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Provisional Peer-Reviewed Toxicity Values for

Technical Toxaphene
(CASRN 8001-35-2)
Weathered Toxaphene, and Toxaphene Congeners

U.S. EPA Office of Research and Development
National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (Cincinnati, OH)

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Questions regarding the content of this PPRTV assessment should 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).

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COMMONLY USED ABBREVIATIONS AND ACRONYMS[1]

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

[1]Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV document.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR TECHNICAL TOXAPHENE (CASRN 8001-35-2), WEATHERED TOXAPHENE, AND TOXAPHENE CONGENERS

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by at least two National Center for Environmental Assessment (NCEA) scientists and an independent external peer review by at least three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

PPRTV assessments are eligible to be updated on a 5-year cycle to incorporate new data or methodologies that might impact the toxicity values or characterization of potential for adverse human-health effects and are revised as appropriate. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. Environmental Protection Agency (EPA) Superfund and Technology Liaison (https://www.epa.gov/research/fact-sheets-regional-science).

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. EPA programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVS

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development's (ORD's) NCEA, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

This PPRTV assessment details the hazard and dose-response assessment pertaining to chronic and subchronic exposures to technical toxaphene (CASRN 8001-35-2), weathered toxaphene, and toxaphene congeners.

TECHNICAL TOXAPHENE

Technical toxaphene, CASRN 8001-35-2, is a yellow, waxy solid with a turpentine odor. It is a manufactured pesticide consisting of a complex mixture of hundreds of chlorinated terpenes produced by the chlorination of camphene under ultraviolet (UV) light (ATSDR, 2014; de Geus et al., 1999; Saleh, 1991). This manufactured mixture, referred to as technical toxaphene in this document, was used extensively as an insecticide, piscicide, and acaricide beginning in the mid-1940s, but the U.S. EPA canceled the registration for most uses as a pesticide or pesticide ingredient in 1982 (ATSDR, 2014; de Geus et al., 1999; Vetter and Oehme, 1993; Saleh, 1991). All registered uses of toxaphene mixtures were subsequently canceled in the United States in 1990 (ATSDR, 2014; Lacayo et al., 2004; de Geus et al., 1999; Saleh, 1991). The use of technical toxaphene was also banned in most of Europe during the 1980s (Barbini et al., 2007; Alder and Vieth, 1996). Table 1 summarizes the physicochemical properties of technical toxaphene.

Table 1. Physicochemical Properties of Technical Toxaphene (CASRN 8001-35-2)

Property (unit)	Value
Physical state	Solid
Boiling point (°C)	NA (dechlorinates at 155°C)[a]
Melting point (°C)	65–90[a]
Density (g/cm^3 at 25°C)	1.65[a]
Vapor pressure (mm Hg at 20°C)	6.69×10^{-6} [a]
pH (unitless)	NV
pKa (unitless)	NV
Solubility in water (mg/L at 20°C)	0.55[a]
Octanol-water partition coefficient (log K_{ow})	5.9[b]
Henry's law constant (atm-m^3/mol at 20°C)	6.0×10^{-6} [a]
Soil adsorption coefficient (log K_{oc})	5[b]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	2.3×10^{-12} (estimated)[b]
Atmospheric half-life (d)	4.7 (estimated)[b]
Relative vapor density (air = 1)	14.3[c]
Molecular weight (g/mol)	431.8[a]
Flash point (°C)	135 (closed cup, 60% solution)[a]; 115 (tag closed cup, 90% solution)[a]

[a]ATSDR (2014).
[b]U.S. EPA (2012c).
[c]NTP (2014).

NA = not applicable; NV = not available.

Congeners (components) in technical toxaphene include chlorinated bornanes, bornenes, bornadienes, camphenes, and dihydrocamphenes, each containing 6–10 chlorine atoms (ATSDR, 2014; de Geus et al., 1999). Figure 1 shows carbon skeleton structures for these congeners. The approximate relative composition of technical toxaphene has been reported to be 76% chlorobornanes, 18% chlorobornenes, 2% chlorobornadienes, 1% other chlorinated hydrocarbons, and 3% nonchlorinated hydrocarbons. The actual composition, however, is likely to have varied depending on manufacturing conditions (ATSDR, 2014; de Geus et al., 1999; Saleh, 1991). Table 2 contains names and CASRNs of selected toxaphene congeners reported in technical toxaphene (or weathered toxaphene residues; see "Weathered Toxaphene" section), as well as alternative names in the Andrews and Vetter (1995) and Parlar (Burhenne et al., 1993) identification systems.

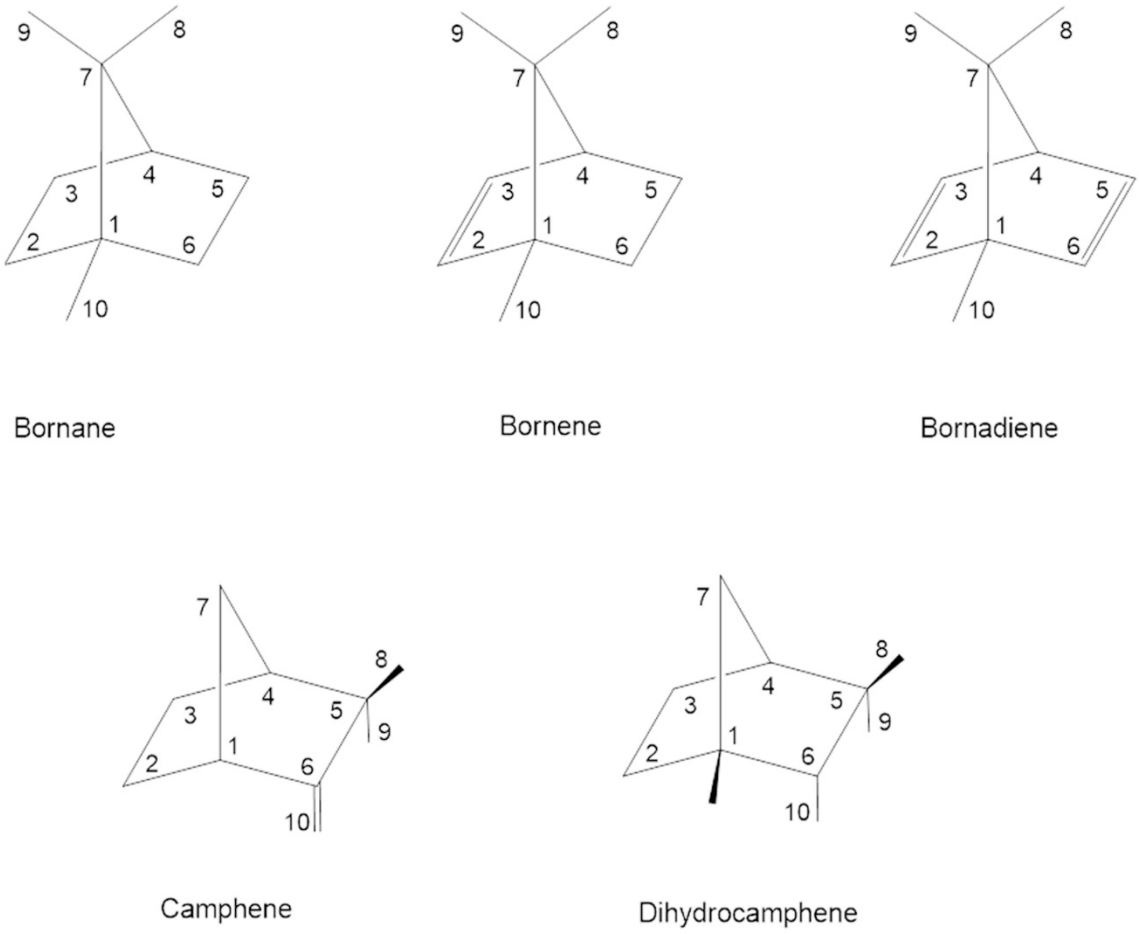

Figure 1. Carbon Skeleton Structures for Congeners (with numbered carbon atoms) in Technical Toxaphene[2]

[2]Congeners typically contain 6−10 chlorine atoms. Sources: ATSDR (2014); de Geus et al. (1999).

Table 2. Names of Selected Congeners in Technical Toxaphene or Weathered Toxaphene[a]

