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Provisional Peer-Reviewed Toxicity Values for

2,4,6-Tribromophenol
(CASRN 118-79-6)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

BMD	Benchmark 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 inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral 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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 2,4,6 TRIBROMOPHENOL (CASRN 118-79-6)

Background

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

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) 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
   - 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 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 2,4,6-tribromophenol is available on IRIS (U.S. EPA, 2009). There are no entries for 2,4,6-tribromophenol in the Chemical Assessments and Related Activities list (CARA; U.S. EPA, 1991a, 1994), the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories lists (U.S. EPA, 2006). The Agency for Toxic Substances Disease Registry (ATSDR, 2009) has not published a Toxicological Profile for 2,4,6-tribromophenol. The World Health Organization (WHO, 2005) has published a Concise International Chemical Assessment Document (CICAD) for 2,4,6-tribromophenol and other simple brominated phenols, but found the existing toxicity data inadequate for derivation of either oral or inhalation criteria to protect human health. 2,4,6-Tribromophenol has been reviewed under the HPV Challenge Program, and robust summaries from sponsors (e.g., Great Lakes Chemical Corporation, 2002) are available online (U.S. EPA, 2008). Data summaries for 2,4,6-tribromophenol have been prepared under the Organization for Economic Cooperation and Development-Screening Information Data System (OECD-SIDS, 2006) program and are available online. The International Agency for Research on Cancer (IARC, 2009) has not reviewed 2,4,6-tribromophenol with respect to chronic toxicity or carcinogenicity in humans or animals. The chronic toxicity and carcinogenicity of 2,4,6-tribromophenol have not been assessed by the National Toxicology Program (NTP, 2005, 2009). The Occupational Safety and Health Administration (OSHA, 2009), National Institute for Occupational Safety and Health (NIOSH, 2005), and the American Conference of Governmental Industrial Hygienists (ACGIH, 2001, 2007) have not established occupational exposure limits for 2,4,6-tribromophenol. The California Environmental Protection Agency (CalEPA, 2002, 2005a, 2005b) has not derived a Recommended Exposure Limit (REL) or cancer potency factor for 2,4,6-tribromophenol.

Except as noted, literature searches were conducted from 1960s through June 2007 for studies relevant to the derivation of provisional toxicity values for 2,4,6-tribromophenol. Databases searched include MEDLINE, TOXLINE (Special), BIOSIS (August 2000 through June 2007), TSCATS 1/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents (December through June 2007). A final search of the literature was conducted for the period from June, 2007 thru July, 2009.

REVIEW OF PERTINENT DATA

Human Studies

No studies regarding the toxicity of 2,4,6-tribromophenol in humans were identified.

Animal Studies

Oral Exposure

Subchronic Studies—Crj:CD Sprague-Dawley rats (12/sex/dose) were exposed orally to 2,4,6-tribromophenol (in corn oil) by gavage at daily doses of 0 (vehicle), 100, 300, or 1000 mg/kg-day in a combined repeat-dose and developmental/reproductive screening toxicity test (OECD Test Guideline 422) (Tanaka et al., 1999). Males were exposed for 14 days prior to mating (plus an additional 34 days; 48 days total) and females were exposed 14 days prior to mating through Day 3 of lactation (41−45 days total). Females that did not mate successfully were exposed for a total of 48 days. Only one female (from the control group) did not mate successfully. Animals were observed daily, and clinical signs of toxicity, body weight, food consumption, and water consumption were assessed for all animals throughout the study. Comprehensive hematological and serum chemistry variables were assessed at study termination for all males, but not for females. Absolute and relative organ weights were evaluated for brain, thymus, liver, spleen, kidneys, adrenals, and reproductive tissues (testes and epididymis for males; ovaries for females). Gross necropsies were conducted on all test animals. Comprehensive histological examination of the digestive system was conducted for all test groups. The thymus and urinary systems were evaluated histologically for all male test groups, but only for control and high-dose females. Histological evaluation of the heart, spleen, testes, ovaries, adrenals, and brain was performed only for control and high-dose animals of both sexes. The reproductive variables assessed in the study, as well as conclusions regarding the reproductive endpoints, are discussed in the *Reproductive/Developmental Studies* section of this document.

Table 1 shows the endpoints relevant to the assessment of systemic toxicity by Tanaka et al. (1999). No parental mortality was observed. In comparison with controls, body weight was statistically significantly decreased in the high-dose males beginning on Day 8 and at every weekly measurement interval through the last measurement on Day 43 of the study (the deficit from controls was approximately 10% throughout this period). Body weights were also decreased among high-dose females relative to controls starting with Day 7 of gestation and persisting through the last measurement on Day 4 of lactation, but the difference was not as pronounced as in the males (deficit of approximately 6% throughout this period). Necropsy body weights were significantly decreased in high-dose males (-12%; $p < 0.0001$, two-tailed *t*-test) and females (-5%; $p < 0.001$, two-tailed *t*-test) with respect to controls (see Table 1). Food consumption was reduced among high-dose animals of both sexes during the first week of the

study, but not in subsequent weeks. A dose-related increase in the occurrence of excessive salivation 5−35 minutes after dosing was observed among males and females exposed to 300 and 1000 mg/kg-day (data not shown by the researchers). This reaction to dosing was more common at 1000 mg/kg-day than at 300 mg/kg-day and in males rather than females.

No treatment-related adverse effects on hematological variables were observed in males (females were not assessed) (Tanaka et al., 1999). A statistically significant increase in prothrombin clotting time in high-dose males relative to controls (15.6 ± 1.2 seconds versus 14.2 ± 0.7 seconds) was not considered toxicologically relevant by the researchers because of the small magnitude of change and because other indicators of potential adverse effects on clotting (APPT [activated partial thromboplastin time] and fibrinogen) were unaffected by treatment. Serum chemistry examination revealed statistically significant, dose-related increases in creatinine in males dosed at 300 and 1000 mg/kg-day (indicative of renal dysfunction), an increase in alkaline phosphatase (ALP) activity in males at 1000 mg/kg-day (possibly indicative of an effect on the liver), and a number of other changes of uncertain biological significance in high-dose males (small 10−15% increases in protein, albumin, albumin-to-globulin ratio [A/G], and chloride [Cl], and decreases in total bilirubin and potassium [K]) potentially related to decreased body weight at this dose (Table 1). Creatinine was the only serum chemistry variable that differed significantly from controls at the 300-mg/kg-day dose group. Blood urea nitrogen (BUN) appeared to be elevated in the high-dose males, providing further support for a renal effect, but it was not statistically increased due to high variability in the treated group. Clinical chemistry was not evaluated in females.

There were statistically increased relative and absolute organ weights with respect to controls for a number of organs in males and females only at the high dose (Table 1) (Tanaka et al., 1999). With the possible exception of the changes in liver weight (increased absolute and relative weights in both sexes) and thymus weight (decreased absolute weight in males), the observed changes (increased relative organ weights) were consistent with, and likely secondary to, the decrease in body weight in this dose group. Liver enlargement was visible upon gross necropsy of high-dose males. Treatment-related histopathologic changes were noted in thymus, kidney, and liver tissue. A statistically significant increase in the incidence of hepatocellular hypertrophy (severity graded as slight -1 on a scale of 1 to 3) was noted in high-dose males (12/12), but not females (0/11), with respect to controls (0/11). There was also a significant decrease in the incidence of fatty change in liver sections from high-dose males. There were statistically significant increases in the incidences of hyaline casts, tubular dilatation, papillary necrosis, and lymphocyte infiltration of kidneys in high-dose males (slight-to-moderate severity), but not females. Histological evaluation of thymus sections revealed slight atrophy in 3/12 high-dose males, but not in control, low-, or mid-dose males or in control or high-dose females. This finding was not statistically significant, but it appears to be biologically relevant given the statistically significant decrease in thymus weight observed in high-dose males.

