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Provisional Peer-Reviewed Toxicity Values for

Tris(2-chloroethyl)phosphate (TCEP)
(CASRN 115-96-8)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
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U.S. Environmental Protection Agency
Cincinnati, OH 45268

Commonly Used Abbreviations

BMD	Benchmark Dose
FEL	frank effect level
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 TRIS(2-CHLOROETHYL)PHOSPHATE (CASRN 115-96-8)

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
   - 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 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

Tris(2-chloroethyl)phosphate (TCEP) is a clear organic liquid that is primarily used in industry as a flame retardant and fire-resistant cellulose resin plasticizer (HSDB, 2008). Figure 1 shows the chemical structure of TCEP. There is no RfD or RfC for TCEP on IRIS (U.S. EPA, 2008), the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006), or in the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997). The CARA list (U.S. EPA, 1991, 1994) does not include any documents pertaining to TCEP. ATSDR (2008) has not prepared a toxicological profile for TCEP. The World Health Organization (WHO) (1998) prepared an Environmental Health Criteria document for TCEP, but it does not derive toxicity values. CalEPA (2008a,b) has not assessed the noncancer toxicity of TCEP. Occupational exposure limits for TCEP have not been derived by the American Conference of Industrial Hygienists (ACGIH) (2008), the National Institute for Occupational Safety and Health (NIOSH) (2008), or the Occupational Safety and Health Administration (OSHA) (2008).

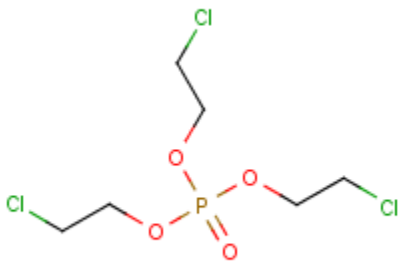

Figure 1. Chemical Structure of Tris-(2-chloroethyl) Phosphate

A cancer assessment for TCEP is not available on IRIS (U.S. EPA, 2008) or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006) or HEAST (U.S. EPA, 1997). NTP (1991) assessed the carcinogenicity of TCEP, concluding that there was clear evidence of carcinogenic activity in male and female rats based on increases in the incidence of

renal tubule adenomas, and equivocal evidence of carcinogenicity in mice based on increased incidences of renal tubule cell neoplasms (males) and Harderian gland adenomas (females). However, TCEP is not included in the 11th Report on Carcinogens (NTP, 2005). CalEPA (2006) included TCEP in its list of Chemicals Known to the State to Cause Cancer or Reproductive Toxicity based on a positive finding of carcinogenicity; however, CalEPA (2008b) has not prepared a quantitative estimate of carcinogenic potential. The International Agency for Research on Cancer (IARC) (1990, 1999) classified TCEP in Group 3: "The agent or mixture is not classifiable as to its carcinogenicity to humans."

Literature searches were conducted from the 1960s through July 2009 for studies relevant to the derivation of provisional toxicity values for TCEP. Databases searched include MEDLINE, TOXLINE (with NTIS), BIOSIS, TSCATS/TSCATS2, CCRIS, DART, GENETOX, HSDB, RTECS, Chemical Abstracts, and Current Contents (last 6 months).

REVIEW OF PERTINENT DATA

Human Studies

No human studies involving oral or inhalation exposure that could be used in dose-response assessment of TCEP were located.

Animal Studies

Oral Exposure

Subchronic Studies—Groups of F344/N rats (10/sex) were administered TCEP (approximately 98% pure) in corn oil by gavage at doses of 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days/week, for 16 weeks (Matthews et al., 1990; NTP, 1991). Animals in the two highest dose groups accidentally received twice the intended dose for three consecutive days during the fourth week of dosing. Following observation of clinical signs in female rats (convulsions, salivation, gasping, and lack of coordination) that did not occur in male rats, dosing was suspended for the fourth scheduled day of dosing during the fourth week and then resumed on the fifth day. Body weight and clinical observations were made prior to the test and at weekly intervals. Serum cholinesterase was assessed from blood drawn at terminal sacrifice. No other clinical chemistry or urinalysis are assessed in this study. Matthews et al. (1990) reported that technical difficulties prevented planned assessment of sperm morphology. All animals were necropsied and pathologic examinations of major tissues and organs were made for animals in the control and two highest dose groups. Additional examination of brain tissue was made for females administered 88 mg/kg-day. Due to the observation of damage in the hippocampal area of the brain during histological evaluation, neuronal damage in the hippocampus was evaluated in a blind study by a pathologist.

Two female rats in each of the two highest dose groups (175 and 350 mg/kg-day) died during the episode of overdosing, and two more females in the second highest group died because of gavage errors (Matthews et al., 1990; NTP, 1991). There was also additional mortality attributable to TCEP treatment at doses of 175 (one male) and 350 mg/kg-day (four males and three females). Final mean body weights were generally similar among dosed and control male rats—although the final mean body weight of surviving high-dose females was

about 20% greater than that of controls. Serum cholinesterase (as a measure of neurotoxicity) was significantly[1] decreased only in female rats treated with doses of 175 (25% decrease relative to controls) or 350 mg/kg-day (41% decrease relative to controls). Absolute liver weights were significantly increased compared to controls in TCEP-treated males at 175 and 350 mg/kg-day (7.5% and 14.6%, respectively) and in females receiving 44–350 mg/kg-day (12.3–83.6%) (see Table 1). Absolute kidney weights were significantly increased at 350 mg/kg-day in males (21.9% relative to controls) and in females receiving 44–350 mg/kg-day (7%–45.6% relative to controls) (see Table 1). Relative (i.e., organ-to-body-weight ratio) liver and kidney weights were significantly increased compared to controls in TCEP-treated males at 350 mg/kg-day (19.9%

Table 1. Absolute and Relative Liver and Kidney Weights of F344/N Rats Given TCEP by Gavage for 16 Weeks[a,b]

Male	Dose (mg/kg-day)					
	0	**22**	**44**	**88**	**175**	**350**
Absolute liver weight (g)	13.4 ± 0.27	13.5 ± 0.74	13.2 ± 0.33	13.2 ± 0.40	14.4 ± 0.31[d]	15.7 ± 0.50[d]
Relative liver weight (mg/g)[c]	37.1 ± 0.64	36.8 ± 1.55	37.4 ± 0.60	38.2 ± 1.23	39.3 ± 1.43	44.5 ± 0.29[d]
Absolute kidney weight (g)	1.28 ± 0.03	1.25 ± 0.03	1.30 ± 0.03	1.28 ± 0.03	1.32 ± 0.04	1.56 ± 0.07[d]
Relative kidney weight (mg/g)[c]	3.54 ± 0.08	3.42 ± 0.07	3.68 ± 0.04	3.68 ± 0.04	3.65 ± 0.09	4.42 ± 0.07[d]
Female						
Absolute liver weight (g)	6.10 ± 0.14	6.34 ± 0.19	6.85 ± 0.14[d]	6.52 ± 0.08[d]	7.56 ± 0.37[d]	11.2 ± 1.34[d]
Relative liver weight (mg/g)[c]	32.0 ± 0.57	33.9 ± 0.73[d]	36.2 ± 0.58[d]	35.3 ± 0.30[d]	38.0 ± 0.60[d]	48.2 ± 2.49[d]
Absolute kidney weight (g)	0.71 ± 0.01	0.72 ± 0.02	0.76 ± 0.01[d]	0.76 ± 0.01[d]	0.83 ± 0.02[d]	1.04 ± 0.07[d]
Relative kidney weight (mg/g)[c]	3.69 ± 0.04	3.83 ± 0.06	4.03 ± 0.04[d]	4.10 ± 0.07[d]	4.18 ± 0.06[d]	4.51 ± 0.06[d]

[a]NTP (1991); Matthews et al. (1993)
[b]Mean ± standard error; $n = 10$ for all groups except 22 mg/kg-day males ($n = 9$), 175 mg/kg-day and 350 mg/kg-day males ($n = 4$), 22 mg/kg-day and 175 mg/kg-day females ($n = 8$), 350 mg/kg-day females ($n = 5$), where noted
[c]Defined as organ-weight to body-weight ratio
[d]Significantly different ($p < 0.05$) from the control (0 mg/kg-day) group by Dunn's or Shirley's test

and 24.9%, respectively) (see Table 1). Relative liver weights were significantly increased in females receiving 22–350 mg/kg-day (5.9–50.6% relative to controls), and relative kidney weights were significantly increased in females receiving 44–350 mg/kg-day (9.2–22.2% relative

[1]Use of the terms "significant" and "significantly" throughout this document refer to statistical significance ($p \leq 0.05$).

to controls) (see Table 1). There were no apparent liver or kidney histological changes accompanying these organ weight changes. Lesions potentially related to TCEP treatment were found in the hippocampal region of in the brain. The lesion was primarily characterized by a loss of CA1 pyramidal neurons (which are involved in learning, memory, and spatial navigation) and was sometimes accompanied by mineralization and microgliosis (i.e., the presence of microglia in neuronal tissue). These lesions were observed in 8 out of 10 and 10 out of 10 females at the 175 and 350 mg/kg-day doses, respectively, with a dose-related increase in severity. Only 2 out of 10 males receiving 350 mg/kg-day were affected, suggesting a greater sensitivity among females. The incidences of brain lesions of females treated with 88 mg/kg-day were not reported (although presumably 0 out of 10 based on the dose selection rationale for the chronic 2-year study), and the incidences were 0 out of 10 for both control males and females. Histopathology was not evaluated in the other male dose groups. Neuronal necrosis was also observed in the thalamus of females receiving 350 mg/kg-day (data not shown; no incidence reported). Due to the fact that only relative liver weight was increased at the lowest dose tested (22 mg/kg-day), as well as the absence of serum liver enzyme alterations, the liver effect at this dose is not considered to be biologically meaningful. Thus, 22 mg/kg-day is identified as a NOAEL. A LOAEL of 44 mg/kg-day is identified from this subchronic study as the dose at which both absolute and relative liver and kidney weights in females were significantly increased. A FEL of 175 mg/kg-day is established due to the observation of treatment-related mortality at this and the highest dose. It is uncertain whether deaths that were not due to the overdose episode were directly related to brain lesions or to other functional derangements.

Groups of $B6C3F_1$ mice (10/sex) were administered TCEP (approximately 98% pure) in corn oil by gavage at doses of 0, 44, 88, 175, 350, or 700 mg/kg-day, for 5 days/week, for 16 weeks (Matthews et al., 1990; NTP, 1991). Body weight and clinical observations were made prior to testing and at weekly intervals. Serum cholinesterase was assessed from blood drawn at terminal sacrifice. No other clinical chemistry or urinalysis are assessed in this study. Sperm counts and morphology were assessed for all males that survived to terminal necropsy. All animals were necropsied and pathologic examinations of major tissues and organs were made for controls and mice exposed to 700 mg/kg-day. Kidneys in mice receiving 44, 88, 175, and 350 mg/kg-day were also examined.

As in the rat study, mice in the two highest dose groups (350 and 700 mg/kg-day) accidentally received twice the intended dose for 3 consecutive days during the fourth week of dosing, received no treatment on the fourth day, and then resumed dosing on the fifth day of that week. Although all female mice in the 350 mg/kg-day dose group appeared to be uncoordinated and two males in the 350-mg/kg-day group had convulsions and labored breathing, there were no other clinical signs and no mortality because of the dosing error (Matthews et al., 1990; NTP, 1991). There were no TCEP-related effects on survival, body weight, or serum cholinesterase in mice of either sex. The authors reported that sperm count was significantly reduced in males treated with 700 mg/kg-day (data not shown). In females, absolute and relative liver weight was significantly increased compared to controls at 175–700 mg/kg-day. The increases in liver weight occurred in the apparent absence of histopathological changes in the 700 mg/kg-day group (the 175 and 350 mg/kg-day dose groups were not examined). Relative kidney weight was significantly decreased in male mice treated with doses of 175 mg/kg-day and higher. Pathology findings were limited to mild enlargement of the nuclei of renal epithelial cells in all high-dose mice of both sexes. These lesions were observed primarily in the proximal

convoluted tubules of the inner cortex and outer stripe of the outer medulla (data not shown). The NOAEL and LOAEL for this study are 88 and 175 mg/kg-day, respectively, and are based on increased absolute and relative liver weight in females and decreased relative kidney weight in males.