Chemical Name (*other ID*)	CASRN	Parlar No.	Andrews-Vetter Code
2,2,3-exo,8,9,10(E)-Hexachlorocamphene	NV	p-11	NV
2-exo,3-endo,8,8,9,10(E)-Hexachlorocamphene	NV	p-12	NV
2,2,5,5,9,10,10-Heptachlorobornane	165820-13-3	p-21	B7-499
2-endo,3-exo,5-endo,6-exo,8,8,10,10-Octachlorobornane *(T2, Tox8)*	142534-71-2	p-26	B8-1413
2,2,5-endo,6-exo,8,9,10-Heptachlorobornane *(Toxicant B)*	51775-36-1	p-32	B7-515
2,2,5,5,9,9,10,10-Octachlorobornane	165820-15-5	p-38	B8-789
2,2,3-exo,5-endo,6-exo,8,9,10-Octachlorobornane	64618-67-3	p-39	B8-531
2-endo,3-exo,5-endo,6-exo,8,9,10,10-Octachlorobornane	166021-27-8	p-40	B8-1414
2-exo,3-endo,5-exo,8,9,9,10,10-Octachlorobornane (*TC6*)	165820-16-6	p-41	B8-1945
2,2,5-endo,6-exo,8,8,9,10-Octachlorobornane *(TC8, Toxicant A1*)	58002-19-0	p-42a	B8-806
2,2,5-endo,6-exo,8,9,9,10-Octachlorobornane (*TC8, Toxicant A2*)	177695-50-0	p-42b	B8-809
2-exo,5,5,8,9,9,10,10-Octachlorobornane (*TC7*)	165820-17-7	p-44	B8-2229
2-endo,3-exo,5-endo,6-exo,8,8,9,10,10-Nonachlorobornane (*Toxicant Ac, T12, Tox9*)	6680-80-8	p-50	B9-1679
2,2,5,5,8,9,10,10-Octachlorobornane	165820-18-8	p-51	B8-786
2,2,5-endo,6-exo,8,8,9,10,10-Nonachlorohornane	64618-71-9	p-56	B9-1046
2,2,5-endo,6-exo,8,9,9,10,10-Nonachlorobornane	155750-49-5	p-59	B9-1049
2,2,5,5,8,9,9,10,10-Nonachlorobornane	154159-06-5	p-62	B9-1025
2-exo,3-endo,5-exo,6-exo,8,8,9,10,10-Nonachlorobornane	182266-92-8	p-63	B9-2206
2,2,5,5,6-exo,8,9,9,10,10-Decachlorobornane	151183-19-6	p-69	B10-1110
2-exo,3-endo,6-exo,8,9,10-Hexachlorobornane (*Hx-Sed*)	57981-29-0	NV	B6-923
2-endo,3-exo,5-endo,6-exo,8,9,10-Heptachlorobornane (*Hp-Sed*)	70649-42-2	NA	B7-1001
2-exo,3-endo,5-exo,8,9,10,10-Heptachlorobornane (*TMX-1*)	NV	NA	B7-1450
2-exo,3-endo,5-exo,9,9,10,10-Heptachlorobornane	NV	NA	B7-1453
2-endo,3-exo,5-endo,6-exo,8,8,9,10-Octachlorobornane	NV	NA	B8-1412

[a]ATSDR (2014); Braekevelt et al. (2001); de Geus et al. (1999); Andrews and Vetter (1995); Burhenne et al. (1993).

NA = not applicable; NV = not available.

WEATHERED TOXAPHENE

Following release of technical toxaphene into the environment, the congeners are expected to undergo differential transformation, and degradation via abiotic and biotic processes, resulting in different mixtures of persistent toxaphene congeners, commonly termed weathered toxaphene [for reviews, see ATSDR (2014); Braekevelt et al. (2001); de Geus et al. (1999); Geygr et al. (1999); Saleh (1991)]. Transformation and degradation processes are expected to include dechlorination and dehydrochlorination. The composition of weathered toxaphene is expected to vary depending on the environmental media and conditions (e.g., soil, sediment, or

air; anaerobic vs. aerobic), distance from source, length of time since release, and the varying biological matrices in which toxaphene congeners may be found [for reviews, see ATSDR (2014); de Geus et al. (1999); U.S. EPA (2010); U.S. EPA (2005a); U.S. EPA (2005b); Saleh (1991)]. Biological processes that can produce different weathered toxaphene profiles include the ways toxaphene is metabolized and excreted, which vary across congeners and species of organisms. For example, studies of tissue samples of aquatic mammals and fish found that the relative amounts of certain octachlorinated and nonachlorinated congeners (p-26 [B8-1413], p-50 [B9-1679], p-62 [B9-1025], and to a lesser extent p-40/41 [B8-1414/B8-1945] and p-44 [B8-2229]), were higher than the relative amounts in technical toxaphene [Ekici et al. (2008); Ruppe et al. (2004); Ruppe et al. (2003); Vetter et al. (2001); Angerhöfer et al. (1999); de Geus et al. (1999); Vetter et al. (1999); Saleh (1991); Vetter and Scherer (1999) as cited in Bernardo et al. (2005)]. In addition, Simon and Manning (2006) showed that the average percentage of three persistent congeners (PCs) (p-26, p-50, and p-62, dubbed ∑3PC) in tissue samples from more than 10 northern-latitude aquatic species (22.45%, based on ng/g wet weight) was greater than the average percentage of these three congeners in tissue from 11 aquatic species sampled from a former U.S. manufacturing plant in Georgia in 1997 (4.47%).

Further support that weathered toxaphene composition varies in different environmental settings comes from observed differences in the compositional distribution of toxaphene congeners in toxaphene-contaminated environmental media (e.g., sediments or air), as well as biological tissues and fluids sampled from different species and regions of the world. Table 3 presents an example of reported compositional differences between a technical toxaphene standard and weathered toxaphene in environmental media and biological tissues, showing a shift to hexachlorinated and heptachlorinated congeners in sediments from a Canadian lake, compared with the proportions of these congeners in technical toxaphene (Braekevelt et al., 2001). The same study found lesser relative amounts of heptachlorinated congeners and greater amounts of nonachlorinated congeners, compared with those in technical toxaphene, in pelagic fish and mammals (i.e., lake trout and beluga whales) and a similar, although less pronounced, pattern in the demersal amphipod *Cyclocaris guilelmi* (see Table 3). In contrast, tissue samples from bottom-dwelling fish species from a tidal creek near a former U.S. toxaphene manufacturing plant showed a clear shift toward hexachlorinated and heptachlorinated congeners that reflected the composition of sediments, with a predominance of Hx-Sed and Hp-Sed among the detected congeners (Maruya et al., 2001b; Maruya et al., 2001a). Because Hx-Sed and Hp-Sed appear to be eliminated more rapidly from fish than octachlorinated and nonachlorinated congeners (Smalling et al., 2000; Fisk et al., 1998), Maruya et al. (2001b) postulated that the predominance of lower chlorinated congeners in bottom-dwelling fish species was due to continued exposure to weathered toxaphene in sediments enriched in these lower chlorinated congeners.

Table 3. Percent Distribution of Chlorine Homologue Groups in Technical Toxaphene, Environmental Media, and Biological Samples[a]

	Hexachloro	Heptachloro	Octachloro	Nonachloro
Technical toxaphene	1.4	26.6	63.1	8.9
Air (Northwest Territory, Canada)	3.8	41.2	48.3	6.7
Sediments (Lake Winnipeg, Canada)	31.2	39.8	25.6	3.5
Demersal amphipod *Cyclocaris guilelmi* (Beaufort Sea, Canada)	1.2	19.2	68.0	11.6
Lake trout (Lake Laberge, Canada)	0.4	11.8	69.3	18.5
Beluga blubber (Nunavut, Canada)	0.4	15.4	67.5	16.7

[a]Braekevelt et al. (2001).

Information about actual exposure levels and toxicokinetic properties of toxaphene congeners in mammalian species is inadequate to explain the congener profile observed in human biological fluids. However, analysis of human fluids shows a congener profile dominated by octachlorinated congeners (p-26, and to a lesser extent p-40/41 and p-44) and nonachlorinated congeners (p-50 and p-62). In an analysis of human serum and breast milk samples collected in five studies, the major detected congeners and their average percentages of total toxaphene congeners detected were as follows: p-26 (32.8%), p-50 (54.7%), p-62 (6.3%), p-44 (3.5%), and p-40/41 (2.7%) (Simon and Manning, 2006). More than 90% of the total congeners detected in these samples was the three major PCs, p-26, p-50, and p-62 (dubbed ∑3PC).

A summary of available toxicity values for technical toxaphene from U.S. EPA and other agencies/organizations is provided in Table 4. No toxicity values are available for weathered toxaphene or individual toxaphene congeners.

Table 4. Summary of Available Toxicity Values for Technical Toxaphene (CASRN 8001-35-2)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2018)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA (RfD)	4×10^{-4} mg/kg-d	NA	U.S. EPA (2012a)
ATSDR (acute-duration oral MRL)	0.05 mg/kg-d	Derived from a NOAEL of 5 mg/kg-d for neurological effects in Beagle dogs exposed for 13 wk (Chu et al., 1986).	ATSDR (2014)
ATSDR (intermediate-duration oral MRL)	0.002 mg/kg-d	Derived from data on depressed humoral immunity in female cynomolgus monkeys.	ATSDR (2014)
IPCS	NV	NA	IPCS (2018); WHO (2018)
WHO (ADI)	Not established; however, reservations remain about the safety of toxaphene in food.	Could not establish an ADI for a material that varied in composition according to the method of manufacture.	WHO (1969); WHO (1974); WHO (1984); WHO (1990)
CalEPA (PHG)	10 ppb in drinking water	Based on a NOAEL of 0.35 mg/kg-d in rats exposed for 90 d (Chu et al., 1986).	CalEPA (2003)
CalEPA (REL)	NV	NA	CalEPA (2016)
CalEPA (Prop 65 List)	NV	Not listed for causing developmental or reproductive toxicity.	CalEPA (2018a)
OSHA (PEL)	0.5 mg/m^3	Skin designation; 8-hr TWA for general industry, construction, and shipyard employment.	OSHA (2017b); OSHA (2017c); OSHA (2017a)
ACGIH (TLV-TWA)	0.5 mg/m^3	Potential for acute CNS effects that include salivation, nausea, vomiting, and muscle spasms that may lead to convulsions; potential for liver damage. Skin notation based on absorption of technical toxaphene through skin of treated rabbits leading to systemic CNS effects and lethality.	ACGIH (2001); ACGIH (2017)
ACGIH (TLV-STEL)	1 mg/m^3	Potential for acute CNS effects that include salivation, nausea, vomiting, and muscle spasms that may lead to convulsions; potential for liver damage. Skin notation based on absorption of technical toxaphene through skin of treated rabbits leading to systemic CNS effects and lethality.	ACGIH (2001); ACGIH (2017)
DOE (PAC)	PAC-1: 1 mg/m^3; PAC-2: 20 mg/m^3; PAC-3: 200 mg/m^3	Based on TEELs.	DOE (2015)

