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Provisional Peer-Reviewed Toxicity Values for

1,3,5-Trimethylbenzene
(CASRN 108-67-8)

Superfund Health Risk Technical Support Center
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ACRONYMS AND ABBREVIATIONS

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
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
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
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 inhalation reference concentration
p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic

ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,3,5-TRIMETHYLBENZENE (CASRN 108-67-8)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.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. U.S. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in U.S. 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
   - U.S. 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 U.S. 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 U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. 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 U.S. 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 U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. 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 U.S. 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 1,3,5-trimethylbenzene (mesitylene) is available on IRIS (U.S. EPA, 2008). The Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997) states that data were inadequate for quantitative risk assessment for trimethylbenzenes, based on a Health and Environmental Assessment (HEA) for Trimethylbenzenes (U.S. EPA, 1987a). The Drinking Water Standards and Health Advisories list (U.S. EPA, 2006) includes a 1-day health advisory of 10 mg/L and a cancer Group D classification for 1,3,5-trimethylbenzene, but no RfD; a Drinking Water Health Advisory document for 1,3,5-trimethylbenzene (U.S. EPA, 1987b) is cited as the source. The Chemical Assessments and Related Activities record (CARA; U.S. EPA, 1991, 1994a) lists only the previously mentioned HEA (U.S. EPA, 1987a) and Drinking Water Health Advisory (U.S. EPA, 1987b) for 1,3,5-trimethylbenzene. The Agency for Toxic Substances and Disease Registry (ATSDR, 2007) has not produced a Toxicological Profile for 1,3,5-trimethylbenzene, and no Environmental Health Criteria document is available from the World Health Organization (WHO, 2008). The chronic toxicity and carcinogenicity of 1,3,5-trimethylbenzene have 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 1,3,5-trimethylbenzene. The National Institute for Occupational Safety and Health (NIOSH, 2005) has set a recommended exposure limit (REL) of 25 ppm (123 mg/m^3) for 1,3,5-trimethylbenzene based on CNS effects, irritation and anemia; the American Conference of Governmental Industrial Hygienists (ACGIH, 2001, 2007) recommends a threshold limit value of 25 ppm for mixed isomers of trimethylbenzene based on the same endpoints. The California Environmental Protection Agency (CalEPA, 2002, 2005a, 2005b) has not derived a REL or cancer potency factor for 1,3,5-trimethylbenzene.

Literature searches were conducted from 1960s through December 2007 for studies relevant to the derivation of provisional toxicity values for 1,3,5-trimethylbenzene. 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 December 2007 through January 2009, in MEDLINE.

REVIEW OF PERTINENT DATA

Human Studies

Oral Exposure

No information was located regarding the oral toxicity of 1,3,5-trimethylbenzene in humans.

Inhalation Exposure

Information regarding the inhalation toxicity of 1,3,5-trimethylbenzene in humans mainly comes from a limited occupational study in which workers were exposed to a mixture of trimethylbenzene isomers. Bättig et al. (1958) examined 27 workers exposed to "Fleet-X-DV-99" solvent in the painting shop of a Swiss transportation plant. Analysis of the solvent showed that it consisted primarily of aromatic hydrocarbons (97.5%) and paraffinic and naphthenic hydrocarbons (2.5%). The aromatic hydrocarbon portion was composed of 1,3,5-trimethylbenzene (>30%), 1,2,4-trimethylbenzene (>50%), and possibly included 1,2,3-trimethylbenzene, 1-methyl-2-ethylbenzene, 1-methyl-3-ethylbenzene, and 1-methyl-4-ethylbenzene. Therefore, up to 20% of the mixture remained unidentified. Analysis of the workplace air indicated that concentrations ranged from 10−60 ppm (sampling time and other monitoring information are not reported). It is unclear if these vapor concentrations were for trimethylbenzene or the solvent mixture. If the vapor were comprised of trimethylbenzene exclusively, the corresponding concentrations in mg/m^3 would be 49−295 mg/m^3. The authors stated that the solvent was used for "a period of some 10 years," but the average exposure duration of the workers was not reported. The control group consisted of 10 workers in other parts of the plant who were apparently not exposed to the solvent. Evaluations of each worker were essentially limited to working history, general clinical status, red and white blood cell counts, and a brief psychiatric assessment. The exposed workers reported CNS symptoms (vertigo, headaches, and drowsiness, which disappeared after work) more often than the control group (70% versus 30%). Chronic asthma-like bronchitis (30% of exposed workers compared to 10% of controls), hyperchromic anemia (defined as <4.5 million erythrocytes/mm^3 and usually combined with normal hemoglobin) (52% versus 20%), and alterations in blood clotting (tendency to hemorrhage) (30% versus 10%) were also observed in the exposed workers. The incidence of CNS effects in the exposed workers was statistically significantly higher than in the controls (19/27 versus 3/10, $p = 0.03$, Fisher's exact test conducted for this assessment), whereas the incidences of the other effects did not achieve statistical significance ($p > 0.05$). A higher incidence of vitamin C deficiency was observed in the control group, suggesting that the two groups may not have been matched for socioeconomic status. If the assumption is made that the solvent exclusively contained trimethylbenzene isomers, then this study identifies a LOAEL in the range of 10−60 ppm (49−295 mg/m^3) for clinical signs of neurotoxicity.