Chronic Studies—Groups of F344 rats (60/sex/group) were administered TCEP (approximately 98% pure) in corn oil by gavage at doses of 0, 44, or 88 mg/kg-day, 5 days/week, for 104 weeks (NTP, 1991; Matthews et al., 1993). Animals were observed twice daily for morbidity and mortality, and clinical signs were recorded monthly. Body weights were recorded weekly for the first 13 weeks, then monthly, and at 3–4 week intervals for the last 3 months. Groups of 10 rats/sex/dose were sacrificed for interim evaluation (organ weights for brain, liver and kidney; hematology[2], clinical chemistry[3] and histological examination of all animals) after 66 weeks of treatment. Gross necropsy was performed on all animals that died or were sacrificed at the end of the study, and the weights of liver, kidney, and brain were recorded. A comprehensive histological examination was conducted for all groups.

There were no treatment-related effects on body weight or clinical signs (NTP, 1991; Matthews et al., 1993). In the 104-week study, survival was reduced in high-dose females starting on about Week 70 of the study. Survival in high-dose males was also reduced—but only during the last month of the study. The Kaplan-Meier survival percentages[4] estimated by NTP (1991) were 78, 68, and 51% for 0, 44, and 88 mg/kg-day males, respectively, and were 66, 71, and 37% for 0, 44, and 88 mg/kg-day females, respectively. The differences in survival between high-dose and control animals is marginally significant for males ($p = 0.043$) and highly significant for females ($p = 0.008$) based on pair-wise comparisons. Females that died early frequently had brain lesions (see below), while males did not.

At the 66-week interim sacrifice, absolute liver and kidney weights were significantly increased compared to controls in TCEP-treated males at 88 mg/kg-day (20.1% and 13.8%, respectively) but not in females (see Table 2). Relative liver weight in males was also significantly increased compared to controls (6.6%) at 44 mg/kg-day (see Table 2). Relative liver and kidney weights were significantly increased compared to controls in high-dose males (18.8% and 12.2%, respectively) (see Table 2). No liver or kidney pathological changes are noted. Decreased serum alkaline phosphatase (ALP) and serum alanine transferase (ALT) was also observed in high-dose (88 mg/kg-day) females but not males (magnitude not reported; data not shown). Lesions that were considered to be treatment-related but not statistically significant at the 66-week interim sacrifice included an adenoma of the renal tubule in one 88 mg/kg-day male and degenerative lesions of the brain (focal lesions in the cerebellum and thalamus) in three 88 mg/kg-day females (NTP, 1991; Matthews et al., 1993). The authors characterized the brain lesions observed at the interim as necrosis of the neuropil with accumulation of inflammatory cells, reactive gliosis, and endothelial hypertrophy and hyperplasia.

[2]Hematocrit, hemoglobin, erythrocytes, leucocytes with differential, mean cell volumes, mean cell hemoglobin, mean cell hemoglobin concentration, and reticulocyte count.
[3]Blood urea nitrogen, serum glucose, creatinine, alkaline phosphatase, serum cholinesterase, cholesterol, sorbitol dehydrogenase, alanine aminotransferase and aspartate aminotransferase.
[4]Survival rates adjusted for gavage deaths, accidents, and interim sacrifice

Histological evaluations conducted at the end of the 104-week duration revealed treatment-related hyperplastic and neoplastic changes in the kidney, thyroid neoplasms, mononuclear cell leukemia, and degenerative lesions in the brain (females only). Table 3 summarizes the incidences of brain lesions. The renal tubule hyperplasia and neoplasms occurred in the cortex. The hyperplasia was focal and multifocal in nature and was characterized by stratification of the epithelial cells with partial to complete obliteration of the lumen. The renal tubule cell hyperplasia may likely be preneoplastic in nature. Similar to the subchronic study, due to the fact that only relative liver weight was increased at the lowest dose tested in the 66-week study (44 mg/kg-day), as well as the absence of serum liver enzyme alterations, the magnitude of the liver effect at this dose is not considered to be biologically meaningful. Thus, 44 mg/kg-day is identified as a NOAEL. A LOAEL of 88 mg/kg-day is identified from the 66-week interim time-point in this chronic study as the dose at which both absolute and relative liver and kidney weights in males were significantly increased. For the 104-week duration, a FEL of 88 mg/kg day is identified for significantly decreased survival in females.

Table 2. Absolute and Relative Liver and Kidney Weights of F344/N Rats Given TCEP By Gavage for 66 Weeks[a,b]

Male	**Dose (mg/kg-day)**		
	0	**44**	**88**
Absolute liver weight (g)	14.9 ± 0.84	16.2 ± 0.33	17.9 ± 0.35 [d]
Relative liver weight (mg/g)[c]	31.9 ± 1.11	34.0 ± 1.55 [d]	37.9 ± 0.50 [d]
Absolute kidney weight (g)	1.52 ± 0.06	1.60 ± 0.03	1.73 ± 0.03 [d]
Relative kidney weight (mg/g)[c]	3.28 ± 0.12	3.37 ± 0.06	3.68 ± 0.06 [d]
Female			
Absolute liver weight (g)	8.86 ± 0.26	8.62 ± 0.20	9.13 ± 0.26
Relative liver weight (mg/g)[c]	31.1 ± 0.96	32.0 ± 0.77	32.8 ± 0.70
Absolute kidney weight (g)	0.87 ± 0.04	0.88 ± 0.03	0.92 ± 0.02
Relative kidney weight (mg/g)[c]	3.03 ± 0.14	3.26 ± 0.13	3.31 ± 0.12

[a]NTP (1991); Matthews et al. (1993)
[b]Mean ± standard error; $n = 10$ for all groups except control (0 mg/kg-day) males and 88 mg/kg-day females ($n = 9$)
[c]Defined as organ-weight-to-body-weight ratio
[d]Significantly different ($p < 0.05$) from the control (0 mg/kg-day) group by Dunn's or Shirley's test

Table 4 summarizes the incidences of neoplastic lesions observed after the 104-week duration. There was a significant increase in the incidence of renal tubule cell adenomas in the high-dose male rats. Smaller, but still significant, increases were also seen for renal adenomas and thyroid follicular cell tumors (adenomas or carcinomas) in female rats and mononuclear cell leukemia in both sexes. NTP (1991) considered the increased renal tubular cell adenomas to be especially noteworthy due to low spontaneous occurrence of renal tubular cell neoplasms in F344/N rats. The incidences of thyroid tumors and mononuclear cell leukemia in the high-dose groups were near the upper limit of the range of historical control values. NTP (1991) concluded

that there was "*clear evidence of carcinogenic activity* for male and female F344/N rats receiving tris(2-chloroethyl) phosphate as shown by increased incidences of renal tubule adenomas. Thyroid follicular cell neoplasms and mononuclear cell leukemia in male and female rats may have been related to chemical administration."

Table 3. Incidence of Nonneoplastic Brain Lesions in F344/N Rats Given TCEP by Gavage for 2 Years[a]

Dose (mg/kg-day, 5/7 days/wk)	0	44	88
	Incidence of Lesions (%)		
Male			
Brain Stem Hemorrhage	0/50 (0)	0/49 (0)	1/50 (2)
Pigment, hemosiderin	1/50 (2)	0/49 (0)	0/50 (0)
Cerebrum Gliosis, focal	0/50 (0)	0/49 (0)	1/50 (2)
Hemorrhage	0/50 (0)	1/49 (2)	1/50 (2)
Pigment, hemosiderin	0/50 (0)	0/49 (0)	1/50 (2)
Pons Hemorrhage	0/50 (0)	0/49 (0)	3/50 (6)
Female			
Brain Stem Gliosis, focal	1/50 (2)	0/50 (0)	15/50 (30)[b]
Hemorrhage	1/50 (2)	0/50 (0)	12/50 (24)[b]
Mineralization	0/50 (0)	0/50 (0)	7/50 (14)[b]
Necrosis	0/50 (0)	0/50 (0)	1/50 (2)
Pigment, hemosiderin	1/50 (2)	0/50 (0)	17/50 (34)[b]
Cerebrum Gliosis	0/50 (0)	0/50 (0)	19/50 (38)[b]
Hemorrhage	1/50 (2)	0/50 (0)	17/50 (34)[b]
Mineralization	0/50 (0)	0/50 (0)	15/50 (30)[b]
Pigment, hemosiderin	0/50 (0)	0/50 (0)	22/50 (44)[b]
Pons Hemorrhage	0/50 (0)	1/50 (2)	0/50 (0)

[a]NTP (1991); Matthews et al. (1993)
[b]$p < 0.01$

Groups of $B6C3F_1$ mice (60/sex/dose) were administered TCEP (approximately 98% pure) in corn oil by gavage at doses of 0, 175, or 350 mg/kg, 5 days/week, for 104 weeks (NTP, 1991; Matthews et al., 1993). Animals were observed twice daily for morbidity and mortality, and clinical signs were recorded monthly. Body weights were recorded weekly for the first 13 weeks, then monthly and at 3–4 week intervals for the last 3 months. Groups of 10 mice/sex/dose were sacrificed for interim evaluation (organ weights for brain, liver and kidneys; hematology[5], clinical chemistry[6], and histological examination of control and high-dose animals) after 66 weeks of exposure. Gross necropsy was performed on all animals that died or were sacrificed at the end of the study, and liver, kidneys, and brain weights were recorded. A comprehensive histological examination was conducted for all controls and high-dose animals, and sections from the Harderian gland, kidney, livers, lung, and stomach were also evaluated for low-dose mice.

There were no significant treatment-related effects on mouse survival, body weight, or clinical signs (NTP, 1991; Matthews et al., 1993). At interim sacrifice after 66 weeks of

[5]Hematocrit, hemoglobin, erythrocytes, leucocytes with differential, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, and reticulocyte count.
[6]Blood urea nitrogen, serum glucose, creatinine, alkaline phosphatase, serum cholinesterase, cholesterol, sorbitol dehydrogenase, alanine aminotransferase, and aspartate aminotransferase.

Table 4. Incidence of Treatment-Related Hyperplasia, Adenomas, and Carcinomas in F344 Rats Given TCEP by Gavage for 2 Years[a]			
Dose (mg/kg-day)	**0**	**44**	**88**
Male			
Kidney Renal Tubule Cell			
Hyperplasia	0/50 (0%)	2/50 (4%)	24/50 (48%)[b]
Adenoma	1/50 (2%)	5/50 (10%)	24/50 (48%)[b]
Carcinoma	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adenoma or Carcinoma	2/50 (4%)	5/50 (10%)	25/50 (50%)[b]
Historical Control Incidence (adenoma or carcinoma)	12/2142 (0.6 ± 0.9%); range = 0–2%		
First Incidence of Adenoma or carcinoma (days)	729	729	575
Thyroid Follicular Cell			
Hyperplasia	0/50 (0%)	0/48 (0%)	0/50 (0%)
Adenoma	1/50 (2%)	2/48 (4%)	3/50 (6%)
Carcinoma	0/50 (0%)	0/48 (0%)	2/50 (4%)
Adenoma or Carcinoma	1/50 (2%)	2/48 (4%)	5/50 (10%)
Historical Control Incidence (adenoma or carcinoma)	51/2106 (2.4 ± 2.3%); range = 0–10%		
First Incidence of Adenoma (days)	729	574	674
First Incidence of Carcinoma (days)	Not applicable	Not applicable	696
Mononuclear Cell Leukemia	5/50 (10%)	14/50 (28%)[c]	13/50 (26%)[c]
Historical Control Incidence	321/2149 (14.9 ± 10.8%); range = 0–44%		
First Incidence (days)	539	620	584
Female			
Kidney Renal Tubule Cell			
Hyperplasia	0/50 (0%)	3/50 (6%)	16/50 (32%)[b]
Adenoma	0/50 (0%)	2/50 (4%)	5/50 (10%)[b]
Carcinoma	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adenoma or Carcinoma	0/50 (0%)	2/50 (4%)	5/50 (10%)[b]
Historical Control Incidence (adenoma)	1/2144 (0.1 ± 0.3%); range = 0–2%		
First Incidence of Adenoma (days)	Not applicable	729	729
Thyroid Follicular Cell			
Hyperplasia	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adenoma	0/50 (0%)	1/50 (2%)	1/50 (2%)
Carcinoma	0/50 (0%)	2/50 (4%)	3/50 (6%)[c]
Adenoma or Carcinoma	0/50 (0%)	3/50 (6%)	4/50 (8%)[c]
Historical Control Incidence (adenoma or carcinoma)	34/2107 (1.6 ± 1.6%); range=0–6%		
First Incidence of Adenoma or carcinoma (days)	Not applicable	697	718
Mononuclear Cell Leukemia	14/50 (28%)	16/50 (32%)	20/50 (40%)[b]
Historical Control Incidence	329/2150 (15.3 ± 10.6%); range = 0–38%		
First Incidence (days)	335	561	469

