FINAL
6-28-2010

Provisional Peer-Reviewed Toxicity Values for

1,2,3-Trimethylbenzene
(CASRN 526-73-8)

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:

Jason Lambert, National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY:

Syracuse Research Corporation
7502 Round Pond Road
North Syracuse, NY 13212

INTERNAL REVIEW PANEL:

National Center for Environmental Assessment, Cincinnati, OH
Dan Petersen
Jay Zhao
Jon Reid

National Center for Environmental Assessment, Research Triangle Park, NC
Anu Mudipalli
Geniece Lehmann
Nicole Hagan
Paul Reinhart

National Center for Environmental Assessment, Washington, D.C.
Audrey Galizia
Martin Gehlhaus
Sanjivani Diwan
Susan Makris

This document was externally peer-reviewed under contract to:
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)

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
IRIS	Integrated Risk Information System
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 (oral)
RfC	reference concentration (inhalation)
RfD	reference dose
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 1,2,3-TRIMETHYLBENZENE (CASRN 526-73-8)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) 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 (PPRTV) 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 Integrated Risk Information System (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 two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program 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 five-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 manuscripts 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 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 manuscript 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 carcinogenicity assessment for 1,2,3-trimethylbenzene (hemimellitene or 1,2,3-TMB) is available on IRIS (U.S. EPA, 2008). The HEAST (U.S. EPA, 1997) states that data were inadequate for quantitative risk assessment for trimethylbenzenes and are based on a Health and Environmental Assessment (HEA) for Trimethylbenzenes (U.S. EPA, 1987). The Drinking Water Standards and Health Advisories list (U.S. EPA, 2006) does not include 1,2,3-trimethylbenzene. The Chemical Assessments and Related Activities record (CARA; U.S. EPA, 1991, 1994a) lists only the previously mentioned HEA (U.S. EPA, 1987). ATSDR (2008) has not produced a Toxicological Profile for 1,2,3-trimethylbenzene, and no Environmental Health Criteria Document is available from the World Health Organization (WHO, 2008). The carcinogenicity of 1,2,3-TMB has not been assessed by the International Agency for Research on Cancer (IARC, 2008) or the National Toxicology Program (NTP, 2005, 2008). The Occupational Safety and Health Administration (OSHA, 2008) has not established a permissible exposure limit (PEL) for 1,2,3-TMB. The National Institute for Occupational Safety and Health (NIOSH, 2008) has set a recommended exposure limit (REL) of 25 ppm (125 mg/m^3) for 1,2,3-TMB based on central nervous system (CNS) effects, irritation, and anemia, and the American Conference of Governmental Industrial Hygienists (ACGIH, 2001, 2007) recommends a threshold limit value (TLV) of 25 ppm for mixed isomers of trimethylbenzene based on the same endpoints. CalEPA (2002, 2005, 2008) has not derived a recommended exposure limit (REL) or a cancer potency factor for 1,2,3-TMB.

Literature searches were conducted from the 1960s through December 2007 for studies relevant to the derivation of provisional toxicity values for 1,2,3-TMB. Databases searched include MEDLINE, TOXLINE (Special), BIOSIS, TSCATS 1/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents. An updated literature search was conducted from January, 2008, through September, 2009, in MEDLINE. Reviews by Delic et al. (1992) and Henderson (2001) were also examined for studies that might inform hazard identification and/or dose-response assessment for 1,2,3-TMB.

REVIEW OF PERTINENT DATA

Human Studies

Oral Exposure

No information was located regarding the oral toxicity of 1,2,3-TMB in humans.

Inhalation Exposure

A single study was located regarding inhalation exposure of humans to 1,2,3-TMB. Jarnberg et al. (1996) studied healthy human volunteers exposed to 1,2,3-TMB in an exposure chamber. Caucasian males (n = 10; average age of 35 years, average weight of 76.5 kg, not occupationally exposed to solvents) were exposed on four separate occasions for 2 hours to 1,2,3-TMB (90–95% purity) at an air concentration of 25 ppm (123 mg/m^3) while pedaling an ergometer bicycle at 50 watts (light physical work). There was an interval of at least 2 weeks between successive exposures. Although the study was focused on the uptake and distribution of 1,2,3-TMB and other trimethylbenzene isomers, the study authors also evaluated irritation and CNS-related symptoms using a questionnaire. The subjects rated symptoms before, during, and after exposure using a 100-mm analog scale ranging from "not at all" to "almost unbearable." No irritation of the eyes, nose, throat, or airways, no CNS-related symptoms (headache, fatigue, nausea, dizziness, intoxication), and no difficulty in breathing were reported by the volunteers. The toxicokinetic data indicated a respiratory uptake of ~56%, moderately rapid elimination (~0.63 L/hr-kg, total blood clearance), a large volume of distribution (~30 L/kg), and long terminal half-life in blood (~78 hr); the study authors indicated that the large volume of distribution and long terminal blood half-life implied a significant accumulation of 1,2,3-TMB in adipose tissue (Jarnberg et al., 1996). Approximately 37% of the total clearance of 1,2,3-TMB was through exhalation. Based on a lack of subjectively reported eye and respiratory tract irritation, and of CNS-related symptoms, the NOAEL for this acute, intermittent-exposure study in humans is 123 mg/m^3. Because this was the only exposure level tested, a LOAEL cannot be determined.

Animal Studies

Oral Exposure

No information was located regarding the oral toxicity of repeated doses of 1,2,3-TMB in animals. Tomas et al. (1999) evaluated locomotor activity in rats (10 males/group) exposed to 1,2,3-TMB (90–95% pure in olive oil) via single gavage doses of 0.002–0.032 mol/kg body weight (240–3850 mg/kg). Locomotor activity, assessed as the number of times the rats crossed square borders in a cage marked with eight equally sized squares, was evaluated in 10-minute intervals before and up to 70 minutes after exposure. Exposure to 1,2,3-TMB was associated with a statistically significant ($p < 0.05$) increase in locomotor activity at the highest dose, which was also a frank-effect level for mortality (4/10), and significant clinical signs (disturbed gait, paresis of hind limbs, tachypnea, tremor, piloerection, and secretion of bloody discharge from the respiratory tract) observed at this dose. The study authors did not indicate whether problems with gavage administration contributed to the clinical signs or mortality. In a similar acute-exposure study, Tomas et al. (2000) evaluated alterations in electrocortical arousal in WAG/Rij rats (6 males/group) exposed to 1,2,3-TMB (90–95% pure in olive oil) via single gavage doses of 0.002–0.032 mol/kg body weight (240–3850 mg/kg). Rats of each dose group were implanted with electrodes bilaterally in the frontoparietal cortex. Electrocortical arousal, assessed as changes in the high-voltage spindle (HVS) activity of the brain, was recorded 20 minutes before

and 20, 40, and 60 minutes after exposure. Exposure to 1,2,3-TMB was associated with a statistically significant ($p < 0.001$) inhibition of HVS activity (i.e., electrocortical function) at all doses tested, with the most pronounced effect occurring in the mid-dose (0.008 mol/kg body weight; 962 mg/kg) group. An acute LOAEL of 240 mg/kg is identified from this single exposure study based upon decreased electrocortical activity in male WAG/Rij rats. An acute NOAEL cannot be determined as the lowest oral dose tested produced a significant effect compared to controls.

