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Provisional Peer-Reviewed Toxicity Values for

Ethyl Methacrylate
(CASRN 97-63-2)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
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
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
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 ETHYL METHACRYLATE (CASRN 97-63-2)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by a panel of six EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may 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), or OSRTI.

INTRODUCTION

No RfD, RfC, or cancer assessment for ethyl methacrylate (see Figure 1 for the chemical structure of ethyl methacrylate; molecular weight = 114.5) is included on IRIS (U.S. EPA, 2009) or on the Drinking Water Standards and Health Advisories (DWSHA) list (U.S. EPA, 2006). The HEAST (U.S. EPA, 1997) reported a value of 0.09 mg/kg-day for both subchronic and chronic oral RfDs based on increased relative kidney weight in a 2-year drinking water study of rats exposed to the related compound, methyl methacrylate (Borzelleca et al., 1964). The methyl methacrylate no-observed-effect-level (NOEL) of 7.5 mg/kg-day was divided by an uncertainty factor (UF) of 100, and then adjusted by multiplying the ratio of molecular weights for ethyl methacrylate and methyl methacrylate (114.5/100.13). The HEAST cited a Health and Environmental Effects Profile (HEEP) for ethyl methacrylate (U.S. EPA, 1986a) as the source for the RfD values. No RfC values are reported in the HEAST or derived in the HEEP. Other than the HEEP (U.S. EPA, 1986a), the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994a, 1991a) do not include any relevant documents. The toxicity of ethyl methacrylate has not been reviewed by ATSDR (2009) or the World Health Organization (WHO, 2009). CalEPA (2009a,b) has not derived toxicity values for exposure to ethyl methacrylate.

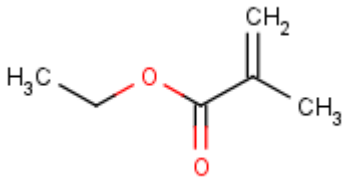

Figure 1. Chemical Structure of Ethyl Methacrylate

No occupational exposure limits have been derived for ethyl methacrylate by the American Conference of Governmental Industrial Hygienists (ACGIH, 2009), the National Institute of Occupational Safety and Health (NIOSH, 2009), or the Occupational Safety and Health Administration (OSHA, 2009). A safety assessment of ethyl methacrylate reviewed by the Cosmetic Ingredient Review Expert Panel was published in 2002, but no occupational exposure limits were presented in this document.

A cancer assessment for ethyl methacrylate is not available on IRIS (U.S. EPA, 2009), the DWSHA list (U.S. EPA, 2006), or in the HEAST (U.S. EPA, 1997). Using the 1986 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986b), the HEEP (U.S. EPA, 1986a) assigned ethyl methacrylate to weight-of-evidence Group D (*Not Classifiable as to Human Carcinogenicity*). Ethyl methacrylate has not been evaluated under the 2005 guidelines (U.S. EPA, 2005). The International Agency for Research on Cancer (IARC, 2009) has not reviewed the carcinogenic potential of ethyl methacrylate. Ethyl methacrylate has not been evaluated for potential carcinogenicity by the National Toxicology Program (NTP, 2009a) and is not included in the 11th Report on Carcinogens (NTP, 2005). CalEPA (2009b) has not prepared a quantitative estimate of carcinogenic potential for ethyl methacrylate.

Literature searches were conducted from 1960s through August 9, 2010 for studies relevant to the derivation of provisional toxicity values for ethyl methacrylate. Databases searched included MEDLINE, TOXLINE (with NTIS), BIOSIS, TSCATS/TSCATS2, CCRIS, DART, GENETOX, HSDB, RTECS, Chemical Abstracts, and Current Contents.

REVIEW OF PERTINENT DATA

HUMAN STUDIES

In a case-control study, Hiipakka and Samimi (1987) measured airborne exposure to ethyl methacrylate (used in nail-sculpting products) in six different sculptured nail salons. Health symptoms data were collected on 20 female nail sculptors and 20 matched controls using standardized, self-administered questionnaires on a range of potential effects including irritation, headaches and dizziness, and neurological signs of clinical adversity. Mean time-weighted average (TWA) concentrations of ethyl methacrylate were estimated to be 4.5 ppm. The only statistically significant ($p < 0.05$ by Chi-Square analysis) health finding was an increase in reporting of throat irritation. Although consistent increases in nose and skin irritation, drowsiness, dizzy spells, and trembling of the hands were reported by sculptors as compared with controls, the differences were not statistically significant. However, these findings could not be attributed solely to ethyl methacrylate because co-occurring exposures to airborne particle dust and other organic vapors, including butyl acetate and toluene, also occurred in the work environment.

ANIMAL STUDIES

Oral Exposure

Data on oral exposure to ethyl methacrylate are available from one subchronic drinking water study by Abou-Donia et al. (2000). Male Sprague-Dawley rats (8/group) were given ethyl methacrylate (99% purity) in drinking water for 60 days at concentrations of 0, 0.1, 0.2, or 0.5%,

(prepared fresh daily). For this assessment, default parameters for drinking water consumption rate and body weight (U.S. EPA, 1988) were used to estimate daily doses of 139, 277, and 693 mg/kg-day for the low-, mid-, and high-dose groups, respectively. Control animals were given untreated water. Animals were observed cage-side daily for mortality and clinical signs of toxicity; observations included overall activity, posture, balance, breathing rate, and evidence of diarrhea. Group-based qualitative observations were recorded weekly. Body weight was also monitored weekly. Following termination of exposure, animals were euthanized, and the brain, spinal cord, and sciatic nerve were removed and examined for histopathology. No other toxicological evaluations were conducted. In addition to administering ethyl methacrylate in drinking water, a subchronic neurotoxicity evaluation was also performed via daily intraperitoneal (i.p.) doses (see summary in "Other Studies" below).

No mortality occurred when ethyl methacrylate was administered in the drinking water (Abou-Donia et al., 2000). Animals in the mid-dose group (277 mg/kg-day) exhibited lethargy, and those in the high-dose group (693 mg/kg-day) showed gait alterations, suggesting an increase in severity of clinical symptoms with increasing dose. No differences in clinical symptoms were observed between low-dose and control animals. Morphological alterations were observed in cross-sections of brain, spinal cord, and sciatic nerve in all treated groups. Major histopathological findings that were statistically significantly ($p < 0.05$) different from control at all doses were (1) an increase in the number of clusters of enlarged axons (>0.05 mm in diameter), primarily at internodal segments, throughout the dorsal, ventral, and lateral columns of the spinal cord; and (2) a reduction in the number of neurons in sections of the ventral horns of the spinal cord. However, the magnitude of these effects was not clearly dose-dependent. Data were only presented in graphical form. Based on visual inspection, the mean numbers of clusters of enlarged axons were approximately 16, 14, and 23 in the low-, mid-, and high-dose groups, respectively, as compared with 0 in the control group. Similarly, based on visual inspection, the numbers of neurons in the ventral horns of a cross-section of the spinal cord were approximately 11, 15, and 13 in the low-, mid-, and high-dose groups, respectively, as compared with 22 in the control group.