[a]NTP (1991); Matthews et al. (1993)
[b]Significantly different ($p < 0.01$) from control by pair-wise comparison (kidney and thyroid) or life table test (leukemia)
[c]Significantly different ($p < 0.05$) from control by pair-wise comparison (kidney and thyroid) or life table test (leukemia)

Table 5. Incidence of Selected Renal Tubule Cell Lesions in B6C3F$_1$ Mice Given TCEP by Gavage for 2 Years[a]

Dose (mg/kg-day)	0	175	350
Male			
Karyomegaly	2/50	16/50[c]	39/50[c]
Hyperplasia	1/50	0/50	3/50
Adenoma	1/50	1/50	3/50
Adenocarcinoma	0/50	0/50	1/50
Female			
Karyomegaly	0/50	5/49[b]	44/50[c]
Hyperplasia	0/50	1/49	2/50
Adenoma	0/50	1/49	0/50
Adenocarcinoma	0/50	0/49	0/50

[a]NTP (1991); Matthews et al. (1993). Incidences hyperplasia, adenoma and adenocarcinoma are for original and step-sections combined
[b]Significantly different ($p \leq 0.05$) from control by logistic regression tests
[c]Significantly different ($p \leq 0.01$) from control by logistic regression tests

treatment, there were no significant treatment-related effects on organ weights, hematology, clinical chemistry, or histopathology. Table 5 summarizes the incidences of nonneoplastic and neoplastic changes in the kidney. The most prominent renal lesion was renal tubular cell karyomegaly (nuclear enlargement), which was significantly increased at both doses in both sexes in a dose-related manner. This lesion was minimal in severity and was observed primarily in the proximal convoluted tubules of the inner kidney cortex and outer stripe of the medulla. Low incidences of hyperplasia and renal tumors (see below) are also reported in the kidney. Based on renal tubule cell karyomegaly, this study identifies a LOAEL of 175 mg/kg-day. A NOAEL is not identified.

None of the neoplastic lesions identified in mice following terminal necropsy and pathologic evaluation of tissues could unequivocally be attributed to treatment with TCEP NTP, 1991; Matthews et al., 1993). Initially, renal tubule adenomas were observed in one control male, one high-dose male, and one low-dose female, and an adenocarcinoma was observed in one high-dose male. Due to the rare occurrence of renal tubule neoplasms in B6C3F$_1$ mice, additional step sections were evaluated, yielding final incidences of 1 out of 50, 1 out of 50, and 3 out of 50 for renal tubular adenomas in 0-, 175-, and 350-mg/kg male mice, respectively (see Table 5). The difference from controls in the high-dose group is not statistically significant. Besides the kidneys, increases in tumors or precursor lesions were also seen in the Harderian gland and the liver. In the Harderian gland, there was an increase in the incidence of combined adenomas and carcinomas in female mice. Incidences were 3 out of 50, 8 out of 60 and 10 out of 60 for 0, 175, and 350 mg/kg, respectively (statistically significant trend; incidence at the high dose was significantly greater than the control incidence). With regard to the liver, there was an increase in the incidence of eosinophilic foci in high-dose males. Incidences were 0 out of 50, 3 out of 50, and 8 out of 50 in 0-, 175-, and 350-mg/kg males, respectively. Although there is a significant trend for increased adenomas in male mice, there are no TCEP-related effects on the incidences of basophilic or clear cell foci, and no significant increases in the incidences of adenoma, carcinoma, or combined adenoma and carcinoma of the liver. Given that the development of eosinophilic, basophilic, and clear-cell foci are considered to be precursors to liver neoplasms, NTP (1991) concluded that the biological importance of the

increase in eosinophilic foci in the absence of the development of neoplastic change is uncertain; they noted that there was "*equivocal evidence of carcinogenic activity* for male $B6C3F_1$ mice as shown by an increased incidence of renal tubular cell neoplasms." Additionally, "*equivocal evidence of carcinogenic activity* for female $B6C3F_1$ mice was shown by an increased incidence of harderian gland adenomas."

In another carcinogenicity study, groups of ddY mice (50/sex/group) were fed TCEP in their diet at concentrations of 0, 0.012, 0.06, 0.3, or 1.5% for 18 months (Takada et al., 1989). This study is written in Japanese, but the information reported here is based on the abstract, tables and figures, all of which are reported in English. Based on measured data for body weight and food consumption, the dietary concentrations used in the study were equivalent to doses of 0, 9.3, 46.6, 232.8, or 1687.5 mg/kg-day for males, and 0, 10.7, 53.3, 266.7, or 1875.0 mg/kg-day for females. Survival, body weight, and food consumption were monitored throughout the study. It is not clear whether clinical chemistry, urinalysis, or hematology were endpoints in this study. A comprehensive evaluation of tissues and organs appears to have been conducted for all dose groups.

The major findings of this study are summarized in Table 6. Mortality (death or moribund sacrifice) was higher in males fed 1687.5 mg/kg-day and in females fed 266.7 or 1875.0 mg/kg-day TCEP than in the control or lower-dose groups (Takada et al., 1989). The early morbidity and mortality may have been associated with neoplastic changes, as the incidence of animals with tumors (including those that died, were sacrificed, or survived to the end of the study) was significantly increased above control values in males fed 1687.5 mg/kg-day and in females fed 266.7 or 1875.0 mg/kg-day. Body weight was significantly decreased (compared to control values) throughout the study (approximately 29–31%) in both males and females fed 1687.5 and 1875.0 mg/kg-day TCEP, respectively, although food consumption was unaffected by addition of TCEP to the diet. Tumors potentially related to treatment were seen in the kidneys, liver, forestomach, and hematopoietic system. In males fed 1687.5 mg/kg-day TCEP, there were statistically significant increases in the incidences of renal cell adenoma, carcinoma and adenoma plus carcinoma combined. These tumors were also seen in females at the same dietary concentration, albeit at low incidences that did not approach statistical significance. In males fed 232.8 or 1687.5 mg/kg-day TCEP, statistically significant increases in hepatocellular adenoma and combined hepatocellular adenoma and carcinoma were seen. A low incidence of these tumors was also seen in the 1875.0-mg/kg-day females. Statistically significant increases of combined forestomach tumors (papillomas and squamous cell carcinomas) and leukemia (specific type not identified) were observed in female mice but not in males. There are no treatment-related tumors in any other organs or tissues. The accessible parts of the report provided few data on nonneoplastic lesions. Renal tubular cell enlargement was apparently observed, as Figure 8 of the report is an image of enlarged nuclei from renal tubular epithelium taken from a male mouse fed 232.8 mg/kg-day TCEP for 79 weeks. No further information on this endpoint is provided.

Reproductive/Developmental Studies—The National Toxicology Program assessed the reproductive/developmental toxicity of TCEP in CD-1 mice using the "*Reproductive Assessment by Continuous Breeding*" (RACB) protocol (Gulati et al., 1991). The RACB protocol consists of four sequentially executed tasks consisting of (1) dose range-finding, (2) continuous breeding, (3) identification of the affected sex, and (4) assessment of the fertility of F1 offspring. Figure 2

illustrates a flow diagram of the RACB protocol. For the range-finding task, mice (8/sex/dose) were administered TCEP in corn oil by gavage at doses of 0, 87.5, 175, 350, 700, or 1000 mg/kg-day for 14 consecutive days. Based on a single treatment-related mortality at the high dose, and the lack of treatment-related effects on body weight and food consumption, doses of 75, 350, and 700 mg/kg-day were selected for the continuous breeding phase of the study.

In the continuous breeding phase (Task 2), groups of male and female mice (40 untreated/control pairs and 20 pairs/dose) were housed together and received TCEP (purity >98% in corn oil) by gavage at doses of 0, 75, 350, or 700 mg/kg-day for 98 consecutive days (Gulati et al., 1991). Endpoints for this task include clinical signs, parental body weight, average water consumption, fertility, litters/pair, live pups/litter, proportion of pups born alive, sex of live pups, and pup weights at birth. There was no significant treatment-related mortality or clinical

Table 6. Effects in ddY Mice Fed TCEP in the Diet for 18 Months[a]

	Dietary Concentration (%)				
Variable	**0**	**0.012**	**0.06**	**0.3**	**1.5**
Male					
Estimated Body Weight (kg)[b]	0.058	0.058	0.058	0.058	0.040
Estimated Food Consumption (kg/day)[b]	0.0045	0.0045	0.0045	0.0045	0.0045
Estimated Dose (mg/kg-day)[c]	0	9.3	46.6	232.8	1687.5
% Mortality (includes moribund sacrifice)	40	36	44	42	62
% with Tumors	68	78	80	83	100[e]
Renal Cell Adenoma	0/50	0/49	0/49	2/47	9/50[e]
Renal Cell Carcinoma	2/50	0/49	2/49	3/47	32/50[e]
Renal Cell Adenoma+Carcinoma	2/50	0/47	2/49	5/47	41/50[e]
Hepatocellular Adenoma	3/50	4/49	3/49	10/47[d]	16/50[d]
Hepatocellular Carcinoma	1/50	1/49	4/49	2/47	3/50
Hepatocellular Adenoma+Carcinoma	4/50	5/49	7/49	12/47[e]	19/50[e]
Leukemia	7/50	4/50	6/49	4/47	4/50
Forestomach Papilloma +Squamous Cell Carcinoma	0/50	0/49	1/49	2/47	2/50
Female					
Estimated Body Weight (kg)[b]	0.045	0.045	0.045	0.045	0.032
Estimated Food Consumption (kg/day)[b]	0.004	0.004	0.004	0.004	0.004
Estimated Dose (mg/kg-day)[c]	0	10.7	53.3	266.7	1875.0
% Mortality (includes moribund sacrifice)	34	38	48	56	64
% with Tumors	61	57	66	80[d]	82[d]
Renal Cell Adenoma	0/49	0/49	0/50	0/49	2/50
Renal Cell Carcinoma	0/49	0/49	0/50	0/49	1/50
Renal Cell Adenoma+Carcinoma	0/49	0/49	0/50	0/49	3/50
Hepatocellular Adenoma	0/49	0/49	0/50	0/49	2/50
Hepatocellular Carcinoma	0/49	0/49	0/50	0/49	0/50
Hepatocellular Adenoma+Carcinoma	0/49	0/49	0/50	0/49	2/50
Leukemia	1/49	3/49	6/50	9/49[d]	9/50[d]
Forestomach Papilloma+Squamous Cell Carcinoma	0/49	0/49	0/50	1/49	7/50[d]

[a]Takada et.al. (1989)
[b]Estimated from graphs shown in study Figures 3 and 4
[c]Estimated dose = (% diet × 10000 × estimated food consumption)/estimated body weight
[d]Statistically significant difference from controls ($p < 0.05$)
[e]Statistically significant difference from controls ($p < 0.01$)