Inhalation Exposure

No chronic inhalation animal studies were located for 1,2,3-TMB.

Korsak et al. (2000) studied the effects of subchronic exposure to 1,2,3-TMB (>97% purity) in male and female outbred Imp:WISTAR rats. Animals (10/sex/group; 20/sex in high-dose group) were exposed in a dynamic inhalation chamber to nominal concentrations of 0 ppm (sham control), 25 ppm (123 mg/m^3), 100 ppm (492 mg/m^3), or 250 ppm (1230 mg/m^3), 6 hours/day, 5 days/week for 3 months. Concentrations in the exposure chamber were measured every 30 minutes using a gas chromatograph with a flame-ionization detector. Actual measured concentrations in the treatment groups were 128 ± 10, 523 ± 38, or 1269 ± 36 mg/m^3. Male and female rats of the 1230-mg/m^3 group were observed for 1 month after termination of exposure. Animals were observed twice a day for overt signs of toxicity. Body weights were recorded prior to the first inhalation exposure and weekly thereafter during the exposure period. Food consumption was measured weekly. One week prior to study termination (and 2 weeks after the end of exposure in the 1230 mg/m^3 recovery group), blood was collected from the tail and analyzed for erythrocyte, leukocyte, and platelet counts, hemoglobin concentration, hematocrit, and clotting time. Clinical laboratory studies were conducted 18 hours after termination of exposure, when rats were exsanguinated and blood samples processed for comprehensive serum chemistry determinations (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, sorbitol dehydrogenase, gamma glutamyltransferase, bilirubin, total cholesterol, glucose, total protein, albumin, creatinine, urea, and electrolytes [calcium, phosphorous, sodium, potassium, and chloride]). All rats were subjected to gross necropsy. Organ weights were determined for the lungs, liver, spleen, kidneys, adrenals, heart, and gonads. The following organs were examined for histopathology: brain, nose, larynx, trachea, thymus, lungs, heart, liver, spleen, kidney, adrenals, thyroid gland, pancreas, gonads, urinary bladder, stomach, duodenum, small and large intestines, and salivary glands. Changes in the lungs reflecting the degree of proliferation of peribronchial lymphatic tissue, lymphoepithelium in bronchial mucosa, interstitial lymphocytic infiltration, macrophage infiltration, and inflammatory processes were graded using an arbitrary scale of 0–3 or 0–4 (0 = normal, 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked).

The study authors did not observe mortality during the course of the study (Korsak et al., 2000). No clinical observations of toxicological relevance were observed. Compared with controls, there were no significant differences in body-weight gain or in food consumption (data not shown). Statistically significant changes in hematological parameters included an increase in percent reticulocytes, decrease in percent segmented neutrophils, decrease in red blood cell counts, and an increase in percent lymphocytes (trend analyses for all indicated $p < 0.05$). A statistically significant increase in percent reticulocytes was seen in females at study termination at 123 mg/m^3 (77%, $p < 0.05$) and 492 mg/m^3 (100%, $p < 0.01$), and at 14 days postexposure at 1230 mg/m^3 (162%, $p < 0.01$), compared to controls. An increase was also observed at study

termination at 1230 mg/m^3, but the difference was not statistically significant and the response was less than that seen at the lower treatment concentrations. A significant increase in percent reticulocytes was observed in males in the 1230 mg/m^3 group at study termination (61%, $p < 0.05$) and 14 days postexposure (146%, $p < 0.01$). A significant decrease in percent segmented neutrophils was observed in females at study termination at 492 mg/m^3 (29%, $p < 0.05$) and 1230 mg/m^3 (48%, $p < 0.01$), and in males at study termination at 1230 mg/m^3 only (29%, $p < 0.05$). Other significant hematological changes, observed only at 1230 mg/m^3 at study termination, were a decreased red blood cell count in males (15%, $p < 0.05$) and an increase in percent lymphocytes in both males (11%, $p < 0.01$) and females (15%, $p < 0.01$).

Statistically significant changes in clinical chemistry included increased alkaline phosphatase activity, increased sorbitol dehydrogenase activity, and decreased alanine aminotransferase activity (Korsak et al., 2000); only sorbitol dehydrogenase activity exhibited a significant trend with 1,2,3-TMB concentration ($p < 0.05$). A significant increase in alkaline phosphatase activity was reported for females at study termination at 492 mg/m^3 (46%, $p < 0.05$) and 1230 mg/m^3 (42%, $p < 0.05$). Females also showed a significant decrease in alanine aminotransferase activity at study termination at 1230 mg/m^3 (23%, $p < 0.05$) only. Males showed a significant increase in sorbitol dehydrogenase activity at study termination at 1230 mg/m^3 (69%, $p < 0.05$) only. The study authors reported a significant increase in relative liver weight in males at study termination at 1230 mg/m^3 (9.3%, $p < 0.05$); absolute liver weight was not significantly increased. A significant decrease in absolute spleen weight was observed in females at study termination at 492 mg/m^3 (9.5%, $p < 0.05$) and 1230 mg/m^3 (11%, $p < 0.05$), but relative spleen weight was not affected at any exposure. Table 1 summarizes the effects of inhaled 1,2,3-TMB on hematology, clinical chemistry, and organ weights (Korsak et al., 2000).

Concentration-related histopathological changes were observed in the lower respiratory tract (Korsak et al., 2000). A significant increase in the number of goblet cells was noted in the bronchi of female rats at 492 mg/m^3 ($p < 0.05$) and 1230 mg/m^3 ($p < 0.01$); a trend analysis indicated significance at $p = 0.001$. At 1230 mg/m^3, there was a significant increase in the intensity of lung perivascular and interstitial infiltration in males ($p < 0.01$); trend analysis significance at $p = 0.006$. Data were reported in terms of the mean severity scores; incidences of the lesions were not reported. Table 2 summarizes the observed pulmonary lesions. No histopathological findings were reported for any other organs or tissues examined.