Table 1. Summary of Significant Findings Following Subchronic Oral (Gavage) Exposure of Rats to 2,4,6-Tribromophenol[a]

Endpoint[b]	Dose (mg/kg-day)							
	0		100		300		1000	
	Male	Female	Male	Female	Male	Female	Male	Female
No. examined[c]	12	11	12	12	12	12	12	11
Body weight (g)[d]	492 ± 34	332 ± 16	478 ± 31	317 ± 27	478 ± 36	333 ± 22	422 ± 25[e]	307 ± 15[e]
Absolute Organ Weights								
Thymus (mg)	299 ± 81	157 ± 46	269 ± 52	134 ± 48	269 ± 66	168 ± 75	201 ± 57[f]	137 ± 32
Liver (g)	13.99 ± 1.72	13.70 ± 0.80	13.18 ± 1.31	13.48 ± 2.07	14.20 ± 1.99	14.39 ± 1.76	16.23 ± 2.32[g]	15.74 ± 1.28[f]
Relative Organ Weights (g%)								
Brain	0.460 ± 0.042	0.613 ± 0.034	0.465 ± 0.033	0.657 ± 0.067	0.473 ± 0.041	0.602 ± 0.038	0.522 ± 0.032[f]	0.665 ± 0.025[g]
Liver	2.834 ± 0.218	4.138 ± 0.287	2.751 ± 0.152	4.230 ± 0.396	2.964 ± 0.285	4.312 ± 0.393	3.837 ± 0.447[f]	5.117 ± 0.265[f]
Kidney	0.678 ± 0.054	0.649 ± 0.072	0.661 ± 0.053	0.694 ± 0.078	0.679 ± 0.083	0.666 ± 0.047	0.824 ± 0.101[f]	0.772 ± 0.094[f]
Adrenals	12.257 ± 1.299	23.171 ± 1.572	11.807 ± 1.277	25.991 ± 3.418	13.494 ± 1.966	25.988 ± 4.091	15.304 ± 1.697[f]	27.315 ± 3.415[f]
Testes	0.721 ± 0.062	NA	0.733 ± 0.067	NA	0.729 ± 0.080	NA	0.794 ± 0.046[g]	NA
Histological Findings (observed/examined)								
Liver								
Fatty change	6/11	2/11	5/12	1/12	3/12	0/12	0/12[f]	0/11
Hepatocyte hypertrophy	0/11	0/11	0/12	0/12	0/12	0/12	12/12[f]	0/11
Kidney								
Hyaline casts[h]	1/11	1/11	1/12	NE	0/12	NE	8/12[f]	0/11
Dilatation, tubules	0/11	0/11	0/12	NE	0/12	NE	7/12[f]	0/11
Mineralization	1/11	3/11	0/12	NE	0/12	NE	1/12	1/11
Papillary necrosis	0/11	0/11	0/12	NE	0/12	NE	5/12[f]	0/11
Lymphocyte infiltration	1/11	0/11	1/12	NE	0	NE	6/12[g]	0/11

Table 1. Summary of Significant Findings Following Subchronic Oral (Gavage) Exposure of Rats to 2,4,6-Tribromophenol[a]

Endpoint[b]	Dose (mg/kg-day)							
	0		100		300		1000	
	Male	Female	Male	Female	Male	Female	Male	Female
Thymus (atrophy)	0/11	0/11	0/12	NE	0/12	NE	3/12	0/11
Blood Chemistry (12 males/dose examined)								
Protein (g/dL)	5.87 ± 0.22	NE	5.84 ± 0.14	NE	5.95 ± 0.26	NE	6.45 ± 0.51[f]	NE
Albumin (g/dL)	3.36 ± 0.13	NE	3.33 ± 0.09	NE	3.39 ± 0.19	NE	3.88 ± 0.29[f]	NE
A/G	1.34 ± 0.06	NE	1.33 ± 0.09	NE	1.33 ± 0.10	NE	1.51 ± 0.08[f]	NE
Creatinine (mg/dL)	0.27 ± 0.03	NE	0.30 ± 0.04	NE	0.33 ± 0.07[g]	NE	0.47 ± 0.26[f]	NE
BUN (mg/dL)	13.3 ± 1.4	NE	13.6 ± 2.1	NE	13.2 ± 2.3	NE	20.9 ± 11.4	NE
Bilirubin (mg/dL)	0.05 ± 0.01	NE	0.05 ± 0.01	NE	0.04 ± 0.01	NE	0.02 ± 0.01[f]	NE
ALP (U/L)	354 ± 74	NE	440 ± 162	NE	342 ± 102	NE	514 ± 155[g]	NE
K (mmol/L)	4.46 ± 0.29	NE	4.40 ± 0.25	NE	4.38 ± 0.30	NE	4.06 ± 0.25[f]	NE
Cl (mmol/L)	106.6 ± 1.2	NE	107.6 ± 1.1	NE	107.8 ± 1.5	NE	119.0 ± 3.6[f]	NE

[a]Tanaka et al., 1999
[b]Values are mean ± SD; NA = Not Applicable; NE = Not Evaluated
[c]The reason why <12 animals per dose were examined for some groups is not clear from the English translation of the study
[d]Values taken from Table 3 of Tanaka et al., 1999; these values differ from body weights depicted in Figures 1 and 2 of Tanaka et al., 1999
[e]Significant difference from control group, $p < 0.001$, two-sided t-test performed for this review
[f]Significant difference from control group, $p < 0.01$ reported by Tanaka et al., 1999
[g]Significant difference from control group, $p < 0.05$ reported by Tanaka et al., 1999
[h]Composition and specific location within the kidney were not addressed

The increase in liver weight and hepatocellular hypertrophy, and the slightly elevated serum ALP levels observed in the high-dose males, are indicative of an adaptive response of the liver to 2,4,6-tribromophenol exposure, but do not suggest an adverse effect. In the thymus, slight atrophy in some individuals and decreased mean absolute organ weight suggest a potential chemical-related effect in high-dose males. The serum chemistry and microscopic evaluation of urinary tract tissues made in this study (Tanaka et al., 1999) suggest that 2,4,6-tribromophenol adversely affects the kidney in male rats. Significant incidences of several types of kidney lesions, including hyaline casts, tubular dilatation, lymphocyte infiltration, and papillary necrosis, were observed in the high-dose males only. The kidney observations appear congruent with the chemically induced globulin accumulation (CIGA alpha$_{2U}$) nephropathy specific to male rats. However, chemicals known to produce alpha$_{2U}$ nephropathy typically produce minimal changes in clinical chemistry and have little-to-no effect on glomerular function (U.S. EPA, 1991b). A dose-related and statistically significant increase in serum creatinine was observed in males exposed to 300 (22%) and 1000 (74%) mg/kg-day, suggesting a treatment-related adverse effect on glomerular function, which, in turn, suggests that alpha$_{2U}$ nephropathy may not be responsible for the observed kidney damage. Unfortunately, no serum chemistries were assessed in females. Based on the dose-related increase in serum creatinine in males and clinical signs (salivation) in both sexes, this study identifies a LOAEL of 300 mg/kg-day for 2,4,6-tribromophenol. The NOAEL is 100 mg/kg-day.

Chronic Studies—No chronic studies of 2,4,6-tribromophenol were identified.