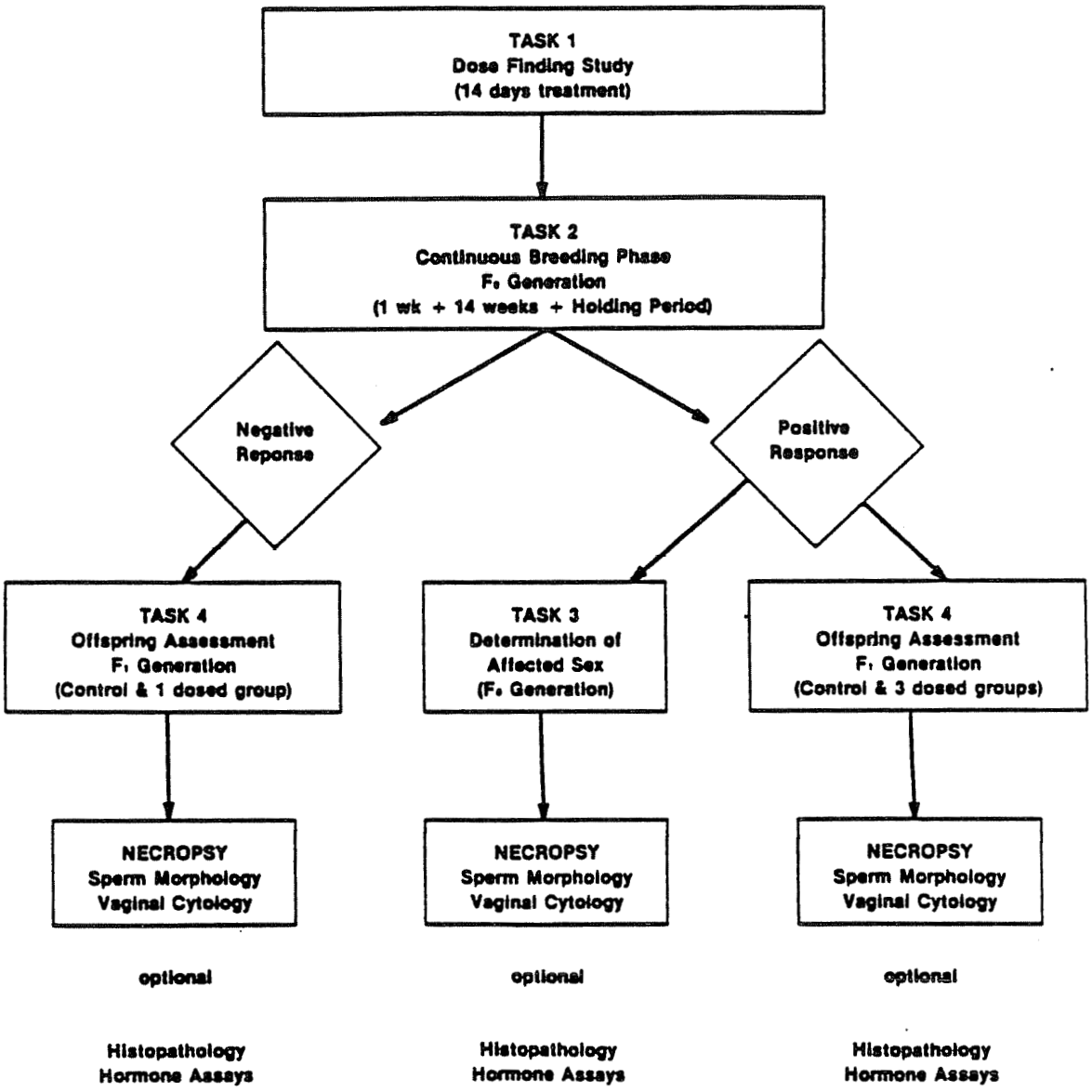

Figure 2. Reproductive Assessment by Continuous Breeding Protocol (Gulati et al., 1991)

signs. Male and female body weights were within 10% of the control values in all test groups throughout the study. Significant decreases in fertility (both litter production and number of live pups per litter) were observed at 350 and 700 mg/kg-day (see Tables 7 and 8). The few dams in the 700-mg/kg-day group that did produce second and third litters took significantly longer to do so than dams in the control or lower-dose groups (see Table 8).

Table 7. Fertility of Breeding Pairs of Swiss CD-1 Mice Given TCEP by Gavage for 98 Days (Task 2)[a]

	Number of Fertile Pairs/Number of Cohabiting Pairs			
	Dose Group (mg/kg-day)			
Litter	0	175	350	700
1	37/38	18/19	18/18	18/18
2	37/38	18/19	18/18	12/18[b]
3	37/38	18/19	16/18	2/18[b]
4	37/38	17/19	16/18	0/18[b]
5	35/38	17/19	13/18[b]	0/18[b]

[a]Gulati et al. (1991)
[b]$p < 0.05$

Table 8. Effects of TCEP (Given By Gavage) on Reproductive Performance of Swiss CD-1 Mice During Continuous Breeding (Task 2)[a]

	Dose (mg/kg-day)[b]			
Variable	0	175	350	700
Average Litters per Pair[c,d]	4.9 ± 0.0 (37)	4.9 ± 0.1 (18)	4.5 ± 0.2 (18)[f]	1.8 ± 0.2 (18)[f]
Live Pups per Litter[c,d]				
Male	6.4 ± 0.3 (37)	6.1 ± 0.3 (18)	5.1 ± 0.4 (18)[f]	3.9 ± 0.3 (18)[f]
Female	6.3 ± 0.3 (37)	6.1 ± 0.3 (18)	5.0 ± 0.2 (18)[f]	4.6 ± 0.5 (18)[f]
Combined	12.7 ± 0.5 (37)	12.1 ± 0.4 (18)	10.1 ± 0.5 (18)[f]	8.6 ± 0.6 (18)[f]
Cumulative Days to Litter[e]				
2nd litter	40.8 ± 0.3 (37)	40.9 ± 0.5 (18)	48.1 ± 4.7 (18)	65.9 ± 6.4 (12)[f]
3rd Litter	61.9 ± 0.3 (37)	60.8 ± 0.5 (18)	61.8 ± 1.2 (16)	102.5 ± 14.5 (2)[g]

[a]Gulati et al. (1991)
[b]Only pairs surviving to the end of Task 2 were included for statistical evaluation
[c]Mean ± standard error (number of fertile pairs)
[d]Each dose is compared to the control group with Shirley's test when a trend is present ($p < 0.1$ from Jonckhere's trend test), otherwise Dunn's test is used
[e]Mean ± standard error (number of dams)
[f]$p < 0.05$
[g]There were too few animals to conduct statistics

Because of the effects on fertility noted in Task 2, a 1-week crossover mating trial (Task 3) was performed to determine which sex had been affected by treatment in Task 2 (Gulati et al., 1991). Three groups of 20 breeding pairs were mated as follows: untreated males were paired with untreated females, untreated males were paired with high-dose (700 mg/kg-day) females, and untreated females were paired with high-dose (700 mg/kg-day) males. The endpoints evaluated for this task included sperm morphology, sperm count, vaginal cytology, weight of reproductive organs, and pathologic examination of reproductive and major organs (in 10 randomly selected high-dose and control mice of each sex). There were no TCEP-related effects on mortality or clinical signs. Effects on fertility were noted in the group with high-dose males bred to untreated females (1 out of 18 pregnancies versus 12 out of

20 pregnancies for untreated pairs) and in the group with high-dose females bred to untreated males (7.2 ± 0.9 live pups/litter versus 10.3 ± 0.7 live pups/litter from untreated pairs). There were no treatment-related effects on vaginal cytology or estrous cycling. Sperm effects in the males at the 700 mg/kg-day dose include significant decreases in mean concentration of sperm (810.8 ± 76.8 per mg caudal tissue versus 1223 ± 68.7 in controls) and percent motile sperm (35.0 ± 8% versus 77.8 ± 1.6 % in controls), as well as a significant increase in the percentage of abnormal sperm (31.5 ± 3.1% versus 9.1 ± 0.59% in controls). The only remarkable treatment-related histological finding is an increase in the incidence of minimal to mild cytomegaly of the renal tubule cells (10 out of 12 males and 5 out of 13 females[7]) in TCEP-treated mice compared with controls (0 out of 10 males and 0 out of 12 females). No treatment-related lesions were found in the brain or ovaries. These results show that both sexes are affected by TCEP, with the males being relatively more sensitive (larger effect at the same dose), and the consequence on male fertility likely being due to an effect on sperm.

In Task 4, members of the last litter born to each pair in Task 2 were allowed to reach sexual maturity, and then they were paired individually with a member of the opposite sex from a separate litter within the same treatment group (Gulati et al., 1991). These pups received the same control or TCEP exposure as their parents. The high-dose (700 mg/kg-day) group was excluded from this phase of the experiment due to an insufficient number of pups. Pairs were mated at approximately 74 days of age and assessed for the same endpoints as in Task 2 (clinical signs, parental body weight, average water consumption, fertility, litters/pair, live pups/litter, proportion of pups born alive, sex of live pups, pup weights at birth, vaginal cytology 12 days before sacrifice and epididymal sperm count and morphology). F1 mice were sacrificed at the end of Task 4, and the presence of morphological and histopathological changes in reproductive organs was assessed. Mating and fertility indices in the control and treated groups were similar, but there was a statistically significant decrease in the number of live F2 pups/litter in the 350 mg/kg-day group (7.6 ± 1.1 versus 11.4 ± 0.5 in controls), specifically males (3.4 ± 0.6 versus 6.4 ± 0.6 in controls). Epididymal sperm count, sperm motility, and the incidence of abnormal sperm were unaffected by TCEP treatment up to the 350 mg/kg-day level in F1 males. There were no apparent effects on estrous cycling or on the average estrous cycle length in treated F1 females. There were no remarkable findings upon histopathologic examination.

Based on the findings of all tasks (Gulati et al., 1991), the NOAEL for reproductive toxicity in Swiss CD-1 mice is 175 mg/kg-day. The LOAEL is 350 mg/kg-day and is based on decreased fertility (decreased number of consecutive litters produced, average litters per pair, and number of live pups per litter), which is likely due, at least in part, to observed effects on sperm count, sperm motility, and sperm morphology.

The developmental toxicity of TCEP (purity unknown) dissolved in olive oil was assessed in groups of Wistar rats (23–30 pregnant females/dose) treated by gavage at doses of 0, 50, 100, or 200 mg/kg-day on Days 7 through 15 of gestation (Kawashima et al., 1983)[8]. Half of the dams were sacrificed on Day 20 of gestation and their uterine contents were examined. The remaining dams were allowed to deliver their litters, and their pups were observed (up to

[7]The tissues examined (reported in Tables 3–-8 and 3-9 of Gulati et al., 1991) include those from an additional two males and three females that died, or were sacrificed, during Task 2.
[8]This report is written in Japanese. The account of this study presented here is based on the abstract and tables that are reported in English.

10 weeks) for physical and neurobehavioral development. The neurobehavioral testing includes assessments of spontaneous motor behavior (ambulation, rearing behavior, defecation) and performance in a water maze.

There was no mortality at doses of 100 mg/kg-day or less, but 7 out of 30 dams treated at 200 mg/kg-day died; food consumption was markedly reduced in this group, and piloerection and general signs of weakness were evident (Kawashima et al., 1983). No effects on body weight, food consumption, or general appearance were reported in dams treated with doses of 50 or 100 mg/kg-day. There were no treatment-related effects on the mean number of corpora lutea, number of implants, implants per corpora lutea or kidney weights among the 15 dams per group killed at term. There were no treatment-related effects on the mean number of live fetuses, sex ratio, fetal body weight, or fetal mortality (including early or late resorptions). No fetuses with malformations were observed in any treatment group, and there were no treatment-related effects on skeletal variations or ossification. Among dams that delivered and reared their pups, there were no treatment-related effects on the number of implantation sites, number of births or any indicator of fetal or pup survival. The only significant effect on spontaneous motor activity was a decrease in rearing among male—but not in female pups born to dams treated with 200 mg/kg-day (9.8 ± 5.6 seconds compared with 19.3 ± 9.4 seconds in controls). There were no treatment-related effects on ambulation or defecation variables. With regard to performance in a water maze (an assessment of memory and learning ability where the test animal has to swim through a maze to find a platform), the only significant effect is an increased time required to find the platform in the fourth of four trials among high-dose males (72.7 seconds versus 35.4 seconds in control males). There were no treatment-related differences in the first three trials for males, or in any of the four trials for females at any treatment level. There are no differences between treatment groups of either sex with regard to the number of errors made. Based on these findings, 100 mg/kg-day is a NOAEL for maternal toxicity and developmental toxicity. The highest dose tested, 200 mg/kg-day, is a FEL for maternal mortality.