Table 1. Effects on Hematology, Clinical Chemistry, and Organ Weights in Rats Exposed to 1,2,3-Trimethylbenzene Through Inhalation for 3 Months[a]

	Control 0 mg/m^3 (n = 10)	123 mg/m^3 (n = 10)	492 mg/m^3 (n = 10)	1230 mg/m^3 (n = 10)	1230 mg/m^3 (14 Days Postexposure) (n = 10)	Trend Analysis
Males (mean ± SD)						
Hematology						
Red blood cell count ($\times 10^6$/mm^3)	9.49 ± 2.03	10.25 ± 1.29	10.11 ± 1.27	8.05 ± 1.38[b]	8.6 ± 1.5	p = 0.0011
Segmented neutrophil (%)	24.8 ± 4.5	25.4 ± 5.8	20.7 ± 5.8	17.7 ± 8.3[b]	27.5 ± 9.2	p = 0.0032
Lymphocyte (%)	71.2 ± 5.0	71.6 ± 6.8	75.4 ± 4.7	79.3 ± 78.0[c]	63.7 ± 11.3	p = 0.0015
Reticulocyte (%)	2.8 ± 1.3	2.1 ± 1.7	3.8 ± 2.1	4.5 ± 1.8[b]	6.9 ± 3.1[c]	p = 0.0017
Clinical Chemistry						
Sorbitol dehydrogenase (U/dL)	1.6 ± 0.7	2.3 ± 1.3	2.5 ± 0.9	2.7 ± 0.7[b]	ND	p = 0.0083
Relative Organ Weight						
Liver	2.208 ± 0.163	2.271 ± 0.129	2.287 ± 0.115	2.414 ± 0.214[b]	ND	p = 0.0117
Females (mean ± SD)						
Hematology						
Segmented neutrophil (%)	23.1 ± 6.1	19.7 ± 3.4	16.4 ± 4.2[b]	11.9 ± 7.1[c]	19.6 ± 8.3	p = 0.0000
Lymphocyte (%)	73.2 ± 7.9	77.5 ± 4.9	80.4 ± 5.1	84.0 ± 78.0[c]	75.7 ± 9.9	p = 0.0003
Reticulocyte (%)	2.6 ± 0.9	4.6 ± 2.5[b]	5.2 ± 0.5[c]	4.4 ± 3.0	6.8 ± 3.5[c]	p = 0.0459
Clinical Chemistry						
Alanine aminotransferase (U/dL)	39.7 ± 3.5	39.5 ± 6.4	36.2 ± 3.3	30.5 ± 9.9[b]	ND	p = 0.1844
Alkaline phosphatase (U/dL)	21.5 ± 2.7	25.8 ± 8.4	31.1 ± 8.6[b]	30.5 ± 9.9[c]	ND	p = 0.1740
Absolute Organ Weight (g)						
Spleen	0.63 ± 0.05	0.61 ± 0.10	0.57 ± 0.05[b]	0.56 ± 0.06[b]	ND	p = 0.0042

[a]Korsak et al., 2000; Tables 1, 2, and 3
[b]$p < 0.05$
[c]$p < 0.01$

ND = Not Determined

Table 2. Pulmonary Lesions (Mean Severity Scores) in Rats Exposed to 1,2,3-Trimethylbenzene Through Inhalation for 3 Months[a]

Change	Control 0 mg/m^3 (n = 10)	123 mg/m^3 (n = 10)	492 mg/m^3 (n = 10)	1230 mg/m^3 (n = 10)	Trend Analysis
Males (mean of 0–3 grading system)					
Interstitial lymphocytic infiltrations	0.4	0.1	0.4	1.5[b,c]	$p = 0.006$
Females (mean of 0–3 grading system)					
Goblet cells	1.3	1.6	2.0[b]	2.4[d]	$p = 0.001$

[a]Korsak et al., 2000, Table 4
[b]$p < 0.05$
[c]Although Table 4 indicated $p < 0.05$, the text indicated $p < 0.01$
[d]$p < 0.01$

The study authors suggested that the signs of anemia (increased percent reticulocytes, decreased red blood cell counts) and increased sorbitol dehydrogenase activity could be associated with hepatotoxic effects (Korsak et al., 2000). Furthermore, a significant increase in relative liver weight was observed in the livers of male rats at the high dose; however, the study authors noted that histological examination of the liver tissue did not show any treatment-related changes in either sex at any 1,2,3-TMB exposure concentration. The study authors, therefore, postulated that the anemia, the increases in white blood cells, and the increase in alkaline phosphatase activity were more likely the result of inflammation in the respiratory tract (indicated by the pulmonary lesions). Although a statistically significant increase in percentage of reticulocytes was seen at the lowest exposure level of 123 mg/m^3, this change is not considered biologically-significant in the absence of related organ/tissue effects at this concentration. Therefore, based on pathological changes in the lower respiratory tract (i.e., an increased number of goblet cells in females), the LOAEL for this subchronic study is 492 mg/m^3; hematologic and clinical chemistry changes were also observed in females exposed to this concentration. The NOAEL is 123 mg/m^3.

Korsak and Rydzynski (1996) examined the neurobehavioral effects of subchronic exposure to 1,2,3-TMB (90–95% purity) in male Wistar rats of IMP:DAK outbred stock. Animals were exposed at concentrations of 0 ppm (sham control), 25 ppm (123 mg/m^3), 100 ppm (492 mg/m^3), or 250 ppm (1230 mg/m^3) in a dynamic inhalation chamber for 6 hours/day, 5 days/week, for 3 months. Animals in the 1230 mg/m^3 group were observed and tested for 2 weeks following exposure termination. Concentrations in the inhalation chamber were measured every 30 minutes using a gas chromatograph with a flame-ionization detector. Animals were observed for clinical signs during the course of the study. Body weights were measured at the beginning and end of the study. Food and water consumption were not measured. Rotarod performance was tested on each group (10/group) prior to the start of the study, weekly during the experiment and 2 weeks following exposure termination (1230-mg/m^3 group only). Rotarod performance, an index of neuromuscular function, tested the ability of the rats to remain on a rotating rod for 2 minutes. Hot-plate behavior was tested in all groups immediately following termination of exposure and 2 weeks after exposure (high-concentration

group only). Hot-plate behavior, a measure of pain sensitivity (analgesia), recorded the latency of the paw-lick response following the placement of the rat on a hot plate.