Table 4. Summary of Available Toxicity Values for Technical Toxaphene (CASRN 8001-35-2)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
USAPHC (air-MEG)	1-hr critical: 200 mg/m^3; 1-hr marginal: 20 mg/m^3; 1-hr negligible: 1 mg/m^3; 8-hr negligible: 0.5 mg/m^3; 14-d negligible: 0.12 mg/m^3; 1-yr negligible: 0.015 mg/m^3	1-hr values based on TEELs for hepatocellular carcinomas and neoplastic nodules, 8-hr and 14-d values based on TLVs for CNS convulsions and liver damage, 1-yr value based on IRIS.	U.S. APHC (2013)
USAPHC (water-MEG)	1-yr negligible: 0.014 mg/L	Based on MRL for mild anisokaryosis.	U.S. APHC (2013)
USAPHC (soil-MEG)	1-yr negligible: 212 mg/kg	Basis: noncancer.	U.S. APHC (2013)
Cancer			
IRIS (WOE)	B2, probable human carcinogen; OSF: 1.1 (mg/kg-d)$^{-1}$; IUR: 3.2 × 10^{-4} (µg/m^3)$^{-1}$	Both values based on increased incidence of hepatocellular tumors in mice and thyroid tumors in rats following oral exposure; states values supported by mutagenicity in *Salmonella*.	U.S. EPA (1988a)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA (WOE)	B2, probable human carcinogen	NA	U.S. EPA (2012a)
NIOSH (REL)	Potential occupational Ca	Skin designation.	NIOSH (2016)
NIOSH (IDLH)	200 mg/m^3; potential occupational Ca	No toxic responses were noted in 25 volunteers exposed to 500 mg/m^3 for 30 min/d for 10 consecutive days [Shelansky (1947) as cited in NIOSH (2014)]. However, the original IDLH of 200 mg/m^3 is not being revised at this time.	NIOSH (2014); NIOSH (2016)
NTP (WOE)	Reasonably anticipated to be a human carcinogen	Based on sufficient evidence of carcinogenicity from studies in mice and rats.	NTP (2014)
IARC (WOE)	Group 2B, possibly carcinogenic to humans	Based on sufficient evidence of carcinogenicity in mice and rats and inadequate evidence in humans.	IARC (2001)
CalEPA (OSF)	1.2 (mg/kg-d)$^{-1}$	PHG of 0.03 ppb in drinking water is based on the OSF.	CalEPA (2003); CalEPA (2018b)
CalEPA (ISF)	1.2 (mg/kg-d)$^{-1}$	NA	CalEPA (2003); CalEPA (2018b)
CalEPA (IUR)	3.4 × 10^{-4} (µg/m^3)$^{-1}$	NA	CalEPA (2003); CalEPA (2018b)

Table 4. Summary of Available Toxicity Values for Technical Toxaphene (CASRN 8001-35-2)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
CalEPA (Prop 65 List)	NV	Listed as cancer causing.	CalEPA (2018a)
ACGIH (WOE)	A3, confirmed animal carcinogen with unknown relevance to humans	Based on induction of hepatocellular carcinomas in mice and an increased incidence of thyroid tumors in rats.	ACGIH (2001); ACGIH (2015)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DOE = U.S. Department of Energy; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; USAPHC = U.S. Army Public Health Command; WHO = World Health Organization.
[b]Parameters: ADI = acceptable daily intake; IDLH = immediately dangerous to life or health concentrations; ISF = inhalation slope factor; IUR = inhalation unit risk; MEG = military exposure guideline; MRL = minimal risk level; OSF = oral slope factor; PAC = protective action criteria; PEL = permissible exposure limit; PHG = public health goal; REL = recommended exposure limit; RfD = reference dose; STEL = short-term exposure limit; TEEL = temporary emergency exposure limit; TLV = threshold limit value; TWA = time-weighted average; WOE = weight of evidence.

Ca = carcinogen; CNS = central nervous system; NA = not applicable; NOAEL = no-observed-adverse-effect level; NV = not available.

Non-date-limited literature searches were conducted in March 2016 and updated in July 2018 for studies relevant to the derivation of provisional toxicity values for technical toxaphene (CASRN 8001-35-2), weathered toxaphene, and toxaphene congeners. Searches were conducted using the U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, ToxLine (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related data: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, U.S. EPA High Production Volume (HPV), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Japan Existing Chemical Database (JECDB), European Chemicals Agency (ECHA), Organisation for Economic Co-operation and Development (OECD) Screening Information Data Sets (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD HPV, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA), and Defense Technical Information Center (DTIC).

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 5A and 5B provide overviews of the relevant noncancer and cancer databases, respectively, for technical toxaphene (CASRN 8001-35-2). The tables include all potentially relevant repeated-dose short-term-, subchronic-, and chronic-duration studies, as well as reproductive and developmental toxicity studies. Principal studies are identified in bold. The phrase "statistical significance," used throughout the document, indicates a p-value of < 0.05 unless otherwise specified.

Table 5A. Summary of Potentially Relevant Noncancer Data for Technical Toxaphene (CASRN 8001-35-2)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Human							
Convulsions (presumably from effects on the nervous system) are the most common effect reported in acute poisoning case reports. A limited number of epidemiological studies have examined possible associations between occupational exposure to TT and noncancer diseases. In U.S. male pesticide applicators, self-reported hypothyroidism was associated with "ever-use" of 50 specific insecticides (including TT) (Goldner et al., 2013), but no statistically significantly elevated ORs were found for amyotrophic lateral sclerosis and "ever-use" of any of the subject pesticides, including TT (Kamel et al., 2012). Additionally, a statistically significant exposure-response trend in association with rheumatoid arthritis was observed for lifetime days of toxaphene use (Meyer et al., 2017).							
Animal							
1. Oral (mg/kg-d)							
Short term	40 M/0 F, S-D, rat, TT in corn oil by gavage; 0, 100 (then 75) mg/kg-d for 28 d	0, 78	Increased TSH serum levels; increased incidences for thyroid follicular hypertrophy and diffuse intrafollicular hyperplasia	NDr	78	Waritz et al. (1996) (Due to dose adjustments after the first 3 d of exposure, a TWA dose of 78 mg/kg-d has been calculated for this assessment.)	PR
Short term	5 M/5 F, S-D, rat, TT in corn oil by gavage; 0, 6 mg/kg-d for 21 d, starting at 5−6 wk-of-age	0, 6	No difference in maze learning and learning transfer testing	6	NDr	Crowder et al. (1980)	PR
Short term	5 M/0 F, B6C3F$_1$, mouse, TT in diet; 0, 10, 40, 80, 160, 320 ppm for 14 d	0, 1.8, 7.3, 15, 29.6, 60.1	Increased absolute and relative liver weight (≥10%)	1.8	7.3	Wang et al. (2015)	PR
Short term	36 M/0 F, B6C3F$_1$, mouse, TT in diet; 0, 3, 32, 320 ppm for up to 28 d (sacrifices at 7, 14, and 28 d)	0, 0.6, 5.9, 60.3	Increased absolute and relative liver weight (≥10%), serum ALT activities, hepatic cell proliferation rates (BrdU labeling index), and MDA concentrations in liver	5.9	60.3	Wang et al. (2015)	PR

Table 5A. Summary of Potentially Relevant Noncancer Data for Technical Toxaphene (CASRN 8001-35-2)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Short term	5 M/0 F, C57BL/6, mouse, TT in diet; 0 or 320 ppm for 14 d	0, 64.5	Decreased body weight; increased absolute and relative liver weight (≥10%); increased hepatic cell proliferation rates (BrdU labeling index); liver enzyme activity changes	NDr	64.5	Wang et al. (2017)	PR
Subchronic	2 M/2 F, cynomolgus, monkey, TT (corn oil) in gelatin capsules; 0, 1 mg/kg-d for 52 wk	0, 1	Increased relative spleen and thymus weights; decreased mean IgG and IgM responses to SRBC, mean percentages of $CD2^+CD4^+$ lymphocytes, and mean CD4:CD8 ratios	NDr	1	Arnold et al. (2001); Bryce et al. (2001); Tryphonas et al. (2000) (The small number of animals limits confidence in the LOAEL)	PR
Subchronic	5 M/10 F, cynomolgus, monkey, TT (corn oil) in gelatin capsules; 0, 0.1, 0.4, 0.8 mg/kg-d for up to 75 wk	M: 0, 0.8 F: 0, 0.1, 0.4, 0.8	Decreased IgM responses to SRBC	NDr (M) 0.1 (F)	0.8 (M) 0.4 (F)	Arnold et al. (2001); Tryphonas et al. (2001)	PR
Subchronic	6 M/6 F, Beagle, dog, TT (corn oil); 0, 0.2, 2.0, 5.0 mg/kg-d in gelatin capsules for 13 wk	0, 0.2, 2.0, 4.5	Increased relative liver weight (≥10%)	2.0 (M) NDr (F)	4.5 (M) 0.2 (F)	Chu et al. (1986) (Due to dose adjustments throughout the exposure duration, an approximate TWA dose of 4.5 mg/kg-d was calculated for the high-dose group for this assessment.)	PR
Subchronic	10 M/10 F, S-D, rat, TT in diet; 0, 4, 20, 100, 500 ppm for 13 wk	M: 0, 0.35, 1.8, 8.6, 45.9 F: 0. 0.50, 2.6, 12.6, 63	Increased incidences of lesions in the thyroid, kidney, and liver in both sexes	0.35 (M) NDr (F)	1.8 (M) 0.50 (F)	Chu et al. (1986)	PR