Inhalation Exposure

Few chronic or subchronic toxicity studies of TCEP conducted by the inhalation route of exposure were located. In a study from the Russian literature, (Shepelskaya and Dyshinevich, 1981) exposed male rats continuously to TCEP in air (no further details of exposure conditions) at concentrations of 0, 0.5, or 1.5 mg/m^3 for 4 months, and then they mated the animals to naïve females. Results are presented here as reported in the English abstract of the report and as discussed by Gulati et al. (1991). There are significant decreases in litter size, and increases in both pre- and postimplantation loss among females mated to males exposed to 1.5 mg/m^3. It is reported that fetal weight and crown-rump length were significantly decreased in pups born to dams mated with males exposed to 0.5 mg/m^3. Effects on the testes were also observed, but the nature of these effects and the concentrations at which they were observed cannot be determined from the report.

Other Studies

Acute/Short-term Studies

No treatment-related effects on spontaneous behavior, memory, or learning were observed when mice were exposed to low doses of TCEP (0.4–40 mg/kg-day) as a single gavage dose during the critical period for brain development (Postnatal Day 10), and then tested as

adults at 2–4 months of age (Eriksson et al., 2004). No other information on study design or findings was presented.

Genotoxicity

The overall weight-of-evidence for the mutagenicity of TCEP is negative. As discussed below, some equivocal results have been obtained, but the majority of studies have yielded negative findings. With one exception, all studies that conducted Ames tests for TCEP reported entirely negative results. TCEP was not mutagenic in *Salmonella typhimurium* strains TA97a, TA98, TA100, TA102, TA104, TA1535, TA1537, or TA1538 when tested with or without S9 in studies by Simmon et al. (1977), Haworth et al. (1983), Kubo et al. (2002), and Follmann and Wober (2006). One other study reported negative results in most strains (TA98, TA100, TA1537, and TA1538), but it did obtain weak positive results for TCEP in TA1535—only in the presence of S9 (Nakamura et al., 1979).

TCEP was not mutagenic in V79 Chinese hamster lung fibroblasts, but it induced sister chromatid exchange (SCE) in the same cell line when tested without S9 (Sala et al., 1982). TCEP was considered to produce equivocal findings in an evaluation of SCE in Chinese Hamster Ovary (CHO) cells, with positive results in one trial and negative results in a second conducted under the same conditions (Galloway et al., 1987). TCEP did not produce any change in chromosomal aberrations in CHO cells incubated with or without S9 (Galloway et al., 1987). TCEP did not induce DNA strand breaks in V79 cells in the Comet assay—with or without metabolic activation (Follmann and Wober, 2006). TCEP gave a negative result for cell transformation in C3H10T1/2 cells but produced transformation in Syrian hamster embryonic cells (Sala et al., 1982).

An in vivo assay for micronucleus production in Chinese hamsters produced equivocal results (Sala et al., 1982). TCEP yielded negative results in a w/w+ bioassay[9] for somatic cell damage that was conducted with *Drosophila melanogaster* (Vogel and Nivard, 1993).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR TRIS(2-CHLOROETHYL)PHOSPHATE

There are no human studies that can be used to quantitatively assess oral or inhalation exposure to TCEP. The oral toxicity database for animals is fairly complete, and Table 9 summarizes the available studies.

Subchronic p-RfD

Subchronic rat studies show significant increases in absolute and relative liver and kidney weights in the absence of frank effects (i.e., mortality) at lower dose levels of TCEP (Matthews et al., 1990; NTP, 1991). Additional support for the consideration of liver and kidney weight changes as critical effects is that significant increases also occurred in rats following a short-term (16-day) TCEP dosing regimen (NTP, 1991), as well as in mice following a subchronic (16-week) dosing regimen (Matthews et al., 1990; NTP, 1991). From these

[9] This assay monitors genetic damage resulting from a loss of heterozygosity and the formation of white spots in the eyes of adult females.

Table 9. Summary of Oral Noncancer Dose-Response Information for TCEP							
Species (n/sex/group)	**Exposure**	**NOAEL (mg/kg-day)**	**LOAEL (mg/kg-day)**	**Duration-adjusted[a] LOAEL (mg/kg-day)**	**Responses at the LOAEL**	**Comments**	**Reference**
Subchronic Studies							
Rat, F344/N (10/sex/dose)	0, 22, 44, 88, 175, or 350 mg/kg-day via gavage in corn oil 5 days/week for 16 weeks.	22	44	31.4	Increased absolute and relative liver and kidney weight in females.	A FEL of 175 mg/kg-day was established for mortality in both sexes.	Matthews et al., 1990; NTP, 1991
Mouse, $B6C3F_1$ (10/sex/dose)	0, 22, 44, 88, 175, or 350 mg/kg-day via gavage in corn oil 5 days/week for 16 weeks.	88	175	125	Increased absolute and relative liver weight in females; decreased relative kidney weight in males.		Matthews et al., 1990; NTP, 1991
Chronic Studies							
Rat, F344/N (50/sex/dose)	0, 44, or 88 mg/kg-day via gavage in corn oil 5 days/week for 104 weeks.	44	88	62.9	Brain lesions (cerebrum, pons, and brain stem) in females; reduced survival in females; renal hyperplasia in males and females.		NTP, 1991; Matthews et al., 1993
Rat, F344/N (10/sex/dose)	0, 44, or 88 mg/kg-day via gavage in corn oil 5 days/week for 66 weeks (interim evaluation).	44	88	62.9	Increased absolute and relative liver and kidney weights in males.		NTP, 1991; Matthews et al., 1993
Mouse, $B6C3F_1$ (10/sex/dose)	0, 175, or 350 mg/kg-day via gavage in corn oil 5 days/week for 104 weeks.	Not defined	175	125	Enlargement of nuclei in renal tubule cells (karyomegaly).		NTP, 1991; Matthews et al., 1993

Table 9. Summary of Oral Noncancer Dose-Response Information for TCEP							
Species (n/sex/group)	**Exposure**	**NOAEL (mg/kg-day)**	**LOAEL (mg/kg-day)**	**Duration-adjusted[a] LOAEL (mg/kg-day)**	**Responses at the LOAEL**	**Comments**	**Reference**
Reproductive/Developmental Toxicity Studies							
Rat, Wistar (20–30 dams/dose)	0, 50, 100, 200 mg/kg-day via daily gavage in olive oil on GD 7–15	100 (maternal and neuro-developmental)	200 (FEL)	200 (FEL)	Maternal mortality.		Kawashima et al., 1983
Mouse, Swiss CD-1 (20 pairs/dose)	0, 175, 350 or 700 mg/kg-day via daily gavage (prior to mating, through mating, gestation, lactation for up to 5 litters and two generations)	175	350	350	Decreased fertility (# consecutive litters produced, mean litters/pair, mean live pups/litter) likely due to adverse effects on sperm count, motility and morphology.		Gulati et al., 1991

[a]Adjusted for continuous exposure

subchronic studies, a NOAEL of 22 mg/kg-day and a LOAEL of 44 mg/kg-day are identified for increased absolute and relative liver and kidney weights in female F344/N rats given TCEP by gavage 5 days/week for 16 weeks (Matthews et al., 1990; NTP, 1991). All available continuous models in the U.S. EPA Benchmark Dose Software (BMDS) version 2.1 beta were applied to the female absolute and relative liver and kidney-weight data. Due to the lack of a dose-response relationship, absolute and relative liver and kidney-weight data in male rats were not suitable for BMD modeling. For females, BMD modeling was performed using the doses administered in the study before duration adjustment. For absolute and relative liver-weight data, as well as absolute kidney-weight data, no adequate model fits were achieved with all of the dose groups—even when the highest two dose groups were dropped from the analysis. For a dose-dependent increase in relative kidney weight in female rats treated with TCEP for 16 weeks, a default benchmark response (BMR) of 1 standard deviation (SD) from the control mean was used in modeling this endpoint. A $BMDL_{1SD}$ of 9.66 mg/kg-day was calculated and identified as the point of departure (POD) for the subchronic p-RfD derivation. Details of the BMD modeling and plots of the models are presented in Appendix A.

The 16-week subchronic rat study involved exposure by oral gavage 5 days/week. Therefore, the $BMDL_{1SD}$ was duration adjusted to 6.9 mg/kg-day for continuous exposure (5/7 days). This duration adjusted $BMDL_{1SD}$ ($BMDL_{1SD[ADJ]}$) was divided by a composite UF of 300 to derive a **subchronic p-RfD** for TCEP as follows:

Subchronic p-RfD	=	$BMDL_{1SD[ADJ]} \div UF$
	=	6.9 mg/kg-day ÷ 300
	=	**0.02 or 2×10^{-2} mg/kg-day**

The composite UF of 300 is composed of the following:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are unavailable.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are unavailable.
- UF_L: A factor of 1 is applied because the POD is based on a BMDL.
- UF_D: The existing database for TCEP consists of subchronic and chronic studies in rats and mice, a reproductive study in mice, and a developmental study in rats that included neurodevelopmental endpoints. However, a partial factor of 3 (i.e., $10^{0.5}$) is applied for database inadequacies, including lack of a comprehensive neurotoxicity study in rats (in light of brain lesions in the subchronic and chronic rat studies) and lack of a multigenerational reproduction study.

Confidence in the principal subchronic rat study (NTP, 1991) is medium. The study is a comprehensive investigation of toxicity in male and female rats. However, deaths due to gavage and dosing errors may have interfered with study findings. Confidence in the database is medium. The database for TCEP includes subchronic and chronic studies in rats and mice, a reproductive study in mice, and a developmental study in rats. However, the database is missing a full neurotoxicity assessment (suggested by hippocampal lesions in the subchronic and chronic rat studies) and a multigenerational assessment of reproduction. Overall confidence in the subchronic p-RfD is medium.

Chronic p-RfD

Chronic studies exist in two laboratory animal species (F344/N rats and B6C3F1 mice) given TCEP by gavage 5 days/week for 66 or 104 weeks (Matthews et al., 1993; NTP, 1991). A high incidence of brain lesions (in the cerebrum, pons, and brain stem) and significantly reduced survival in female rats (with brain lesions observed in many of these animals) occurred after treatment with 88 mg/kg-day for 104 weeks. Renal tubular hyperplasia seen in association with renal tumors in both males and females in the 104-week study duration was may likely be preneoplastic in nature.

Similar to the subchronic study, significantly increased absolute and relative liver and kidney weights were the most sensitive effects occurring in the absence of frank effects following 66 weeks of TCEP exposure. However, at the interim 66-week sacrifice, increased absolute and relative liver and kidney weights were only observed in male rats at 88 mg/kg-day (LOAEL). This dose is twice that of the LOAEL of 44 mg/kg-day identified for the similar liver and kidney effects observed only in female rats from the subchronic study (Matthews et al., 1990; NTP, 1991). The only change in serum enzymes from any group tested are decreases in serum ALP and ALT in high-dose female rats in the 66-week study, which is not indicative of biological and/or functional liver alterations. Likewise, no accompanying liver or kidney pathological changes were observed in 175 and 350 mg/kg-day rats or 700 mg/kg-day mice (≥44 mg/kg-day for kidney) exposed subchronically or 88 mg/kg-day rats and mice exposed chronically. The explanation for the discrepancy between significantly increased absolute and relative liver and kidney weights between the subchronic study (treatment-dependent effects observed only in female rats at a LOAEL of 44 mg/kg-day) and the 66-week study (duration-dependent effects observed only in male rats at a LOAEL of 88 mg/kg-day) is unclear because these two studies were performed concurrently by the same laboratory.