Several acute experimental studies provide additional information on health effects in humans. Jarnberg et al. (1996) studied healthy human volunteers exposed to 1,3,5-trimethylbenzene. Caucasian males (n = 10; average 35 years of age and of average weight) were exposed four times for 2 hours to 1,3,5-trimethylbenzene (99% pure) at a vapor concentration of 25 ppm (123 mg/m^3; the NIOSH REL) while pedaling an ergometer bicycle at 50 watts. While the study was focused on the uptake and distribution of 1,3,5-trimethylbenzene, the authors also evaluated irritation and CNS-related symptoms using a questionnaire. No irritation of eyes, nose, or airways was reported, and no CNS-related symptoms were reported. The data indicated high respiratory uptake (>60% at 25 ppm) and moderately rapid elimination (~1 L/hour-kg). A large volume of distribution (~39 L/kg) and long terminal half-life in blood (120 hours) implied extensive accumulation of 1,3,5-trimethylbenzene in adipose tissue. Kostrewski et al. (1995, 1997) conducted two studies wherein five healthy human volunteers were exposed to 1,3,5-trimethylbenzene at air concentrations as high as 150 mg/m^3 for 8 hours (the intervals between two consecutive exposures were 3−4 weeks). The subjects showed no abnormalities in routine clinical (internal, laryngologic, neurologic, and hematologic) examinations conducted before and after the exposures. The study authors found that trimethylbenzene was eliminated from capillary blood in accordance with an open three-compartment model ($t_{1/2}$ = 2 minutes, 43 minutes, and 46 hours for the triphasic elimination from blood). The primary metabolite reported in urine was 3,5-dimethylbenzoic acid.

Animal Studies

Oral Exposure

In a good laboratory practices (GLP) study conducted for TSCA §4 compliance, Sprague-Dawley CD rats (10/sex) were administered 0 (vehicle control), 60, 150, or 600 mg/kg-day of 1,3,5-trimethylbenzene (99.2% pure) in corn oil vehicle by gavage for 14 consecutive days (Koch Industries, 1995a). An additional group of rats (10/sex) was administered 600 mg/kg-day for 14 consecutive days and retained without treatment for an additional 14 days to evaluate recovery from any toxic effects. Indices used to assess toxicity included daily physical examinations and clinical observations, ophthalmological examinations at initiation and termination of treatment, weekly body weights and food consumption, and hematology (11 parameters) and serum chemistry (17 parameters) at the end of the treatment and recovery periods. Complete necropsy and select organ weight measurements (adrenal glands, brain, gonads, kidneys, liver, and lungs) were performed at death and at the end of the treatment and recovery periods. Comprehensive histological examinations were performed on the control and high-dose non-recovery animals. Tissues examined in the low- and mid-dose non-recovery animals were limited to the liver, lungs, and any gross lesions observed at necropsy. Histological examinations in the recovery animals were limited to the liver and any gross lesions observed at necropsy.

No rats died during the study, and wet inguinal fur was the most prominent clinical finding, occurring predominantly in the 600 mg/kg-day males (Koch Industries, 1995a). Mean body weight and cumulative body weight gain were not significantly affected in the treated rats (either sex) compared to vehicle controls. Exposure-related effects after 14 days of dosing included statistically significant ($p \leq 0.05$) increases in white blood cell count (with corresponding increases in neutrophils and lymphocytes) in males at 600 mg/kg-day (35.4% higher than controls) and serum cholesterol in females at 150 and 600 mg/kg-day

(34.5% and 51.8% higher than controls); both effects appeared to be reversible based on results at the end of the recovery period. The authors noted that the increased serum cholesterol levels in the 150 and 600 mg/kg-day females were above the range of in-house historical control values for rats of the strain and age used in this study. No changes in serum enzymes (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, or gamma glutamyl transpeptidase) were observed. Absolute and relative liver weights were significantly increased in females at 150 mg/kg-day (12.2 and 9.1% higher than controls) and 600 mg/kg-day (25.1 and 25.6% higher) and in males at 600 mg/kg-day (18.8% and 22.0% higher), and relative adrenal weight was significantly increased in males at 600 mg/kg-day (14.3% higher). All of these organ-weight changes appeared to be reversible. The only exposure-related histopathology finding was minimal centrilobular hepatocyte hypertrophy in the liver of 10/10 males and 3/10 females at 600 mg/kg-day at the termination of treatment; this effect was not observed at lower dose levels or in controls and was not present in recovery animals, demonstrating its reversibility. The study authors concluded that the centrilobular hepatocellular hypertrophy (and presumably the increases in liver weight) most likely resulted from the induction of microsomal enzymes. Based on the observed increases in absolute and relative liver weight and serum cholesterol, this study identified a 14-day NOAEL of 60 mg/kg-day and LOAEL of 150 mg/kg-day.

In another GLP study conducted for TSCA §4 compliance, Koch Industries (1995b) evaluated the subchronic toxicity of 1,3,5-trimethylbenzene. Sprague-Dawley CD rats (10/sex) were administered 0, 50, 200, or 600 mg/kg-day of 1,3,5-trimethylbenzene (99.2% pure) in corn oil by gavage 5 days/week for 90 days. An additional group of rats (10/sex) was treated at the same dose levels for 90 days and retained without treatment for 28 days to evaluate recovery from any toxic effects. Indices used to assess toxicity included daily physical examinations and clinical observations, ophthalmological examinations at initiation and treatment termination, weekly body weights and food consumption, and hematology (11 parameters) and serum chemistry (17 parameters) evaluated at Treatment Day 30 and at the end of the treatment and recovery periods. All rats were subjected to complete necropsy, and select organs (adrenals, brain, gonads, kidneys, liver, and lungs) were weighed at necropsy. Comprehensive histological examinations were performed on all control and high-dose non-recovery animals. Tissues examined in the low- and mid-dose non-recovery animals were limited to the lungs and any gross lesions observed at necropsy. No histological examinations were performed in the recovery animals.

