Rohm and Haas Company, 1992a}} \times (MW \div 24.45) \times (\text{hours exposed} \div 24 \text{ hours}) \\ &\quad \times (\text{days exposed} \div 7 \text{ days per week}) \\ &= 15.6 \text{ ppm} \times (86 \div 24.45) \times (6 \text{ hours} \div 24 \text{ hours}) \times (5 \text{ days} \div 7 \text{ days}) \\ &= 15.6 \times 0.628 \\ &= 9.8 \text{ mg/m}^3 \end{aligned}$$

It is not necessary to calculate the HEC for cornea lesions because the effect is due to direct exposure of the chemical. Dosimetric adjustments for respiratory effects (i.e., nasal lesions) are described in *Derivation of Subchronic Provisional RfC*.

The chronic p-RfC for methyl acrylate, based on the $NOAEL_{HEC}$ of 2.2 mg/m^3 from an increased incidence of nasal lesions in the female rat (Rohm and Haas, 1992a), is derived as follows:

$$\begin{aligned} \textbf{Chronic p-RfC} &= NOAEL_{HEC,\,RESP} \div UF_C \\ &= 2.2 \div 100 \\ &= \mathbf{2 \times 10^{-2} \text{ mg/m}^3} \end{aligned}$$

Table 9 summarizes the uncertainty factors for the chronic p-RfC for methyl acrylate, and the confidence descriptors are provided in Table 10.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

IRIS provides the cancer WOE descriptor of D for methyl acrylate: not classifiable as to human carcinogenicity (U.S. EPA, 2011a).

Table 9. Uncertainty Factors for Chronic p-RfC of Methyl Acrylate		
UF	**Value**	**Justification**
UF_A	3	A UF_A of 3 is applied for animal-to-human extrapolation to account for the toxicodynamic portion of the UF_A because the toxicokinetics portion ($10^{0.5}$) has been addressed in dosimetric conversions.
UF_D	3	A UF_D of 3 is selected because the database includes one acceptable developmental study in rats (Saillenfait et al., 1999), but no acceptable two-generation reproduction studies. Also, all available studies were performed on a single species of rats, and there are no human toxicity data available negating the possibility of a lower uncertainty factor for this parameter.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied for using a POD based on a NOAEL.
UF_S	1	A UF_S of 1 is applied because a chronic study was utilized as the critical study.
UF_C	100	

Table 10. Confidence Descriptor for Chronic p-RfC for Methyl Acrylate		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in Study	M	The study is given a medium confidence level because the study included most of the data expected to be reported for a combined chronic toxicity/carcinogenicity study.
Confidence in Database	M	The database is given a medium confidence level because acceptable toxicity and developmental toxicity studies were located in the absence of an acceptable two-generation reproductive toxicity study.
Confidence in Chronic p-RfC[b]	M	The overall confidence in the subchronic p-RfC is designated as medium, because both the study and the database received designations of medium.

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than the lowest entry in table.

MUTAGENICITY INFORMATION

Methyl acrylate was not mutagenic in *S. typhimurium* GA46, C3076, D3052, TA98, TA100, TA1535, TA1537, or TA1538, or *E. coli* CM881 or CM891, with or without metabolic activation. Measures were taken to limit volatilization in some assays. No mutations in *D. melanogaster* (sex-linked recessive lethal mutation assay) were observed without metabolic activation. In mammalian cells treated in vitro, methyl acrylate induced mutations at the *tk*-locus in mouse cells, in the absence of exogenous metabolic activation, but not at the *hprt*-locus in Chinese hamster ovary cells. Methyl acrylate induced chromosomal aberrations in mouse and Chinese hamster cells in vitro; and also induced chromosome damage and micronuclei formation in vivo, using the micronucleus test with mice. There is no adequate evidence of carcinogenic potential in humans or animals.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

No suitable human or animal studies examining the carcinogenicity of methyl acrylate following oral exposure were identified. Therefore, derivation of p-OSF is precluded.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

No suitable human or animal studies examining the carcinogenicity of methyl acrylate following inhalation exposure were identified. Therefore, derivation of p-IUR is precluded. Although inhalation carcinogenicity studies were located, no increase in neoplasia was evident at the concentrations tested.

APPENDIX A. PROVISIONAL SCREENING VALUES

No screening values are presented.

APPENDIX B. DATA TABLES

Table B.1. Incidence of Rats (# Affected/# Examined [%]) with Cornea Parenchymal Changes (Degeneration or Vascularization) After Inhalation of Methyl Acrylate Vapor[a]

Exposure (mo)	Dose Group (ppm)			
	0	15 (9.8 mg/m^3 HEC)	45 (29 mg/m^3 HEC)	135 (88 mg/m^3 HEC)
Males				
12	0/12 (0)	1/13 (8)	1/12 (8)	6/12[b] (50)
18	0/15 (0)	1/15 (7)	2/15 (13)	10/15 (67)
24	1/50 (2)	6/50 (12)	12/53[b] (23)	31/52[b] (60)
Total	1/77 (1)	8/78[c] (10)	15/80[d] (19)	47/79[d] (59)
Females				
12	0/13 (0)	0/12 (0)	1/13 (8)	2/12 (17)
18	0/15 (0)	2/15 (13)	3/15 (20)	9/15 (60)
24	0/51 (0)	4/50 (8)	18/48[b] (38)	29/49[b] (59)
Total	0/79 (0)	6/77[c] (8)	22/76[d] (29)	40/76[d] (53)

[a]Rohm and Haas Company (1992a). Data were obtained from Table D on page 7−11 of the cited publication. HEC equivalents for the mean measured concentrations corresponding to 0, 15, 45, and 135 ppm are 0, 9.8, 29, and 88 mg/m^3 in both males and females, respectively.
[b]Significantly different ($p \leq 0.05$) from the control group as determined by Fisher's exact test.
[c]Significantly different ($p \leq 0.05$) from the control group as determined by chi-square test.
[d]Significantly different ($p \leq 0.001$) from the control group as determined by chi-square test.