The LOAEL of 44 mg/kg-day for increased absolute and relative liver and kidney weights in female rats from the 16-week subchronic study is more sensitive than the LOAEL of 88 mg/kg-day for the same endpoints in male rats from the 66-week study. In light of the available data on TCEP, and because the shorter exposure duration provided the most sensitive response, the $BMDL_{1SD[ADJ]}$ of 6.9 mg/kg-day for increased relative kidney weight from the subchronic 16-week study serves as the POD for deriving the chronic p-RfD value. The subchronic $BMDL_{1SD[ADJ]}$ was divided by a composite UF of 1000 to derive a **chronic p-RfD** for TCEP, as follows:

Chronic p-RfD	=	Subchronic $BMDL_{1SD[ADJ]} \div$ UF
	=	6.9 mg/kg-day ÷ 1000
	=	**0.007 or 7×10^{-3} mg/kg-day**

The composite UF of 1000 is composed of the following:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are unavailable.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are unavailable.
- UF_L: A factor of 1 is applied because the POD was based on a BMDL.

- UFs: A partial factor of 3 (i.e., $10^{0.5}$) is applied. A full factor of 10 for extrapolation from a subchronic to chronic exposure duration is not warranted because the available data suggests that severity of the critical effects (i.e., increased absolute and relative liver and kidney weights in female rats) did not increase from a 16 week exposure compared with a 66 week exposure duration.
- UFD: The existing database for TCEP consists of subchronic and chronic studies in rats and mice, a reproductive study in mice, and a developmental study in rats that included neurodevelopmental endpoints. However, a partial factor of 3 (i.e., $10^{0.5}$) is applied for database inadequacies, including lack of a comprehensive neurotoxicity study in rats (in light of brain lesions in the subchronic and chronic rat studies) and lack of a multigenerational reproduction study.

Confidence in the principal study is medium. The NTP study employs appropriate dose levels, uses sufficient numbers of animals, is comprehensive in scope, and includes a 66-week interim sacrifice as well as an evaluation over the lifespan of the animal. However, the significantly increased mortality in male and female rats in the high-dose group complicates the dose-response assessment of noncancer effects after a 104-week exposure duration. Confidence in the database is medium. However, the database is missing a full neurotoxicity assessment (suggested by brain lesions in the subchronic and chronic rat studies) and a multigenerational assessment of reproduction. Overall confidence in the chronic p-RfD is medium.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR TRIS(2-CHLOROETHYL)PHOSPHATE

No subchronic or chronic toxicity studies of inhaled TCEP were located. An inadequately reported developmental toxicity study from the Russian literature (Shepelskaya and Dyshinevich, 1981) was located, but it does not provide an adequate basis for derivation of p-RfC values.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR TRIS(2-CHLOROETHYL)PHOSPHATE

Weight-of-Evidence Descriptor

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the available evidence suggests that TCEP is ***"Likely to be Carcinogenic to Humans"*** based on (1) clear evidence of renal tubule cell adenomas in male and female F344/N rats, (2) suggestive evidence of renal tubule cell adenomas in $B6C3F_1$ mice, (3) clear evidence of renal tubule adenomas and carcinomas in male ddY mice, (4) the rarity of spontaneous renal tubule cell tumors in F344/N rats and $B6C3F_1$ mice, (5) suggestive evidence of hepatocellular adenomas in two strains of male mice, (6) suggestive evidence of leukemia in female ddY mice and in rats of both sexes, (7) suggestive evidence of Harderian gland adenomas in female $B6C3F_1$ mice, and (8) equivocal evidence of thyroid follicular cell carcinoma in female F344/N rats.

Chronic toxicity studies with male and female F344/N rats (NTP, 1991) and with male ddY mice (Takada et al., 1989) yielded clear evidence of a dose-related significant increase in renal tubular cell adenomas in response to oral (gavage) administration of TCEP for 2 years (male and female F344N rats) and following dietary administration for 18 months (male ddY mice). In the Takada et al. (1989) study, the incidence of renal cell carcinomas in male mice was also significantly increased. Evidence for TCEP-induced mononuclear cell leukemia in male and female F344/N rats was considered equivocal in the (NTP, 1991) study because although the incidences of this cancer were significantly elevated in both sexes, they were within the range of incidences observed for historical controls. A significantly increased incidence of leukemia was also observed among female—but not male—ddY mice in the Takada et al. (1989) dietary study, but no historic control values are presented. The incidences of thyroid follicular cell carcinoma and combined carcinoma plus adenoma were significantly increased in female—but not male—rats (NTP, 1991). However, this result provides only equivocal evidence of carcinogenicity due to a low incidence in high-dose rats (8%) that only marginally exceeded the upper limit of the historical control range for this neoplasm (6%) in NTP corn oil gavage studies. Results from the NTP (1991) mouse bioassay provide no clear evidence of carcinogenicity. Nonsignificant increases in renal tubule cell adenomas or carcinomas in male mice, and in Harderian gland adenomas and carcinomas in female mice, were considered by NTP (1991) to provide equivocal evidence of carcinogenicity. In the NTP (1991) study, there is a significant trend for increased hepatocellular adenomas. In the Takada et al. (1989) study, the incidences of hepatocellular adenomas and combined adenomas plus carcinomas are significantly elevated in males exposed to estimated dietary doses of approximately 233 and 1688 mg/kg-day. A significant increase in forestomach papillomas and squamous cell carcinomas is also documented in female ddY mice (Takada et al. 1989).

Mode-of-Action Discussion

The U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment* defines mode of action as "a sequence of key events and processes, starting with the interaction of an agent with a cell, proceeding through operational and anatomical changes and resulting in cancer formation." Toxicokinetic processes leading to the formation or distribution of the active agent (i.e., parent material or metabolite) to the target tissue are not part of the mode of action. Examples of possible modes of carcinogenic action include mutagenic, mitogenic, antiapoptotic (inhibition of programmed cell death), cytotoxic with reparative cell proliferation and immunologic suppression.

Ames tests are primarily negative in five studies reported by different investigators. One study reported a weakly positive result for one strain in the presence of S9 (Nakamura et al., 1979), but these results are not replicated in studies reported by four other groups of investigators (Simmon et al., 1977; Haworth et al., 1983; Kubo et al., 2002; Follmann and Wober, 2006). TCEP did not induce mutation in V79 cells (Sala et al., 1982). Most tests for other types of genetic damage (DNA strand breaks, clastogenic effects) were negative as well. The overwhelmingly negative response in the Ames tests conducted for TCEP is consistent with a general observation that the majority of chemical carcinogens that act on the kidney test negative in mutation tests with *Salmonella typhimurium* (Gold et al., 1993; Dybing and Sanner, 1999).

A potential mode of action for the development of renal tumors in male rats is one associated with the accumulation of α-2u-globulin[10]. However, several lines of evidence show that this mode of action is not relevant to TCEP. First, both male and female rats had significantly increased incidences of the renal tumors, and male ddY mice also exhibited an increased incidence of renal cell tumors (Takada et al., 1989). When cancer develops due to α-2u-nephropathy, the male rat is the only sex and species affected. Second, none of the renal findings typically associated with α-2u-globulin formation were observed in the study; neither hyaline droplets nor tubular casts are reported in the kidneys of either sex. Finally, TCEP was used as a negative control in a recent study investigating the mechanism of compound-mediated induction of α-2u-globulin formation in male F344N rats (Pahler et al., 1999). In that study, TCEP did not induce α-2u-globulin formation in circumstances that were positive for other compounds.

Proliferative and preneoplastic lesions were found in association with the renal tumors in rats (hyperplasia) and mice (karyomegaly) and with the liver tumors in mice (eosinophilic foci) (NTP, 1991). There was no evidence of degenerative lesions in either organ (NTP, 1991). The continuum of cellular changes (hyperplasia, renal tubular cell enlargement, and adenoma/carcinoma) observed with rats and mice are similar to that which has been observed in the expression of renal tubular cell cancers in humans (Beckwith, 1999). However, beyond the general association with known proliferative and preneoplastic lesions, there are no data available outlining specific potential key events in the mode of action for TCEP-induced tumors in the kidney or in other organs.

Quantitative Estimates of Carcinogenic Risk

Oral Exposure

The three data sets that were considered to derive an oral slope factor for TCEP are (1) the combined incidence of renal tubule cell adenomas and carcinomas in male F344/N rats (NTP, 1991; Table 10), (2) the combined incidence of renal tubule cell adenomas and carcinomas in female F344/N rats (NTP, 1991), and (3) the combined incidence of renal tubule cell adenomas and carcinomas in male ddY mice (Takada et al., 1989; Table 11). Tables 4 and 6 summarize these data . The incidences of other tumor types were lower and considered equivocal evidence of carcinogenicity, so those tumor types are not further considered. BMD modeling was conducted for male F344/N rats and male ddY mice. Renal tumor incidence in female rats is considerably lower than in males, so this data set is not modeled. The data modeled for male F344/N rats and ddY mice are summarized in Tables 10 and 11, including the calculation of human equivalent doses (HED). Appendix B presents the details of BMD modeling.

[10]Some compounds that induce tumors in the kidneys of male rats act through a mechanism involving the α-2u globulin protein—a component that is not produced in the kidneys of female rats or in other species (including humans). Therefore, kidney tumors that are known to occur as a consequence of α-2u-globulin nephropathy in male rats are not considered relevant to the assessment of carcinogenic potential in humans.

Table 10. Dose-Response Data for the Combined Incidence of Renal Tubular Cell Adenomas and Carcinomas in Male F344/N Rats[a] Given TCEP by Gavage		
Animal Dose (mg/kg-day, adjusted to 7d/wk)	**Human Equivalent Dose[b] (mg/kg-day)**	**Incidence**
0	0	2/50
31.4	8.8	5/50
62.9	17.7	25/50

[a]NTP (1991)
[b]Human Equivalent Dose = animal dose × (animal bw/human bw)$^{0.25}$, where animal body weights = 0.439 kg (control), 0.434 kg (low dose) and 0.438 (high dose), and human body weight = 70 kg

Table B-1 and Figure B-1 of Appendix B shows model predictions for the combined incidence of renal tubular cell adenomas and carcinomas in male F344/N rats. The 2-degree multistage cancer model provides the best fit to the data on combined incidence of renal tubular cell carcinomas and adenomas in male F344/N rats, yielding a $BMDL_{10[HED]}$ value of 5.41 mg/kg-day (human-equivalent dose). Model predictions for the combined incidence of renal tubular cell adenomas and carcinomas in male ddY mice are shown in Table B-2 and Figure B-2 of Appendix B. The 2-degree model also yielded the best fit to the data on combined incidence of renal tubular cell adenomas and carcinomas in male ddY mice, with a $BMDL_{10[HED]}$ value of 21.45 mg/kg-day (human-equivalent dose).

Table 11. Dose-Response Data for the Combined Incidence of Renal Tubular Cell Adenomas and Carcinomas in Male ddYY Mice[a] Given TCEP by Gavage		
Animal Dose (mg/kg-day, adjusted to 7d/wk)	**Human Equivalent Dose[b] (mg/kg-day)**	**Incidence**
0	0	2/50
9.3	1.5	0/47
46.6	7.4	2/49
232.8	37.1	5/47
1687.5	261	41/50

[a]Takada et al. (1989)
[b]Human Equivalent Dose = animal dose × (animal bw/human bw)$^{0.25}$, where animal body weights = 0.045 kg (all but highest dose) and 0.040 kg (highest dose), and human body weight = 70 kg

In the absence of a defined mode of action for TCEP, a linear low-dose extrapolation is applied. Using the lower $BMDL_{10[HED]}$ of 5.41 mg/kg-day for the combined incidence of renal tubular cell adenomas and carcinomas in male F344/N rats (NTP, 1991; Matthews et al., 1993) as the POD, a **p-OSF** for TCEP is calculated as follows:

$$\begin{aligned} \textbf{p-OSF} &= 0.1 \div BMDL_{10[HED]} \\ &= 0.1 \div 5.41 \text{ mg/kg-day} \\ &= \textbf{0.02 or } \mathbf{2 \times 10^{-2}\ (mg/kg\text{-}day)^{-1}} \end{aligned}$$

The oral slope factor for TCEP should not be used with exposures exceeding the POD ($BMDL_{10[HED]}$ = 5.4 mg/kg-day) because at exposures above this level, the fitted dose-response

model better characterizes what is known about the carcinogenicity of TCEP. Table 12 shows the doses associated with specific levels of cancer risk based on the p-OSF estimated herein.