The study authors reported no mortalities during the study (Korsak and Rydzynski, 1996). No remarkable clinical signs or significant changes in final body weights were observed in any group (data not shown). Exposure to 1,2,3-TMB was associated with time- and dose-dependent decreases in both rotarod performance and pain sensitivity. The rotarod data were reported graphically; only the results for the testing conducted at study initiation, 4 and 8 weeks following study initiation, exposure termination, and 2 weeks following exposure termination were presented. Changes in rotarod performance (increased percent of failures compared with the control) were reported to be statistically significant ($p < 0.005$) in the 492 mg/m^3 group at study termination, and in the 1230 mg/m^3 group at 4 and 8 weeks following study initiation, at exposure termination, and 2 weeks following exposure termination. The study authors observed no statistically significant changes in rotarod performance in the 123 mg/m^3 group. The hot-plate behavior data were reported in tabular form. Changes in hot-plate behavior (increased latency of the paw-lick response compared with the control) were reported to be statistically significant ($p < 0.05$) at study termination in all treatment groups. The mean latency of the paw-lick response, when compared with the control group, was increased by 22%, 68%, and 78% in the 123-, 492-, and 1230-mg/m^3 groups, respectively. Partial recovery in behavior (13% increase in latency compared with the control) was observed 2 weeks after cessation of exposure. Table 3 presents the data for the hot-plate behavior test. Based on an increased latency of the paw-lick response, the study identifies a subchronic LOAEL of 123 mg/m^3 for neurobehavioral impairment. Because the LOAEL was the lowest inhalation exposure concentration tested, a NOAEL cannot be determined for the study.

Table 3. Effects of a 3-Month Inhalation Exposure to 1,2,3-Trimethylbenzene on the Latency of the Paw-Lick Response (Hot-Plate Behavior) in Rats[a]

Group	Number of Animals (n)	Latency of the Paw-Lick Response (seconds, mean ± SD)[b]
Control (0 mg/m^3)	30	9.7 ± 2.1
123 mg/m^3	20	11.8 ± 3.8[b]
492 mg/m^3	10	16.3 ± 6.3[c]
1230 mg/m^3	10	17.3 ± 3.4[d]
1230 mg/m^3 (2 weeks after exposure termination)	10	11.0 ± 2.4

[a]Korsak and Rydzynski, 1996, Table 1
[b]$p \leq 0.05$
[c]Although the text of the original study reported that the results were statistically significant at all exposure concentrations, Table 1 of the paper did not indicate significance at 492 mg/m^3; this may have been a typographical error. The results of an ad-hoc Kruskal-Wallis test performed for this review indicated $p < 0.01$.
[d]$p \leq 0.01$

Neurobehavioral effects were studied in male Wistar rats exposed to 1,2,3-TMB (purity not reported) in a dynamic inhalation chamber at concentrations of 0 ppm (sham control, $n = 13$), 25 ppm (123 mg/m^3, $n = 13$), 100 ppm (492 mg/m^3, $n = 14$), or 250 ppm (1230 mg/m^3, $n = 13$) 6 hours/day, 5 days/week for 4 weeks (Wiaderna et al., 1998). Air samples from the inhalation chambers were collected at 30-minute intervals and analyzed using a gas chromatograph with a flame-ionization detector. Body weights were determined at the onset of exposure, weekly during exposure, and every 2 weeks up to 60 days following the last exposure. The study authors did not measure food and water consumption, but they did conduct the following neurobehavioral battery of tests, primarily during the postexposure period: (1) radial maze (test of spatial working memory, conducted 1 week preexposure and 14–18 days postexposure), (2) open-field activity (test of spontaneous activity, conducted 25 days postexposure), (3) passive avoidance (test of long-term memory, and learning ability, conducted 39–48 days postexposure), (4) hot-plate test (test of sensitivity to pain, conducted 50 and 51 days postexposure), and (5) conditioned active avoidance reaction (test of long-term memory and learning ability, conducted 54 and 60 days postexposure).

No mortalities were noted by the study authors (Wiaderna et al., 1998). There were no treatment-related effects on body weight at any test concentration (data not shown). Data for the behavioral tests were shown graphically. Compared with the control group, significant effects of 1,2,3-TMB exposure were noted for the passive avoidance test (reduced ability to withhold a locomotor response, i.e., stepping down) in the 123 mg/m^3 group during Trial 4 ($p < 0.05$), Trial 5 ($p < 0.05$), and Trial 6 ($p < 0.001$) and in the 492 mg/m^3 group during Trial 6 ($p < 0.001$). There were no significant differences noted for the high-dose (1230 mg/m^3) group. In the active avoidance test (impaired acquisition of avoiding an unconditioned stimulus, i.e., footshocks, after the presentation of a conditioned stimulus, i.e., pulsing tone), when compared with the control group, a significant difference was noted during training in the 492 mg/m^3 group ($p < 0.05$)—but not in the 123 mg/m^3 or 1230 mg/m^3 groups. The study authors observed no significant differences from control in any treatment group during retraining or retention testing. Significant differences between the treatment and control groups were not reported for the hot-plate test. No significant differences between the treatment and control groups for the radial maze performance and open-field activity tests were noted by the study authors. Based on impairment of the passive avoidance response, the study identifies a subchronic LOAEL of 123 mg/m^3 for neurobehavioral impairment. Because the LOAEL was the lowest exposure concentration tested, a NOAEL cannot be determined.

Neurobehavioral effects were studied in male Wistar rats (10–11/treatment group) that were exposed to 0 or 100 ppm (492 mg/m^3) of 1,2,3-TMB (purity not reported) 6 hours/day, 5 days/week for 4 weeks in whole-body dynamic inhalation chambers (Gralewicz and Wiaderna, 2001). Air samples from the inhalation chambers were collected for analysis 20 minutes after exposure onset and at 30-minute intervals thereafter, and analyzed using a gas chromatograph with a flame-ionization detector. The purpose of the study was to compare the effects of *m*-xylene to the effects of each of the trimethylbenzene isomers (1,2,3-, 1,2,4-, and 1,3,5-). The tests conducted were the same as those used in a previous study using 1,2,3-TMB (Wiaderna et al., 1998) and were performed on the same schedule. No mortalities were reported. Body-weight gain was not affected by exposure to 1,2,3-TMB (data not shown). The data for the behavioral tests are shown graphically. In the active avoidance test, 1,2,3-TMB caused a statistically significant ($p < 0.05$) impairment of acquisition—but not retention—of the two-way active avoidance response (i.e., increase in number of trials to the avoidance criterion). The

mean number of trials to criterion during training was significantly higher than the control in all solvent-exposed groups—but was lowest in the 1,2,3-TMB group; the differences between solvent-exposed groups were not statistically significant. There were no statistically significant differences between groups during retraining (data not shown). No statistically significant differences between the 1,2,3-TMB and control groups were found for any of the other behavioral tests; some differences were noted between the 1,2,3-TMB group and the other isomer groups. These results were inconsistent with those of Wiaderna et al. (1998), which indicated significant differences in both the active and passive avoidance tests at the 492 mg/m^3 exposure level. Gralewicz and Wiaderna (2001) suggested that the discrepancies between the results for the two studies may have been due to different sensitivities in the rat population or to "undetected differences in other experimental variables." Based on the impairment of acquisition in the active avoidance response test, the study identified a subchronic LOAEL of 492 mg/m^3 for neurobehavioral impairment. Because this was the only exposure concentration tested, a subchronic NOAEL could not be determined.