Table 5A. Summary of Potentially Relevant Noncancer Data for Technical Toxaphene (CASRN 8001-35-2)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Subchronic	12 M/0 F, S-D, rat, TT in diet; 0, 30, 300 ppm for 9 wk	0, 2.6, 25.8	Transient immunosuppression (decreased KLH IgG titers at 15 d, but not at 21 d) and increased relative liver weight	NDr	2.6	Koller et al. (1983)	PR
Subchronic	0 M/23−26 F, Swiss-Webster, mouse, TT in diet; 0, 10, 100, 200 ppm for 8 wk	0, 1.9, 19.1, 39.2	Immune suppression (decreased BSA IgG titers). Increased absolute and relative liver weight (≥10%) and variation in hepatocyte size	1.9	19.1	Allen et al. (1983)	PR
Chronic	50 M/50 F per exposed group; 10 M/10 F controls, Osborne-Mendel, rat, TT in diet; 0, 556, 1,112 TWA ppm (M); 0, 540, 1,080 TWA ppm (F) for 80 wk followed by 28−30 wk on control diet	M: 0, 38.9, 77.88 F: 0, 41.6, 83.29	Statistically and biologically significant (≥10%) decreased body weight in females and clinical signs in both sexes	38.9 (M) 41.6 (F)	77.88 (M) 83.29 (F)	NCI (1979)	PR
Chronic	50 M/50 F per exposed group; 10 M/10 F controls, $B6C3F_1$, mouse, TT in diet; 0, 99, 198 TWA ppm for 80 wk followed by 10−11 wk on control diet	M: 0, 17, 34.0 F: 0, 17, 34.2	No effects at the low dose in either sex.	17	NDr	NCI (1979) (Increased late mortality in high-dose males and females may have been secondary to high incidence of hepatocellular carcinomas in these groups.)	PR

Table 5A. Summary of Potentially Relevant Noncancer Data for Technical Toxaphene (CASRN 8001-35-2)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Reproductive	3 M/6 F, S-D, rat, TT in diet; 0, 4, 20, 100, 500 ppm for up to 29 wk; F0 dams and sires exposed for 13 wk prior to mating and throughout mating, gestation, and lactation (~29 wk). F1a pups were exposed to same diet as parents at weaning, culled to 15 M and 30 F at 5 wk, and maintained on same diet for an additional 26 wk. F0 rats were maintained on diets after F1a weaning and production of F1b litters	F0 M: 0, 0.36, 1.8, 9.2, 45 F0 F: 0, 0.36, 1.9, 8.5, 46 F1a M: 0, 0.29, 1.4, 7.5, 37 F1a F: 0, 0.38, 1.9, 9.4, 49	Reproductive: No effects on F0 fertility and gestation indices, litter sizes, or pup survival. Systemic: Increased absolute liver weight (≥10%) in F0 females; increases in lesions in the thyroid, kidney, and liver, in the F0 and F1a adults and F1b pups.	45 (F0 M) 46 (F0 F) NDr (F1a M) NDr (F0 F)	NDr (F0 M) NDr (F0 F) 0.29 (F1a M) 0.36 (F0 F)	Chu et al. (1988)	PR, PS

Table 5A. Summary of Potentially Relevant Noncancer Data for Technical Toxaphene (CASRN 8001-35-2)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Reproductive	8 M/16 F, S-D, rat, TT in diet; 0, 25, 100 ppm for up to 42 wk; F0 dams and sires exposed from 28−100 d-of-age, when mating occurred, continuing for the dams through gestation, lactation, and production of two litters. This procedure was continued through three successive two-litter generations until F3b pups were born. F0 dams were sacrificed after 42 wk of exposure; F1b and F2b parents were sacrificed after 39 wk of exposure	M: 0, 1.7, 6.88 F: 0, 2.0, 7.99	Reproductive: No effects on F0 fertility and pregnancy indices, mean litter size, live birth index, number of pups at birth through lactation, or growth of pups through lactation Systemic: Increased relative liver weight (≥10%)	6.88 (F0 M) 7.99 (F0 F) NDr (M) NDr (F)	NDr (F0 M) NDr (F0 F) 1.7 (F1 M) 2.0 (F0 F)	Kennedy et al. (1973) (NOAEL/LOAEL determinations are of low confidence due to reporting deficiencies in the available report and uncertainties regarding the reliability of studies conducted by Industrial Bio-Test Laboratories. Reporting of results is inadequate to conduct BMD analysis on endpoints evaluated.)	PR

Table 5A. Summary of Potentially Relevant Noncancer Data for Technical Toxaphene (CASRN 8001-35-2)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Reproductive	4 M/14 F, Swiss-white, mouse, TT in diet; 0, 25 ppm through 5 generations; exposure to parental dams and sires before mating and continuing through production of two litters until F5b litters were delivered. The report did not clearly specify F0 exposure duration before mating, but specified that parental animals in all generations were sacrificed at 120 d-of-age	M: 0, 4.7 F: 0, 5.1	Parental reproductive: No effects on fertility, pup viability, or pup survival indices	4.7 (M) 5.1 (F)	NDr NDr	Keplinger et al. (1970) (Although histology, serum chemistry, and hematology endpoints were reported to be evaluated, reporting of results was inadequate for NOAEL/LOAEL determination for parental systemic effects from TT.)	PR
Developmental	16−39 pregnant F, CD, rat, TT in corn oil by gavage; 0, 15, 25, 35 mg/kg-d on GDs 7−16; dams sacrificed on GD 21 and fetuses examined for ossification centers	0, 15, 25, 35	Maternal: Decreased weight gain Developmental: Decreased number of sternal, but not caudal, ossification centers in fetuses; biologically significant (≥5%) decreased fetal body weight	NDr NDr	15 15	Chernoff and Carver (1976)	PR

Table 5A. Summary of Potentially Relevant Noncancer Data for Technical Toxaphene (CASRN 8001-35-2)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Developmental	26−90 pregnant F, CD-1, mouse, TT in corn oil by gavage; 0, 15, 25, 35 mg/kg-d on GDs 7−16; dams were sacrificed on GD 18 and fetuses examined for ossification centers	0, 15, 25, 35	Maternal: Increased relative liver weight Developmental: No statistically significant changes observed	NDr 35	15 NDr	Chernoff and Carver (1976)	PR
Developmental	25 pregnant F, CD-1, mouse, TT in corn oil by gavage; 0, 75 mg/kg-d on GDs 8−12; dams gave birth and litters were counted and weighed on PNDs 1 and 3	0, 75	Maternal: Decreased body-weight gain Developmental: Decreased pup body weight on PND 1, but not PND 3	NDr NDr	75 75	Chernoff and Kavlock (1983) (Comprehensive examination of fetuses for visceral or skeletal variations or anomalies was not conducted.)	PR
Developmental	~25 exposed pregnant F, ~50 control pregnant F, S-D, rat, TT in corn oil by gavage; 0, 32 mg/kg-d on GDs 6−15; sacrifice on GD 20	0, 32	Maternal: Increased mortality and decreased body-weight gain Developmental: Increased mean proportion of fetuses with supernumerary ribs	NDr NDr	32 (FEL) 32	Chernoff et al. (1990)	PR
Developmental	3 pregnant F, S-D, rat, TT in corn oil by gavage; 0, 6 mg/kg-d on GDs 7−21; righting, grasp-hold, and startle reflexes assessed in all offspring, starting at PND 7; 5 M/5 F offspring evaluated in maze tests, PNWs 14−16	0, 6	Developmental: Delayed attainment of righting reflex ability in offspring	NDr	6	Crowder et al. (1980) (LOAEL is considered potentially minimal; righting reflex was delayed, but not grasp-hold or startle reflexes.)	PR

Table 5A. Summary of Potentially Relevant Noncancer Data for Technical Toxaphene (CASRN 8001-35-2)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Developmental	3 pregnant F, Holtzman albino, rat; TT, Toxicant A (p-42), or Toxicant B (p-32) in diet; 0, 0.050 (TT), 0.002 (p-42), 0.002 (p-32) mg/kg-d from GD 5 through weaning and PND 30; offspring received same diet as dams through PND 90; due to insufficient p-32 test substance, p-32-exposed offspring received p-42 from PNDs 40−90	0, 0.050 (TT) 0.002 (p-42) 0.002 (p-32)	Developmental: No clear effects in offspring neurobehavioral tests (righting reflex and swimming ability at PNDs 7−17 [all offspring]; maze testing of motivational behavior, learning, and learning retention between PNDs 70−90 [*n* = 15−16 per group])	NDr (TT) 0.002 (p-42) 0.002 (p-32)	NDr (TT) NDr (p-42) NDr (p-32)	Olson et al. (1980) (Delays in righting reflex were noted in TT-exposed rats [but not in p-42 or p-32 groups]; however, the magnitude of effect was not reported, precluding the determination of an effect level.)	PR
Developmental	0 M/12 F, Swiss-Webster, mouse, TT in diet; 0, 10, 100, 200 ppm for 3 wk before mating and throughout gestation and lactation (~9 wk)	0, 1.9, 19.1, 39.2	Immune suppression (decreased ability of macrophages to engulf SRBCs) in offspring	NDr	1.9	Allen et al. (1983) (Offspring received control diet at weaning and were aged 8 wk prior to immune testing.)	PR

Table 5A. Summary of Potentially Relevant Noncancer Data for Technical Toxaphene (CASRN 8001-35-2)							
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
2. Inhalation (mg/m^3)							
ND							

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days−2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: Values are presented as ADDs (mg/kg-day) for oral noncancer effects. In contrast to other repeated exposure studies, values from animal gestational exposure studies are not adjusted for exposure duration in calculation of the ADD or HEC.
[c]Notes: PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; ALT = alanine aminotransferase; BMD = benchmark dose; BrdU = bromodeoxyuridine; BSA = bovine serum albumin; F = female(s); FEL = frank effect level; GD = gestation day; HEC = human equivalent concentration; IgG = immunoglobulin G; IgM = immunoglobulin M; KLH = keyhole limpet hemocyanin; LOAEL = lowest-observed-adverse-effect level; M = male(s); MDA = malondialdehyde; ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; OR = odds ratio; PND = postnatal day; PNW = postnatal week; S-D = Sprague-Dawley; SRBC = sheep red blood cell; TSH = thyroid stimulating hormone; TT = technical toxaphene; TWA = time-weighted average.