Reproductive/Developmental Studies—As discussed in the Subchronic Studies section, Tanaka et al. (1999) exposed groups of male and female rats by gavage to 2,4,6-tribromophenol (0, 100, 300, or 1000 mg/kg-day) in a combined repeated-dose/reproductive/developmental toxicity screening study (OECD Test Guideline 422). The reproductive variables assessed in the study included numbers of pairs copulated, numbers of pregnant females, copulation index, fertility index, mean days of estrous cycle, numbers of dams delivering live pups, mean duration of gestation, mean number of total corpora lutea, mean number of total implants, mean number of total pups born, mean number of total live pups born, mean sex ratio, mean stillbirths (cannibalism evaluated separately), gestation index, mean implantation index, mean liver birth index, and mean viability index (male and female) on Day 4. All of the reproductive variables were presented as totals per dose-group as well as means per litter per dose-group where appropriate. There were no treatment-related adverse effects on any endpoint except for neonatal growth (decreased body weight relative to controls; both sexes; Days 0 and 4 of lactation) and viability (Day 4 of lactation) in the 1000 mg/kg-day test group. Table 2 summarizes the results for the viability endpoints. Data for pup body weight were not reported. Based on these observations, the LOAEL for reproductive toxicity was 1000 mg/kg-day for decreased neonatal viability (both sexes) on Day 4 of lactation and decreased neonatal body weight on Days 0 and 4 of lactation. The NOAEL is 300 mg/kg-day.

Table 2. Summary of Significant Reproductive/Developmental Endpoints Following Oral (Gavage) Exposure of Rats to 2,4,6-Tribromophenol Prior to Mating and Throughout Gestation and Early Lactation[a]

Dose (mg/kg-day)	0	100	300	1000
No. Live Pups on Day 4 (per litter mean ± SD)				
Male	83 (7.3 ± 1.2)	87 (7.3 ± 2.8)	86 (7.2 ± 2.3)	42 (3.5 ± 2.4) [b,c]
Female	72 (6.5 ± 1.9)	84 (7.0 ± 2.2)	80 (6.7 ± 1.2)	49 (4.1 ± 2.9)[b,d]
Mean ± SD Day 4 Viability Index[e]				
Male	92.6 ± 8.6	88.6 ± 23.7	97.4 ± 6.3	53.3 ± 34.2[c]
Female	97.6 ± 5.4	92.7 ± 15.5	94.0 ± 9.6	50.4 ± 35.1[c]

[a]Tanaka et al., 1999
[b]Not clear whether the investigator's assessment of statistical significance applies to the total numbers, the means or both
[c]Significant difference from control group, $p < 0.01$
[d]Significant difference from control group, $p < 0.05$
[e]Per litter: (Number of live pups on Day 4 ÷ number live pups born) × 100

A pilot teratology study was conducted in which 2,4,6-tribromophenol (purity not reported) in corn oil was administered by gavage to groups of five Charles River CD female rats at doses of 0, 10, 30, 100, 300, 1000, or 3000 mg/kg-day on Gestation Days (GD) 6−15 (International Research and Development Corporation, 1978a). The dams were observed for clinical signs, changes in body weight, and mortality and were sacrificed on GD 20 for uterine observations. Numbers of viable and nonviable fetuses, early and late resorptions, total implantations, and corpora lutea were recorded, but the fetuses were not examined for skeletal or visceral malformations. All rats in the 3000-mg/kg-day group died by GD 7. Significant effects at the 1000-mg/kg-day dose included a 12.7% decrease, relative to controls, in maternal weight gain between GD 6 and 12 and a 16% decrease in the number of live fetuses (13.7, 12.0, 13.6, 13.0, 13.6, and 11.5% at 0, 10, 30, 100, 300, and 1000 mg/kg-day, respectively; standard deviations [SDs] not reported). Postimplantation loss was increased 500% at 1000 mg/kg-day, but this effect was not clearly dose-related (increased 433, 100, 100, and 33% at 10, 30, 100, and 300 mg/kg-day, respectively). The LOAEL for maternal and fetal toxicity in this study is 1000 mg/kg-day for decreased maternal weight gain and decreased fetal viability. The NOAEL is 300 mg/kg-day.

Inhalation Exposure

Subchronic Studies—Groups of five male and five female Charles River COBS rats were exposed via whole-body inhalation to 2,4,6-tribromophenol (purity 99.5 to 99.7%) dust at nominal concentrations of 0, 0.1, or 1 mg/L (mean analytical concentrations of 0, 0.10, or 0.92 mg/L (0, 100, or 920 mg/m^3); mean gravimetric concentrations of 0, 0.15, or 0.98 mg/L) for 2 or 6 hours/day, 5 days/week, for 3 weeks (Industrial Biotest Laboratories, Inc., 1977). Particle sizes ranged from 1−74 microns, with 78% of the particles ≤10 microns and 65% = 1−5 microns. A mass median aerodynamic diameter (MMAD) was not reported and one cannot be estimated from the data presented. Clinical signs, body weight, mortality, hematology (three/sex/group), clinical chemistry (three/sex/group), urinalysis endpoints (three/sex/group), and gross pathology

were evaluated in all groups. Animals were observed daily, body weights were measured weekly, and clinical chemistry, urinalysis, and hematological variables were assessed on Study Day 0 and at study termination. Histopathology was assessed in surviving animals in the control and high-concentration groups. No statistical analyses were reported by the researchers.

Deaths occurred in the high-dose group (1/5 males and 1/5 females) after 10−11 exposures (Industrial Biotest Laboratories, Inc., 1977). No control or low-dose animals died. Clinical signs of toxicity (primarily hypoactivity, salivation, lacrimation, and red nasal discharge) were observed at both exposure concentrations. Hypoactivity and salivation were observed in all high- and low-dose animals on every exposure day of the study. Mean terminal body weights were markedly reduced in high-dose males (-30%) and females (-25%), in comparison to controls; the animals in these groups actually lost weight during the course of the study (the loss in weight occurred during the third week of the study). In the low-dose group, terminal body weights did not differ significantly from controls, but body weight gain over the course of the study was marginally reduced in females only ($p = 0.045$, two-tailed t-test performed for this review). Hematology and urinalysis findings were unremarkable. Although the researchers suggested that serum chemistry findings were likewise normal, there were statistically significant ($p < 0.05$, two-tailed t-tests performed for this review) 1.5 to 3-fold increases in BUN (males and females) and alanine aminotransferase (ALT) (males) in the high-dose group; small group sizes ($n = 2$ or 3) limit the reliability of these data, however. At gross necropsy, 4/5 males and 5/5 females in the high-dose group were visibly emaciated. Pathologic changes were observed in the liver and kidneys of high-dose animals. Histologic alterations included dilatation of renal tubules in 3/5 rats of each sex and a solitary area of submassive hepatic necrosis in one female. Proteinaceous casts (unilateral) were observed in the renal tubules of 2/5 high-dose males, but in none of the control males and in none of the females (either control or high-dose). There were no treatment-related effects on the lungs or trachea of high-dose rats in comparison with controls. The LOAEL for this study is 100 mg/m^3 (lowest dose tested) based on clinical signs of toxicity (especially hypoactivity and salivation) in males and females and marginally decreased body weight gain in females. A NOAEL was not identified.

Chronic Studies—No chronic inhalation studies were identified.