No compound-related deaths were observed (Koch Industries, 1995b). Clinical signs, mainly consisting of discolored and/or wet inguinal fur and salivation occurred predominantly at 600 mg/kg-day. There were no statistically significant changes in body weight. Body-weight gain was significantly ($p \leq 0.05$) reduced in the 600 mg/kg-day males at week 5 (36.4% less than controls), although cumulative body-weight gain after 90 days was only slightly, but not significantly, affected (10.8% less than controls, $p > 0.05$). In the male rats receiving 600 mg/kg, significant increases in serum alkaline phosphatase and phosphorus levels and a decrease in glucose level were observed. In the female rats dosed with 600 mg/kg, significant increases in serum cholesterol and phosphorus levels, and decreases in sodium and chloride levels were observed; serum alkaline phosphatase was also increased in female rats at the high dose but did not reach statistical significance compared to control. No significant alterations in serum chemistry parameters were observed at the lower dose levels. The study authors noted that with the exception of the increased serum phosphorus levels, the serum chemistry values were within normal historical ranges, or, in the case of alkaline phosphatase, due to exceptionally high values

for 2 (out of 10) animals in the group (additional information on these particular animals not reported). The increased phosphorus levels were considered to be treatment-related; the serum phosphorus levels were 16.9 and 22.9% higher in the 600 mg/kg male and female rats, respectively, than in the control group. No significant alterations in serum phosphorus or other serum chemistry parameters occurred in the recovery group. No significant alterations in erythrocyte parameters or total leukocyte levels were observed. Statistically significant increases in monocyte levels occurred in the 200 and 600 mg/kg groups, but were not related to dose (200 mg/kg-day was highest) or considered treatment-related. No significant alterations in hematological parameters occurred in the recovery group. Relative liver and kidney weights were increased in males at 600 mg/kg-day (15.9 and 13.8% higher than controls, respectively), and absolute and relative liver weights were increased in females at 600 mg/kg-day (24.5 and 25.7% higher than controls, respectively) at the end of the treatment period. No significant changes in organ weights occurred in the recovery group. No exposure-related alterations in gross or microscopic histopathology of the liver, kidneys, or other tissues were observed. As indicated above, all treatment-related effects (i.e., wet/discolored inguinal fur, salivation, slightly decreased body-weight gain, increased serum phosphorus levels, and increased liver and kidney weights) appeared to be reversible since these effects were no longer apparent at the end of the 28-day recovery period.

The toxicological significance of the increased serum phosphorus levels observed by Koch Industries (1995b) is unclear. The finding that the serum phosphorus levels returned to normal in the recovery group suggests that the serum phosphorus level alterations were related to 1,3,5-trimethylbenzene exposure. Although kidney weights were increased, no unusual increases in other serum electrolytes or effects on blood urea nitrogen or kidney histopathology were observed, suggesting that the increased serum phosphorus levels may not have been related to renal damage. Possible non-renal causes of increased serum phosphorus levels include parathyroid diseases (pseudohyperparathyroidism and hypoparathyroidism cause phosphate retention, although parathyroid histology was normal in this study), decreased liver degradation of vitamin D (excessive vitamin D increases intestinal phosphate uptake and stimulates bone resorption), glucose intolerance (hyperphosphatemia results from decreased glucose phosphorylation and can occur in glucose-intolerant states such as Diabetes mellitus and Cushing's disease), and muscle damage (muscle lysis releases large amounts of intracellular phosphate, although muscle histology was normal in this study) (Riley and Cornelius, 1989). However, none of these potential etiological factors related to increased serum phosphorus have been examined following exposure to 1,3,5-trimethylbenzene. Regarding increased liver weight, the study authors concluded that this effect most likely resulted from the induction of microsomal enzymes. This is a reasonable conclusion considering evidence for microsomal enzyme induction by 1,3,5-trimethylbenzene in acute studies (summarized below), as well as the normal liver histopathology and normal serum alanine aminotransferase, aspartate aminotransferase, and gamma glutamyl transpeptidase levels. Although serum alkaline phosphatase was increased, this is not necessarily due to liver damage. Taken together, the clinical observations, slight decrease in body-weight gain, increase in serum phosphorus levels, and increases in liver and kidney weights indicate that this study identified a LOAEL of 600 mg/kg-day and a NOAEL of 200 mg/kg-day for subchronic oral exposure in rats.

The hepatic effects observed in the 14- and 90-day studies by Koch Industries (1995a,b) are supported by two acute studies: Pyykko (1980) and Ungvary et al. (1981). Pyykko (1980) administered 0 or 10 mmol/kg-day (0 or 1202 mg/kg-day) of 1,3,5-trimethylbenzene (97% pure) in corn oil by gavage to groups of 8−10 male Sprague-Dawley rats for 3 days. Treatment with 1,3,5-trimethylbenzene resulted in significant increases in liver weight and in the cytochrome b5 content of the liver and kidney. Increases in the activity of various microsomal enzymes were also reported by Ungvary et al. (1981). 1,3,5-Trimethylbenzene (purity not reported) was administered orally to male and female CFY rats (eight/sex/group) at 13.7 mmol/kg-day (1647 mg/kg-day) for 4 days. In both sexes, reduced body-weight gain, statistically significant increases in hepatic cytochrome P450 and cytochrome b5, and a statistically significant increase in liver weight were reported following administration of 1,3,5-trimethylbenzene. Electron microscopy revealed that acute administration of 1,3,5-trimethylbenzene produced extensive proliferation of the smooth endoplasmic reticulum in the centrilobular zone of the liver (Ungvary et al., 1981).