Table 5B. Summary of Potentially Relevant Cancer Data for Technical Toxaphene (CASRN 8001-35-2)

Category	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[a]	Critical Effects	Reference (comments)	Notes[b]
Human					
Several epidemiological studies of agricultural workers have exhibited some statistically significant associations between self-reported past occupational exposure to TT or regional indicators of agricultural use of toxaphene and increased risk for several types of cancer as follows: rectal cancer (Lee et al., 2007; Purdue et al., 2007), melanoma (Purdue et al., 2007), leukemia or non-Hodgkin's lymphoma (Mills et al., 2005; Schroeder et al., 2001), and breast cancer (Mills and Yang, 2006). In spouses of the male pesticide applicators in the Lee et al. (2007) and Purdue et al. (2007) studies, glioma was significantly associated with "ever-use" of any of the subject insecticides (including TT) (Louis et al., 2017). Additionally, based on the observation that telomere length in surrogate tissues is associated with some cancer types in other epidemiological studies, mean relative telomere length in buccal DNA decreased significantly with toxaphene use in male pesticide applicators (Hou et al., 2013). No significant association between exposure to toxaphene and the occurrence of non-Hodgkin's lymphoma was reported in several studies (Louis et al., 2017; Purdue et al., 2007; Mills et al., 2005; De Roos et al., 2003; Cantor et al., 1992). In contrast to the Mills et al. (2005) study, the study by Purdue and colleagues did not see a significant association between exposure to toxaphene and leukemia (Purdue et al., 2007).					
Animal					
1. Oral (mg/kg-d)					
Carcinogenicity	54 M/54 F, B6C3F$_1$, mouse, TT in diet; 0, 7, 20, or 50 ppm for 18 mo followed by a 6-mo observation period	0, 0.91, 2.6, 6.5	Statistically significantly increased incidence of combined hepatocellular adenomas and carcinomas in male mice at 6.5 mg/kg-d. No significantly elevated tumor incidences in exposed-female groups	Litton Bionetics (1978) (The IRIS OSF of 1.1 [mg/kg-d]$^{-1}$ is based on the liver tumor data in male mice.)	U.S. EPA (1988a); NPR
Carcinogenicity	50 M/50 F, B6C3F$_1$, mouse, TT in diet; 99, 198 ppm (TWA) for 80 wk (10 M/10 F in matched 0-ppm control group)	M: 0, 17, 34.0 F: 0, 17, 34.2	Statistically significantly increased incidences of combined hepatocellular carcinomas and adenomas in exposed-male and female groups	NCI (1979)	PR
Carcinogenicity	50 M/50 F, Osborne-Mendel, rat, TT in diet; 556, 1,112 ppm (TWA) (M); 540, 1,080 ppm (TWA) (F) for 80 wk (10 M/10 F in matched 0-ppm control group)	M: 0, 38.9, 77.88 F: 0, 41.6, 83.29	Statistically significantly increased incidences of thyroid tumors in high-dose males and females	NCI (1979)	PR

Table 5B. Summary of Potentially Relevant Cancer Data for Technical Toxaphene (CASRN 8001-35-2)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[a]**	**Critical Effects**	**Reference (comments)**	**Notes[b]**
2. Inhalation (mg/m^3)					
Human					
ND					
Animal					
ND					

[a]Dosimetry: The units for oral exposures are expressed as ADDs (mg/kg-day).
[b]Notes: PR = peer reviewed; NPR = not peer reviewed.

ADD = adjusted daily dose; DNA = deoxyribonucleic acid; F = female(s); IRIS = Integrated Risk Information System; M = male(s); ND = no data; OSF = oral slope factor; TT = technical toxaphene; TWA = time-weighted average.

HUMAN STUDIES

Technical Toxaphene

Case reports of humans intentionally or accidentally ingesting products containing technical toxaphene reported convulsions as the principal and common effect in both fatal and nonfatal poisoning events (Wells and Milhorn, 1983; McGee et al., 1952). For some of these cases, other reported effects included changes in liver and kidney function, cardiac dilatation, swelled kidneys, and temporary memory loss.

Two reports of acute or short-term exposure of human subjects to airborne technical toxaphene were identified in the literature search. No changes in blood cell profiles, urinalysis, or gross appearance of the skin were found in a group of 25 human subjects (15 males, 10 females) following 10 daily 30-minute exposures to an aerosol containing a maximum of 500 mg technical toxaphene/m^3 or following three additional 30-minute exposures after a 3-week nonexposure period (Keplinger, 1963). Acute pulmonary insufficiency and changes in chest x-rays were noted in two Egyptian agricultural workers who applied a spray containing 60% technical toxaphene, 35% kerosene, 3% xylol, and 2% emulsifier during a 2-month period in 1958 (Warraki, 1963). Treatment with cortisone, streptomycin, and isoniazid produced rapid recovery in both subjects.

Several epidemiological studies of pesticide applicators or agricultural workers have reported some statistically significant associations between self-reported past occupational exposure to technical toxaphene, or regional indicators of agricultural use of toxaphene, with increased risk for several types of cancer. These positive associations included rectal cancer (Lee et al., 2007; Purdue et al., 2007), melanoma (Purdue et al., 2007), leukemia or non-Hodgkin's lymphoma (Mills et al., 2005; Schroeder et al., 2001), and breast cancer (Mills and Yang, 2006). Louis et al. (2017) evaluated possible associations between various types of cancer and the use of seven specific organochlorine insecticides (including technical toxaphene) in female spouses of male pesticide applicators from the Lee et al. (2007) and Purdue et al. (2007) studies. A statistically significant association was observed between "ever-use" of any of the subject organochlorine insecticides and increased glioma risk. Although statistically significant associations were observed between specific organochlorine insecticide (e.g., lindane) use and increased risk of cancer, no association was observed specifically for toxaphene use.

No significant association between exposure to toxaphene and the occurrence of non-Hodgkin's lymphoma was reported in several studies (Louis et al., 2017; Purdue et al., 2007; Mills et al., 2005; De Roos et al., 2003; Cantor et al., 1992). In contrast to the Mills et al. (2005) study, the study by Purdue and colleagues did not see a significant association between exposure to toxaphene and leukemia (Purdue et al., 2007).

Goldner et al. (2013) evaluated possible associations between self-reported thyroid disease and use of 50 specific insecticides (including technical toxaphene), herbicides, and fungicides within a cohort of U.S. male pesticide applicators. Hypothyroidism was associated with "ever-use" of eight insecticides, including technical toxaphene. Additionally, results from exposure-response analyses using the intensity-weighted exposure measure showed technical toxaphene had an association at low exposure, but not high exposure.

Hou et al. (2013) evaluated possible associations between telomere length in buccal cell deoxyribonucleic acid (DNA) samples and the use of 48 specific pesticides (including technical

toxaphene) within the Agricultural Health Study cohort of U.S. male pesticide applicators. Mean relative telomere length (measured with real-time polymerase chain reaction) decreased significantly with two metrics of pesticide use (lifetime days of use, and lifetime intensity-weighted days of use) for technical toxaphene and six other pesticides. No significant associations were found for relative telomere lengthening and use of any of the pesticides. The rationale for examining telomere length in DNA from buccal cells was based on the observation from other case-control studies that telomere length in surrogate tissues (e.g., blood or buccal cells) is associated with some, but not all, cancer types [see Hou et al. (2013) for a list of references]. Some studies found associations between cancer and shorter telomeres, and others found associations with longer telomeres (Hou et al., 2013).

In another case-control analysis of data collected within the U.S. Agricultural Health Study of male pesticide applicators, no statistically significantly elevated odds ratios (ORs) were found for amyotrophic lateral sclerosis and "ever-use" of any of the subject pesticides, including toxaphene (Kamel et al., 2012). The OR for toxaphene (adjusted for age and sex) was elevated, but not to a statistically significant degree (OR = 2.0, 95% confidence interval [CI] = 0.8−4.9; 7 cases, 6,937 controls).

In a recent case-control analysis of data collected within the U.S. Agricultural Health Study of male pesticide applicators, a statistically significant exposure-response trend in association with rheumatoid arthritis was observed for the top tertile of lifetime days of toxaphene use (Meyer et al., 2017). The OR for rheumatoid arthritis and "ever-use" of toxaphene (adjusted for age, state of enrollment, pack-years smoking, and education) was elevated, but not statistically significantly (OR = 1.44, 95% CI = 0.90−2.14; 23 cases, 1,487 controls).

A hospital-based prospective cohort study was designed to evaluate possible associations between levels of 29 persistent organochlorine pesticides in blood samples of pregnant women and health outcomes of offspring during infancy and early childhood. In a report of preliminary findings, concentrations of a considerable number of these chemicals (including the toxaphene congeners p-26 and p-50) showed significant increases associated with increasing age of the subject. Additionally, decreases in congener concentrations were associated with with increasing number of pregnancies experienced (gravidity) or carried to a viable gestation age (parity) (Kanazawa et al., 2012). Health outcome data for offspring from this study has not been identified.