Table B.2. Incidence of Rats (# Affected/# Examined [%]) with Nasal Reserve Cell Hyperplasia with Loss of Olfactory and Ciliated Cells After Inhalation of Methyl Acrylate Vapor, Nasal Cavity Sectional Plane II[a]

Exposure (mo)	Dose Group (ppm) for Males			
	0	**15 (3.1 mg/m^3 HEC)**	**45 (9.2 mg/m^3 HEC)**	**135 (28 mg/m^3 HEC)**
12	0/10 (0)	0/9 (0)	9/10[b] (90)	10/10[b] (100)
18	0/14 (0)	0/14 (0)	15/15[b] (100)	15/15[b] (100)
24	0/46 (0)	4/49[b] (8)	49/53[b] (92)	52/52[b] (100)
Total[d]	0/86 (0)	4/82[c] (5)	80/86[c] (93)	84/85[c] (99)
	Dose Group (ppm) for Females			
	0	**15 (2.2 mg/m^3 HEC)**	**45 (6.4 mg/m^3 HEC)**	**135 (19 mg/m^3 HEC)**
12	0/10 (0)	0/9 (0)	6/10[b] (60)	10/10[b] (100)
18	0/15 (0)	0/15 (0)	11/15[b] (73)	15/15[b] (100)
24	0/48 (0)	0/48 (0)	41/46[b] (89)	46/46[b] (100)
Total[d]	1/85 (1)	0/85 (0)	67/85[c] (79)	84/86[c] (98)

[a]Rohm and Haas Company (1992a). Data were obtained from Table B on page 7−7 of the cited publication. HEC equivalents for the mean measured concentrations corresponding to 0, 15, 45, and 135 ppm are 0, 3.1, 9.2, and 28 mg/m^3 in males or 0, 2.2, 6.4, or 19 mg/m^3 in females, respectively.
[b]Significantly different ($p \leq 0.05$) from the control group as determined by Fisher's exact test.
[c] Significantly different ($p \leq 0.001$) from the control group as determined by chi-square test.
[d]Including rats dying spontaneously and terminated when moribund.

Table B.3. Effects on Body-Weight Gain and Food Consumption During Gestation Days 6−20 in Dams Treated by Whole Body Exposure to Methyl Acrylate Vapor[a,b]

Parameter	Dose Group (ppm)			
	0	**25 (22 mg/m^3 HEC)**	**50 (44 mg/m^3 HEC)**	**100 (88 mg/m^3 HEC)**
Number of dams	25	21	23	23
Body weight on GD 6 (grams)	277 ± 20	279 ± 21	284 ± 20	282 ± 21
Absolute weight gain[c] (grams)	30 ± 14	26 ± 20	−8 ± 21[d]	−40 ± 36[d]
Estimated final body weight[e] (grams)	307	305	276	242
Food consumption (GDs 6−20) (grams/dam/day)	24 ± 2	24 ± 2	20 ± 3 (↓17)[d]	16 ± 4 (↓33)[d]
Fetal body weight (grams) for males and Females	5.69 ± 0.42	5.60 ± 0.29 (↓1.6)	5.31 ± 0.50 (↓6.7)	4.73 ± 0.89 (↓17)[d]
Fetal body weight (grams) for males	5.81 ± 0.46	5.71 ± 0.31 (↓1.7)	5.43 ± 0.52 (↓6.5)	4.84 ± 0.93(↓17)[d]
Fetal body weight (grams) for females	5.55 ± 0.39	5.47 ± 0.31(↓1.4)	5.18 ± 0.50 (↓6.7)	4.58 ± 0.87(↓17)[d]

[a]Saillenfait et al. (1999). Data were obtained from Tables 2, 3, and 4 on pages 243−244 of the cited publication. HEC equivalents for the mean measured concentrations corresponding to 0, 25, 50, and 100 ppm are 0, 22, 44, and 88 mg/m^3, respectively. Percent difference from controls is presented within parentheses.
[b]Values are expressed as means ± SD.
[c]Calculated as Day 21 body weight − gravid uterus weight − Day 6 body weight.
[d]Significantly different ($p \leq 0.01$) from the control group.
[e]Calculated by the sum of body weight on GD 6 and absolute weight gain.