Inhalation Exposure

Bättig et al. (1958) exposed groups of 8 male rats (strain not reported) to air concentrations of 0 or 1700 ppm of Fleet-X-DV-99 solvent for 4 months (8 hours/day, 5 days/week). Another group of rats (sex, strain, and number not reported) was exposed to approximately 500 ppm for 70 days (8 hours/day, 5 days/week). As described earlier in the human studies, Fleet-X-DV-99 is a solvent containing 97.5% aromatic hydrocarbons (>30% 1,3,5-trimethylbenzene and >50% 1,2,4-trimethylbenzene) and 2.5% of paraffinic and naphthenic hydrocarbons. Furthermore, up to 20% of the mixture remained unidentified. It is unclear if the reported exposure concentrations are for trimethylbenzenes or the solvent. If the aromatic hydrocarbon fraction of the vapors was comprised exclusively trimethylbenzenes, the 500 and 1700 ppm concentrations would be approximately 2523 and 8155 mg/m^3, respectively. Evaluations included mortality, behavior, body weight, food and water consumption, red and white blood cell counts, and histopathology (liver, kidney, spleen, pancreas, heart, lung, and adrenal). Of the 8 rats exposed to 1700 ppm, 4 died within 2 weeks of exposure and were replaced. During exposure, the 1700 ppm animals were initially "highly excited and aggressive" followed by a period of narcosis and ataxia. There was a loss of body weight during the first month of 1700 ppm exposure with subsequent recovery although control values were never regained. The changes in body weight were paralleled by reduced food intake. Other effects at 1700 ppm included increased drinking water consumption (43−58% higher than in the control group) and alterations in differential white blood cell counts (increased percentage of neutrophils and decreased percentage of lymphocytes), with no changes in total white or red blood cell counts or hemoglobin content. Histopathological examinations at the end of the exposure period showed effects at 1700 ppm that included marked congestion of the pulmonary capillaries with alveolar wall thickening, cloudy swelling and fatty infiltration in the kidneys, peripheral fatty infiltration in the liver and an increase in secondary nodules in the spleen. Little information was provided on the results in the 500 ppm group, and it is unclear whether all of the endpoints evaluated at 1700 ppm were evaluated at 500 ppm. None of the 500 ppm animals died. Effects at 500 ppm appear to have been limited to clinical signs of neurotoxicity (the "phenomena of severe excitation with subsequent narcosis and ataxia were only indicated") and decreased body-weight gain (data not reported) that were less pronounced than at 1700 ppm. Due to the insufficient reporting of these results and the limited scope of the study, it cannot be determined whether 500 ppm is a NOAEL or LOAEL. The high concentration of 1700 ppm, however, is a frank effect level (FEL) for mortality.

The hematological effects of 1,3,5-trimethylbenzene reported by Bättig et al. (1958) are supported by Wiglusz et al. (1975a,b) and Bernshtein (1972). Wiglusz et al. (1975a,b) exposed groups of 5−8 male Wistar rats to 1,3,5-trimethylbenzene vapors (purity not reported) at 0, 1.5, 3, or 6 mg/L (0, 1500, 3000, or 6000 mg/m^3; 0, 305, 610, or 1220 ppm, respectively) for 6 hours or at 0 or 3 mg/L (3000 mg/m^3; 610 ppm) for 6 hours/day, 6 days/week, for 5 weeks. Blood samples were collected 3 days before exposure and on exposure days 1, 7, 14, and 28. In the single 6-hour exposure, a slight (not statistically significant) reduction in hemoglobin was observed on day 7 at 6000 mg/m^3. In the 5-week exposure, slight alterations in differential white blood cell counts (increase in the proportion of segmented neutrophilic granulocytes and a decrease in the proportion of lymphocytes), as well as a significant elevation of serum aspartate aminotransferase levels, were found in the rats exposed to 3000 mg/m^3. Bernshtein (1972) exposed rats (number, sex, and strain not specified) to 1 mg/L (1000 mg/m^3; 200 ppm) of trimethylbenzene (not further specified) 4 hours/day, 6 days/week, for 6 months. An inhibition of phagocytic activity of the leukocytes was reported. This study was summarized by Henderson (2001) and further experimental details were not provided.

Behavioral effects were studied in male Wistar rats (5 months old; 11 rats in treated group and 10 rats in sham-exposed control group) that were exposed to 100 ppm (492 mg/m^3) of 1,3,5-trimethylbenzene (≥98.0% pure) for 4 weeks (6 hours/day, 5 days/week) in whole-body dynamic inhalation chambers (Gralewicz and Wiaderna, 2001). Beginning 2 weeks after exposure, the following tests were conducted: (1) radial maze test (assay of short-term spatial memory, at 14−18 days post-exposure), (2) open-field test (assays of spontaneous locomotor, exploratory, and grooming activities, at 25 days post-exposure), (3) passive avoidance test (assay of long-term memory, at 39−48 days post-exposure), (4) hot-plate test (assay of sensitivity to pain and pain-related stress level, at 50−51 days post-exposure), and (5) conditioned active avoidance reaction test (assay of ability to learn and memorize, at 54 and 60 days post-exposure). Body-weight gain and radial maze performance were not affected by exposure. As compared to control rats, 1,3,5-trimethylbenzene exposure caused statistically significant increases in spontaneous locomotor activity in the open-field test and latency in heat-induced paw-lick 24 hours after electric foot shock in the hot plate test, and impairments in passive avoidance learning and acquisition, but not retention, of the active avoidance response. (Descriptions of these tests are provided below in the summary of the Wiaderna et al., 2002 study.) This study identified a LOAEL of 492 mg/m^3 and no NOAEL for neurobehavioral impairment.

In a follow-up behavioral assessment, groups of 12 male outbred LOD:WIST rats (5 months old) were exposed to 0, 25, 100, or 250 ppm (0, 123, 492, or 1230 mg/m^3) of 1,3,5-trimethylbenzene (≥99.8% pure) for 6 hours/day, 5 days/week for 1 month in whole-body dynamic inhalation chambers (Wiaderna et al., 2002). Beginning 2 weeks after exposure, the following tests were conducted: (1) radial maze test (14−19 days post-exposure), (2) open-field test (25 days post-exposure), (3) passive-avoidance test (35−45 days post-exposure), (4) hot plate test (50−51 days post-exposure), and (5) conditioned active avoidance reaction test (54−60 days post-exposure). The design and conduct of these tests are essentially identical to those in the Gralewicz and Wiaderna (2001) study summarized above. Body weight gain, radial maze performance, and open-field behavior (locomotor activity, exploratory activity, or number of grooming episodes) were not affected by exposure. Effects were observed in the hot plate test at 492 mg/m^3 (but not 1230 mg/m^3) and in the passive avoidance and active avoidance tests at ≥123 mg/m^3. The hot plate test measured the latency of the paw-lick reaction when the rat was placed on the hot plate. The test comprised three trials, in which the rat received a 2-minute series of electric shocks immediately following the first trial. The second trial was performed