Reproductive/Developmental Studies—Pregnant Wistar rats (25/dose) were exposed via whole-body inhalation to research-grade 2,4,6-tribromophenol (no further characterization) at nominal concentrations of 0, 0.03, 0.1, 0.3, or 1.0 mg/m^3, 24 hr/day, 7 days/wk, on Days 1−21 of gestation (Lyubimov et al., 1998). No details regarding the methods for generating the test atmosphere, particle sizes, or measurement of test concentrations were reported. CNS effects were monitored in pregnant dams (Day 21 of gestation) and pups (postnatal days [PND] 30 and 60 by assessing skin pain threshold (SPT) and behavior in an open field (mobility, orientation, horizontal and vertical movement, etc.), but these methods were not described in detail. Maternal body weight, rectal temperature, lipid peroxidation (liver and placenta), total amino nitrogen in the urine and blood, phenol excretion (urine), and serum hormone and enzyme levels were recorded. Nonspecific immunological status of the dams was assessed by evaluating phagocytosis and antimicrobial activity (test not specified) of the blood. On Day 21 of pregnancy, 15 dams per dose group were sacrificed and examined for corpora lutea, numbers of implants, resorptions, and live and dead fetuses. Half of the fetuses were examined for skeletal variations and half were examined for visceral malformations. Groups of 10 dams per dose were

allowed to deliver pups, which were then observed for two months and evaluated in the aforementioned SPT and behavioral tests. These pups were sacrificed on PND 60 and relative organ weights were determined for heart, liver, kidneys, spleen, adrenals, and reproductive organs (ovaries and testes).

No mortality and no effects on maternal body-weight gain were reported (data not shown by researchers) (Lyubimov et al., 1998). Dams exposed to the highest concentration had significant decreases in mean orientation reactions (i.e., vertical head movements), relative to controls (3.8 ± 0.59 versus 11.11 ± 2.73 in controls), but no other behavioral changes. Significant increases in serum ALP (65.0 versus 29.0 mEQ in controls, no measure of error reported), serum progesterone (93.5 ± 7.3 versus 61.3 ± 7.1 mg/L in controls), urinary total amino nitrogen (~22% higher than controls), and total excretion of phenols (~23% higher than controls) were also observed in dams exposed at the highest concentration. Data were not shown for the aforementioned variables at the other exposure concentrations. There were no treatment-related effects on immune function, serum corticosterone levels, or serum estradiol concentrations (data not shown). Statistically significant dose-related increases in embryolethality (combined pre- and postimplantation loss) were found at test concentrations of 0.1 mg/m^3 and above (approximately 7, 8, 18, 22, and 36% embryolethality for the control, 0.03, 0.1, 0.3, and 1.0 mg/m^3 groups, respectively; data presented graphically in the original report). Fetal weight was significantly decreased at concentrations of 0.1 and 1 mg/m^3, but not at 0.3 mg/m^3. Delayed sternal ossification was reported in exposed groups; this manifest as a significant decrease in the number of centers for sternal ossification (6.5 ± not reported, 3.85 ± 0.42, 4.98 ± 0.27, and 4.95 ± 0.27 in control, 0.1, 0.3, and 1.0 mg/m^3 groups; data for 0.03 mg/m^3 were not reported). No other meaningful treatment-related findings regarding skeletal or visceral malformations or other variables that were assessed are apparent from the data presented in the report.

A somewhat detailed discussion of postnatal development and neurobehavioral effects is presented in the report (Lyubimov et al., 1998), but the meaning of these findings is unclear. The reported behavioral changes that had statistical significance (grooming behavior and"emotionality") were not dose-related, and, in the case of"emotionality," which is defined by the investigators as a measure of the number of defecations made during the observation period, the mean and SDs were extremely small. Changes in relative organ weights are discussed for 2-month-old neonates, but no data are presented. With the possible exception of reduced relative testes weight in high-dose males, the reported changes do not appear to be dose-related. In addition to the absence of data to discern the magnitude of the reported changes, the lack of absolute organ weights and the lack of organ histopathology preclude the assignment of meaning to any of the reported findings with respect to organ weights.

Deficiencies in reporting of the study (Lyubimov et al., 1998) limit the utility of these data for toxicity assessment. Using the data reported, the LOAEL for maternal toxicity in this study is 1.0 mg/m^3 on the basis of increases in serum ALP and progesterone and urinary amino nitrogen, and the NOAEL is 0.3 mg/m^3. For fetotoxicity, the study appears to identify a LOAEL of 0.1 mg/m^3 for embryolethality and delayed sternal ossification, with a NOAEL of 0.03 mg/m^3. These findings suggest that the developing fetus may be a sensitive target for 2,4,6-tribromophenol. However, the reliability of these data is uncertain due to inadequate reporting of study methods and results.

Other Studies

Toxicokinetics

Absorption, distribution, and elimination were evaluated in 11 rats (strain not reported) that were treated with a single dose of ^{14}C-2,4,6-tribromophenol (purity 99.98%) in aqueous ethanol by gavage (Velsicol Chemical Corporation, 1977). Groups of 2−3 females and 2 males were given 4.0−5.3 mg/kg and sacrificed 8, 17, 48, and 96 hours after treatment, respectively, for measurement of radiocarbon in tissues. Blood radiocarbon was measured in four rats at 1, 2, 4, 8, 17, 24, and 48 hours after treatment. 2,4,6-Tribromophenol appears to have been rapidly absorbed and readily excreted. Radiocarbon in the blood peaked 1 hour after dosing and then decreased log-linearly to negligible levels within 24 hours. Blood level kinetics are apparently first order and the elimination rate constant (k_e) and half-life are calculated to be 0.3 and 2.03 hours, respectively. In tissues, the levels of radiocarbon reached maximum values 8 hours following dosing, with the highest levels occurring in the blood, muscle, fat, kidneys, liver, and lungs. The only tissues containing detectable residues after 48 hours were kidneys, liver, and lungs. Tissues retained approximately 4.9% and 0.01% of the administered radiocarbon at 8 and 48 hours following treatment, respectively. Most of the administered radioactivity was eliminated via urine (~70−90%) and feces (~4−6%) within 48 hours. Elimination of radioactivity in the urine was proportional to the decreasing concentrations in the blood.

Accumulation of 2,4,6-tribromophenol (purity 99.3%) in adipose tissue was evaluated in groups of 8 male Charles River rats (3 control and 5 test rats/group) by gas chromatography (Industrial Biotest Laboratories, Inc., 1975). Rats were fed a diet containing 1000 ppm of 2,4,6-tribromophenol and then sacrificed after 7 days of exposure followed by 0, 7, or 14 days of recovery or 21 days of exposure followed by 0, 14, or 42 days of recovery. Compared to control values ranging from not detectable (<0.01 ppm) to 0.016 ppm, the fat tissue analysis showed, increased 2,4,6-tribromophenol concentration at the end of the 7- and 14-day exposure periods (0.56 and 0.30 ppm, respectively), as well as an increase (0.06 ppm) in 2/5 animals given 7 days recovery after 7 days of treatment. None of the animals given 14-day or longer recovery periods had detectable residue. No treatment-related changes in food consumption or body weight were observed during the study.

Acute/Short-term Toxicity

Crj:CD Sprague-Dawley rats (5/sex/dose) were given a single oral dose of 2,4,6-tribromophenol (99.8% purity by weight) in corn oil by gavage at doses of 1000, 1300, 1690, 2197, or 2856 mg/kg and observed for 14 days (Tanaka et al., 1999). Hypoactivity was observed at all doses and excessive salivation was observed in most treated animals. Mortality, convulsions, tremors, and prone or lateral body position were observed in both sexes at doses ≥1300 mg/kg. All deaths occurred within 1 day of exposure. The combined LD_{50} for both sexes is 1486 mg/kg. No macroscopic abnormalities were observed at necropsy.