APPENDIX C. BENCHMARK DOSE CALCULATIONS FOR THE SUBCHRONIC AND CHRONIC p-RfC

MODELING PROCEDURE FOR DICHOTOMOUS DATA

The BMD modeling of dichotomous data was conducted with U.S. EPA's BMDS (version 2.1.2). For these data, all of the dichotomous models (i.e., Gamma, Multistage, Logistic, Log-logistic, Probit, Log-probit, and Weibull models) available within the software were fit using a BMR of 10% extra risk. Adequacy of model fit was judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. Among all models providing adequate fit, the lowest BMCL was selected if the BMCLs estimated from different models varied greater than 3-fold; otherwise, the BMCL from the model with the lowest AIC was selected as a potential POD from which to derive the RfC. In addition, in the absence of a mechanistic understanding of the biological response to a toxic agent, data from exposures much higher than the study LOAEL do not provide reliable information regarding the shape of the response at low doses. Such exposures, however, can have a strong effect on the shape of the fitted model in the low-dose region of the dose-response curve. Thus, if lack of fit is due to characteristics of the dose-response data for high doses, then the EPA Benchmark Dose Technical Guidance Document allows for data to be adjusted by eliminating the high-dose group (U.S. EPA, 2012). Because the focus of BMD analysis is on the low dose region of the response curve, eliminating high-dose groups is deemed reasonable.

MODELING PROCEDURE FOR CONTINUOUS DATA

The BMD modeling of continuous data was conducted with EPA's BMDS (version 2.1.2). For maternal food consumption, all continuous models available within the software were fit using a BMR of 1 standard deviation from the control mean. For decreased fetal body weight, all continuous models available within the software were fit using a BMR of 5% extra risk. An adequate fit was judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was homogeneous. If a homogeneous variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2), the final BMD results were estimated from a homogeneous variance model. If the test for homogeneity of variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model did not adequately fit the data (i.e., Test 3; *p*-value < 0.1), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMCL was selected if the BMCLs estimated from different models varied greater than 3-fold; otherwise, the BMCL from the model with the lowest AIC was selected as a potential POD from which to derive the RfC.

DECREASED FOOD CONSUMPTION IN RAT DAMS EXPOSED TO METHYL ACRYLATE VAPOR (Saillenfait et al., 1999)

All available continuous models in BMDS (version 2.1.2) were fit to the decreased maternal food consumption data from S-D rat dams exposed to methyl acrylate via inhalation during gestation (for a total of 15 days) (Saillenfait et al., 1999; see Table B.3). The Hill model in BMDS provided an adequate fit to the data, (see Table C.1 and Figure C.1). Estimated doses

associated with 1 standard deviation relative risk and the 95% lower confidence limit on these doses (BMC_{1SD} values and $BMCL_{1SD}$ values, respectively) were 41 and 29 mg/m^3.

Table C.1. Goodness-of-Fit Statistics, BMC_{10}, and $BMCL_{10}$ Values for Continuous Models for Food Consumption in the Female Rat Treated with Methyl Acrylate

Model	Goodness-of-Fit *p*-Value	AIC	BMC_{1SDHEC} (mg/m^3)	$BMCL_{1SDHEC}$ (mg/m^3)
Without Constant Variance				
Hill	**0.9970**	**276.25**	**41**	**29**
Linear	0.0020	268.71	23	18
Polynomial	<0.0001	368.36	−1000	47
Power	0.0020	285.78	31	22
Constant Variance				
Hill	NA	292.05	42	31
Linear	0.0240	295.51	30	25
Polynomial	<0.0001	366.36	−1000	240
Power	0.0163	295.82	38	27