Other Studies

Acute Studies

Korsak and Rydzynski (1996) examined the neurobehavioral effects of acute-exposure to 1,2,3-TMB (90–95% purity) in male Wistar rats of IMP:DAK outbred stock. Animals were exposed in a dynamic inhalation chamber at concentrations of 0 ppm (sham control) or 250–2000 ppm (1230–9840 mg/m^3) for 4 hours (10/dose group). Rotarod performance and hot-plate behavior were tested on each group as described above for the subchronic study conducted by Korsak and Rydzynski (1996). No mortalities were noted by the study authors. Acute-exposure caused concentration-related decreases in rotarod performance and pain sensitivity. The acute EC_{50} (median effective concentration) for impaired rotarod performance was calculated to be 768 ppm (3779 mg/m^3), with 95% confidence intervals of 578–942 ppm (2832–4615 mg/m^3). The acute EC_{50} for the hot-plate test (concentration that increased the latency of the paw-lick response to 50% over control) was calculated to be 848 ppm (4155 mg/m^3), with 95% confidence intervals of 694–982 ppm (3400–4811 mg/m^3).

Respiratory irritation resulting from acute-exposure to 1,2,3-TMB (90–95% purity) was investigated in male Balb/c mice (Korsak et al., 1997). Animals (8–10/group) were exposed in dynamic inhalation chambers at 266 ppm (1309 mg/m^3), 511 ppm (2514 mg/m^3), 842 ppm (4143 mg /m^3), or 1591 ppm (7828 mg/m^3) for 6 minutes. The respiratory rate, measured by the whole-body plethysmographic method, was recorded continuously 10 minutes before the exposure, during 6 minutes of exposure, and 6 minutes after termination of exposure. No mortalities were reported. The maximum decrease in respiratory rate at each exposure concentration, observed in the second minute of exposure, was used for the calculation of an RD_{50} (concentration depressing the respiratory rate to 50% of control). The RD_{50} was calculated to be 2662 mg/m^3 (95% confidence intervals of 1343–4074 mg/m^3). During the 6-minute period following termination of exposure, the respiratory rate for the 1309 and 2514 mg/m^3 exposure groups recovered to approximately 80% of the control; the respiratory rate for the 4143-mg/m^3 and 7828-mg/m^3 exposure groups recovered to close to 100% of the control.

Genotoxicity

Genotoxicity of 1,2,3-TMB was evaluated in vitro and in vivo by Janik-Spiechowicz et al. (1998). Mutagenicity was tested in a standard Ames assay using the *S. typhimurium* strains TA97a, TA98, TA100, and TA102 in the presence or absence of rat

S9 cytosolic protein fraction. 1,2,3-TMB exhibited characteristics of a direct-acting mutagen as the mutation frequency was significantly elevated in at least one or more exposure groups for each tester strain in the absence of metabolic activation. 1,2,3-TMB was also evaluated in a micronucleus assay and sister chromatid exchange (SCE) assay in bone marrow cells from male and female Imp:Balb/c mice exposed by intraperitoneal injection. 1,2,3-TMB was negative for a micronucleus response in polychromatic erythrocytes of the bone marrow of male mice exposed to doses of 1468 or 2936 or mg/kg, or female mice exposed to 2160 mg/kg. 1,2,3-TMB did, however, exhibit clastogenic potential, as a statistically significant dose-dependent increase in SCE frequency was observed at all doses tested (730, 1470, and 2200 mg/kg).

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 1,2,3-TRIMETHYLBENZENE

There were no oral studies on which to base the derivation of oral p-RfDs for 1,2,3-TMB.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 1,2,3-TRIMETHYLBENZENE

A review of the existing literature failed to identify any chronic duration human or animal studies evaluating inhalation exposure to 1,2,3-TMB. Dose-response data addressing the toxicological effects of inhalation exposure to 1,2,3-TMB include the results of one intermittent-exposure study in humans (Jarnberg et al., 1996), two acute-exposure studies in animals (Korsak and Rydzynski, 1996; Korsak et al., 1997), and four subchronic duration animal studies (Korsak et al., 2000; Korsak and Rydzynski,1996; Wiaderna et al., 1998; Gralewicz and Wiaderna, 2001). Of the available studies, only the data from the four subchronic animal studies are relevant to the derivation of p-RfC values for 1,2,3-TMB. The durations of exposure in the human study (four 2-hour exposures at a minimum of 2-week intervals) and acute animal studies (single exposures of 4 hours or 6 minutes) do not inform the derivation of either subchronic or chronic p-RfC values.

Subchronic p-RfC

Of the subchronic studies, all conducted in rats, one (Korsak et al., 2000) was a comprehensive systemic study that evaluated body weight, hematological parameters, clinical chemistry, organ weights, gross necropsy, and histopathology. The other three studies assessed neurobehavioral effects using performance testing (Korsak and Rydzynski, 1996; Wiarderna et al., 1998; Gralewicz and Wiaderna, 2001).

In the comprehensive subchronic toxicity study (Korsak et al., 2000), a LOAEL of 492 mg/m^3 is identified based on an increase in goblet cells in the bronchi of female rats; the NOAEL is identified to be 123 mg/m^3. No formal assessment of neurobehavioral function was included in the Korsak et al. (2000) study. Conversely, no other available repeated exposure inhalation studies of 1,2,3-TMB evaluated endpoints beyond neurological function. In one of the neurobehavioral studies, Korsak and Rydzynski (1996) exposed rats to 0, 123, 492, or 1230 mg/m^3 1,2,3-TMB for 6 hours/day, 5 days/week, for 3 months. Wiaderna et al. (1998) exposed rats to the same inhalation concentrations on the same exposure schedule for 4 weeks.