immediately following the termination of the shocks and the third trial was performed approximately 24 hours later. The latency in heat-induced paw-lick 24 hours after electric foot shock in the 492 mg/m^3 group was significantly longer than in controls, but this effect was not observed at 1230 mg/m^3. The passive avoidance test compared the time of staying on a platform in six consecutive trials. In trial three, leaving the platform was punished by an electric shock. Trials one, two, three, and four were performed at 24-hour intervals, while trials five and six were performed 3 and 7 days after trial three, respectively. In trial six, the 123, 492, and 1230 mg/m^3 groups of rats remained on the platform significantly shorter than the control group. The active avoidance test compared the number of trials (attempts) required to reach the avoidance criterion (four shock avoidances) in five consecutive trials (attempts) during a training session (post-exposure Day 54) and a retraining session (post-exposure Day 60). In the training session, the 123, 492, and 1230 mg/m^3 groups of rats required significantly more trials to produce the active-avoidance reaction than in the control group. The magnitudes of the effects in both the passive- and active-avoidance tests were not significantly different among the groups (i.e., were not concentration-related). This study identified a LOAEL of 123 mg/m^3 and no NOAEL for neurobehavioral impairment.

Korsak and Rydzynski (1996) examined neurobehavioral effects in male Wistar rats of IMP:DAK outbreed stock (10/group) that were exposed to 250−2000 ppm (1227−9816 mg/m^3) 1,3,5-trimethylbenzene (>99% pure) for 4 hours. Exposure caused concentration-related decreases in rotarod performance (EC_{50} = 4738 mg/m^3) and pain sensitivity (hot plate behavior, as measured by increased paw-lick response latency) (EC_{50} = 5963 mg/m^3).

Developmental toxicity was evaluated in groups of 24−25 bred (17−24 pregnant) Sprague-Dawley rats that were exposed to 0, 100, 300, 600, or 1200 ppm (0, 492, 1475, 2949, or 5900 mg/m^3) of 1,3,5-trimethylbenzene (99% pure) for 6 hours/day on gestation days (GD) 6−20 (Saillenfait et al., 2005). Maternal animals were evaluated for mortality, clinical signs, food consumption (GD 6−13 and 13−21), and body weight (GD 0, 6, 13, and 21) and sacrificed on GD 21, at which time the uterus was weighed and examined for numbers of *corpora lutea*, implantation sites, resorptions, and live and dead fetuses. All live fetuses were weighed, sexed, and examined for external abnormalities (including those of the oral cavity). Half of the live fetuses from each litter had internal soft tissue examinations and the other half had skeletal examinations. Maternal body-weight gain was significantly reduced compared to controls at 1475 mg/m^3 on GD 13−21 (13.6% lower, $p < 0.05$), 2949 mg/m^3 on GD 6−13 (36.0% lower, $p < 0.01$) and 13−21 (27.3% lower, $p < 0.01$), and 5900 mg/m^3 on GD 6−13 (60.0% lower, $p < 0.01$) and 13−21 (42.7% lower, $p < 0.01$). When body-weight gains were corrected for gravid uterine weights, weight gain throughout the exposure period (GD 6−21) was significantly reduced at 2949 mg/m^3 and weight loss occurred at 5900 mg/m^3. Maternal food consumption was significantly reduced throughout exposure at ≥1475 mg/m^3. The only other exposure-related effect was a concentration-related decrease in fetal body weight that achieved statistical significance in males at 2949 mg/m^3 ($p < 0.05$) and all fetuses at 5900 mg/m^3 ($p < 0.01$). At 492, 1475, 2949, and 5900 mg/m^3, body weight was 0.7, 5.2, 7.1, and 12.1% lower than controls in male fetuses, respectively, and 0.5, 4.2, 5.8, and 12.5% lower than controls in female fetuses, respectively. Based on the reductions in maternal and fetal body weight, this study identified a NOAEL of 492 mg/m^3 and LOAEL of 1475 mg/m^3 for maternal toxicity and a NOAEL of 1475 mg/m^3 and LOAEL of 2949 mg/m^3 for developmental toxicity. These results suggest that the fetus is not a sensitive target of 1,3,5-trimethylbenzene toxicity.

Other Studies

Limited genotoxicity data suggest that 1,3,5-trimethylbenzene is not mutagenic but may be clastogenic. 1,3,5-Trimethylbenzene did not induce reverse mutations in *Salmonella typhimurium* strains TA97a, TA98, TA100, TA102, or TA2637 when tested *in vitro* with or without rat liver S9 metabolic activation (Janik-Spiechowicz et al., 1998; Nohmi et al., 1985). *In vivo* micronucleus and sister-chromatid exchange (SCE) tests were conducted with bone marrow cells of Imp:Balb/c mice treated by intraperitoneal injection (Janik-Spiechowicz et al., 1998). The frequency of micronucleated polychromatic erythrocytes in the bone marrow was not increased in male mice administered a total dose of 1800 or 3600 mg/kg (40 or 80% of LD_{50}) or female mice administered a total dose of 2960 mg/kg (80% of LD_{50}); each dose was divided into two equal parts and given at a 24-hour interval. In the SCE test, a single 900, 1800, or 2700 mg/kg dose was administered to male mice; weakly positive results were obtained at the middle- and high-dose level.

DERIVATION OF A PROVISIONAL SUBCHRONIC ORAL RfD VALUE FOR 1,3,5-TRIMETHYLBENZENE

Limited information is available on the oral toxicity of 1,3,5-trimethylbenzene and only one study, the Koch Industries (1995b) study, is of a duration sufficient for assessing effects associated with subchronic oral exposure to this compound. However, based upon current standard operating procedure and standards, unpublished principal or influential studies must be peer-reviewed before they can be considered for reference value derivation. Since the Koch Industries (1995b) study is an unpublished TSCA 4 submission, it is not known if the information has been peer-reviewed. As such, while an oral reference value cannot be derived here, a "screening" level evaluation of oral 1,3,5-trimethylbenzene toxicity is provided in the Appendix.