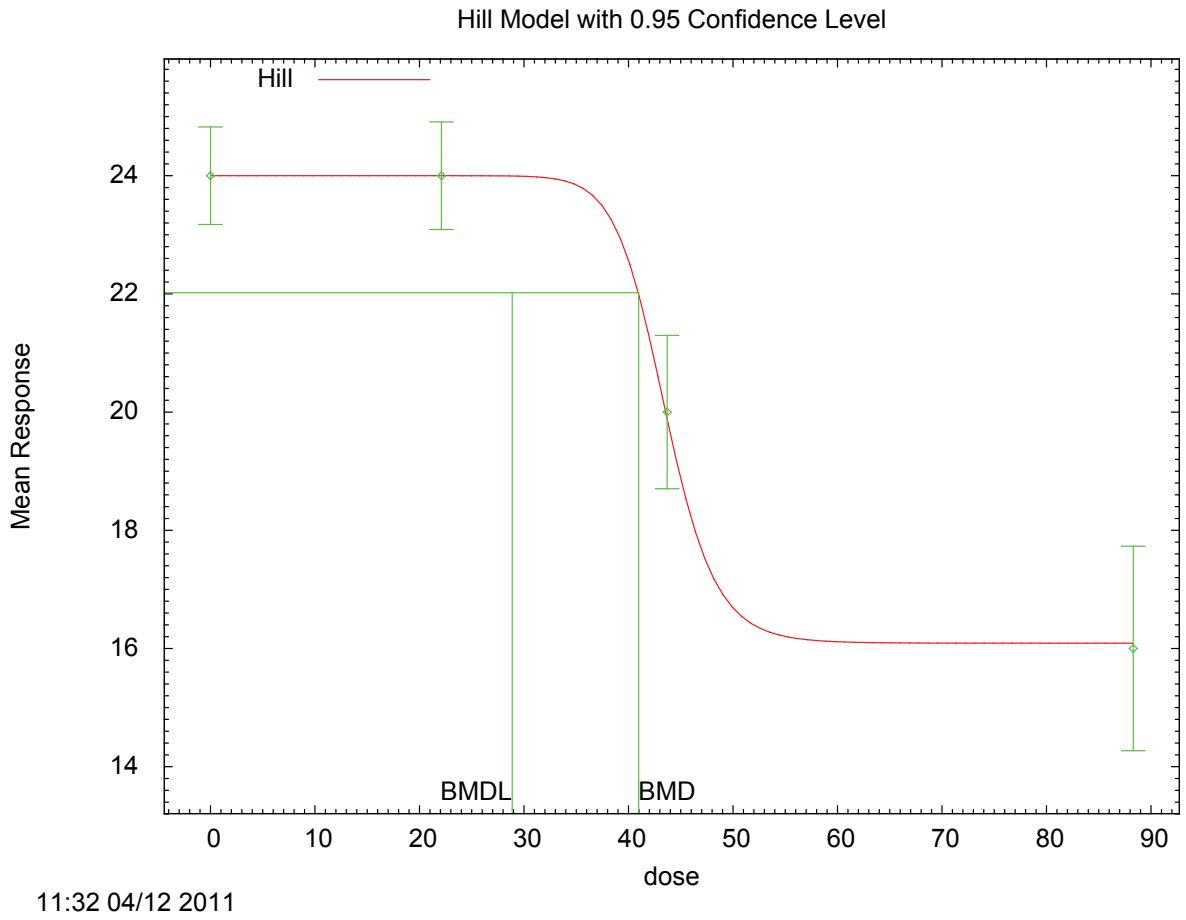

Figure C.1. Hill (Without Constant Variance) BMD Model for Food Consumption Data (Saillenfait et al., 1999)

DECREASED FETAL BODY WEIGHT IN RAT PUPS EXPOSED TO METHYL ACRYLATE VAPOR DURING GESTATION (Saillenfait et al., 1999)

All available continuous models in BMDS (version 2.1.2) were fit to the decreased fetal body weight data from S-D rat pups exposed to methyl acrylate vapor during gestation for a total of 15 days (Saillenfait et al., 1999; see Table B.3). No available model in BMDS provided an adequate fit to the data as the goodness-of-fit *p*-value for all models was less than 0.1. All of the BMD modeling results shown in Table C.2 were obtained from nonconstant variance models. Because all models for these data failed, a BMD output graph is not provided.

Table C.2. Goodness-of-Fit Statistics, BMC_{10}, and $BMCL_{10}$ Values for Continuous Models for Fetal Body Weight in S-D Pups Exposed to Methyl Acrylate During Gestation (GDs 6−20)

Model	Goodness-of-Fit *p*-Value	AIC	BMC_{5HEC} (mg/m^3)	$BMCL_{5HEC}$ (mg/m^3)
Males and Females				
Hill	NA	−495.903	45	NA
Linear	<0.0001	−423.807	34	31
Polynomial	<0.0001	−474.781	49	44
Power	<0.0001	−478.737	47	43
Males				
Hill	NA	−163.33	45	NA
Linear	<0.0001	−128.548	36	32
Polynomial	0.0016	−155.338	52	45
Power	0.0037	−156.911	50	44
Females				
Hill	NA	−268.504	44	40
Linear	<0.0001	−240.715	34	30
Polynomial	0.0022	−261.127	47	40
Power	0.0063	−263.045	46	40

INCIDENCE OF CORNEA LESIONS AT 12 MONTHS IN MALE RATS EXPOSED TO METHYL ACRYLATE VAPOR (Rohm and Haas Company, 1992a)

All dichotomous models available in BMDS (version 2.1.2) were fit to the incidence data of cornea lesions at 12 months in male S-D rats exposed to methyl acrylate via inhalation for 12 months (Saillenfait et al., 1999; see Table B.1). As assessed by the χ^2 goodness-of-fit statistic, all available models adequately fit the data. The Log-logistic model provided the best fit, as assessed by lowest BMCL, for data from male rats (see Table C.3 and Figure C.2). Estimated doses associated with 10% extra risk and the 95% lower confidence limit on these doses (BMC_{10} values and $BMCL_{10}$ values, respectively) were 20 and 7.7 mg/m^3.

Table C.3. Goodness-of-Fit Statistics, BMC_{10}, and $BMCL_{10}$ Values for Dichotomous Models for Cornea Lesions at 12 Months in the Male Rats Treated with Methyl Acrylate[a]

Model	Goodness-of-Fit *p*-Value[b]	AIC	BMC_{10HEC} (mg/m^3)	$BMCL_{10HEC}$ (mg/m^3)
Gamma[a]	0.6506	35.457	19	9.5
Logistic	0.6935	35.59	39	26
Log-Logistic[c]	**0.6071**	**35.579**	**20**	**7.7**
Log-Probit[c]	0.3234	37.902	37	16
Multistage[b]	0.7003	35.254	22	9.7
Probit	0.6878	35.543	36	24
Weibull[a]	0.6563	35.417	20	9.6

[a]Restrict power ≥1.
[b]Restrict betas ≥0; degree of polynomial = 2; lowest degree polynomial with an adequate fit reported.
[c]Slope restricted to >1.