A LOAEL of 123 mg/m^3 is identified for each of these studies based on neurobehavioral impairment; NOAELs could not be determined. Korsak and Rydzynski (1996) reported a statistically significant decrease in pain sensitivity, manifested as an increased latency in paw-lick response in the hot-plate test, at all treatment concentrations, and disturbances in rotarod performance at 492 and 1230 mg/m^3. Wiaderna et al. (1998) also performed a hot-plate test, however, in contrast to the results for the Korsak and Rydzynski (1996) study, there were no statistically significant differences between the treatment and control groups. In addition, data for the hot-plate test in the Korsak and Rydzynski (1996) study were linear, whereas neurobehavioral changes observed in the Wiaderna et al. (1998) study exhibited a nonlinear (inverted U-shaped) relationship to exposure. The differences in results for the two hot-plate tests in these studies may be due, at least in part, to the differences in duration of exposure, 3 months vs. 4 weeks, and the time of testing, immediately following exposure vs. 50–51 days postexposure, for the Korsak and Rydzynski (1996) and Wiaderna et al. (1998) studies, respectively. In the Wiarderna et al. (1998) study, statistically significant impairments in performance were also observed in the passive avoidance test at 123 and 492 mg/m^3—but not at 1230 mg/m^3—and in the active avoidance test at 492 mg/m^3—but not at 123 or 1230 mg/m^3. Due to the uncertain dose-response characteristics of the neurobehavorial effects observed in rats of the Wiaderna et al. (1998) study, this study was not further considered in the derivation of a p-RfC.

Decreased pain sensitivity in rats, as reported in the Korsak and Rydzynski (1996) study, was chosen as the critical effect as it provided the lowest effect level (LOAEL = 123 mg/m^3) from a positively correlated concentration-response for inhaled 1,2,3-TMB. The results of the hot-plate test, which were presented quantitatively in tabular form, showed a concentration-dependent and statistically-significant effect on neurobehavioral performance at exposure concentrations of 123, 492, and 1230 mg/m^3. Table 3 summarizes these data. The pain sensitivity data (i.e., latency in paw-lick response) for rats from the Korsak and Rydzynski (1996) study was evaluated to determine suitability for benchmark dose (BMD) modeling. Appendix A provides details of the BMD modeling and results. The recommended Benchmark Response (BMR) of 1 standard deviation (SD) from the control mean (U.S. EPA, 2000) was used in the absence of a biologically based benchmark response level for this neurobehavioral endpoint. No model fit was achieved with all of the exposure groups. However, adequate fit was achieved when the highest-exposure group was dropped from the analysis. For the reduced data set, the nonhomogenous variance model in the software provided adequate fit to the variance data, and the linear model provided adequate fit to the means. The benchmark concentration (BMC_{1SD}) and the 95% lower confidence limit ($BMCL_{1SD}$) resulting from this model were 152 and 97 mg/m^3 (unadjusted concentrations), respectively.

The rat $BMCL_{1SD}$ of 97 mg/m^3 was converted to a human equivalent concentration (HEC) ($BMCL_{[HEC]}$) in accordance with U.S. EPA guidance (U.S. EPA, 1994b). The $BMCL_{1SD}$ was first converted to an equivalent continuous exposure concentration ($BMCL_{[ADJ]}$) by adjusting for the exposure frequency and duration of the study (i.e., number of hours/day and days/week). The $BMCL_{HEC}$ was then calculated from the duration-adjusted effect level ($BMCL_{ADJ}$) by multiplying by the appropriate dosimetric adjustment (rat-to-human blood:air partition coefficient ratio). For the Korsak and Rydzynski (1996) study data, the BMCL was based on an extrarespiratory effect, thus, as a Category 3 gas, the ratio of blood:air partition coefficients was used in the dosimetric adjustment (EPA, 1994b). Blood:air partition coefficients for several volatile organic compounds, including 1,2,3-TMB, have been reported

for human and rat in Meulenberg and Vijverberg (2000). The reported partition coefficients of 66.5 (human) and 62.6 (rat) for 1,2,3-TMB are used in the calculation of a $BMCL_{HEC}$ shown below:

$$BMCL_{ADJ} = 97\ mg/m^3 \times 6\ hours \div 24\ hours \times 5\ days \div 7\ days$$
$$= 17\ mg/m^3$$

$$BMCL_{HEC} = BMCL_{ADJ} \times (H_{b/g})_A \div (H_{b/g})_H$$
$$= 17\ mg/m^3 \times 0.94$$
$$= 16\ mg/m^3$$

where,

$(H_{b/g})_A \div (H_{b/g})_H$ = rat-to-human blood:air partition coefficient ratio

and,

$(H_{b/g})_A = 62.6$; $(H_{b/g})_H =$ 66.5 (Meulenberg and Vijverberg, 2000)

This $BMCL_{HEC}$ value is used as the point of departure for both the subchronic and chronic p-RfCs for 1,2,3-TMB. The $BMCL_{HEC}$ of 16 mg/m^3 is divided by a composite UF of 300 to derive a subchronic p-RfC as follows:

$$\textbf{Subchronic p-RfC} = BMCL_{HEC} \div UF$$
$$= 16\ mg/m^3 \div 300$$
$$= \mathbf{5 \times 10^{-2}\ mg/m^3}$$

The composite UF of 300 includes component factors of 3 for extrapolation from rats to humans, 10 for human variability, and 10 for database insufficiencies, as explained below.

- An UF of 1 for extrapolation from a LOAEL to NOAEL (UF_L) is applied because the current approach is to address this extrapolation as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR of 1 standard deviation increase over the control mean for latency in paw-lick response was selected under an assumption that it represents a minimal biologically significant change.

- A 3-fold UF is applied for interspecies extrapolation (UF_A). This factor comprises two areas of uncertainty: pharmacokinetics and pharmacodynamics. In this assessment, the pharmacokinetic component is addressed by the dosimetric adjustment—i.e., calculation of the HEC according to the procedures in the RfC methodology (U.S. EPA, 1994b). Consequently, only the pharmacodynamic area of uncertainty remains as a partial factor of 3 for interspecies extrapolation.

- A 10-fold UF for intraspecies differences is applied to account for potentially susceptible human subpopulations (UF_H). In the absence of information on the variability in response of humans to 1,2,3-TMB, the full factor of 10 is applied.

- A 10-fold UF is applied to account for deficiencies in the available 1,2,3-TMB database (UF_D). No subchronic human studies are available. The relevant inhalation database

includes one 3-month comprehensive systemic toxicity study and one 3-month and two 4-week neurobehavioral studies, all in rats. Developmental and reproductive toxicity studies are lacking for both the inhalation and oral routes, as are subchronic studies in a second species, therefore a full factor of 10 is applied.

Confidence in the principal study (Korsak and Rydzynski, 1996) is low-to-medium. Although several exposure levels are used, a NOAEL is not identified, and only one species and sex was tested. Confidence in the database is low; supporting neurobehavioral studies and a comprehensive 3-month study are available, but a second species has not been tested and no tests of reproductive or developmental effects have been located. Low confidence in the subchronic p-RfC follows.