Other abnormalities were reported to occur in all treated groups, but neither raw data nor statistical significance was presented (Abou-Donia et al., 2000). These included (1) spongiform alterations in myelin and clusters of enlarged axons in white matter tracts in the brainstem and forebrain (fornix, cerebral peduncles, and internal capsule); and (2) shrunken axons with separated myelin lamellae and large axons with thinner-than-normal myelin sheaths dispersed throughout the sciatic nerve. The study authors concluded that daily administration of ethyl methacrylate in drinking water to rats for 60 days produces clinical signs of neurotoxicity and a range of adverse neuropathological effects consistent with the induction of myelinopathy rather than a primary axonopathy. They also suggested that neuronal loss, as indicated by decreased neuronal density, may be either secondary to demyelination or a primary effect of ethyl methacrylate treatment. The study authors do not identify effect levels. Based on the neuropathology findings, a lowest-observed-adverse-effect level (LOAEL) of 139 mg/kg-day, the lowest dose tested, is identified. A no-observed-adverse-effect level (NOAEL) could not be identified.

Inhalation Exposure

An inhalation developmental toxicity study (Saillenfait et al., 1999) was the only inhalation study located for ethyl methacrylate. Nulliparous mated female Sprague-Dawley rats (23−27 bred rats; 19−25 pregnancies) were exposed to ethyl methacrylate (99% purity) for 6 hours/day, on gestation days (GDs) 6−20, at airborne concentrations of 0, 600, 1200, 1800, or 2400 ppm (equivalent to 0, 2800, 5600, 8400, and 11,200 mg/m^3, respectively). For ethyl methacrylate exposures, the pregnant rats were placed in stainless-steel wire mesh exposure cages that were moved into 200-L glass/stainless-steel inhalation chambers with dynamic and adjustable laminar airflow. Control animals were exposed concurrently to filtered room air in an adjacent chamber identical to those of the exposure groups. Chamber concentrations of ethyl methacrylate were monitored continuously by gas chromatography. Food and water were provided ad libitum but not during exposures. Maternal body weights were recorded on GDs 0, 6, 13, and 21. Food consumption was measured for the intervals: GDs 6−13 and 13−21. Following euthanasia of dams on GD 21, the uterus was removed and weighed. The numbers of corpora lutea, implantation sites, resorptions, and dead and live fetuses were recorded. Uteri with 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 ethanol (70%), eviscerated, and examined for skeletal abnormalities following staining with alizarin red S. The litter was used as the basis for analysis of fetal variables.

Saillenfait et al. (1999) did not observe mortality during the study. Clinical signs of toxicity during treatment and any neurotoxicity findings were not reported. Table 1 presents statistically significant changes in maternal body-weight gain and food consumption, as well as fetal body weight on a per-litter basis. Maternal body-weight gain was significantly reduced between GDs 6 and 13 at concentrations ≥5600 mg/m^3, and between GDs 13 and 21 at 11,200 mg/m^3. Overall weight gain between GDs 6 and 21 was significantly decreased at concentrations ≥5600 mg/m^3, and there was a concentration-related reduction in corrected (adjusted for gravid uterine weight) weight gain relative to controls (see Table 1). Maternal food consumption was significantly less than controls between GDs 6 and 13, between GDs 13 and 21, and for the entire exposure period (between GDs 6 and 21) at concentrations ≥5600 mg/m^3. With the exception of fetal body weights, no reproductive or developmental effects were observed for any measured endpoint. Mean fetal body weight per litter was significantly reduced in males at concentrations ≥5600 mg/m^3, and in females and both sexes combined at concentrations ≥8400 mg/m^3 (see Table 1). The percent decreases in mean fetal body weight relative to controls were 5.2, 7.6, and 7.1% at 5600, 8400, and 11,200 mg/m^3, respectively, for males; 5.1 and 5.6% at 8400 and 11,200 mg/m^3, respectively, for females; and 6.4 and 6.4% at 8400 and 11,200 mg/m^3, respectively, for males and females combined. The study authors concluded that inhalation exposure to ethyl methacrylate did not produce evidence of embryolethality or teratogenicity in any treatment group. Decreases in mean fetal body weight on a per-litter basis were only observed at maternally toxic doses, as measured by significant decreases in dam bodyweight gain, absolute body weight, and decreased food consumption. The study authors do not identify maternal effect levels. Based on statistically significant ($p < 0.05$) reduced body-weight gain, a maternal NOAEL of 2800 mg/m^3 and a LOAEL of 5600 mg/m^3 are identified. Based on a significant decrease in mean male fetal body weight per litter, the study authors identified a developmental NOAEL of 2800 mg/m^3 and a LOAEL of 5600 mg/m^3.

Table 1. Statistically Significant Changes in Female Sprague-Dawley Rats and Their Litters Treated with Ethyl Methacrylate via Inhalation on GDs 6−20

	Exposure Concentration in mg/m^3 (ppm)				
	Control (0 ppm)	2800 (600 ppm)	5600 (1200 ppm)	8400 (1800 ppm)	11,200 (2400 ppm)
Parameter	HEC[a] 0	HEC 700	HEC 1400	HEC 2100	HEC 2800
Number of animals treated	25	24	25	24	24
Number of dams/litters examined	23/25[b]	22/24	20/25	23/24	19/24
Body weight on GD 6 (g)	261 ± 18[c]	264 ± 20	259 ± 20	260 ± 19	264 ± 19
Body-weight gain (g)					
GDs 6−13	29 ± 9	24 ± 6	19 ± 6[d]	16 ± 5[d]	9 ± 7[d]
GDs 13−21	96 ± 22	103 ± 14	89 ± 15	85 ± 13	68 ± 18[d]
GDs 6−21	125 ± 26	127 ± 15	107 ± 18[d]	101 ± 14[d]	77 ± 21[d]
Absolute weight gain (g)[e]	28 ± 14	19 ± 9	13 ± 12[d]	4 ± 9[d]	−7 ± 18[d]
Food consumption (g)					
GDs 6−13	21 ± 2	20 ± 2	17 ± 2[d]	17 ± 2[d]	15 ± 2[d]
GDs 13−21	25 ± 2	25 ± 2	22 ± 2[d]	22 ± 2[d]	20 ± 1[d]
GDs 6−21	24 ± 2	22 ± 1	20 ± 2[d]	19 ± 2[d]	18 ± 1[d]
Average fetal body weight per litter (g)					
Males	5.79 ± 0.26	5.65 ± 0.28	5.49 ± 0.35[d]	5.35 ± 0.34[d]	5.38 ± 0.41[d]
Females	5.43 ± 0.32	5.34 ± 0.20	5.24 ± 0.34	5.14 ± 0.35[d]	5.10 ± 0.44[d]
Males and females	5.61 ± 0.28	5.49 ± 0.22	5.37 ± 0.32	5.25 ± 0.32[d]	5.25 ± 0.42[d]

[a]HEC = Human Equivalent Concentration in mg/m^3 (see RfC derivation text for calculation)
[b]Number examined/number treated
[c]Mean ± SD
[d]Significantly different from control at $p < 0.05$ by Dunnett's test
[e](Day 21 body weight) − (gravid uterus weight) − (Day 6 body weight)

Source: Saillenfait et al. (1999).