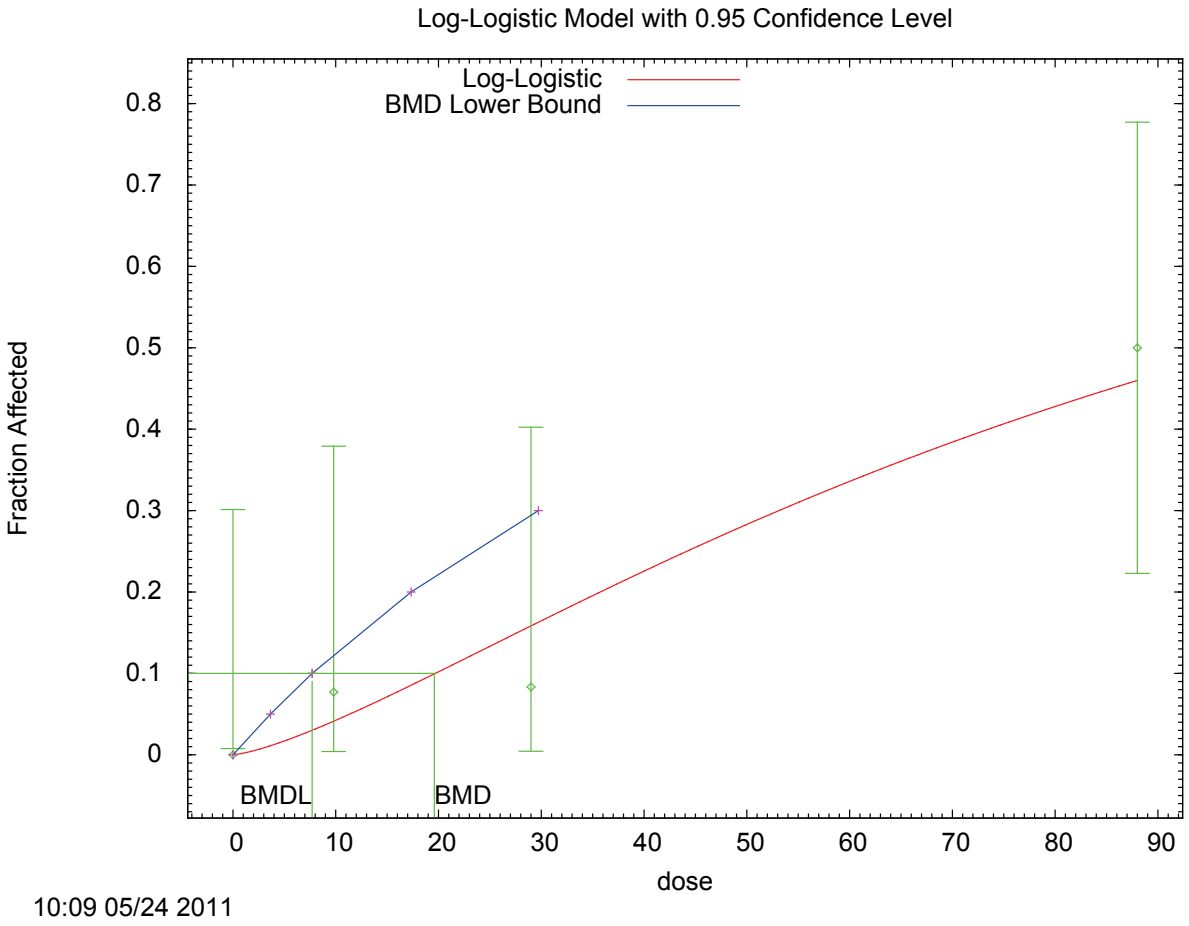

Figure C.2. Log-logistic BMD Model for Corneal Lesions at 12 Months in Male Rats (Rohm and Haas Company, 1992a)

INCIDENCE OF CORNEA LESIONS AT 24 MONTHS IN MALE RATS EXPOSED TO METHYL ACRYLATE VAPOR (Rohm and Haas Company, 1992a)

All dichotomous models available in BMDS (version 2.1.2) were fit to the incidence data of cornea lesions at 24 months in male S-D rats exposed to methyl acrylate via inhalation for 24 months (Saillenfait et al., 1999; see Table B.1). As assessed by the χ^2 goodness-of-fit statistic, all available models adequately fit the data. The Log-logistic model provided the best fit, as assessed by lowest BMCL, for data from male rats (see Table C.4 and Figure C.3). Estimated doses associated with 10% extra risk and the 95% lower confidence limit on these doses (BMC_{10} values and $BMCL_{10}$ values, respectively) were 12 and 6.7 mg/m^3.

Table C.4. Goodness-of-Fit Statistics, BMC_{10}, and $BMCL_{10}$ Values for Dichotomous Models for Cornea Lesions at 24 Months in the Male Rats Treated with Methyl Acrylate[a]

Model	Goodness-of-Fit *p*-Value[b]	AIC	BMC_{10HEC} (mg/m^3)	$BMCL_{10HEC}$ (mg/m^3)
Gamma[a]	0.5297	179.743	12	8.6
Logistic	0.1885	181.414	27	22
Log-Logistic[c]	**0.3926**	**180.073**	**12**	**6.7**
Log-Probit[c]	0.2696	179.966	19	15
Multistage[b]	0.5782	179.651	12	8.6
Probit	0.2389	180.776	25	21
Weibull[a]	0.5363	179.728	12	8.6

[a]Restrict power ≥1.
[b]Restrict betas ≥0; degree of polynomial = 2; lowest degree polynomial with an adequate fit reported.
[c]Slope restricted to >1.