Spartan rats (5/sex/dose) were treated by gavage with a single dose of 2,4,6-tribromophenol (suspended in 0.5% Methocel) at 1585, 2512, 3980, 6308, 10,000, or 15,848 mg/kg and were observed for 14 days (International Research and Development Corporation, 1974a). LD_{50} values of 5012 mg/kg for males and 5012 mg/kg for females were calculated based on zero, one (male), one (female), nine (five males, four females), nine (four males, five females) and nine (four males, five females) deaths in the low- to high-dose groups. Clinical signs of toxicity, including nasal and ocular discharge (clear and porphyrin-containing), lacrimation, decreased motor activity, tachypnea, and/or tachycardia, were observed in all dose

groups. Ataxia, tremors, flaccidity, prostration, and/or cyanosis occurred at ≥6308 mg/kg. Gross necropsy revealed a dose-related increase in congestion with some hemorrhage in lung, stomach, and liver.

Charles River CD rats (5/sex/dose) were given a single oral dose (by gavage) of 631, 1000, 1585, 2512, 3980, or 6308 mg/kg and were observed for 14 days (International Research and Development Corporation, 1978b). One female at 1585 mg/kg and all animals in the higher-dose groups died. LD_{50} values were estimated to be 1995 mg/kg for males and 1819 mg/kg for females. No information on clinical signs of toxicity or pathology was reported.

Mortality was observed in guinea pigs given a single oral dose of 2,4,6-tribromophenol at 3000 mg/kg, but no mortality was observed following similar exposure to 1000 mg/kg (Dow Chemical Company, 1946). No additional information (e.g., numbers tested and deceased, observation period, animal sex, and strain) was reported.

Spartan rats (5/sex) that were exposed by inhalation to 50 mg/L (50,000 mg/m^3) of 2,4,6-tribromophenol for 4 hours and observed for 14 days showed clinical signs that included decreased motor activity, slight dyspnea, erythema, ocular porphyrin discharge, and clear nasal discharge (International Research and Development Corporation, 1974b). Clinical signs of toxicity observed in Charles River rats (5/sex) during inhalation exposure to 1.63 mg/L (1630 mg/m^3) for 4 hours included ptosis (drooping eyelids) and red nasal discharge; the nasal discharge continued for 8−18 hours following exposure (Industrial Biotest Laboratories, Inc., 1977).

Genotoxicity

2,4,6-Tribromophenol was not mutagenic in assays conducted by three different laboratories with *Salmonella typhimurium, Escherichia coli*, or *Saccharomyces cerevisiae*. 2,4,6-Tribromophenol dissolved in dimethyl sulfoxide (DMSO) is not mutagenic in preincubation assays with *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2uvrA (Tanaka et al., 1999). Assays were conducted both with and without metabolic activation (rat liver S9) at six different concentrations up to 500 μg/plate in *Salmonella* strains TA98, 100, and 1535, and up to 1000 μg/plate in TA1537. Toxicity was observed at higher test concentrations, and the results at these concentrations are not reported. In *E. coli*, assays were conducted with six different concentrations up to 5000 μg/plate, and toxicity was observed only at 5000 μg/plate. All test results were negative. Positive and negative controls responded appropriately. 2,4,6-Tribromophenol is not mutagenic in preincubation assays with *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 (Zeigler et al., 1987). These assays were conducted with and without Aroclor 1254-induced rat and hamster liver homogenate. 2,4,6-Tribromophenol was also not mutagenic in plate incorporation assays with *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *Saccharomyces cerevisiae* strain D4 (Litton Bionetics, Inc., 1978). These assays were conducted with, and without, Aroclor 1254-induced rat liver homogenate.

2,4,6-Tribromophenol dissolved in DMSO induced chromosomal aberrations in Chinese hamster lung (CHL/IU) cells following short-term treatment (Tanaka et al., 1999). The lowest effective concentrations are 0.050 mg/L in the absence of metabolic activation and 0.10 mg/L in the presence of metabolic activation (phenobarbital and 5,6-benzoflavone-induced rat liver S9).

These were the highest concentrations tested. No polyploidy was observed. 2,4,6-Tribromophenol did not induce chromosome fragmentation in *Allium cepa* root cells (Levan and Tjio, 1948).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 2,4,6-TRIBROMOPHENOL

Subchronic p-RfD Derivation

The toxicity database for 2,4,6-tribromophenol is limited to a combination repeated-dose reproductive/developmental screening toxicity study (Tanaka et al., 1999) and a pilot teratology study (International Research and Development Corporation, 1978a), both of which were conducted with rats. The repeated-dose study was conducted for 41−48 days. None of the available studies examined fetuses for malformations. There are no human studies. Table 3 shows the dose-response information from the available animal studies.

Table 3. Summary of Oral Noncancer Dose-Response Information

Species	Sex	Dose (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Subchronic Exposure								
Rat	M,F	0, 100, 300, or 1000 mg/kg-day	Gavage, 14 days prior to mating through Day 3 of lactation	100	300	Increased serum creatinine (M), clinical signs (salivation)	OECD Guideline Study for combined repeated-dose, reproductive, and developmental toxicity screening.	Tanaka et al., 1999
Reproductive/Developmental Toxicity								
Rat	M,F	0, 100, 300, or 1000 mg/kg-day	Gavage, 14 days prior to mating through Day 3 of lactation	300	1000	Decreased neonatal viability (both sexes) on Day 4; decreased neonatal body weight (Days 0 and 4)	OECD Guideline Study for combined repeated-dose, reproductive, and developmental toxicity screening; no exams for fetal malformations.	Tanaka et al., 1999
Rat	F	0, 10, 30, 100, 300, 1000, or 3000 mg/kg-day	Gavage, Days 6−15 gestation	300	1000	Decrease in maternal weight gain between Gestation Days 6 and 12 and a 16% decrease in the mean number of live fetuses per litter	Pilot study; no exams for fetal malformations; 100% mortality by GD 7 at 3000 mg/kg-day.	International Research and Development Corporation, 1978a

The observed treatment-related effects following the lowest repeated exposure in the animal database were increased serum creatinine and clinical signs of toxicity (excessive salivation) (Tanaka et al., 1999). These effects were observed at a concentration of 300 mg/kg-day. The next highest dose tested (1000 mg/kg-day) was associated with a larger increase in serum creatinine, greater occurrence of salivation, histopathologic evidence of kidney damage (males), increased absolute and relative liver weight, hepatocellular hypertrophy, increased serum ALP, other serum chemistry changes in males (increased protein, albumin, chloride, and decreased potassium), possible thymic atrophy in males (decreased thymus weight and histological evidence of atrophy), and decreased body weight in both sexes. The observed liver changes (increased liver weight, hepatocellular hypertrophy, and increased serum ALP levels) appear to represent an adaptive response to exposure, rather than toxicity. Despite the similarity in lesions and pattern of occurrence, the observed effects on the kidney in males may not be $alpha_{2u}$-related nephropathy; increased serum creatinine is indicative of an effect on glomerular function that is not typical of $alpha_{2u}$ nephropathy. Unfortunately, no serum chemistries were assessed in females, making further characterization of potential effects on the kidney in females impossible.

Data from the reproductive phase of the combined study and from the pilot teratology study are supportive of adverse effects at the 1000 mg/kg-day level of exposure. Decreases in maternal weight gain during exposure and in neonatal growth and viability were observed in both the screening reproductive and pilot teratology studies at 1000 mg/kg-day (Tanaka et al., 1999; International Research and Development Corporation, 1978a;). No treatment-related effects were observed at 300 mg/kg-day in either the reproductive phase of the combined study or in the pilot teratology study.