DERIVATION OF A PROVISIONAL SUBCHRONIC INHALATION RfC VALUE FOR 1,3,5-TRIMETHYLBENZENE

Information relevant to derivation of a p-RfC value for 1,3,5-trimethylbenzene is available from one human study and several animal studies. In the human study, increases in the incidence of CNS toxicity (vertigo, dizziness, headaches) and non-significant increases in the incidences of respiratory effects (bronchitis) and hematological effects (hyperchromic anemia and blood clotting alterations) have been observed in workers exposed to 10−60 ppm of Fleet-X-DV-99 solvent mixture containing >30% 1,3,5-trimethylbenzene and >50% 1,2,4-trimethylbenzene isomers (Battig et al., 1958). Some of the effects reported in the occupationally exposed humans have been observed in animals repeatedly exposed to 1,3,5-trimethylbenzene or mixtures of trimethylbenzene isomers. For example, in rats exposed to the Fleet-X-DV-99 solvent for 8 hours/day, 5 days/week, for up to 4 months, effects included CNS alterations (excitation followed by narcosis and ataxia) and decreased body-weight gain at 500 and 1700 ppm, as well as hematological effects (alterations in differential white blood cell counts), fatty changes in the liver and kidneys, and mortality at 1700 ppm (Battig et al., 1958). Hematological effects also have been reported in rats exposed to 200 ppm of trimethylbenzene (not further described) 4 hours/day, 6 days/week, for 6 months (inhibition of phagocytic activity

of leukocytes) (Bernshtein, 1972) and rats exposed to 610 ppm of 1,3,5-trimethylbenzene for 6 hours/day, 6 days/week, for 5 weeks (alterations in differential white blood cell counts) (Wiglusz et al., 1975a). Neurobehavioral testing showed CNS effects in rats exposed to 1,3,5-trimethybenzene at concentrations as low as 25 ppm for 6 hours/day, 5 days/week, for 1 month (impairments in learning and memory) (Gralewicz and Wiaderna, 2001; Wiaderna et al., 2002). Developmental toxicity testing showed reductions in maternal and fetal body-weight gain in rats gestationally exposed to 300 and 600 ppm of 1,3,5-trimethybenzene, respectively (Saillenfait et al., 2005).

The lowest estimated level of occupational exposure to the solvent Fleet-X-DV-99 (>30% 1,3,5-trimethylbenzene and >50% 1,2,4-trimethylbenzene) in the human study (Battig et al., 1958) was 10 ppm. Assuming that the mixture exclusively contained trimethylbenzenes, the 10 ppm (49 mg/m^3) exposure concentration is a LOAEL for CNS effects in humans. This concentration is the lowest LOAEL of any inhalation study, but it is an unsuitable basis for p-RfC derivation for a number of reasons. For example, the reliability of the 10 ppm exposure level is uncertain because a range of 10−60 ppm was the only reported monitoring data (sampling time, number of samples, and other information was not reported). Additionally, because up to 50% of the mixture contained 1,2,4-trimethylbenzene, contained up to 2.5% of paraffinic and naphthenic hydrocarbons, and up to 20% of the mixture was undefined, it is not possible to confidently attribute the observed health effects of the Fleet-X-DV-99 solvent to 1,3,5-trimethybenzene. Other study concerns include unreported exposure duration and an inappropriate control group due to vitamin C deficient nutritional status.

Neurobehavioral impairment was the most sensitive effect of 1,3,5-trimethylbenzene inhalation exposure in the animal studies, occurring at concentrations as low as 25 ppm in the Wiaderna et al. (2002) study. In this study, behavioral effects were evaluated in rats that were exposed to 0, 25, 100, or 250 ppm 1,3,5-trimethylbenzene for 6 hours/day, 5 days/week, for 1 month. Impairments in passive-avoidance and active-avoidance tests, indicative of effects on learning and memory, occurred at ≥25 ppm. These findings corroborated those of an earlier study in which rats were similarly exposed to a single exposure level of 100 ppm of 1,3,5-trimethylbenzene (Gralewicz and Wiaderna, 2001) and are consistent with the results of the human study indicating that low concentrations of a mixture containing 1,3,5-trimethylbenzene can affect the CNS.

Subchronic p-RfC

The LOAEL of 25 ppm (123 mg/m^3) for neurobehavioral impairment in rats (Wiaderna et al., 2002) is used to derive the subchronic p-RfC; BMD analysis is precluded by insufficient quantitative data (results of the passive-avoidance and active-avoidance tests were imprecisely reported as bar graphs with undefined error bars). Derivation of the p-RfC first involves converting the rat LOAEL to a human equivalent concentration (HEC). The U.S. EPA (1994b) default procedure for calculating a HEC for an extrarespiratory effect from a vapor is to adjust the LOAEL for intermittent exposure and multiply the duration-adjusted LOAEL by the ratio of animal-to-human blood:air partition coefficients, as follows:

$$\begin{aligned} LOAEL_{ADJ} &= 123\ mg/m^3 \times 6\ hours/24\ hours \times 5\ days/7\ days \\ &= 22\ mg/m^3 \end{aligned}$$

$$LOAEL_{HEC} = LOAEL_{ADJ} \times (H_{b/g})_A/(H_{b/g})_H$$
$$= 22\ mg/m^3 \times 55.7/43.0$$
$$= 22\ mg/m^3 \times 1.3$$
$$= 29\ mg/m^3$$

where,

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

and,

$(H_{b/g})_A = 55.7$; $(H_{b/g})_H = 43.0$ (Meulenberg and Vijverberg, 2000)

The $LOAEL_{HEC}$ of 29 mg/m^3 is divided by a composite uncertainty factor (UF) of 3000 to derive a **subchronic p-RfC of 1E-2 mg/m^3**, as follows:

$$\textbf{Subchronic p-RfC} = LOAEL_{HEC} \div UF$$
$$= 29\ mg/m^3 \div 3000$$
$$= \textbf{0.01 or 1E-2 } \textbf{mg/m}^3$$

The composite UF of 3000 includes component factors of 10 for extrapolation from a LOAEL to a NOAEL, 3 for extrapolation from rats to humans, 10 for human variability, and 10 for database insufficiencies, as explained below.