OTHER STUDIES

Toxicokinetics

No standard toxicokinetic studies have been conducted with ethyl methacrylate. However, metabolic studies of the acrylate esters (primarily conducted on ethyl and methyl acrylates) in male Holtzman rats demonstrate that they are hydrolyzed by carboxylases to acrylic acid and the corresponding alcohol (Silver and Murphy, 1981).

Toxicokinetic data are available for methyl methacrylate, a closely related structural analog of ethyl methacrylate. Methyl methacrylate is rapidly absorbed following oral, inhalation, and dermal administration, and it is metabolized to methanol and methacrylic acid, and, eventually, to CO_2 via the citric acid cycle (reviewed by U.S. EPA, 1998). Similar toxicokinetics have been observed with intravenous administration. Very little parent compound is retained in the body. According to EPA (1998), exposure duration did not affect tissue concentrations, suggesting that methyl methacrylate does not bioaccumulate. In rats,

metabolism was observed to occur in the blood, with the rate of disappearance of parent compound showing a first-order dose dependency and suggesting a simple serum enzymatic reaction involving esterase-catalyzed hydrolysis to methanol and methacrylic acid (U.S. EPA, 1998). Substrate saturation can occur at elevated doses and several studies suggest that, in the absence of available carboxylesterases, binding of parent compound with nonprotein sulfhydryl compounds can occur. In in vitro experiments with methyl methacrylate, the enzymatic substrate-saturation curve was reduced by the addition of inhibitors of nonspecific carboxylesterase (U.S. EPA, 1998). In an in vivo study by Silver and Murphy (1981), pretreatment with tri-o-cresyl phosphate (a carboxylesterase inhibitor) potentiated the acute toxicity and reduced the level of tissue nonprotein sulfhydryls following a 4-hour inhalation exposure of rats to either methyl or ethyl acrylate (Silver and Murphy, 1981). Methyl methacrylate is also metabolized to methacrylic acid by carboxylesterase enzymes in the upper respiratory tract of rats (primarily in olfactory tissue) following inhalation exposure and can induce in situ toxicity (U.S. EPA, 1998). However, the rate of metabolism of ethyl methacrylate may differ from methyl methacrylate, and the possibility of formation of other metabolite(s) cannot be excluded.

Acute or Short-term Studies

Deichman et al. (1941) reported oral LD_{50} values for ethyl methacrylate ranging from 12.70 to 14.51 g/kg for rats and from 3.63 to 5.44 g/kg for rabbits.

To investigate structure-toxicity relationships and mechanisms, Ghanayem et al. (1985b) tested the comparative gastric toxicities of methyl and ethyl acrylates and their substituted esters, methyl methacrylate and ethyl methacrylate (99% purity), in male Fischer 344 rats (15/dose group). A previous study in the same laboratory (Ghanayem et al., 1985a) had shown that single or repeated gavage dose administration of ethyl acrylate caused extensive gastric toxicity in both the forestomach and glandular stomach. In the Ghanayem et al. (1985b) study, the results of a single dose of ethyl acrylate treatment were the same as in Ghanayem et al. (1985a). However, an equimolar concentration (2 mmol/kg dissolved in corn oil) of ethyl methacrylate did not induce gastric toxicity, as measured by an increase in the size of the stomach and forestomach edema and changes in the flattening of the glandular stomach rugae 4 hours following dosing. The study authors concluded that the methyl substitution at Carbon 2 decreases the direct toxicity of ethyl acrylate, likely due to an increase in the chain length, which alters the polarity and/or detoxification process of ethyl methacrylate.

Lawrence and Autian (1972) investigated whether ethyl methacrylate (used as a volatile ingredient of dental products) might affect response to sedatives used in dentistry. Male ICR mice (10/dose group) were exposed to vapors of ethyl methacrylate (purity not reported) in an inhalation chamber at a target concentration of 84.79 mg/m^3. The duration of exposure was 3.85, 7.70, or 19.25 minutes. Control mice were placed in the inhalation chamber for the longest exposure time, but they received only air. Following treatment, mice were given a standard dose of sodium pentobarbital (route not reported but, presumably, via injection), and the length of sleeping time was monitored. Mean sleeping time was increased only in the group with 19.25 minutes of exposure as compared with controls (94.93 versus 50.63 minutes, respectively).

Other Routes

In a subchronic neurotoxicity study, ethyl methacrylate (99% purity) was administered (neat) to male Sprague-Dawley rats (10/dose group) via daily i.p. doses of 0, 100, 200, 400, or 800 mg/kg, 7 days/week, for 60 days (Abou-Donia et al., 2000). The volume of injected compound varied with body weight and dose, and ranged from 0.02 to 0.16 mL/rat at the beginning of the experiment and from 0.04 to 0.32 mL/rat at the end. Control animals received 0.1 mL/kg saline daily. Animals were monitored daily for mortality and clinical signs of toxicity. Body weight was recorded weekly. In the control, 100-, 200-, and 400-mg/kg groups, motor activity was assessed at the end of the exposure period and was followed by evaluation of spatial memory in the Morris water maze. Behavioral testing was conducted by a single trained observer who was blind to treatment. No other toxicological evaluations were conducted.

Motor activity was measured using sets of photobeam devices, placed strategically to detect both horizontal and vertical movements, with computer data collection. Photobeam interruptions were recorded at 5-minute intervals and subsequently summed over the 1-hour test session. In the circular Morris water maze, a closed-circuit video camera was mounted above the tank to track and transmit images of the swimming rat to a television monitor as well as to a computer for data analysis. The image of the pool was divided into four separate quadrants, and a submerged hidden Plexiglas platform was randomly placed in one of the quadrants. Each animal was released into the pool from one of the quadrants not containing the platform and allowed to swim for 60 seconds or until it located and climbed onto the escape platform. Rats were given five trials per day with a 1-minute rest period between each trial. Animals were trained daily until they successfully found the escape platform within 60 seconds on the last four trials of a given day or until they had reached the 25^{th} trial (5 days). Escape latencies were then summed across the number of trials required to meet the designated criterion or through the 25^{th} trial (Abou-Donia et al., 2000).