Weathered Toxaphene and Toxaphene Congeners

Studies evaluating possible associations between health effects in humans and exposure to weathered toxaphene or individual toxaphene congeners have not been identified.

ANIMAL STUDIES

Oral Exposures

Short-Term-Duration Studies

Technical Toxaphene

Waritz et al. (1996)

Groups of 40 male Sprague-Dawley (S-D) rats (8 weeks old) were given 100 mg/kg-day technical toxaphene in corn oil by gavage for 3 days, followed by a lower dose, 75 mg/kg-day, for 25 days, due to deaths of two rats on Day 4. A time-weighted average (TWA) dose of 78 mg/kg-day has been calculated for this assessment. A group of 40 control rats received the corn oil vehicle for 28 days. Technical toxaphene (purity unknown) was mixed with corn oil and administered once daily by intragastric gavage. Feed consumption and body weight were measured at study initiation (Day 0) and weekly thereafter. Ten animals per group were sacrificed on exposure Days 1, 8, and 15, and 1 day following the last administered dose (Day 29). Blood was immediately collected from the aorta. Levels of serum thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), reverse triiodothyronine (rT3), and corrected triiodothyronine (CrT3) were determined by radioimmunoassay (RIA). At necropsy, the thyroids, parathyroid glands, pituitary glands, and brains were grossly examined, fixed in formalin, and weighed. Slices of thyroids including the parathyroids and slices of pituitary glands were prepared for sectioning and stained with hematoxylin/eosin for microscopic examination. Colloid levels in thyroid follicles were determined by follicle cell sizes as follows: (1) small, nondistended follicles were taken as indicators of no or little colloid storage, typically found in young rats; and (2) large, >60% distended follicles were taken as indicators of large stores of colloid, typically found in older rats.

No differences in mean thyroid or brain weights, or in thyroid:brain-weight ratios between exposed and control groups were observed. Other organ-weight results were not described. TSH levels significantly increased with exposure time (39, 141, and 192% increases over controls after 7, 14, and 28 days of exposure, respectively). Mean differences between exposed and control values for levels of T3, T4, rT3, and CrT3 were reported as not statistically significant at any exposure interval. Histological features of pituitary sections were reported to be similar between control and exposed groups. Thyroid follicular hypertrophy (indicated by columnar thyroid follicular epithelial cells) was not found in control rats or exposed rats sacrificed on Day 1, but occurred in 70% of exposed rats sacrificed on Days 8 and 15, and 100% of exposed rats on Day 29. Diffuse intrafollicular hyperplasia also was found in thyroids of 10, 90, and 80% of exposed rats on Days 8, 15, and 21, but was not found in control rats. The percentage of exposed rats with small follicle sizes (indicative of low stores of colloid) increased with exposure duration: 0% on Day 1; 20% on Day 8; 30% on Day 15; and 50% on Day 29.

The results of this study indicate that 78 mg/kg-day, the only dose tested, is a lowest-observed-adverse-effect level (LOAEL) for increased TSH levels in serum and increased incidences of thyroid follicular hypertrophy and diffuse intrafollicular hyperplasia in male S-D rats given gavage doses of technical toxaphene for 28 days. Waritz et al. (1996) postulated that the study results, along with other observations showing that technical toxaphene induces cytochrome P450 (CYP450) enzymes in the liver (including UDP-glucuronyl transferases), are consistent with the hypothesis that technical toxaphene perturbs thyroid homeostasis in rats (i.e., induces thyroid hyperactivity) via stimulation of the synthesis of UDP-glucuronyl transferases.

Crowder et al. (1980)

Groups of 5- to 6-week-old S-D rats (five/sex/group) were administered technical toxaphene (Boots-Hercules, Inc.; purity 99.9%) at doses of 0 or 6 mg/kg-day, once daily by gavage (in 0.1 mL corn oil) for 21 days. Animals were given free access to food and water. Body-weight measurements, feed consumption, or clinical observations were not reported by the study authors. Approximately 6−8 weeks after the exposure ended and between 14−16 weeks-of-age, five male and five female rats/group were chosen randomly for evaluation of learning and learning transfer abilities using maze testing. Each rat received 10 maze trials/day.

No statistically significant differences in maze learning or learning transfer between the exposed and control groups were described. The study authors concluded that exposure to 6 mg/kg-day technical toxaphene did not interfere with the learning ability of adult rats.

The study results indicate a no-observed-adverse-effect level (NOAEL) of 6 mg/kg-day for the lack of prolonged effects on learning and learning transfer abilities in maze testing of adult male and female S-D rats exposed to technical toxaphene via gavage for 21 days, starting at 5−6 weeks-of-age. No LOAEL could be determined.

Wang et al. (2015)

In an initial 14-day range-finding study, $B6C3F_1$ mice (five males/group) were exposed to technical toxaphene in the diet at concentrations of 0, 10, 40, 80, 160, and 320 ppm for 14 days. Based on group averages between reported means for initial and final body weights and and an allometric equation for food consumption (food consumption in kg/day = 0.056 × [body weight in $kg^{0.6611}$]) described by U.S. EPA (1988b), estimated daily intakes of 1.8, 7.3, 15, 29.6, and 60.1 mg/kg-day were calculated. In a follow-up 28-day mechanistic study, $B6C3F_1$ mice (36 males/exposure group) were exposed to 0, 3, 32, and 320 ppm for up to 28 days (sacrifices occurred at 7, 14, and 28 days). Based on group averages between reported means for initial and final body weights at 28 days and an allometric equation for food consumption (food consumption in kg/day = 0.056 × [body weight in $kg^{0.6611}$]) described in U.S. EPA (1988b), estimated daily intakes of 0.6, 5.9, and 60.3 mg/kg-day were calculated. In a final knockout study, a total of 30 male mice (15 wild-type C57BL/6 and 15 constitutive androstane receptor knockout [$CAR^{-/-}$] mice) were exposed to 0 or 320 ppm for 14 days. Because body-weight or food-consumption data for the wild-type C57BL/6 or $CAR^{-/-}$ knockout mice were not reported, an estimated daily intake of 60.4 mg/kg-day was calculated for the exposed groups based on the mean reference body weights and food-consumption rates for BAF_1 and $B6C3F_1$ mice in a subchronic-duration study.[3] Groups of male mice exposed to 750 ppm phenobarbital (PB) in food were included as a positive control. Food and water were available ad libitum. Seven days prior to sacrifice, all of the range-finding and knockout study animals and five randomly selected mice/group from the mechanistic study were given bromodeoxyuridine (BrdU, 0.8 mg/mL in drinking water with 1% glucose) to measure hepatic DNA synthesis to provide an indicator of cell proliferation. Body weights of all animals were recorded weekly, although only initial and terminal weights were provided in the report. For the range-finding and mechanistic studies, liver weight and weights of other major organs were recorded. Blood was collected to determine

[3]Dose estimates were calculated using the mean reference body weight and food-consumption rate values for male BAF_1 and $B6C3F_1$ mice in a subchronic-duration study (U.S. EPA, 1988b). Mean reference body weight = 0.0270 kg, and mean reference food-consumption rate = 0.0051 kg/day.

serum activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Survival data were obtained and necropsies were performed on all animals from each study. Portions of the liver and gut (in the range-finding and mechanistic studies) were fixed for histopathological analysis and for immunohistochemistry staining for anti-BrdU. Liver tissues from sacrificed animals in the mechanistic study and the constitutive androstane receptor (CAR) knockout study were also analyzed for concentrations of total protein, acyl-CoA oxidase (ACO) activity, 8-isoprostane, and malondialdehyde (MDA) (to test for lipid peroxidation), as well as 8-hydroxydeoxyguanasine (8-OHdG) (to test for oxidative DNA damage). Quantitative real-time polymerase chain reaction (PCR) was used for gene expression analysis of CAR, aryl hydrocarbon receptor (AhR), peroxisome proliferator-activated receptor alpha (PPAR-alpha) target genes, cell growth genes, and oxidative stress-related genes in the liver.

No mortalities or clinical signs of toxicity were recorded in any of the control or exposed groups in any of the studies. In the 14-day range-finding and 28-day mechanistic studies, mean terminal body weights were statistically significantly decreased only in the high-dose groups by about 8 and 6% respectively, compared with control groups. In the 14-day study, the mean initial body weight within the 60.1-mg/kg-day group was higher than the terminal body weight (28.79 g vs. 27.57 g), indicating a significant decrease in body-weight gain during exposure. In the 28-day study, control mean body-weight values increased by about 8% during the study period, but the increase during exposure was only about 0.5% in the 60.3-mg/kg-day group. In the CAR knockout 14-day study, body weights and body-weight gain were reported to be not significantly different between exposed (60.4 mg/kg-day) groups and untreated controls. In the 14-day range-finding study, absolute and relative liver weights were increased by ≥10% (compared with controls) at concentrations ≥7.3 mg/kg-day (see Table B-1). In the 28-day mechanistic study, absolute and relative liver weights were increased by ≥10% (compared with controls) in the 60.3-mg/kg-day group only (see Table B-2), with similar magnitudes of increase observed across all exposure durations. After a 14-day exposure of wild-type (WT) C57BL/6 mice to 60.4 mg/kg-day, increased absolute and relative liver weights were seen (27 and 57% increase compared with WT controls; see Table B-1), but the liver weight responses were diminished in $CAR^{-/-}$ knockout mice (−5 and +7%, respectively, compared with $CAR^{-/-}$ controls). In the 14- and 28-day studies of $B6C3F_1$ mice, serum ALT activities were statistically significantly increased only in the highest dose groups (the increases ranged from 68−98%, see Tables B-1 and B-2). Histopathological examinations were reported to be similar between the exposed and control groups in the 28-day study; no necrosis or compensatory hyperplasia was reportedly observed (no incidence data were reported).