A UF of 10 is applied for extrapolation from a LOAEL to a NOAEL because the lowest exposure concentration examined in the principal study was associated with neurobehavioral impairment; a NOAEL was not established.

A 3-fold UF is applied for interspecies extrapolation. 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. In the absence of information on the variability in response of humans to 1,3,5-trimethylbenzene, the full value of 10 is applied.

A 10-fold UF is applied to account for deficiencies in the available 1,3,5-trimethylbenzene database. A database UF of 10 is appropriate because the key neurobehavioral study was only 1 month in duration and did not identify a NOAEL, and the database lacks a comprehensive 90-day systemic toxicity study, a developmental toxicity study in a second species and a reproductive toxicity study.

Confidence in the principal study is low. Although a variety of neurobehavioral endpoints and three dose levels were evaluated, the study was only 1 month in duration, did not identify a NOAEL, and did not report results adequately to support BMD modeling. Confidence in the database is low, as discussed above. As such, a low confidence in the subchronic p-RfC result.

Chronic p-RfC

No chronic inhalation toxicity study of 1,3,5-trimethybenzene was located.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1,3,5-TRIMETHYLBENZENE

There are no human or animal carcinogenicity data for 1,3,5-trimethylbenzene. Limited genotoxicity data suggest that 1,3,5-trimethylbenzene is not mutagenic but may be clastogenic. 1,3,5-Trimethylbenzene did not induce reverse mutations in several strains of *Salmonella typhimurium* when tested *in vitro* with or without rat liver S9 metabolic activation (Janik-Spiechowicz et al., 1998; Nohmi et al., 1985). Mice that were treated with 1,3,5-trimethylbenzene by intraperitoneal injection had weak induction of sister-chromatid exchanges, but no induction of micronuclei, in bone marrow cells (Janik-Spiechowicz et al., 1998).

In accordance with current U.S. EPA cancer guidelines (U.S. EPA, 2005), the available data are characterized as "*Inadequate Information to Assess Carcinogenic Potential.*"

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APPENDIX. DERIVATION OF ORAL SCREENING VALUES FOR 1,3,5-TRIMETHYLBENZENE (CASRN 108-67-8)

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional oral toxicity values directly from the Koch Industries (1995b) 90-day rat study. Specifically, as an unpublished, presumably non-peer-reviewed TSCA submission, any useful data provided in such a reference is currently deemed inappropriate for the derivation of provisional toxicity values. However, the qualitative and quantitative information in the Koch Industries (1995b) study may be used to support derivation of provisional "Screening Values" that may be of use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix. 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.

Limited information is available on the oral toxicity of 1,3,5-trimethylbenzene and only one study, the Koch Industries (1995b) study, is of an exposure duration sufficient for deriving oral screening values. This is a comprehensive subchronic study in which male and female rats were administered 1,3,5-trimethylbenzene by gavage in doses of 0, 50, 200, or 600 mg/kg-day, for 5 days/week, for 90 days (Koch Industries, 1995b). The study identified a NOAEL of 200 mg/kg-day and LOAEL of 600 mg/kg-day based on clinical signs of discolored/wet inguinal fur and salivation, slightly decreased body-weight gain, increased liver and kidney weights, and increased serum alkaline phosphatase and phosphorus levels. The clinical signs may be possible neurotoxic effects of exposure that occurred in a majority of the high-dose animals. However, discolored/wet inguinal fur and salivation are also typical of a more generalized stress response in experimental rodents (Selye, 1936) and, as such, were not further considered. Likewise, the toxicological significance of increased serum phosphorus levels was not clear and not directly attributable to tissue/organ toxicity and, therefore, was not considered further. The increased liver and kidney weights are the most relevant effects because the decrease in body-weight gain was not statistically significant at the end of the study and not accompanied by a change in body weight. Liver and kidney weight increases were observed only in male and female rats of the high-dose (600 mg/kg-day) group, and were not accompanied by histopathological changes indicative of injury. Indeed, the authors of the Koch Industries (1995b) study suggested that the increased liver weight was likely due to induction of metabolic enzyme systems. This suggestion is supported by observations from earlier studies that indicated an association between significantly increased liver weight, cytochrome b5 content, and proliferation of smooth endoplasmic reticulum in rats exposed acutely to oral 1,3,5-trimethylbenzene (Pyykko, 1980; Ungvary et al., 1981). However, it should be noted that significantly increased serum alkaline

phosphatase (ALP) and cholesterol levels were observed only in male and female rats, respectively, of the 600 mg/kg-day exposure group. It is conservatively assumed that 1,3,5-trimethylbenzene-induced increased serum ALP may be indicative of injury to the hepatic biliary epithelium, although this enzyme is also found in bone, kidney, and intestine. Increased serum cholesterol in female rats exposed to 600 mg/kg-day may also be suggestive of altered hepatic function, as this organ is involved in cholesterol synthesis and storage. These increased serum biomarker levels further suggest the liver as the target of 1,3,5-trimethylbenzene toxicity via the oral route.

Subchronic Oral Screening Value

Potential points of departure (POD) for the subchronic oral screening value were identified in the Koch Industries (1995b) 90-day rat study. The serum phosphorus data and clinical signs were initially considered for POD identification. However, these effects were not clearly associated with an alteration in the structure or function of a given tissue or organ in rats. A benchmark dose (BMD) modeling approach was considered for the increased liver weight data, however it was not modeled because the responses were effectively limited to the high-dose group. As such, a LOAEL/NOAEL approach was used to identify the NOAEL of 200 mg/kg-day as the POD for significantly increased liver weight in male and female rats.