Significant mortality occurred in all treatment groups ≥200 mg/kg but was not dose-dependent (Abou-Donia et al., 2000). Clinical signs of toxicity were increased in a dose-dependent manner at doses of ≥200 mg/kg. Body-weight gains varied across treatment groups, but the differences from control were sporadic, transient, and unrelated to dose. In the motor activity test, a statistically significant, dose-dependent decrease in both horizontal and vertical activity was observed in the 100-, 200-, and 400-mg/kg groups as compared with controls. The effect of trial was also significant, but there was no significant interaction between trial and treatment. In the Morris water maze, a significant decrease in escape latency was observed across the 5 days of treatment, demonstrating that the platform location was being learned. The effect of treatment was significant only in the 400-mg/kg group, with a significant interaction between day and treatment on Test Days 3 and 5. The study authors concluded that subchronic i.p. administration of ethyl methacrylate can produce dose-dependent clinical abnormalities and impairment of motor activity, as well as disruption of spatial memory at the highest dose tested (400 mg/kg).

Singh et al. (1972) examined the developmental toxicity of ethyl methacrylate and other methacrylates administered intraperitoneally on GDs 5, 10, and 15 in female Sprague-Dawley rats (5/dose group) following successful mating with untreated males. Single administered doses of ethyl methacrylate (purity not mentioned) were 0.122, 0.245, and 0.408 mL/kg (equivalent to 0.111, 0.224, and 0.373 mg/kg, respectively) in the low-, mid-, and high-dose groups,

respectively. No diluent was used. An untreated group of rats was maintained as controls. For comparative purposes, cottonseed oil, distilled water, or normal saline were administered to other groups of rats at a dose of 0.822 mL/kg to test the effects of various vehicles. Five female rats were housed with a single male, and the onset of gestation was established by the presence of sperm in the vaginal smear (designated as GD 0). Data on maternal toxicity were not presented. Statistical tests used for data analysis were not reported; however, the fetus, rather than the litter, was the unit of analysis. Endpoints examined were number of resorptions, stillbirths, gross (external) and skeletal malformations, and mean fetal body weight. All dosed groups showed a small, but statistically significant, increase in the number of fetal resorptions ($p < 0.05$) relative to untreated controls. However, there did not appear to be significant differences in this endpoint relative to the number of resorptions occurring in rat treated with only distilled water or normal saline vehicle. A small—but statistically significant—increase in the number of fetuses with gross abnormalities (e.g., hemangiomas on various parts of the fetus, twisted hind legs, no tail) was reported to occur in all treated groups relative to pooled controls (3/51, 5/42, and 8/48 in the low-, mid-, and high-dose groups, respectively, versus 0/59, 0/36, 1/50, and 1/50 in untreated, distilled water, normal saline, and cottonseed oil groups, respectively). No effects on skeletal abnormalities were observed. Mean fetal body weights were significantly decreased in the mid- and high-dose groups as compared with untreated, but not vehicle, controls; the mean fetal body weights of all vehicle control groups were also statistically significantly decreased relative to untreated controls. The numerous limitations of this study preclude interpretation of the findings. No data on maternal toxicity, including mortality, were given. Statistical methodology was not reported, and the litter was not used as the unit of statistical analysis, so it is possible that the observed effects occurred only in a single litter. Additionally, the sample size was small (5/dose group). Finally, similar effects on resorption and mean fetal body weight were observed in vehicle controls, suggesting that these findings were associated, at least in part, with i.p. injection procedures. Thus, the observed effects could not be clearly attributed to ethyl methacrylate treatment.

Genotoxicity

Ethyl methacrylate was negative in the Ames bacterial mutagenicity assay using *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537, and TA1538, with and without Aroclor 1254- or phenobarbital-induced S9 mix (Zeiger et al., 1987; Waegemaekers and Bensink, 1984). Preincubation of cell cultures prior to treatment also produced negative findings with and without metabolic activation (Zeiger et al., 1987).

Ethyl methacrylate was also evaluated for mutagenicity and clastogenicity without exogenous activation in L578Y mouse lymphoma cells at concentrations ranging from 900 to 2100 µg/mL (Moore et al., 1988). A weakly positive response (approximately twice the background rate) was induced at cytotoxic concentrations >1000 µg/mL and then only at 10−20% survival rates. The dose-response curve was nonlinear, and the study authors attribute these findings to possible induction of chromosomal aberrations rather than point mutations. A weakly positive clastogenic response (less than twice the background rate) was also observed in cell cultures treated separately for analysis of chromatid and chromosomal aberrations (Moore et al., 1988).

In in vitro genotoxicity testing using Chinese hamster ovary (CHO) cells, ethyl methacrylate was negative for chromosomal aberrations at plate concentrations ranging from

1000 to 3000 µg/mL with and without exogenous rat liver S9 activation (NTP, 2009b). Ethyl methacrylate was positive for sister chromatid exchanges (SCEs) at plate concentrations ranging from 1000 to 4000 µg/mL, with cytotoxicity occurring at higher doses (NTP, 2009b). No information on genotoxicity endpoints examined in animals treated with ethyl methacrylate in vivo was located in the available literature.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR ETHYL METHACRYLATE

SUBCHRONIC p-RfD

Oral toxicity data are limited to a single neurotoxicity study (Abou-Donia et al., 2000) in which ethyl methacrylate was administered in drinking water to male Sprague-Dawley rats for 60 days. However, if this study were to be used as the principal study for the derivation of the subchronic RfD, the composite UF would be 10,000. Based on current guidelines and SOPs, a composite UF >3000 cannot be considered for reference value derivation. As such, while a subchronic p-RfD cannot be derived here, Appendix A of this document contains an oral "screening value" that may be useful in certain instances. Please refer to Appendix A for details.

CHRONIC p-RfD

There are no chronic oral studies of ethyl methacrylate. A subchronic neurotoxicity study using only one species (rat) and sex (male) has been conducted, and this study did not identify a NOAEL. Data for evaluating systemic effects other than neurotoxicity and reproductive/developmental toxicity via i.p. exposure are not available nor are any oral toxicological data in another species or in female animals. Due to these database deficiencies, the data do not support the derivation of a chronic p-RfD.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR ETHYL METHACRYLATE

The only available inhalation study of ethyl methacrylate is a developmental toxicity study (Saillenfait et al., 1999) in Sprague-Dawley rats. Table 1 summarizes the results of this study. The only treatment-related effects were large, statistically significant decreases in maternal body-weight gain (both before and after adjustment for gravid uterine weight) at exposure concentrations ≥5600 mg/m^3 and decreases in male fetal body weight (on a per-litter basis) at ≥5600 mg/m^3, and in female and combined male and female fetal body weights at ≥8400 mg/m^3. No other effects on reproductive and developmental parameters were observed.