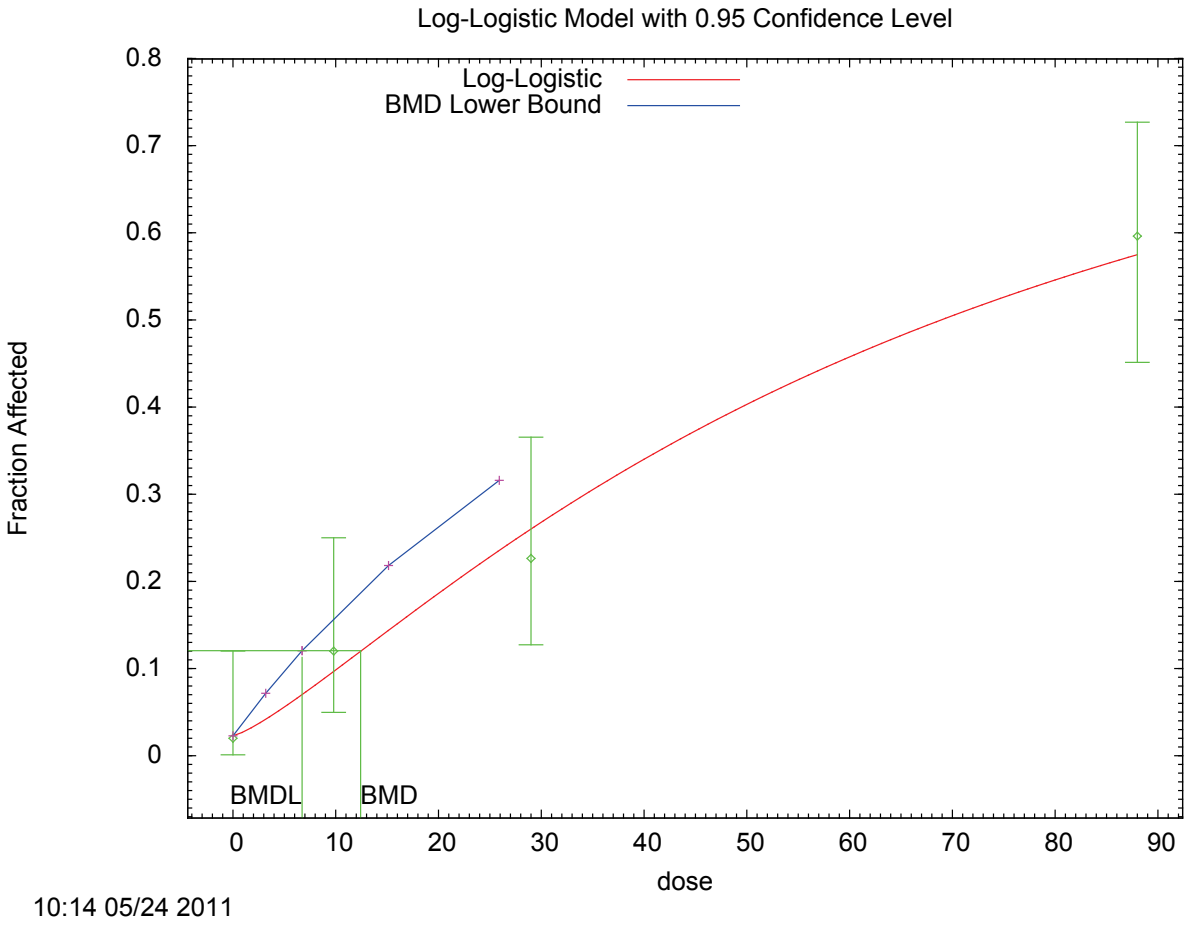

Figure C.3. Log-logistic BMD Model for Corneal Lesions at 24 Months in Male Rats (Rohm and Haas Company, 1992a)

INCIDENCE OF CORNEA LESIONS AT 24 MONTHS IN FEMALE RATS EXPOSED TO METHYL ACRYLATE VAPOR (Rohm and Haas Company, 1992a)

All dichotomous models available in BMDS (version 2.1.2) were fit to the incidence data of cornea lesions at 24 months in female S-D rats exposed to methyl acrylate via inhalation for 24 months (Saillenfait et al., 1999; see Table B.1). As assessed by the χ^2 goodness-of-fit statistic, all available models except for the Logistic and Probit adequately fit the data. The Multistage model provided the best fit, as assessed by lowest AIC, for data from female rats (see Table C.5 and Figure C.4). Estimated doses associated with 10% extra risk and the 95% lower confidence limit on these doses (BMC_{10} values and $BMCL_{10}$ values, respectively) were 9.1 and 7.3 mg/m^3.