These observations suggest that 300 mg/kg-day is a LOAEL for short-term oral exposure on the basis of increased serum creatinine in male rats. The dose-related statistically significant ($p < 0.05$) increase in creatinine in male rats (Tanaka et al., 1999) is the most sensitive treatment-related endpoint in the database. Although clinical signs (salivation) were observed at 300 mg/kg-day, the data are not presented. The serum creatinine data are used as the basis for benchmark dose (BMD) modeling. Table 4 summarizes the data set used in the BMD modeling. Appendix B presents the results of the BMD model. A linear model with modeled variance provided adequate fit to the data set and yields a $BMDL_{1SD}$ of 92 mg/kg-day.

Table 4. Data Set for Increased Serum Creatinine in Male Rats[a]

Dose (mg/kg-day)	0	100	300	1000
Mean	0.27	0.30	0.33	0.47
Standard Deviation	0.08	0.04	0.07	0.26
Number Animals	12	12	12	12

[a]Tanaka et al., 1999

Applying a composite uncertainty factor (UF) of 1000 to the $BMDL_{1SD}$ of 92 mg/kg-day yields a **subchronic p-RfD** for 2,4,6-tribromophenol as follows:

Subchronic p-RfD = $BMDL_{1SD}$ ÷ Composite UF
= 92 mg/kg-day ÷ 1000
= **0.092, rounded to 0.09 mg/kg-day or 9×10^{-2} mg/kg-day**

The Composite UF of 1000 is composed of the following:

- A full UF of 10 is applied for interspecies extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between rats and humans.
- A full UF of 10 is applied for intraspecies differences in order to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A full UF of 10 is applied to account for database deficiencies. The toxicological database for oral exposure to 2,4,6-tribromophenol is composed solely of two studies conducted on only one species and lacks true subchronic, reproductive, and developmental toxicity studies. Neither of the existing studies examined fetuses for malformations.

A UF for LOAEL-to-NOAEL extrapolation is not applied because BMD modeling is used to identify the POD; a UF for subchronic-to-chronic extrapolation is not applied because a subchronic study was available.

Confidence in the principal study (Tanaka et al., 1999) is **medium** because the rats were exposed for only 41−48 days (approximately half of the typical 90-day duration of a subchronic toxicity study in rats), and females were not evaluated for clinical chemistry and hematology. Confidence in the database is **low**. Toxicity is investigated in only one species—rats—and the existing studies were designed as screening-level and, as such, employed small numbers of animals and less-than-complete analyses. Also, as discussed above, neither of the existing studies examined fetuses for malformations. Consequently, confidence in the subchronic p-RfD is **low**.

Chronic p-RfD Derivation

There are no chronic toxicity studies for 2,4,6-tribromophenol, and, as discussed in the previous section, there are only screening-level, repeated-dose, reproductive and developmental toxicity studies. It is a commonly accepted practice to use a subchronic p-RfD as the basis for a chronic RfD by applying an additional UF of 10 to account for the use of a subchronic study to approximate a chronic duration of exposure. However, given that the subchronic p-RfD for 2,4,6-tribromophenol derived in the previous section already incorporates an UF of 1000 for intraspecies variability, interspecies variability, and database uncertainties, employing an additional UF of 10 to account for less-than-chronic duration would yield a total UF of 10,000. Provisional reference values are usually not developed for studies that exceed a composite UF of 3000 because of the high level of uncertainty. Therefore, **no chronic p-RfD** is derived for 2,4,6-tribromophenol. However, Appendix A of this document contains a screening value that may be useful in certain instances. Please see the Appendix A for details.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION p-RfC VALUES FOR 2,4,6-TRIBROMOPHENOL

The relevant inhalation studies for 2,4,6-tribromophenol are restricted to two 21-day studies (one with gestational exposure); neither of which is suitable for quantitative risk assessment. Table 5 summarizes the data from these studies.

The study by Industrial Biotest Laboratories, Inc. (1977) used only two test concentrations and does not establish a NOAEL. Clinical signs of toxicity, most notably hypoactivity and excessive salivation, were observed at both test concentrations in males and females. Body weight gain was marginally decreased in females at the low concentration. At the high concentration, body weights were markedly reduced in both sexes and most of the animals were visibly emaciated. Histopathologic examination and serum chemistry analyses suggested effects on the liver and kidneys in rats at the high concentration. Histological examination was not performed for the low-exposure animals. There are two further deficiencies in this study that preclude its use in quantitative human risk assessment. Only the lungs and trachea are examined microscopically, limiting the usefulness of the study in determining critical respiratory endpoints. In addition, no information on aerodynamic particle sizes is reported, making it impossible to determine the mass aerodynamic diameter variables necessary to extrapolate from a particulate animal exposure concentration to a human equivalent concentration (HEC).

The developmental toxicity study by Lyubimov et al. (1998) has many deficiencies in reporting. The most important deficiency with respect to the quantification of dose is a complete lack of discussion about how the test atmosphere was generated and whether the nominally reported exposure concentrations were validated. If the reported nominal concentrations are correct, then the LOAELs for maternal toxicity (1 mg/m^3) and embryolethality (0.1 mg/m^3) observed in this study occur at concentrations 18 times and 180 times lower, respectively, than the duration-adjusted LOAEL for adult toxicity (18 mg/m^3) reported for rats in the 21-day Industrial Biotest Laboratories, Inc. (1977) study. As in the previous study, no information on particle sizes is reported. Therefore, it is not possible to know—with confidence—the conditions and concentrations for animal exposure, and it is, therefore, not possible to extrapolate a HEC from the available information. Based on these deficiencies, the study by Lyubimov et al. (1998) is not useful for quantitative human health risk assessment.

In conclusion, there are no suitable inhalation data from which to derive a subchronic or a chronic p-RfC for 2,4,6-tribromophenol.

Table 5. Summary of Inhalation Noncancer Dose-Response Information

Species	Sex	Exposure Concentration[a] (mg/m^3)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses	Comments	Reference
Short-term Exposure								
Rat	M, F	Mean analytical concentrations of dust at 0, 100, or 920 mg/m^3 adjusted to 0, 18 or 164 mg/m^3 (mg/m^3 × 6/24 × 5/7)	Whole-body, 6 hr/day, 5 days/wk, for 3 wk	Not established	18	Clinical signs of toxicity (hypoactivity and excessive salivation) in males and females and marginally decreased body-weight gain in females	No information on MMAD or data from which to generate MMAD were provided. Histopathologic examination of the respiratory tract included only lungs and trachea.	Industrial Biotest Laboratories, Inc., 1977
Reproductive/Developmental Toxicity								
Rat	F	Nominal: 0, 0.03, 0.1, 0.3, and 1.0 mg/m^3	Whole body continuous, Days 1-21 of gestation	Maternal 0.3 Fetal 0.03	Maternal 1.0 Fetal 0.1	Maternal: Increased serum ALP, serum progesterone, urinary total amino nitrogen, and urinary excretion of total phenols Fetal: Embryolethality (combined pre- and postimplantation loss), delayed sternal ossification	No information on generation of the test atmosphere, measurement of test concentrations or particle size distribution was reported; many deficiencies in methodology and data reporting.	Lyubimov et al., 1998

[a]Concentrations cannot be adjusted to human equivalent concentrations (HEC) due to the lack of information on mean aerodynamic particle diameters for these studies

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2,4,6-TRIBROMOPHENOL

Weight-of-Evidence Descriptor

No data have been located on the carcinogenicity of 2,4,6-tribromophenol in humans or animals. The available toxicity studies were conducted for very short durations and, as such, are not useful for assessing potential carcinogenicity. Mutagenicity data in bacteria and yeast are negative—although positive results have been obtained for chromosomal aberrations in Chinese hamster lung cells. In accordance with *Guidelines for Carcinogen Risk Assessment and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005), there is"*Inadequate Information to Assess* [the] *Carcinogenic Potential"* of 2,4,6-tribromophenol in humans.