Table 12. Doses of TCEP Associated with Some Specific Levels of Cancer Risk

Risk Level	Dose (mg/kg-day)
10^{-4}	5×10^{-3}
10^{-5}	5×10^{-4}
10^{-6}	5×10^{-5}

Inhalation Exposure

There are no inhalation studies that address the carcinogenic potential of inhaled TCEP. Therefore, it is not possible to derive a p-IUR for TCEP.

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APPENDIX A. DETAILS OF BENCHMARK DOSE MODELING FOR THE PROVISIONAL RfDs

Model Fitting Procedure for Continuous Data

The BMD modeling for continuous data (i.e., relative kidney weight changes) was conducted with the U.S. EPA's BMD software (BMDS version 2.1 beta). The original data were modeled with all the continuous models available within the software employing a BMR of 1 SD. An adequate fit was judged based on three criteria: (1) the goodness-of-fit *p* value ($p > 0.1$), (2) magnitude of scaled residuals in the vicinity of the BMR, and (3) visual inspection of the model fit. In addition to the three criteria for judging the adequate model fit, whether the variance needed to be modeled, and if so, how it was modeled also determined final use of the model results. If a constant variance model was deemed appropriate based on the statistical test provided in the BMDS (i.e., Test 2), the final BMD results were estimated from a constant variance model. If the test for constant variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonconstant variance. If this nonconstant variance model did not adequately fit the data (i.e., Test 3; *p*-value < 0.1), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL was selected if the BMDLs estimated from different models varied > 3-fold; otherwise, the BMDL from the model with the lowest AIC was selected as a potential POD from which to derive an RfD.

Model Predictions for Relative Kidney Weight in Female F344/N Rats Given TCEP by Gavage for 16 Weeks

All available continuous models in the BMDS (version 2.1 beta) have been fit to the relative kidney-weight data from the subchronic study (Matthews et al., 1990; NTP, 1991) (see Table A1). BMD modeling has been performed using the doses administered in the study before duration adjustment. A default BMR of 1SD from the control mean was used in the BMD modeling because no specific criteria on the magnitude of change of relative kidney weight that would be considered biologically significant of changes could be identified. Due to the lack of a dose-response relationship, relative kidney-weight data in male rats are not suitable for BMD modeling. For relative kidney-weight data in females, only the Hill model run with constant variance met the goodness of fit *p* value > 0.1 criteria and the scaled residual criteria for assessing adequate model fit, and Test 2 ($p = 0.4089$) also indicated that using a constant variance model was appropriate for modeling these data (see Table A-1, Figure A-1). Visual inspection of the dose-response curve suggested that the dose-response relationship is better characterized in the low-dose region. Thus, the highest dose was removed from the analysis for biological considerations, which significantly improved model fit (Figure A-2). Thus, the estimated BMD_{1SD} and $BMDL_{1SD}$ based on relative kidney-weight data are 22.74 and 9.66 mg/kg-day, respectively.

Table A-1. BMD Modeling Results Based on Relative Kidney-Weight Data from Female F344/N Rats Given TCEP By Gavage for 16 Weeks						
Model	**Test 2**	**Test 3**	**Goodness of fit *p* value**	**AIC**	**BMD_{1SD}**	**$BMDL_{1SD}$**
All Doses						
Linear[a,b]	0.4546	0.3421	0.0056	-117.304	96.14	65.93
Polynomial[a,b]	0.4546	0.3421	0.0056	-117.304	96.14	65.93
Power[b,c]	0.4546	0.3421	0.0056	-117.304	96.14	65.93
Hill[b,c]	0.4546	0.3421	0.1494	-124.579	17.24	9.06
5 Doses (without the highest dose group)						
Linear[a,d]	0.4089	0.4089	0.0060	-105.457	68.36	51.47
Polynomial[a,d]	0.4089	0.4089	0.0060	-105.457	68.36	51.47
Power[c,d]	0.4089	0.4089	0.0060	-105.457	68.36	51.47
Hill[c,d]	**0.4089**	**0.4089**	**0.4770**	**-113.407**	**22.74**	**9.66**

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

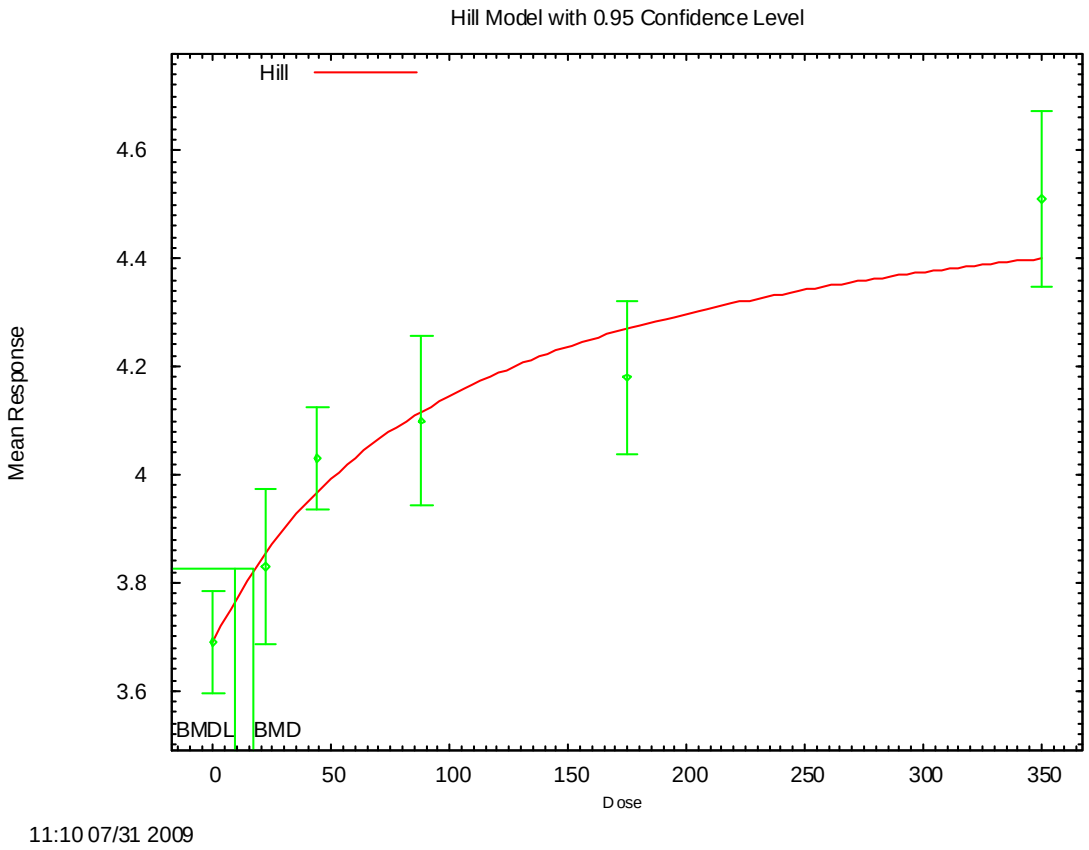

Figure A-1. Dose-Response Modeling of Relative Kidney Weight (All Dose Groups) in Female F344/N Rats Given TCEP By Gavage for 16 Weeks

```
================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\USEPA\BMDS21Beta\Data\1HilTCEHil.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21Beta\Data\1HilTCEHil.plt
                                          Fri Jul 31 11:10:17 2009
 ================================================================

 BMDS Model Run
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   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 6
   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 =	-3.61439
rho =	0
intercept =	3.69
v =	0.82
n =	0.207813
k =	262

Asymptotic Correlation Matrix of Parameter Estimates

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

	lalpha	rho	intercept	v	k
lalpha	1	-1	0.08	0.33	0.31
rho	-1	1	-0.082	-0.33	-0.31
intercept	0.08	-0.082	1	0.12	0.55
v	0.33	-0.33	0.12	1	0.84
k	0.31	-0.31	0.55	0.84	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-10.2762	5.54513	-21.1445	0.592029
rho	4.77951	3.99085	-3.04242	12.6014
intercept	3.69228	0.0416158	3.61071	3.77384
v	0.915182	0.16943	0.583105	1.24726
n	1	NA		
k	101.282	48.289	6.63697	195.926

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	3.69	3.69	0.13	0.133	-0.0541
22	8	3.83	3.86	0.17	0.148	-0.49
44	10	4.03	3.97	0.13	0.158	1.21
88	10	4.1	4.12	0.22	0.173	-0.325

175	8	4.18	4.27	0.17	0.189	-1.38
350	5	4.51	4.4	0.13	0.203	1.19

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	69.858620	7	-125.717241
A2	72.204625	12	-120.409251
A3	69.952821	8	-123.905642
fitted	67.289523	5	-124.579046
R	39.035206	2	-74.070412

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	66.3388	10	<.0001
Test 2	4.69201	5	0.4546
Test 3	4.50361	4	0.3421
Test 4	5.3266	3	0.1494

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

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

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 = 17.2397

BMDL = 9.05952

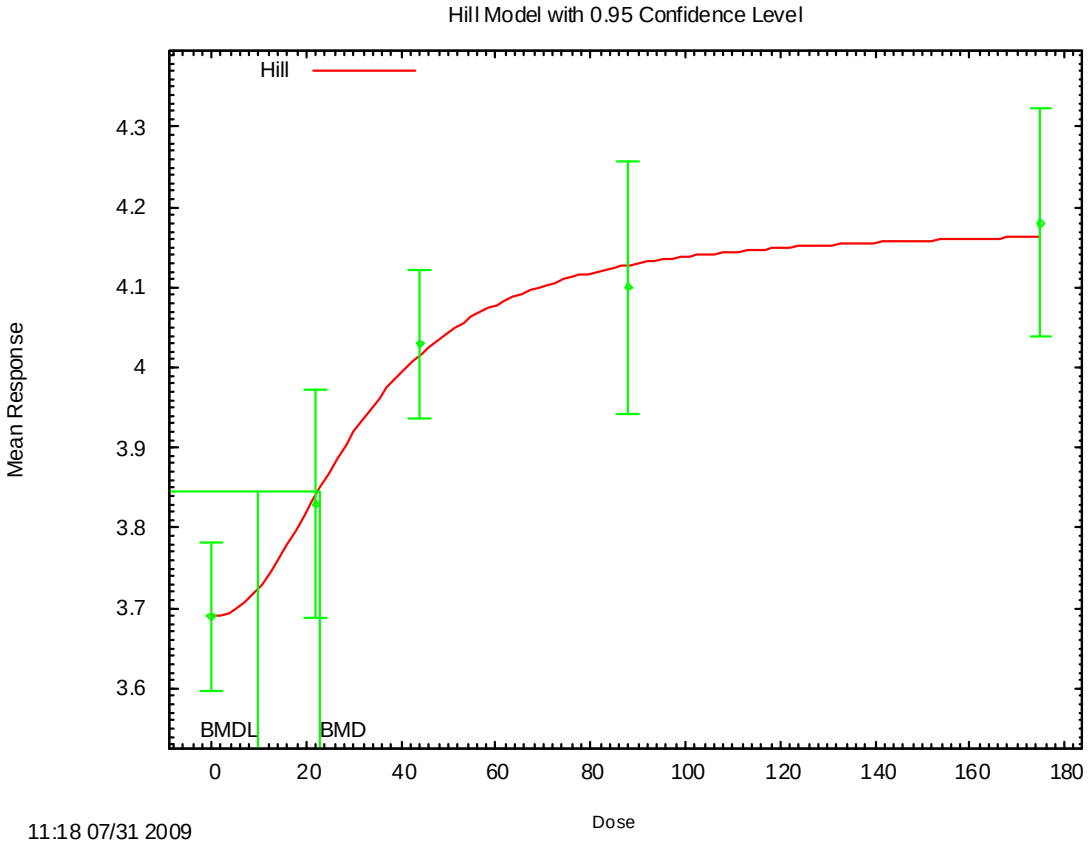

Figure A-2. Dose-Response Modeling of Relative Kidney Weight (Without the Highest Dose Group) in Female F344/N Rats Given TCEP by Gavage for 16 Weeks

```
=================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\USEPA\BMDS21Beta\Data\1HilTCEHil.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21Beta\Data\1HilTCEHil.plt
                                          Fri Jul 31 11:18:58 2009
 =================================================================