Table C.5. Goodness-of-Fit Statistics, BMC_{10}, and $BMCL_{10}$ Values for Dichotomous Models for Cornea Lesions at 24 Months in the Female Rats Treated with Methyl Acrylate[a]

Model	Goodness-of-Fit *p*-Value[b]	AIC	BMC_{10HEC} (mg/m^3)	$BMCL_{10HEC}$ (mg/m^3)
Gamma[a]	0.4301	162.338	9.1	7.3
Logistic	0.0004	179.942	25	20
Log-Logistic[c]	0.4363	163.327	8.8	5.2
Log-Probit[c]	0.1131	165.197	14	11
Multistage[b]	**0.4301**	**162.338**	**9.1**	**7.3**
Probit	0.0007	178.477	23	19
Weibull[a]	0.4301	162.338	9.1	7.3

[a]Restrict power ≥1.
[b]Restrict betas ≥0; degree of polynomial = 2; lowest degree polynomial with an adequate fit reported.
[c]Slope restricted to >1.

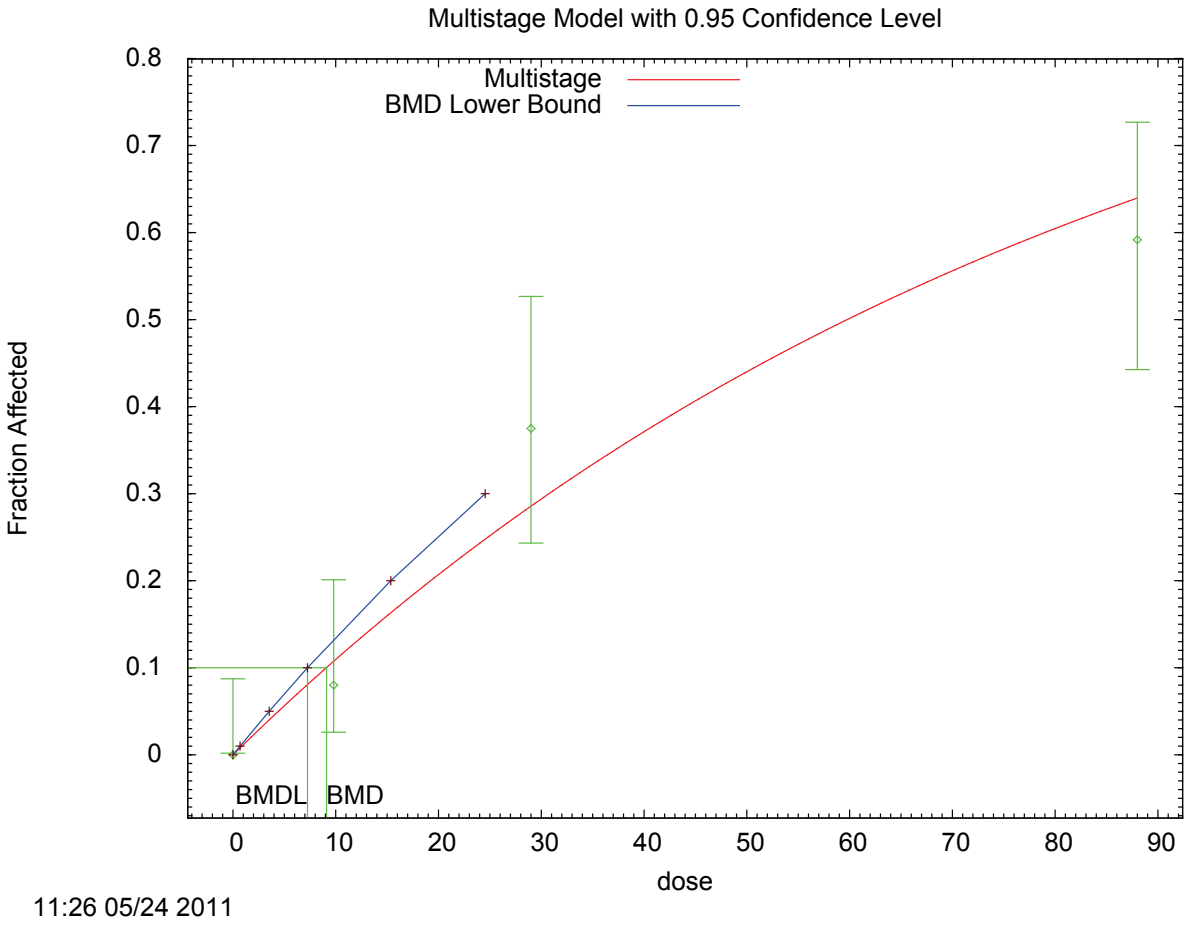

Figure C.4. Multistage BMD Model for Corneal Lesions at 24 Months in Female Rats (Rohm and Haas Company, 1992a)

INCIDENCE OF NOSE LESIONS IN MALE RATS EXPOSED TO METHYL ACRYLATE VAPOR (Rohm and Haas Company, 1992a)

All dichotomous models available in BMDS (version 2.1.2) were fit to the total incidence data of nose lesions in male S-D rats exposed to methyl acrylate via inhalation for 24 months (Saillenfait et al., 1999; see Table B.1). The initial modeling of all the data including all dose groups failed to provide an adequate fit to the data, as assessed by the χ^2 goodness-of-fit test. After excluding the highest dose group, all models besides the Multistage adequately fit the data. The Gamma, Log-logistic, Log-probit, and Weibull models provided the best fit, as assessed by lowest AIC, for data from male rats (see Table C.6 and Figure C.5). Modeling results shown in Table C.6 and Figure C.5 are with the highest dose group excluded. Estimated doses associated with 10% extra risk and the 95% lower confidence limit on these doses (BMC_{10} values and $BMCL_{10}$ values, respectively) were 3.5 and 3.1 mg/m^3.