SUBCHRONIC p-RfC

Dose-response modeling was performed for corrected (adjusted for gravid uterine weight) body-weight gain in dams and for mean fetal body weight per litter in males (Saillenfait et al., 1999). For fetal males, the data were modeled on a per-litter basis as the litter is considered to be the experimental unit in developmental toxicity studies (U.S. EPA, 1991b).

Exposure concentrations were adjusted for intermittent dosing (as per guidance provided by U.S. EPA, 2002) and human equivalent concentrations (HECs) were determined prior to modeling. The maternal and developmental $NOAEL_{HEC}$ of 700 mg/m^3 was calculated from the rat NOAEL of 2800 mg/m^3 using EPA (1994b) methodology for an extrarespiratory effect produced by a Category 3 gas, as follows:

$$\begin{aligned} NOAEL_{ADJ} &= 2800 \text{ mg/m}^3 \times 6 \text{ hours} \div 24 \text{ hours} \\ &= 700 \text{ mg/m}^3 \end{aligned}$$

$$\begin{aligned} NOAEL_{HEC} &= NOAEL_{ADJ} \times (H_{b/g})_A \div (H_{b/g})_H \\ &= 700 \text{ mg/m}^3 \times 1 \\ &= 700 \text{ mg/m}^3 \end{aligned}$$

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 ethyl methacrylate, the default value of 1 was used, as specified in EPA (1994b) guidance.

Appendix B contains details of the BMD modeling. For maternal data, a benchmark response (BMR) of 1 standard deviation (SD) from the mean was used. The BMC_{HEC} and $BMCL_{HEC}$ associated with the best fitting model for this data set were 1103 and 854 mg/m^3, respectively.

For male fetal body-weight data, a BMR of a 5% change from the control mean (relative deviation) was used. This BMR level is considered to be less sensitive to background variability in fetal body weight than a change of 1 SD from the control mean and yields a BMD that more closely approximates a NOAEL (Allen et al., 1996; Kavlock et al., 1995). The BMC_{05HEC} and $BMCL_{05HEC}$ associated with the best-fitting model were 1794 and 1386 mg/m^3, respectively.

The lowest $BMCL_{HEC}$ value of 854 mg/m^3 (Saillenfait et al., 1999) was selected as the point of departure (POD) for derivation of a subchronic p-RfC because it is protective of both fetal and maternal toxicity. This $BMCL_{HEC}$ was divided by a composite UF of 300 to derive a subchronic p-RfC for ethyl methacrylate, as follows:

$$\begin{aligned} \textbf{Subchronic p-RfC} &= BMCL_{HEC} \div UF \\ &= 854 \text{ mg/m}^3 \div 300 \\ &= \textbf{3 mg/m}^3 \textbf{ or } \mathbf{3 \times 10^0 \text{ mg/m}^3} \end{aligned}$$

The composite UF of 300 is composed of the following UFs:

- UF_A: A factor of 3 ($10^{0.5}$) is applied for animal-to-human extrapolation because derivation of a HEC from the animal data partially adjusts for interspecies sensitivity (U.S. EPA, 1994b).

- UF_D: The database contains a developmental toxicity study in one species. However, because subchronic, chronic, developmental toxicity in a second species, and multigeneration reproductive toxicity studies have not been conducted, the identification of more sensitive endpoints from ethyl methacrylate inhalation could have been potentially missed. Thus, a factor of 10 is applied for database limitations.
- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating a susceptible human response are insufficient.
- UF_L: A factor of 1 is applied for extrapolation from a LOAEL to a NOAEL because a BMCL was used as the POD.

Confidence in the principal study (Saillenfait et al., 1999) is high. This study included 24−25 animals per group and five exposure levels, utilized appropriate statistical methodology, assessed litter effects, investigated a suitable range of endpoints, and established both a NOAEL and LOAEL. Confidence in the database is, however, low. Subchronic, chronic, and multigeneration reproductive toxicity studies have not been conducted and developmental toxicity data in a second species are also lacking. Low confidence in the subchronic p-RfC value follows.

CHRONIC p-RfC

To derive the chronic p-RfC using the POD of 854 mg/m^3 for decreased maternal body-weight gain in the developmental toxicity study (Saillenfait et al., 1999), a composite UF is applied that includes the same areas of uncertainty enumerated above for the subchronic p-RfC, as well as an additional 10-fold UF, as follows:

- UF_S: A factor of 10 is applied for using data from a less-than-lifetime study to assess potential effects from chronic exposure.

This results in a composite UF of 3000 for derivation of the chronic p-RfC.

A chronic p-RfC for ethyl methacrylate is derived from the $BMCL_{HEC}$ of 854 mg/m^3 (Saillenfait et al., 1999) as follows:

$$\begin{aligned} \textbf{Chronic p-RfC} &= BMCL_{HEC} \div UF \\ &= 854\ mg/m^3 \div 3000 \\ &= \textbf{0.3 mg/m}^{\mathbf{3}}\textbf{ or } \mathbf{3 \times 10^{-1}\ mg/m^3} \end{aligned}$$

As discussed for the subchronic p-RfC, confidence in the principal study is high, confidence in the database is low, and overall confidence in the chronic p-RfC is low.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR ETHYL METHACRYLATE

WEIGHT-OF-EVIDENCE DESCRIPTOR

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "*Inadequate Information to Assess [the] Carcinogenic Potential"* of ethyl methacrylate. No information was located on the potential carcinogenicity of ethyl methacrylate in either humans or animals. A limited number of in vitro studies suggest that ethyl methacrylate is not mutagenic but may be weakly genotoxic. In bacterial mutagenicity assays conducted in two different laboratories, ethyl methacrylate was not observed to be mutagenic with or without exogenous metabolic activation in all *S. typhimurium* strains tested (Zeiger et al., 1987; Waegemaekers and Bensink, 1984). In L5178Y mouse lymphoma cells, ethyl methacrylate was weakly positive for both mutagenicity and clastogenicity at cytotoxic plate concentrations with 10−20% cell survival rates (Moore et al., 1988). In CHO cells, ethyl methacrylate was negative for chromosomal aberrations and positive for SCE (NTP, 2009b). No in vivo genotoxicity studies are available for ethyl methacrylate.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Derivation of quantitative estimates of cancer risk for ethyl methacrylate ether is precluded by the lack of available data.