Statistically significant increases in hepatic DNA synthesis (BrdU labeling index), compared with controls, were observed at concentrations of 29.6 mg/kg-day (~8-fold) and 60.1 mg/kg-day (~14-fold) in the 14-day study (see Table B-1), and at 60.3 mg/kg-day (~3-fold) in the 28-day study (see Table B-2). Statistically significant increases in hepatic DNA synthesis also were observed in 60.4-mg/kg-day C57BL/6 mice (>10-fold increase compared with control) exposed for 14 days, but no increase was observed in exposed $CAR^{-/-}$ knockout mice. Liver levels of PPAR-alpha and 8-OHdG were comparable to controls in $B6C3F_1$ mice at 7, 14, and 28 days, but MDA concentrations were elevated in 60.3-mg/kg-day animals at 7, 14, and 28 days (27−35% increase compared with controls) (see Table B-2). In 14-day exposed wild-type C57BL/6 mice, hepatic MDA concentrations were elevated by 22%; no MDA changes were observed in exposed $CAR^{-/-}$ knockout mice.

Results for several endpoints in the positive control (PB) $B6C3F_1$ group were not significantly different from the negative control (i.e., body weight, serum ALT activities, and hepatic MDA concentrations) at any time point evaluated, but statistically significant increased relative liver-weight values were found at 7, 14, and 28 days, and increased hepatic BrdU labeling index values were found at Days 7 and 14, but not at 28 days.

In $B6C3F_1$ mice, statistically significant changes in expression of genes in liver tissue (>2-fold change) were primarily limited to the highest-dose group at 7, 14, and 28 days and included increased expression of the CAR responsive genes *Cyp3a11* and *Cyp2b10* (up to a 1,973-fold increase), a decrease in the PPAR-alpha related gene *Acot1* (occurring at 7 and 14 days at ≥5.9 mg/kg-day, with no other PPAR-alpha related gene changes), increased expression of the cell growth-related gene, *c-myc*, suppression of *p21* expression, and increased expression of the oxidative-stress related gene, *Aox1*. In 60.4-mg/kg-day wild-type C57BL/6 mice exposed for 14 days, increased hepatic expression of the following genes was found: *Cyp3a11*, *Cyp2b9*, *Cyp2b10, c-myc*, and *Aox1*. These gene expression changes were not observed in the exposed $CAR^{-/-}$ mice.

Results from the 14-day range-finding study indicate a LOAEL of 7.3 mg/kg-day and a NOAEL of 1.8 mg/kg-day for increased absolute and relative liver weight in male $B6C3F_1$ mice. At 29.6 mg/kg-day, significantly increased hepatic cell proliferation rates (BrdU labeling indices) were observed, and at 60.1 mg/kg-day, significantly increased serum ALT activity was also observed. The 28-day study identified a LOAEL of 60.3 mg/kg-day and a NOAEL of 5.9 mg/kg-day for increases in absolute and relative liver weight, serum ALT activities, hepatic cell proliferation rates, and hepatic MDA concentrations in male $B6C3F_1$ mice. Histological examination of livers from the exposed groups reportedly revealed no evidence for necrosis or compensatory hyperplasia. Changed expression of examined genes was only observed in livers of high-dose $B6C3F_1$ mice (increased expression for *Cyp3a11*, *Cyp2b10, c-myc,* and *Aox1* and decreased expression of *p21*). In the 14-day CAR knockout study, exposure of technical toxaphene to wild-type C57BL/6 male mice to 60.4 mg/kg-day increased relative liver weight, hepatic cell proliferation rates, and hepatic MDA concentrations, but these changes were absent in $CAR^{-/-}$ knockout mice exposed to 60.4 mg/kg-day. The study authors submit that taken together, the results implicate a nongenotoxic, CAR-mediated mode of action (MOA). However, the data do not unequivocally prove this to be the primary MOA.

Wang et al. (2017)

In a follow-up knockout study by Wang and colleagues, a total of 50 male mice (15 wild-type C57BL/6 and $CAR^{-/-}$, and 10 pregnane X receptor knockout mice [$PXR^{-/-}$] and PXR/CAR double knockout mice [$PXR^{-/-}/CAR^{-/-}$]; 5 mice/group) were exposed to 0 or 320 ppm technical toxaphene in the diet for 14 days. Due to increased mortality (3/5 mice) observed in $PXR^{-/-}/CAR^{-/-}$ mice in initial studies, the dose was lowered to 160 ppm for subsequent studies in the double knockout mice. Based on group averages between reported means for initial and final body weights and an allometric equation for food consumption (food consumption in kg/day = 0.056 × [body weight in $kg^{0.6611}$]) described by U.S. EPA (1988b), estimated daily intakes were calculated as follows: 64.5 mg/kg-day for C57BL/6 mice, 63.7 mg/kg-day for $CAR^{-/-}$ mice, 64.6 mg/kg-day for $PXR^{-/-}$ mice, and 32.6 mg/kg-day for $PXR^{-/-}/CAR^{-/-}$ mice. Groups of male mice exposed to 750 ppm PB in food were included as a positive control. Food and water were available ad libitum. Seven days prior to sacrifice, mice were given BrdU (0.8 mg/mL in drinking water with 1% glucose) to measure hepatic DNA

synthesis to provide an indicator of cell proliferation. Body weights of all animals were recorded weekly, although only initial and terminal weights were provided in the report. Survival data were obtained and necropsies were performed on all animals from each study. The liver was removed and weighed, portions of the liver were fixed for histopathological analysis and for immunohistochemistry staining for anti-BrdU, and the remainder was snap frozen for enzyme activity and gene expression analysis. Hepatic microsomal ethoxyresorufin-*O*-deethylase (EROD; as a measure of AhR activation), pentoxyresorufin-*O*-dealkylase (PROD; as a measure of CAR activation), and 7-benzyloxyquinoline (BQ; as a measure of PXR activation) activities were determined. Quantitative real-time PCR was used for gene expression analysis of CAR, PXR, and AhR target genes in the liver, as well as cell growth-related genes.

After the dose change in the $PXR^{-/-}/CAR^{-/-}$ mice, no mortalities or clinical signs of toxicity were recorded in the control or exposed groups tested, of any strain tested. Mean terminal body weights were statistically significantly decreased (13−18%) in all exposed groups compared with controls. The mean initial body weight for $PXR^{-/-}$ mice was higher than the terminal body weight (24.0 g vs. 21.3 g), indicating a significant decrease in body-weight gain during exposure. This decrease was also observed in $PXR^{-/-}/CAR^{-/-}$ but to a much lesser extent. Control mean body-weight values increased by 5−14% during the study period. Absolute and relative liver weights were increased by ≥10% (compared with controls) in exposed C57BL/6 and $PXR^{-/-}$ mice, but the liver weight responses were greatly diminished in $CAR^{-/-}$ knockout mice (−13 and +7%, respectively, compared with $CAR^{-/-}$ controls). Relative liver weight increased by 21% in $PXR^{-/-}/CAR^{-/-}$ double knockout mice, which the study authors contributed to the significantly lower body weight compared to controls.

Statistically significant increases in hepatic DNA synthesis (BrdU labeling index), compared with controls, were observed in C57BL/6 and $PXR^{-/-}$ mice, but no increase was observed in exposed $CAR^{-/-}$ or $PXR^{-/-}/CAR^{-/-}$ mice. Statistically significant liver enzyme activity changes were as follows: increased PROD in $PXR^{-/-}$ mice, increased BQ in C57BL/6 and $PXR^{-/-}$ mice, decreased BQ in $PXR^{-/-}/CAR^{-/-}$ mice, and increased EROD in C57BL/6, $CAR^{-/-}$ and $PXR^{-/-}$ mice. Statistically significant changes in expression of genes in liver tissue induction of CAR, PXR, and AhR target genes generally followed the same pattern seen with the induction of enzyme activities. The expression levels of CAR/PXR target genes (*Cyp3a11*, *Cyp2b9*, and *Cyp2b10*) were significantly increased (30- to 570-fold) in exposed C57BL/6 and $PXR^{-/-}$ mice compared to controls. *Cyp3a11* and *Cyp2b9* expression levels were not significantly altered in exposed $CAR^{-/-}$ mice compared to controls. *Cyp2b10*, however, was significantly increased in $CAR^{-/-}$ mice. *Cyp3a11*, *Cyp2b9*, and *Cyp2b10* expression levels were unchanged in exposed $PXR^{-/-}/CAR^{-/-}$ mice compared to untreated controls. Among the AhR target genes examined, expression of *Cyp1a1* and *Cyp1a2* was significantly increased in exposed C57BL/6 and $PXR^{-/-}$ mice compared to untreated controls. *Pon1* was significantly increased in C57BL/6 mice but not in $PXR^{-/-}$ mice, and *Cyp1b1* was unchanged in C57BL/6 and significantly decreased in $PXR^{-/-}$ mice. No change in expression of *Cyp1a2*, *Cyp1b1*, or *Pon1* was observed in $CAR^{-/-}$ or $PXR^{-/-}/CAR^{-/-}$ mice compared to controls, whereas *Cyp1a1* was significantly decreased in $CAR^{-/-}$ mice. Of the cell growth-related genes examined (*C-myc*, *Ccnd1*, *Cdc25a*, and *P21*), the only significant increase in expression observed was that of *C-myc* in exposed $PXR^{-/-}$ mice. As with the Wang et al. (2015) study, the results of this study implicate a nongenotoxic, CAR-mediated MOA, but do not unequivocally prove this to be the primary MOA.