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APPENDIX A. DERIVATION OF A CHRONIC SCREENING RfD FOR 2,4,6-TRIBROMOPHENOL

For reasons noted in the main PPRTV document, it is inappropriate to derive a chronic p-RfD for 2,4,6-tribromophenol. However, information is available for this chemical, which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a"screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

Tanaka et al. (1999) observed that 300 mg/kg-day is a LOAEL for short-term oral exposure on the basis of increased serum creatinine in male rats. The dose-related statistically significant ($p < 0.05$) increase in creatinine in male rats (Tanaka et al., 1999) is the most sensitive treatment-related endpoint in the database. The serum creatinine data are used as the basis for benchmark dose (BMD) modeling. Table 4 of the main text summarizes the data set used in the BMD modeling. Appendix B presents the results of the BMD model. A linear model with modeled variance provided adequate fit to the data set and yields a $BMDL_{1sd}$ of 92 mg/kg-day.

Applying a composite uncertainty factor (UF) of 10,000 to the $BMDL_{1SD}$ of 92 mg/kg-day yields a **chronic screening p-RfD** for 2,4,6-tribromophenol as follows:

Chronic Screening p-RfD = $BMDL_{1SD}$ ÷ Composite UF
= 92 mg/kg-day ÷ 10,000
= **0.0092 mg/kg-day or 9×10^{-3} mg/kg-day**

The Composite UF of 10,000 is composed of the following:

- A full UF of 10 is applied for interspecies extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between rats and humans.
- A UF of 10 is applied for intraspecies differences in order to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A UF of 10 is applied for extrapolation from subchronic-to-chronic exposures in order to account for additional effects that may be observed with longer exposure periods.
- A full UF of 10 is applied to account for database deficiencies. The toxicological database for oral exposure to 2,4,6-tribromophenol is composed solely of two studies conducted on only one species and lacks true subchronic, reproductive, and developmental toxicity studies. Neither of the existing studies examined fetuses for malformations.

A UF for LOAEL-to-NOAEL extrapolation is not applied because BMD modeling was used to identify the POD.

APPENDIX B. DETAILS OF BENCHMARK DOSE MODELING FOR CHRONIC SCREENING p-RfD

The data have been analyzed using all available models for continuous data in the BMD dose software (BMDS) program (version 2.1) developed by the U.S. EPA (2000). Risk was calculated as extra risk. For the continuous data, the original data were modeled with all the continuous models available within the software with a default BMR of 1 SD. An adequate fit was judged based on the goodness of fit *p*-value ($p > 0.1$), scaled residual at the range of BMR, and visual inspection of the model fit. In addition to the three criteria for judging the adequate model fit, whether the variance needed to be modeled, and if so, how it was modeled, also determined final use of the model results. If a homogenous variance model was recommended based on statistics (Test 2) provided from the BMD model runs, the final BMD results would be estimated from a homogenous variance model. If the test for homogenous variance (Test 2) was negative (i.e., $p < 0.1$), the model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance (known as nonhomogenous model). If the nonhomogenous variance model did not provide an adequate fit to the variance data (Test 3: p value < 0.1), the data set would be considered unsuitable for BMD modeling. Among all the models providing adequate data fit (goodness of fit p-value ≥ 0.1), the lowest BMDL will be selected if the BMDLs estimated from different models varies over a wide range (not quantified); otherwise, the BMDL from the model with the lowest AIC would be considered appropriate for the data set. Confidence bounds were automatically calculated by the BMDS using a maximum likelihood profile method.

Results of Model Fitting for 2,4,6-Tribromophenol

BMD modeling was conducted for the increased incidence of serum creatinine in male rats observed in the Tanaka et al. (1999) study. Table B-1 shows the BMD modeling results for the data set. As shown in Table B-1, the linear model with constant variance fit the means but not the variance. Running the linear model with modeled variance provides adequate fit to both the means and the variance and, therefore, is chosen as the basis for BMD derivation. Figure B-1 illustrates the best-fitting model. Complete model runs are appended.

Table B-1. Model Predictions for Increased Serum Creatinine in Male Rats

Model	Variance *p*-Value[a]	Means *p*-Value[a]	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
All dose groups					
Linear (constant variance)[b]	<0.0001	0.977	-141.006	NA	NA
Linear (modeled variance)[c]	0.8892	0.8339	-205.141	143.115	92.1898

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria
[b]Coefficients restricted to be positive
[c]Coefficients restricted to be positive

NA = not applicable; model does not fit the data adequately

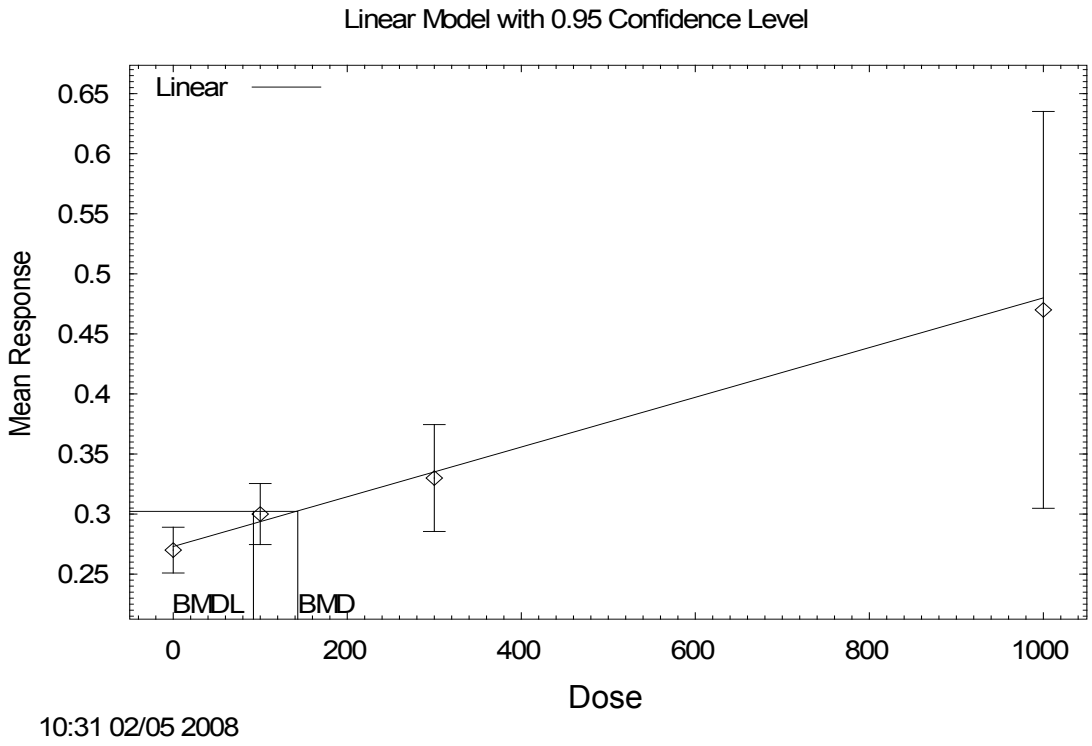


Figure B-1. Fit of Linear Model with Nonhomogeneous (Modeled) Variance to Data on Increased Serum Creatinine in Male Rats from Tanaka et al., 1999