Since the gavage exposure protocol employed in the Koch Industries (1995b) principal study was 5 days/week, derivation of the subchronic oral screening value involves adjusting the NOAEL for partial weekly exposure and dividing the duration-adjusted $NOAEL_{ADJ}$ by an uncertainty factor (UF) of 1000. The **subchronic oral screening value of 1E-1 mg/kg-day** is calculated as follows:

$$NOAEL_{ADJ} = 200 \text{ mg/kg-day} \times 5 \text{ days}/7 \text{ days}$$
$$= 143 \text{ mg/kg-day}$$

$$\textbf{Subchronic Oral Screening Value} = NOAEL_{ADJ} \div UF$$
$$= 143 \text{ mg/kg-day} \div 1000$$
$$= \textbf{0.1 or 1E-1 mg/kg-day}$$

The composite UF of 1000 includes component factors of 10 for extrapolation from rats to humans, 10 for human variability, and 10 for database insufficiencies, as explained below.

A 10-fold UF is applied to account for laboratory animal-to-human interspecies differences. No information is available on the oral toxicity of 1,3,5-trimethylbenzene in humans; limited inhalation data suggest that the CNS is a target of 1,3,5-trimethylbenzene toxicity in humans as well as rats. No other information is available to assess possible differences between animals and humans in pharmacokinetic and pharmacodynamic responses to oral 1,3,5-trimethylbenzene.

A 10-fold UF for intraspecies differences is applied to account for potentially susceptible human subpopulations. In the absence of information on the variability in response of humans to 1,3,5-trimethylbenzene, the full value of 10 is applied.

A 10-fold UF is applied to account for deficiencies in the available 1,3,5-trimethylbenzene database. The oral database is essentially limited to a single 90-day systemic toxicity study. This is a well-designed study, but oral neurotoxicity, and developmental and reproductive toxicity studies are lacking. Neurotoxicity and developmental toxicity have been tested by the inhalation route. The inhalation data indicate that neurotoxicity, but not developmental toxicity, is a sensitive effect of exposure that needs to be assessed following oral exposure. In the absence of neurotoxicity studies by the oral route, and considering the lack of reproductive toxicity testing by any route, the full UF of 10 is applied.

Confidence in the principal study is medium. Although this study was comprehensive for systemic toxicity and identified both a LOAEL and NOAEL, only one species was tested and neurotoxicity, a known sensitive endpoint by the inhalation route, was not assessed. Confidence in the database is low, as discussed above. Confidence in the subchronic p-RfD is low due to the significant deficiencies in the database.

Chronic Oral Screening Value

No chronic oral toxicity study of 1,3,5-trimethybenzene was located. The same 90-day study (Koch Industries, 1995b) used to derive the subchronic oral screening value is used to derive a chronic oral screening value, based upon liver effects in rats. An additional uncertainty factor of 10 for extrapolation from subchronic to chronic duration is applied to the NOAEL of 200 mg/kg-day for significantly increased liver weight in male and female rats.

Since the gavage exposure protocol employed in the Koch Industries (1995b) principal study was 5 days/week, derivation of the chronic oral screening value involves adjusting the NOAEL for partial weekly exposure and dividing the duration-adjusted $NOAEL_{ADJ}$ by an uncertainty factor (UF) of 10,000. The **chronic oral screening value of 1E-2 mg/kg-day** is calculated as follows:

$NOAEL_{ADJ}$ = 200 mg/kg-day × 5 days/7 days
= 143 mg/kg-day

Chronic Oral Screening Value = $NOAEL_{ADJ}$ ÷ UF
= 143 mg/kg-day ÷ 10,000
= **0.01 or 1E-2 mg/kg-day**

The composite UF of 10,000 includes component factors of 10 for extrapolation from rats to humans, 10 for human variability, 10 for database insufficiencies, and 10 for subchronic to chronic duration, as explained below.

A 10-fold UF is applied to account for laboratory animal-to-human interspecies differences. No information is available on the oral toxicity of 1,3,5-trimethylbenzene in humans; limited inhalation data suggest that the CNS is a target of 1,3,5-trimethylbenzene toxicity in humans as well as rats. No other information is available to assess possible differences between animals and humans in pharmacokinetic and pharmacodynamic responses to oral 1,3,5-trimethylbenzene.

A 10-fold UF for intraspecies differences is applied to account for potentially susceptible human subpopulations. In the absence of information on the variability in response of humans to 1,3,5-trimethylbenzene, the full value of 10 is applied.

A 10-fold UF is applied to account for deficiencies in the available 1,3,5-trimethylbenzene database. The oral database is essentially limited to a single 90-day systemic toxicity study. This is a well-designed study, but oral neurotoxicity, and developmental and reproductive toxicity studies are lacking. Neurotoxicity and developmental toxicity have been tested by the inhalation route. The inhalation data indicate that neurotoxicity, but not developmental toxicity, is a sensitive effect of exposure that needs to be assessed following oral exposure. In the absence of neurotoxicity studies by the oral route, and considering the lack of reproductive toxicity testing by any route, the full UF of 10 is applied.

A 10-fold UF is applied to account for extrapolating from a subchronic study to chronic exposure scenarios. No chronic oral toxicity study of 1,3,5-trimethybenzene was located. Therefore, since the relationship between prolonged (chronic) oral exposure to 1,3,5-trimethylbenzene and liver effects observed following subchronic exposure, or potentially some other effect(s), cannot be confidently characterized, a full UF of 10 is applied.

Confidence in the principal study is medium. Although this study was comprehensive for systemic toxicity and identified both a LOAEL and NOAEL, only one species was tested and neurotoxicity, a known sensitive endpoint by the inhalation route, was not assessed. Confidence in the database is low, as discussed above. Confidence in the chronic p-RfD is low due to the significant deficiencies in the database.