Table C.6. Goodness-of-Fit Statistics, BMC_{10}, and $BMCL_{10}$ Values for Dichotomous Models for Total Nose Lesions in the Male Rats Treated with Methyl Acrylate[a]

Model	Goodness-of-Fit *p*-Value[b]	AIC	BMC_{10HEC} (mg/m^3)	$BMCL_{10HEC}$ (mg/m^3)
Gamma[a]	**1**	**79.487**	**3.6**	**3.1**
Logistic	0.6102	79.971	4.1	3.4
Log-Logistic[c]	**1**	**79.487**	**3.6**	**3.1**
Log-Probit[c]	**1**	**79.487**	**3.5**	**3.1**
Multistage[b]	0.0005	97.422	2.1	1.9
Probit	0.8237	79.583	3.9	3.2
Weibull[a]	**1**	**79.487**	**3.8**	**3.1**

[a]Restrict power ≥1.
[b]Restrict betas ≥0; degree of polynomial = 2; lowest degree polynomial with an adequate fit reported.
[c]Slope restricted to >1.

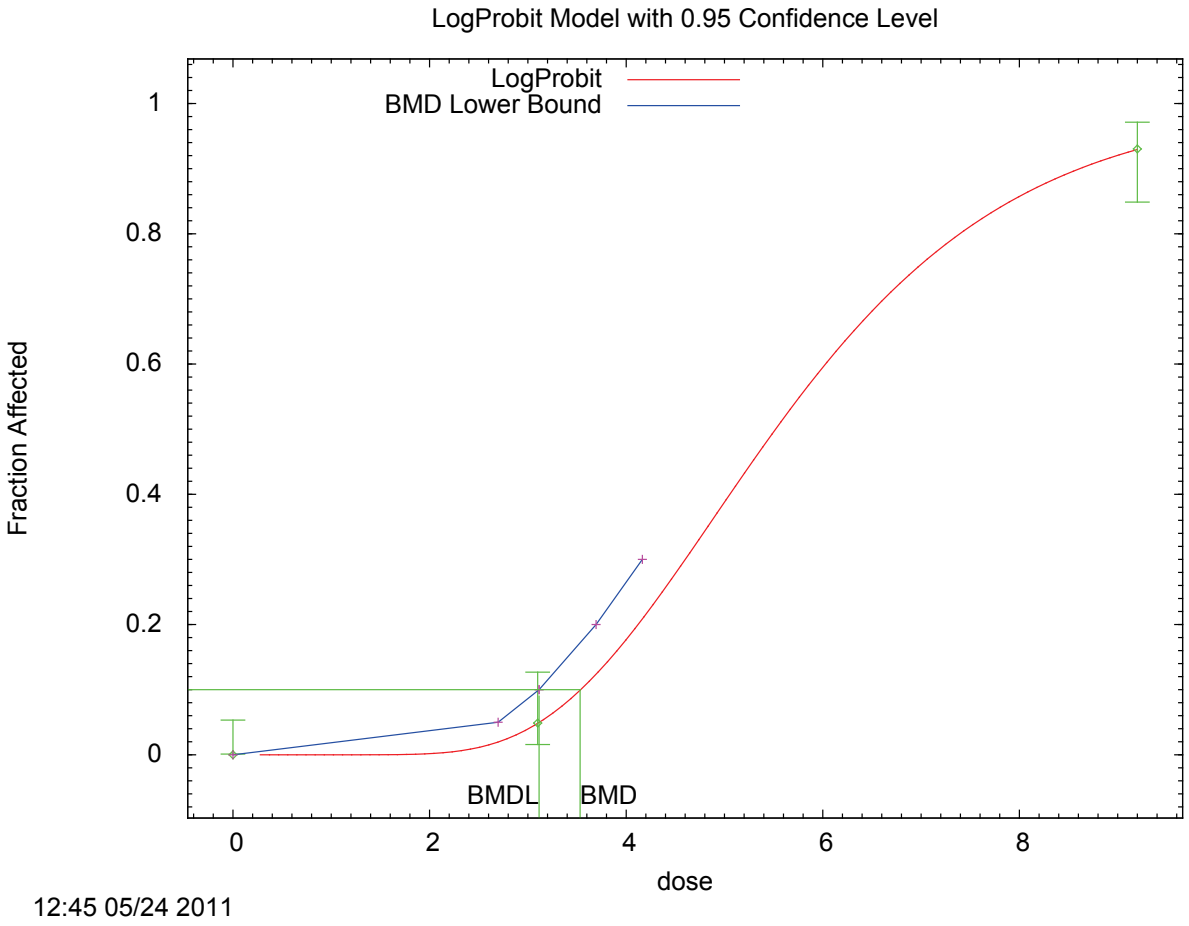

Figure C.5. Log-probit BMD Model for Total Nasal Lesions at 24 Months in Male Rats (Rohm and Haas Company, 1992a)

APPENDIX D. REFERENCES

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