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

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

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

Default Initial Parameter Values

alpha =	0.0279122	
rho =	0	Specified
intercept =	3.69	
v =	0.49	
n =	1.47172	
k =	54.45	

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	intercept	v	n	k
alpha	1	2.3e-009	-1.3e-008	3.3e-008	-1.7e-008
intercept	2.3e-009	1	-0.59	0.19	0.35
v	-1.3e-008	-0.59	1	-0.75	0.37
n	3.3e-008	0.19	-0.75	1	-0.41
k	-1.7e-008	0.35	0.37	-0.41	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.0251533	0.00524483	0.0148736	0.035433
intercept	3.68803	0.0496782	3.59066	3.7854
v	0.483805	0.0951159	0.297381	0.670228
n	2.19378	1.35239	-0.456867	4.84442
k	31.5522	8.20197	15.4766	47.6277

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	3.69	3.69	0.13	0.159	0.0393
22	8	3.83	3.84	0.17	0.159	-0.16
44	10	4.03	4.01	0.13	0.159	0.31
88	10	4.1	4.13	0.22	0.159	-0.513
175	8	4.18	4.16	0.17	0.159	0.342

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           61.956501            6    -111.913002
             A2           63.945662           10    -107.891324
             A3           61.956501            6    -111.913002
          fitted          61.703602            5    -113.407204
              R           42.726595            2     -81.453190


                   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              42.4381          8          <.0001
   Test 2              3.97832          4          0.4089
   Test 3              3.97832          4          0.4089
   Test 4             0.505798          1           0.477

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

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


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

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


        Benchmark Dose Computation

Specified effect =            1

Risk Type        =     Estimated standard deviations from the control mean
```

```
Confidence level =           0.95

             BMD =        22.7443

            BMDL =       9.65587
```

APPENDIX B. DETAILS OF BENCHMARK DOSE MODELING FOR THE PROVISIONAL ORAL SLOPE FACTOR

Model-Fitting Procedure for Cancer Incidence Data

The model fitting procedure for dichotomous cancer incidence data is as follows. The multistage-cancer model in the U.S. EPA BMDS is fit to the incidence data using the extra risk option. The multistage-cancer model is run for all polynomial degrees up to *n*-1 (where *n* is the number of dose groups including control). Adequate model fit is judged by three criteria: goodness-of-fit *p*-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMDL is selected as the POD when the difference between the BMDLs estimated from these models are more three-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with U.S. EPA (2000) guidance, benchmark doses (BMDs) and lower bounds on the BMD (BMDLs) associated with an extra risk of 10% are calculated.

Model Predictions for Renal Tubular Cell Neoplasms (Combined Adenoma and Carcinoma) in Male F344/N Rats (NTP, 1991)

Model predictions for the combined incidence of renal tubular cell carcinomas and adenomas in male F344/N rats are shown in Table B-1 and Figure B-1. The 2-degree multistage cancer model provides adequate fit, yielding a $BMDL_{10}$ value of 5.41 mg/kg-day (human-equivalent-dose) and a p-OSF of 0.018 $(mg/kg\text{-}day)^{-1}$.

Table B-1: Model Predictions for Renal Tubular Cell Neoplasms (Combined Adenoma and Carcinoma) in Male F344/N Rats (NTP, 1991)

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[b]	AIC	$BMD_{10\ HED}$ (mg/kg-day)	$BMDL_{10\ HED}$ (mg/kg-day)	Cancer slope factor
Multistage-Cancer (1-degree)[c]	1	7.46	0.0063	130.95	4.03	2.94	0.034028
Multistage-Cancer (2-degree)[c]	**1**	**1.85**	**0.1734**	**124.63**	**7.55**	**5.41**	**0.018481**

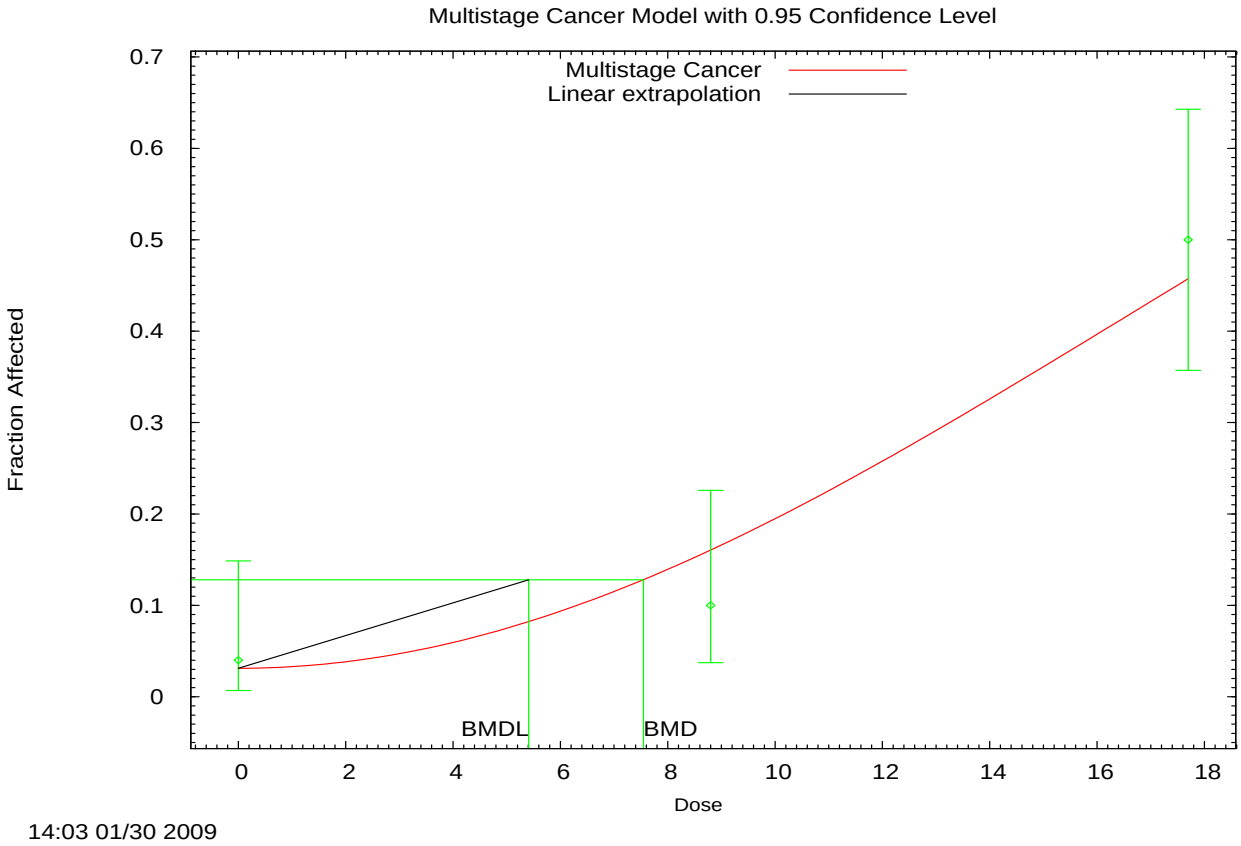

Figure B-1. Fit of the 2-Degree Multistage Cancer Model to Data on the Combined Incidence of Renal Tubular Cell Adenomas and Carcinomas in Male F344/N Rats (NTP, 1991)

BMDs and BMDLs indicated are associated with an extra risk of 10%, and are human-equivalent doses in units of mg/kg-day

Model Predictions for Renal Tubular Cell Neoplasms (Combined Adenoma and Carcinoma) in Male ddY Mice (Takada et al., 1989)

Model predictions for the combined incidence of renal tubular cell adenomas and carcinomas in male ddY mice are shown in Table B-2 and Figure B-2. The 2-degree multistage cancer model provides adequate fit, yielding a $BMDL_{10}$ value of 21.45 mg/kg-day (human-equivalent-dose) and a p-OSF of 0.005 $(mg/kg\text{-}day)^{-1}$.

Table B-2: Model Predictions for Renal Tubular Cell Neoplasms (Combined Adenoma and Carcinoma) in Male ddY Mice (Takada et al., 1989)

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[b]	AIC	$BMD_{10\ HED}$ (mg/kg-day)	$BMDL_{10\ HED}$ (mg/kg-day)	Cancer slope factor
Multistage-Cancer (1-degree)[c]	3	6.53	0.0886	124.02	19.27	14.92	0.00670225
Multistage-Cancer (2-degree)[c]	**2**	**1.95**	**0.3775**	**121.49**	**42.48**	**21.45**	**0.00466094**
Multistage-Cancer (3-degree)[c]	2	1.95	0.3775	121.49	42.48	21.23	0.00471001
Multistage-Cancer (4-degree)[c]	2	1.95	0.3775	121.49	42.48	21.18	0.00472245

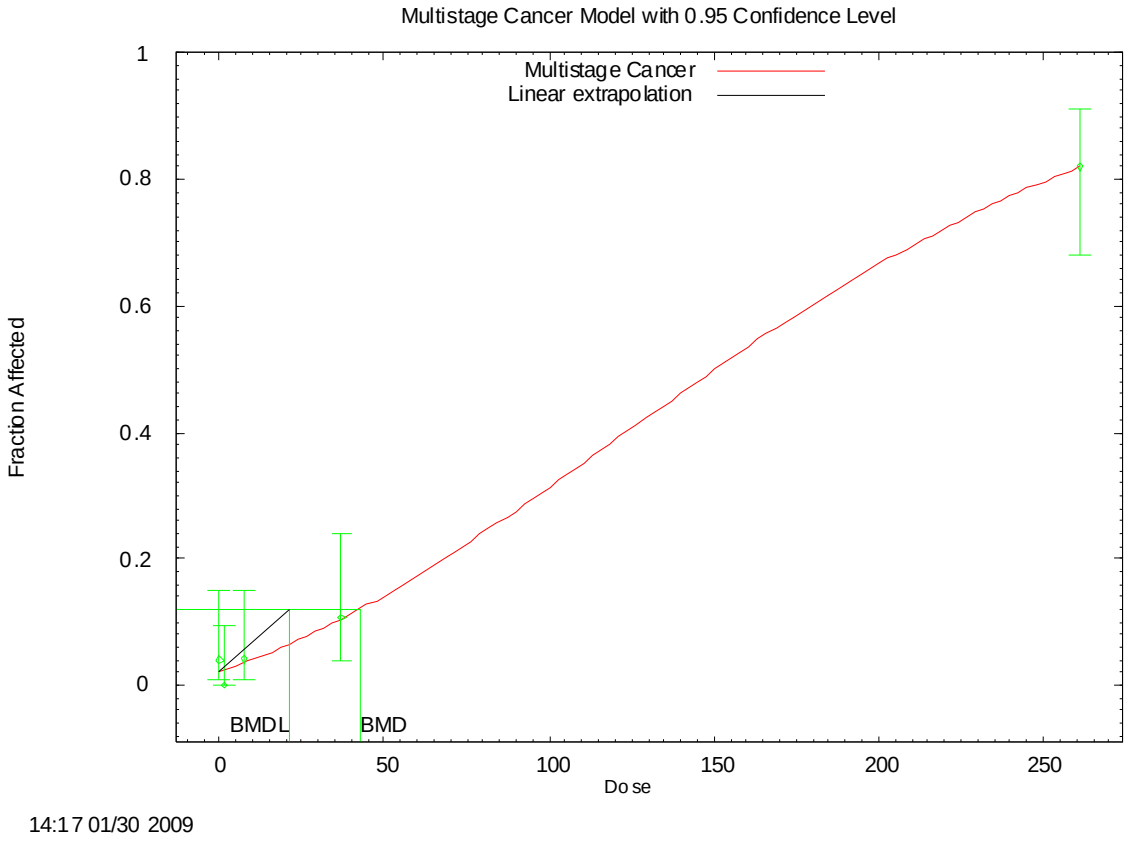

Figure B-2. Fit of the 2-Degree Multistage Cancer Model to Data on the Combined Incidence of Renal Tubular Cell Adenomas and Carcinomas in Male ddY Mice

BMDs and BMDLs indicated are associated with an extra risk of 10%, and are human-equivalent doses in units of mg/kg-day