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APPENDIX A. DERIVATION OF A SCREENING VALUE FOR ETHYL METHACRYLATE

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for ethyl methacrylate. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Hazard identification and dose-response information contained in an Appendix receives the same level of internal and external scientific peer review as the main body of PPRTV documents, to ensure their appropriateness within the limitations detailed in the document. In the OSRTI hierarchy, screening values are considered to be *below* Tier 3, "Other (Peer-Reviewed) Toxicity Values."

Screening values are intended for use in limited circumstances when no Tier 1, 2, or 3 values are available. Screening values may be used, for example, to rank relative risks of individual chemicals present at a site to determine if the risk developed from the associated exposure at the specific site is likely to be a significant concern in the overall cleanup decision. Screening values are not defensible as the primary drivers in making cleanup decisions because they are based on limited (e.g., scope, depth, validity, etc.) information. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

SCREENING SUBCHRONIC ORAL VALUE

As noted earlier, oral toxicity data are limited to a single neurotoxicity study (Abou-Donia et al., 2000) in which ethyl methacrylate was administered in drinking water to male Sprague-Dawley rats for 60 days. The endpoints measured were limited to mortality, clinical signs of toxicity, body weight, and histopathology of the brain, spinal cord, and sciatic nerve. Dose-dependent clinical signs of neurotoxicity were observed at the two highest doses, and significant central nervous system histology was observed at all treatment levels ($p < 0.05$). The major histopathological findings were as follows: (1) a statistically significant increase in the number of clusters of enlarged axons (>0.05 mm in diameter), primarily at internodal segments, throughout the dorsal, ventral, and lateral columns of the spinal cord; and (2) a statistically significant reduction in the number of neurons in sections of the ventral horn of the spinal cord.

Abou-Donia et al. (2000) presented no raw data. Therefore, benchmark dose-response modeling could not be conducted and, consequently, the lowest-observed-adverse-effect level [LOAEL] of 139 mg/kg-day for neurotoxicity was selected as the point of departure (POD) for derivation of a screening subchronic p-RfD (a no-observed-adverse-effect level [NOAEL] was not identified in this study). No adjustment was needed for exposure duration as ethyl

methacrylate was administered continuously in drinking water for 60 days. This LOAEL was divided by a composite uncertainty factor (UF) of 10,000 to derive a screening subchronic p-RfD for ethyl methacrylate, as follows:

Screening Subchronic p-RfD = LOAEL ÷ UF
= 139 mg/kg-day ÷ 10,000
= **0.01 mg/kg-day or 1×10^{-2} mg/kg-day**

The composite UF of 10,000 is composed of the following UFs:

- UF_A: A factor of 10 is applied for animal-to-human extrapolation because the data for evaluating relative interspecies sensitivity are insufficient.
- UF_D: A subchronic neurotoxicity study using only one species (rat) and sex (male) has been conducted. Data for evaluating systemic effects other than neurotoxicity and reproductive/developmental toxicity via i.p. exposure are not available. A developmental study by inhalation exposure was conducted in only one species (rats). A factor of 10 is applied for database inadequacies because the data for evaluating systemic toxicity and developmental and reproductive toxicity are insufficient.
- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because the data for evaluating a susceptible human response are insufficient.
- UF_L: A factor of 10 is applied for extrapolating from a LOAEL to a NOAEL.

APPENDIX B. DETAILS OF BENCHMARK DOSE MODELING FOR THE PROVISIONAL RfCs

MODEL-FITTING PROCEDURE FOR CONTINUOUS DATA

The benchmark dose (BMD) modeling for continuous data was conducted with the EPA's BMD software (BMDS). The original data were modeled with all the continuous models available within the software employing a BMR of 1 SD. An adequate fit was judged based on three criteria: (1) the goodness-of-fit *p* value ($p > 0.1$), (2) magnitude of scaled residuals in the vicinity of the benchmark response (BMR), and (3) visual inspection of the model fit. In addition to the three criteria for judging the adequate model fit, whether the variance needed to be modeled, and if so, how it was modeled also determined final use of the model results. If a constant variance model was deemed appropriate based on the statistical test provided in the BMDS (i.e., Test 2), the final BMD results were estimated from a constant variance model. If the test for constant 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 nonconstant variance. If this nonconstant 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 >3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was selected as a potential point of departure (POD) from which to derive an RfD.