Chronic p-RfC

No chronic inhalation toxicity study of 1,2,3-trimethybenzene was located. However, the study on which the subchronic p-RfC is based is of sufficient duration (3 months) to support the derivation of a chronic p-RfC. The same uncertainty factors (UFs) described in the derivation of a subchronic p-RfC are applied here, with an additional UF of 10 applied to extrapolate from a subchronic to chronic exposure duration. Application of the composite UF of 3000 to the $BMCL_{HEC}$ of 16 mg/m^3 results in a chronic p-RfC as follows:

$$\begin{aligned} \textbf{Chronic p-RfC} &= BMCL_{HEC} \div UF \\ &= 16\ mg/m^3 \div 3000 \\ &= \mathbf{5 \times 10^{-3}\ mg/m^3} \end{aligned}$$

The composite UF of 3000 includes component factors of 3 for extrapolation from rats to humans, 10 for human variability, 10 for database insufficiencies, and a factor of 10 for extrapolation from subchronic-to-chronic exposure duration.

Confidence in the subchronic toxicity study used to derive the chronic p-RfC is low-to-medium, and confidence in the database is low, as discussed in the subchronic p-RfC derivation. Confidence in the database is further reduced by the lack of chronic toxicity data. Low confidence in the chronic p-RfC follows.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1,2,3-TRIMETHYLBENZENE

Weight-of-Evidence Descriptor

Studies evaluating the carcinogenic potential of oral or inhalation exposure to 1,2,3-TMB in humans or animals were not identified in the available literature. A limited number of genotoxicity studies exist for 1,2,3-TMB. Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "*Inadequate Information to Assess [the] Carcinogenic Potential*" of 1,2,3-TMB.

Quantitative Estimates of Carcinogenic Risk

Derivation of quantitative estimates of cancer risk for 1,2,3-TMB is precluded by the lack of carcinogenicity data.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2001. Documentation of the threshold limit values for chemical substances. 7th Edition. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 2007. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 2008. Toxicological Profile Information Sheet. U.S. Department of Health and Human Services, Public Health Service. Online. http://www.atsdr.cdc.gov/toxpro2.html.

CalEPA (California Environmental Protection Agency). 2002. Hot Spots Unit Risk and Cancer Potency Values. Online. http://www.oehha.ca.gov/air/hot_spots/pdf/TSDlookup2002.pdf.

CalEPA (California Environmental Protection Agency). 2005. Air Chronic Reference Exposure Levels Adopted by OEHHA as of February 2005. Online. http://www.oehha.ca.gov/air/chronic_rels/AllChrels.html.

CalEPA (California Environmental Protection Agency). 2008. OEHHA/ARB Approved Chronic Reference Exposure Levels and Target Organs. Online. http://www.arb.ca.gov/toxics/healthval/chronic.pdf.

Delic, J., R. Gardner, J. Cocker et al. 1992. Trimethylbenzenes: Criteria document for an occupational exposure limit. HMSO Books, London, United Kingdom. p. 33.

Gralewicz, S. and D. Wiaderna. 2001. Behavioral effects following subacute inhalation exposure to m-xylene or trimethylbenzene in the rat: A comparative study. Neurotoxicology. 22(1):79–89.

Henderson, R.F. 2001. Aromatic Hydrocarbons – Benzene and Other Alkylbenzenes. In: Patty's Industrial Hygiene and Toxicology, 5th Edition. Bingham, E., B. Cohrssen and C.H. Powell (eds.). John Wiley & Sons, Inc., New York, NY.

IARC (International Agency for Research on Cancer). 2008. Search IARC Monographs. Online. http://monographs.iarc.fr/ENG/Monographs/allmonos90.php.

Janik-Spiechowicz, E., K. Wyszyńska and E. Dziubałtowska. 1998. Genotoxicity evaluation of trimethylbenzenes. Mutation Research 412:299–305.

Jarnberg, J., G. Johanson and A. Lof. 1996. Toxicokinetics of inhaled trimethylbenzenes in man. Toxicol. Appl. Pharmacol. 140:281–288.

Korsak, Z. and K. Rydzynski. 1996. Neurotoxic effects of acute and subchronic inhalation exposure to trimethylbenzene isomers (pseudocumene, mesitylene, hemimellitene) in rats. Int. J. Occup. Med. Environ. Health. 9:341–349.

Korsak, Z., K. Rydzynski and J. Jajte. 1997. Respiratory irritative effects of trimethylbenzenes: an experimental animal study. Int. J. Occup. Med. Environ. Health. 10:303–311.

Korsak, Z., J. Stetkiewicz, W. Majcherek, I. Stetkiewicz, J. Jajte and K. Rydzynski. 2000. Subchronic inhalation toxicity of 1,2,3-trimethylbenzene (hemimellitene) in rats. Int. J. Occup. Med. Environ. Health. 13:223–232.

Meulenberg C.J.W. and H.P.M. Vijverberg. 2000. Empirical relations predicting human and rat tissue:air partition coefficients of volatile organic compounds. Toxicol. Appl. Pharmacol. 165:206–216.

NIOSH (National Institute for Occupational Safety and Health). 2008. NIOSH Pocket Guide to Chemical Hazards. Online. http://www.cdc.gov/niosh/npg/.

NTP (National Toxicology Program). 2005. 11th Report on Carcinogens. Online. http://ntp.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932.

NTP (National Toxicology Program). 2008. Management Status Report. Online. http://ntp.niehs.nih.gov/index.cfm?objectid=78CC7E4C-F1F6-975E-72940974DE301C3F.

OSHA (Occupational Safety and Health Administration). 2008. OSHA Standard 1910.1000 Table Z-1. Part Z, Toxic and Hazardous Substances. Online. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992.

Tomas, T., P. Lutz, and D. Wiaderna. 2000. Changes in electrocortical arousal following acute trimethylbenzene administration in rats. Int. J. Occup. Med. Environ. Health. 13(1):67–78.

Tomas, T., R. Swiercz, D. Wiaderna et al. 1999. Effects of acute-exposure to aromatic hydrocarbons C9 on locomotor activity in rats. Trimethylbenzene isomers. Int. J. Occup. Med. Environ. Health. 12(4):331–343.

U.S. EPA. 1987. Health Effects Assessment for Trimethylbenzenes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA/600/8-88/060.

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994a. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1994b. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Office of Research and Development, Washington, DC. EPA/600/8-90/066F.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS PB97-921199.

U.S. EPA. 2000. Benchmark Dose Technical Guidance Document [external review draft]. EPA/630/R-00/001. Online. http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. 2005. Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. EPA/630/P-03/001B. Online. http://www.thecre.com/pdf/20050404_cancer.pdf.