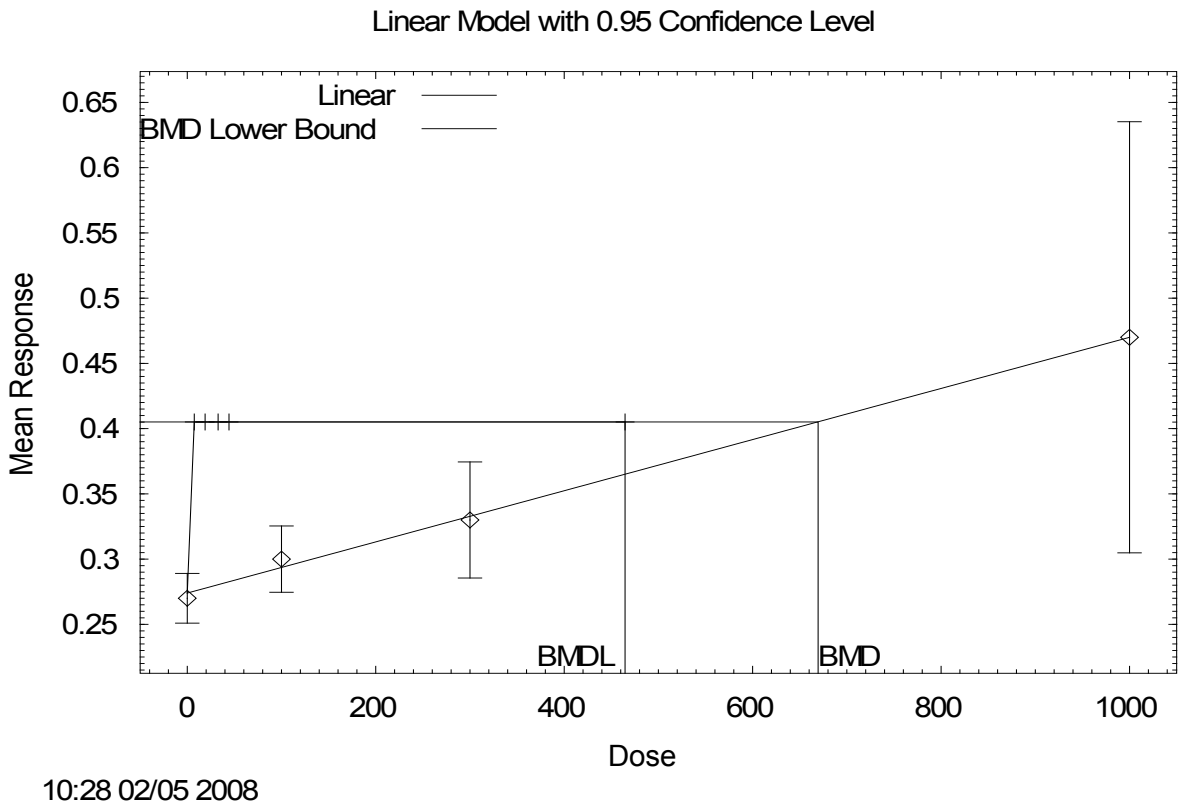
BMDs and BMDLs indicated are associated with a change of 1 SD from the control and are in units of mg/kg-day. BMDL computation failed for one or more points on the curve, therefore, the BMDL curve is not plotted.

BMD Model Runs for Tanaka et al. 1999
Serum Creatinine in Male SD Rats

```
 ======================================================================
        Polynomial Model. (Version: 2.12;  Date: 02/20/2007)
        Input Data File: C:\BMDS\TANAKA99.(d)
        Gnuplot Plotting File: C:\BMDS\TANAKA99.plt
                                          Tue Feb 05 10:28:53 2008
 ======================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

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


   Dependent variable = MEAN
   Independent variable = dose
   rho is set to 0
   The polynomial coefficients are restricted to be positive
   A constant variance model is fit

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



                  Default Initial Parameter Values
                          alpha =      0.01875
                            rho =            0   Specified
                         beta_0 =     0.273934
                         beta_1 =  0.000195902


           Asymptotic Correlation Matrix of Parameter Estimates

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

                   alpha       beta_0       beta_1

     alpha             1    -2.7e-011     3.8e-011

    beta_0    -2.7e-011            1        -0.67

    beta_1     3.8e-011        -0.67            1


                                Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha        0.0172037       0.00351169           0.0103209
0.0240865
         beta_0         0.273934        0.0254227            0.224107
0.323762
```

```
         beta_1      0.000195902     4.84792e-005         0.000100884
0.000290919


     Table of Data and Estimated Values of Interest

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

    0    12       0.27        0.274         0.03        0.131         -0.104
  100    12        0.3        0.294         0.04        0.131          0.171
  300    12       0.33        0.333         0.07        0.131         -0.0714
 1000    12       0.47         0.47         0.26        0.131         0.00433


 Model Descriptions for likelihoods calculated


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

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

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

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


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          73.525750            5    -137.051499
             A2         106.869482            8    -197.738964
             A3          73.525750            5    -137.051499
         fitted          73.503155            3    -141.006311
              R          66.475642            2    -128.951283


                   Explanation of Tests

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

                     Tests of Interest

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

   Test 1              80.7877          6          <.0001
   Test 2              66.6875          3          <.0001
   Test 3              66.6875          3          <.0001
   Test 4            0.0451889          2          0.9777

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

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

The p-value for Test 2 is less than .1.  Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

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


             Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        669.534


            BMDL =        464.636
```



```
 ================================================================
        Polynomial Model. (Version: 2.12;  Date: 02/20/2007)
        Input Data File: C:\BMDS\TANAKA99.(d)
        Gnuplot Plotting File: C:\BMDS\TANAKA99.plt
                                        Tue Feb 05 10:31:17 2008
 ================================================================

 BMDS MODEL RUN
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   The form of the response function is:

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


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

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


                    Default Initial Parameter Values
                           lalpha =     -3.97656
                              rho =            0
                           beta_0 =     0.273934
                           beta_1 =  0.000195902


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho       beta_0       beta_1

    lalpha             1         0.98      -0.0046        0.016

       rho          0.98            1      -0.0034        0.014

    beta_0       -0.0046      -0.0034            1        -0.49

    beta_1         0.016        0.014        -0.49            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         2.85154          1.06185           0.770343
4.93273
            rho         7.61417          0.95684             5.7388
9.48954
         beta_0        0.272686       0.00731748           0.258344
0.287028
         beta_1      0.000206555     4.92665e-005         0.000109994
0.000303115
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	12	0.27	0.273	0.03	0.0296	-0.315
100	12	0.3	0.293	0.04	0.039	0.591
300	12	0.33	0.335	0.07	0.0645	-0.25
1000	12	0.47	0.479	0.26	0.253	-0.127

Model Descriptions for likelihoods calculated

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

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

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

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

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	73.525750	5	-137.051499
A2	106.869482	8	-197.738964
A3	106.752006	6	-201.504012
fitted	106.570308	4	-205.140616
R	66.475642	2	-128.951283

Explanation of Tests

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

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	80.7877	6	<.0001
Test 2	66.6875	3	<.0001
Test 3	0.234952	2	0.8892
Test 4	0.363396	2	0.8339

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

The p-value for Test 2 is less than .1. A non-homogeneous variance

```
model appears to be appropriate

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

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


             Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        143.115


            BMDL =        92.1898


BMDL computation failed for one or more point on the BMDL curve.
 The BMDL curve will not be plotted
```