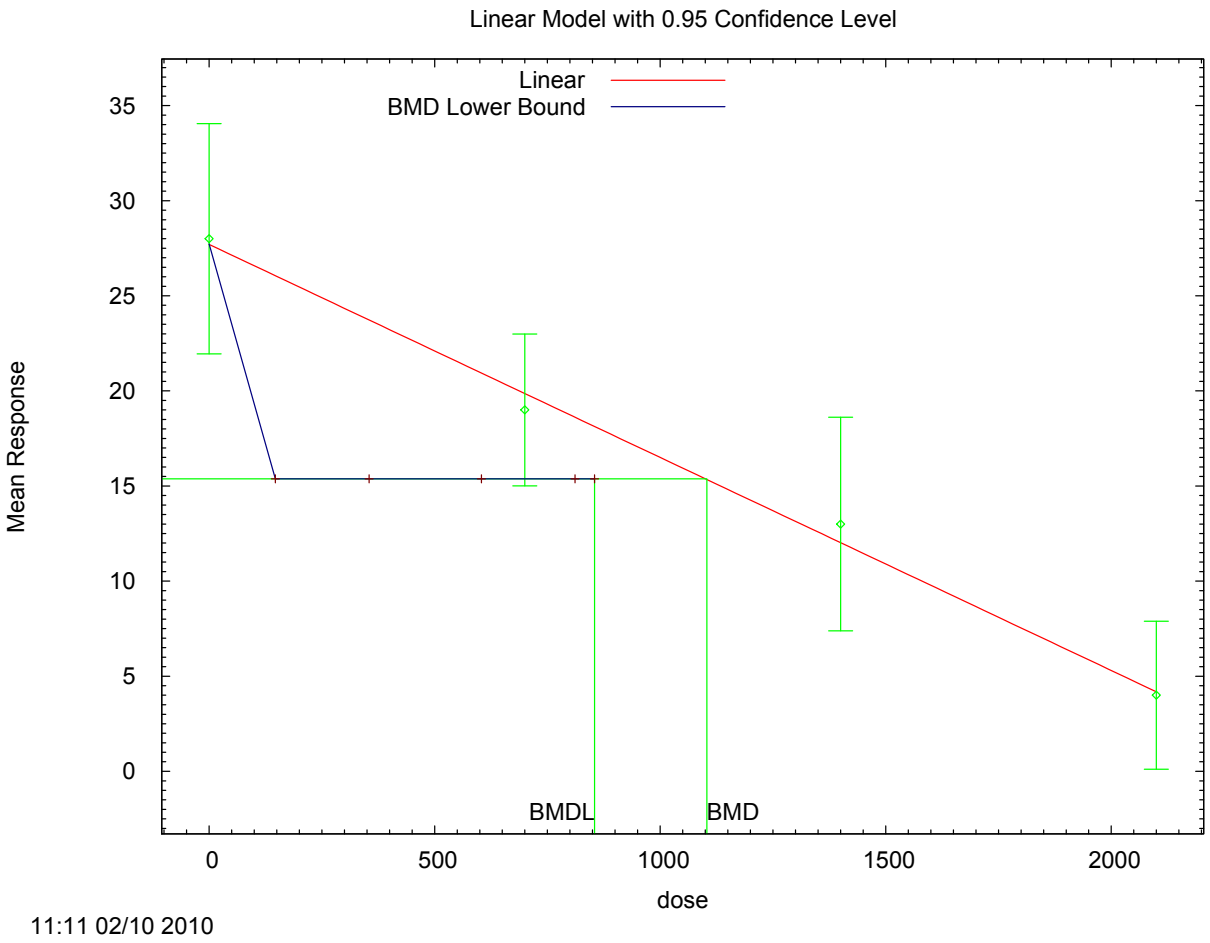
MODEL FITTING RESULTS FOR CORRECTED WEIGHT GAIN IN DAMS

All available continuous models in the BMDS (version 2.1.1) have been fit to the corrected weight gain in Sprague-Dawley dams treated with ethyl methacrylate via inhalation on Gestation Days (GDs) 6−20 (Saillenfait et al., 1999) (see Table B-1). BMD modeling has been performed using the calculated human equivalent concentrations (HECs). A BMR of 1 SD from the control mean was used in the BMD modeling. No adequate model fits were provided with constant and nonconstant variance. However, visual inspection of the dose-response curve suggested that the dose-response relationship is better characterized in the low-dose region. Thus, the highest dose was removed from the analysis for statistical and biological considerations. Again, no adequate model fits were provided with constant variance after removing the highest dose, but an adequate fit to the means was provided with nonconstant variance for all of the continuous models. The linear and power models were determined to be the best fitting models based on AIC, and the BMC_{1SDHEC} and $BMCL_{1SDHEC}$ are predicted to be 1103 and 854 mg/m^3, respectively (see Table B-1 and Figure B-1).

Table B-1. BMD Modeling Results Based on Corrected Body-Weight Gain (g) in Sprague-Dawley Dams Treated with Ethyl Methacrylate via Inhalation on GDs 6−20

Model	Test 2	Test 3	Goodness-of-Fit *p*-Value	AIC	BMC_{1SDHEC} (mg/m^3)	$BMCL_{1SDHEC}$ (mg/m^3)
All Doses						
Linear[a,b]	0.0048	0.0019	0.8248	654.098	1025.99	853.15
Polynomial[a,b]	0.0048	0.0019	0.7943	655.656	1172.92	866.05
Power[b,c]	0.0048	0.0021	<0.0001	650.347	1119.84	N/A
Hill[b,c]	0.0048	<0.0001	<0.0001	751.228	N/A	N/A
Four Doses (without the highest dose group)						
Linear[a,b]	**0.0855**	**0.1777**	**0.7208**	**514.559**	**1103.36**	**854.33**
Polynomial[a,b]	0.0855	0.1777	0.4184	516.559	1103.77	854.33
Power[b,c]	**0.0855**	**0.1777**	**0.7208**	**514.559**	**1103.36**	**854.33**
Hill[b,c]	0.0855	0.1777	0.4177	516.561	1092.27	846.36

[a]Restrict betas ≤ 0
[b]Nonconstant variance
[c]Restrict power ≥ 1



BMCs and BMCLs indicated are HECs associated with a change of 1 SD from the control and are in units of mg/m^3.

Figure B-1. Fit of Linear Model (Nonconstant Variance) to Data (Without the Highest Dose Group) on Corrected Weight Gain (g) in Sprague-Dawley Dams Treated with Ethyl Methacrylate via Inhalation on GDs 6−20

```
 ================================================================
        Linear Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\USEPA\BMDS21\Data\lin_Et_Meth_Weight_Gain_Lin-
ModelVariance-BMR1Std.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\lin_Et_Meth_Weight_Gain_Lin-
ModelVariance-BMR1Std.plt
                                              Wed Feb 10 11:11:02 2010
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   The polynomial coefficients are restricted to be negative
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                         lalpha =      4.83126
                            rho =            0
                         beta_0 =         27.7
                         beta_1 =   -0.0111429


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho       beta_0       beta_1

    lalpha            1        -0.96      -0.0084        0.014

       rho        -0.96            1       0.0085       -0.014

    beta_0      -0.0084       0.0085            1        -0.84

    beta_1        0.014       -0.014        -0.84            1


                                Parameter Estimates

                                                      95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
         lalpha          3.85113         0.546795             2.77943
4.92283
            rho         0.353818         0.205436          -0.0488302
0.756466
         beta_0          27.7234          2.09431             23.6186
31.8281
```

```
        beta_1       -0.0111892       0.00141385          -0.0139603         -
0.00841809


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    23         28         27.7           14         12.3          0.107
  700    22         19         19.9            9         11.6         -0.359
 1400    20         13         12.1           12         10.7          0.395
 2100    23          4         4.23            9         8.85         -0.122


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)}August10 = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1         -254.528637            5     519.057274
            A2         -251.224514            8     518.449028
            A3         -252.952258            6     517.904516
        fitted         -253.279623            4     514.559245
             R         -276.957118            2     557.914236


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              51.4652          6          <.0001
   Test 2              6.60825          3         0.08549
   Test 3              3.45549          2          0.1777
   Test 4             0.654729          2          0.7208

The p-value for Test 1 is less than .05.  There appears to be a
```

difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 1103.36

BMDL = 854.334

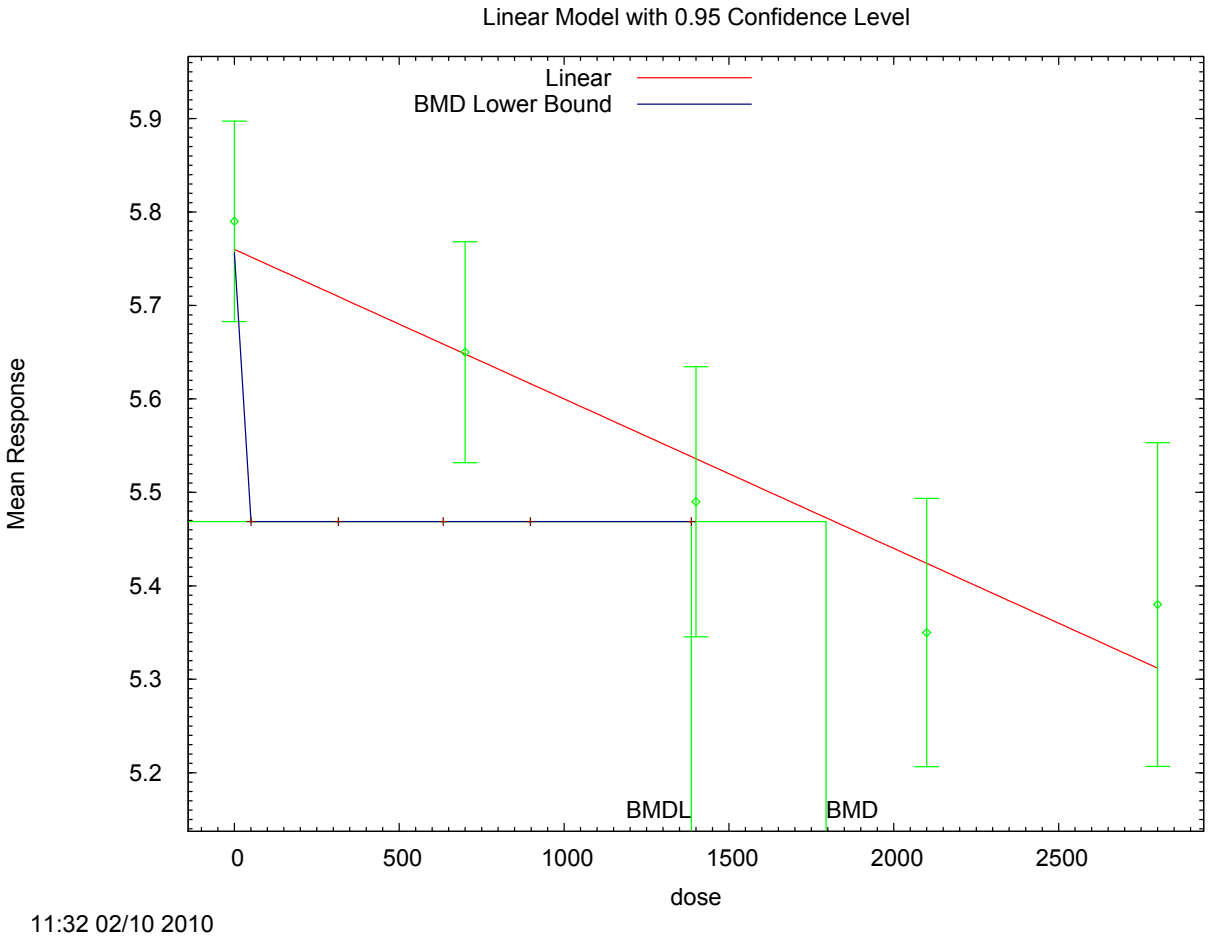
MODEL-FITTING RESULTS FOR AVERAGE FETAL BODY WEIGHT PER LITTER IN MALES

All available continuous models in the BMDS (version 2.1.1) have been fit to the average fetal body weight in male offspring of Sprague-Dawley dams (on a per-litter basis) treated with ethyl methacrylate via inhalation on GDs 6−20 (Saillenfait et al., 1999) (see Table B-1). BMD modeling has been performed using the calculated HECs. For this data set, a BMR of a 5% change from the control mean (relative deviation) was used. All of the continuous models provided an adequate fit to the means. The difference between the BMCLs from these models was less than 3-fold, so the best fitting model was determined using the AIC. The linear, polynomial, and power models all converged on the same result with the lowest AIC. Thus, the BMC_{05HEC} and $BMCL_{05HEC}$ are 1794 and 1386 mg/m^3, respectively (see Table B-2 and Figure B-2).

Table B-2. BMD Modeling Results Based on Changes in Average Fetal Body Weight (g) in Male Offspring of Sprague-Dawley Dams (on a Per-Litter Basis) Treated with Ethyl Methacrylate via Inhalation on GDs 6−20

Model	Test 2	Test 3	Goodness-of-Fit *p*-Value	AIC	BMC_{05HEC} (mg/m^3)	$BMCL_{05HEC}$ (mg/m^3)
Linear[a,b]	**0.1689**	**0.1689**	**0.3989**	**−143.243**	**1794.43**	**1385.69**
Polynomial[a,b]	**0.1689**	**0.1689**	**0.3989**	**−143.243**	**1794.43**	**1385.69**
Power[b,c]	**0.1689**	**0.1689**	**0.3989**	**−143.243**	**1794.43**	**1385.69**
Hill[b,c]	0.1689	0.1689	0.4463	−141.617	1251.34	725.78

[a]Restrict betas ≤ 0
[b]Constant variance
[c]Restrict power ≥ 1



BMCs and BMCLs indicated are HECs associated with a BMR of 5% change from the control (relative deviation) and are in units of mg/m^3.

Figure B-2. Fit of Linear Model (Constant Variance) to Data on Average Fetal Weight per Litter in Male Offspring of Dams Treated with Ethyl Methacrylate via Inhalation on GDs 6–20

```
 ================================================================
        Linear Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\USEPA\BMDS21\Data\lin_Et_Meth_Fetal_BW_Lin-
ConstantVariance-BMR05.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\lin_Et_Meth_Fetal_BW_Lin-
ConstantVariance-BMR05.plt
                                                Wed Feb 10 11:32:07 2010
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The polynomial coefficients are restricted to be negative
   A constant variance model is fit

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =     0.110177
                            rho =            0   Specified
                         beta_0 =        5.756
                         beta_1 =     -0.00016


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                    alpha       beta_0       beta_1

     alpha             1    -3.8e-011     2.9e-011

    beta_0    -3.8e-011            1        -0.81

    beta_1     2.9e-011        -0.81            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
          alpha          0.10825        0.0138601           0.0810853
0.135416
```

```
        beta_0          5.75649        0.0513143             5.65591
5.85706
        beta_1     -0.000160399      3.0092e-005        -0.000219378         -
0.00010142
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	25	5.79	5.76	0.26	0.329	0.509
700	24	5.65	5.64	0.28	0.329	0.0862
1400	25	5.49	5.53	0.35	0.329	-0.637
2100	24	5.35	5.42	0.34	0.329	-1.04
2800	24	5.38	5.31	0.41	0.329	1.08

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	76.098410	6	-140.196821
A2	79.316053	10	-138.632106
A3	76.098410	6	-140.196821
fitted	74.621747	3	-143.243495
R	61.850991	2	-119.701982

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	34.9301	8	<.0001
Test 2	6.43529	4	0.1689
Test 3	6.43529	4	0.1689

```
   Test 4              2.95333          3          0.3989

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


             Benchmark Dose Computation

Specified effect =          0.05

Risk Type        =     Relative risk

Confidence level =          0.95

             BMD =        1794.43


            BMDL =        1385.69
```