U.S. EPA. 2006. 2006 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. EPA 822-R-06-013. Washington, DC. Online. http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf.

U.S. EPA. 2008. Integrated Risk Information System (IRIS). Online. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. http://www.epa.gov/iris/.

Wiaderna, D., S. Gralewicz and T. Tomas. 1998. Behavioural changes following a four-week inhalation exposure to hemimellitene (1,2,3-trimethylbenzene) in rats. Int. J. Occup. Med. Environ. Health. 11:319–334.

WHO (World Health Organization). 2008. Online catalogs for the Environmental Health Criteria Series. Online. http://www.who.int/ipcs/publications/ehc/ehc_alphabetical/en/index.html.

APPENDIX A. DETAILS OF BENCHMARK DOSE MODELING FOR SUBCHRONIC AND CHRONIC INHALATION p-RfCs

Model Fitting Procedure for Continuous Data:

The model fitting procedure for continuous data is as follows. The simplest model (linear) in the EPA BMDS (version 1.4.1c) is first applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then, all of the available models are fit to the data while assuming constant variance. Among the models providing adequate fit to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the test for constant variance is negative, the linear model is run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then all of the available models are fit to the data and evaluated while the variance model is applied. Among those providing adequate fit to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the test for constant variance is negative and the nonhomogenous variance model does not provide an adequate fit to the variance data, then the data set is considered unsuitable for modeling.

Model Fitting Results for Latency of Paw-Lick Response in Rats (Korsak and Rydzynski, 1996)

The data on latency of paw-lick response were modeled according to the procedure outlined above using BMDS version 1.4.1 with default parameter restrictions. Table A-1 shows the data modeled.

In the absence of a biologically relevant response level, the BMR was chosen to be 1 standard deviation from the control mean, as recommended by U.S. EPA (2000). Neither the constant nor modeled variance models in the software provided adequate fit to the variance data for the full data set, indicating that the full data set is not suitable for BMD. The high-dose group was dropped from the model in an effort to achieve model fit. Using the reduced data set, the test for homogenous variance was negative, but the variance model in the software provided adequate fit to the variance information, and the linear model provided adequate fit to the means (see Table A-2). With only three dose groups (including controls) available for modeling, other model forms requiring more parameters either reverted to linear or left insufficient degrees of freedom to test model fit. A BMC_{1SD} and $BMCL_{1SD}$ of 152.07 and 97.19 mg/m^3, respectively, were predicted using these data. Figure A-1 shows the fit of the linear model (nonconstant variance) to these data.

Table A-1. Latency of Paw-Lick Response in Rats Exposed to 1,2,3-Trimethylbenzene for 90 Days[a]

Effect	Exposure Concentration (mg/m^3)			
	0	**123**	**492**	**1230**
Latency of paw-lick (sec, mean ± SD)	9.7 ± 2.1 (n = 30)	11.8 ± 3.8 (n = 20)	16.3 ± 6.3 (n =10)	17.3 ± 3.4 (n = 10)

[a]Korsak and Rydzynski, 1996

Table A-2. Model Predictions for Latency (sec) of Paw-Lick in Rats Exposed to 1,2,3-Trimethylbenzene for 90 Days[a]

Model	Variance p-Value[b]	Means p-Value[b]	AIC	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)
All exposure concentrations					
Linear (constant variance)[c]	0.0001146	0.01728	259.99	577.56	442.59
Linear (modeled variance)[c]	0.07076	0.00032	254.41	319.65	195.99
High-exposure group dropped					
Linear (constant variance)[c]	<0.0001	0.6445	218.51	265.69	195.64
Linear (Modeled Variance)[c]	**0.5008**	**0.2016**	**201.71**	**152.07**	**97.19**
2-Degree polynomial (modeled variance)[c]	0.5008	0.2016	201.71	152.07	97.19
Power (modeled variance)[d]	0.5008	0.2016	201.71	152.07	97.19
Hill (modeled variance)[d]	NA	NA	NA	NA	NA

[a]Korsak and Rydzynski, 1996
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria
[c]Coefficients restricted to be positive
[d]Power restricted to ≥1

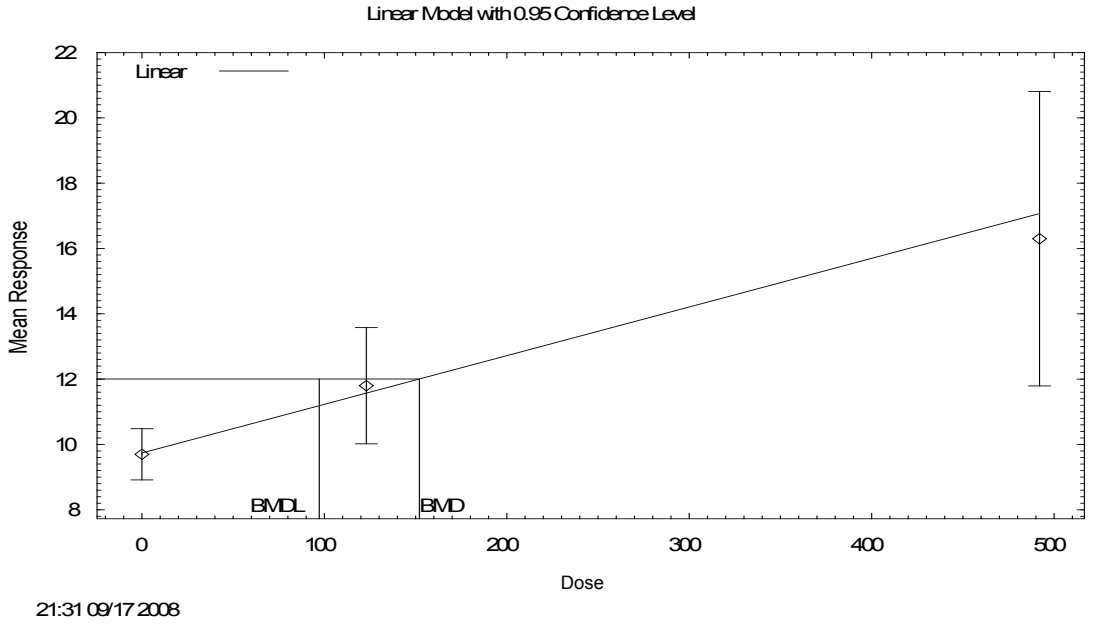

Figure A-1. Fit of Linear Model (Nonconstant Variance) to Data on Latency of Paw-Lick Response (Korsak and Rydzynski, 1996)

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