Results from this 14-day study indicate a LOAEL of 64.5 mg/kg-day for increased absolute and relative liver weight in male C57BL/6 mice (wild-type). No NOAEL could be determined.

Weathered Toxaphene

No short-term-duration toxicity studies of weathered toxaphene in laboratory animals by oral exposure have been identified.

Toxaphene Congeners

No short-term-duration toxicity studies of individual toxaphene congeners in laboratory animals by oral exposure have been identified.

Subchronic-Duration Studies

Technical Toxaphene

Arnold et al. (2001); Bryce et al. (2001); Tryphonas et al. (2000) (52 weeks)

Cynomolgus monkeys (*Macaca fascicularis*) (two males and two females/group; ~3.5 to ~3.9 years old) were administered technical toxaphene (Hercules Powder Company Inc., Wilmington, DE, Lot #71-132-b8-17-20) in gelatin capsules (glycerol/corn oil vehicle) at doses of 0 or 1 mg/kg-day, 7 days/week, for 52 weeks. Animals were allotted ~240 g of monkey chow daily along with small amounts of fruit and vegetables (quantities not reported). Water was available ad libitum and supplemented once/week with a vitamin preparation. Monkeys were provided with environmental enrichment activities and allowed time for paired exercise runs (within groups only).

On a daily basis, feed and water consumption were measured, visual inspections for general health and behavior status were conducted, and menstrual status of female monkeys was determined by vaginal swabbing. Body weight and detailed clinical evaluations were performed weekly, including examination of the animals' skin/coat; lymph glands; eyelids; hydration status; ears; mouth; teeth; nares; heart and respiration rate; body temperature; cardiac, pulmonary and abdominal sounds; and abdominal, uterine, or prostate status. Monthly blood samples were collected for 26 comprehensive standard serum biochemistry endpoints including cholesterol, chloride, potassium, sodium, ALT, alkaline phosphatase (ALP), AST, thyroxine (T4), and thyroxine unbound (TU). Additionally, comprehensive hematology endpoints were measured bimonthly (Arnold et al., 2001).

Immune system endpoints were evaluated between Weeks 36−50 (Tryphonas et al., 2000). Flow cytometry analysis and measurement of phagocytic and respiratory burst activities in peripheral blood of the control and exposed monkeys were performed during Week 35. Natural killer cell (NKC) activity and the response of fractionated peripheral blood leukocytes to several mitogens (phytohemagglutinin, Concanavalin A, pokeweed mitogen) were measured during exposure Week 36. Monkeys in exposed and control groups were immunized intravenously with sheep red blood cells (SRBCs) (1×10^9 per kg body weight) on Weeks 36 and 42. Blood was collected just prior to the initial immunization (Day 0) and then weekly (to Day 63 postimmunization), and titers to SRBC immunoglobulin M (IgM) and immunoglobulin G (IgG) were determined. On treatment Week 46, monkeys were immunized intramuscularly with 0.5 mL pneumococcus antigens (pneumovax-23; Merk, Shar and Dohme, Canada, Kirkland, Quebec) and 0.5 mL of tetanus toxoid. Blood was collected just prior to

immunizations (Day 0) and then weekly (to Day 35 postimmunization). IgG titers to pneumovax and tetanus toxoid were determined using enzyme-linked immunosorbent assays (ELISAs).

All exposed monkeys and two control (one/sex) animals were necropsied after 1 year (52 weeks) of exposure. Organ weights were obtained for liver, spleen, kidneys, adrenals, thyroid, thymus, ovaries/testes, brain, and pituitary. Sections of these and 21 other internal organs were processed for light microscopy; however, no histopathological incidence data were provided in the available reports. Hearts were subsectioned to include atrium, septum, ventricles, and conducting system. Microsomal fractions were prepared immediately from liver samples to test for CYP450 oxygenase activities (aminopyrine, methoxyresorufin, and ethoxyresorufin metabolism). Toxaphene contents were determined in blood samples, nuchal fat pad samples biopsied at the time of blood sampling, portions of one kidney, and liver samples from necropsied monkeys, as well as 24-hour urine and fecal samples 1 day prior to fat pad biopsy.

Food consumption, body weights, and all hematology and serum biochemistry endpoints (including T4 and TU) were plotted versus time on test for each control and exposed monkey, as well as mean and standard deviation (SD) values for the control and exposed groups for visual examination of time trends, or differences in exposed and control animals. Serum data for cholesterol, sodium, potassium, and chloride levels were fit to polynomial models and assessed for fit to the models by analysis of variance (ANOVA) techniques. Statistical analyses for phagocytosis and respiratory burst activities used ANOVA, and a paired *t*-test was used for IgG titer data for SRBC, pneumococcus, and tetanus toxoid.

No exposure-related changes in body weight, feed consumption, or water intake were reported, but these data were not shown. Relative spleen and thymus weights were increased in each exposed monkey of each sex, compared with values for one control monkey of each sex. The magnitudes of increase following exposure ranged from about 22−100% for spleens and from 66−216% for thymuses, but were reported to be "not explained" by the histological examinations. Absolute and relative liver weights were increased by 30 and 32%, respectively, in one exposed female monkey. Absolute and relative liver weights in the other three exposed monkeys were generally within about 10% of reported control values (in one male, relative liver weight was decreased by 11% compared with control). Clinical monitoring identified increased inflammation and/or enlargement of tarsal glands (3/4 treated animals vs. 0/4 control) during treatment Weeks 8−13, and impacted diverticulae in the upper and lower eyelids (4/4 vs. 0/4 control) during Weeks 10−41. One exposed female showed additional clinical signs including edema-like swelling on the eyelids and excessive dry skin, as well as increased serum potassium and sodium levels and a steady significant decrease in cholesterol during the study. Serum chemistry in the remaining animals was comparable to controls, with the exception of a slight increase in chloride levels in exposed animals. Based on graphically presented data, there was an increase in liver microsomal metabolic activities, with average increases of ~35% (methoxyresorufin), ~55% (ethoxyresorufin), and ~50% (aminopyrine) in exposed animals (average of two males and one female) compared with controls, excluding the female with swollen eyelids and dry skin. No differences in T4 or TU serum levels, or hematologic endpoints were reported in exposed monkeys, compared with control monkeys. No statistically significant differences in immune endpoints were observed between the exposed and control groups, but there were consistent (across most time points) decreases in mean percentages of $CD2^+CD4^+$ lymphocytes (16% lower compared with control), mean CD4:CD8 ratios

(~25% reduction), and mean IgG and IgM responses to SRBCs (~10−30% lower than control values), all suggesting a possible immune suppression effect. The study authors noted that no remarkable histological changes in examined tissues due to toxaphene treatment were found.

The single exposure level in this study, 1 mg/kg-day, is a LOAEL for increased relative spleen and thymus weights, clinical signs of toxicity (e.g., inflammation and enlargement of tarsal glands), and small (but not statistically significant) decreases in three endpoints indicative of possible immune suppression. Confidence in this determination is low because of the limited number of animals in the study and the small magnitude of changes in the immune suppression indicators.

Arnold et al. (2001) and Tryphonas et al. (2001) (up to 75 weeks)

Groups of cynomolgus monkeys (*Macaca fascicularis*) (10 females and 5 males/group) were administered technical toxaphene (Hercules Powder Company Inc., Wilmington, DE, Lot #71-132-b8-17-20) in gelatin capsules (glycerol/corn oil vehicle) at doses of 0, 0.1, 0.4, or 0.8 mg/kg-day (females) and 0 or 0.8 mg/kg-day (males) for up to 75 weeks. The monkeys were obtained from the Animal Breeding Colony, Health Canada, Ottawa, Ontario and housed individually in stainless-steel cages in rooms maintained at 22 ± 3°C with a relative humidity of 50 ± 10% where they acclimatized for at least 5 months. Age-matched females were randomly distributed into four test groups, which were then assigned to one of two test rooms (20 females/room). Older males that were proven sires were assigned to the control group. Younger males, similar in age to females, formed the exposed groups, and males were randomly assigned to either test room (6 or 4 males/room). Male and female animals were daily allotted ~200 and ~165 g of Laboratory Monkey Chow, respectively, along with small amounts of fruits and vegetables; water was available ad libitum. For enrichment, female monkeys were paired (within groups) and moved to exercise cages at least 1 day/week; males were exercised individually.

General health status, feed and water consumption, and menstrual status in females were recorded daily, and body weight was measured weekly. Comprehensive hematology endpoints were measured 4 months prior to dosing and during Weeks 5, 11, 19, 23, 41, and 64; samples for analysis of 26 standard serum biochemistry endpoints (including ALT, ALP, AST, T4, and T4 binding capacity) were taken 4 months prior to dosing and during Weeks 9, 18, 36, and 63 after the start of dosing. Because of the age difference between the control and exposed males, serum biochemistry endpoints were measured in females only. In females, estrogen and progesterone were monitored daily throughout a complete menstrual cycle during Weeks 22−31. Serum hydrocortisone (i.e., cortisol) and toxaphene concentrations in blood and adipose tissue collected from the nuchal fat pad were determined at least monthly. Available reports for this study, however, did not present the blood and tissue toxaphene concentration results. Immunological testing was initiated on study Week 33 and performed in blocks until completion at Week 70. Results from a pilot study indicated that, by Week 20, steady-state concentrations of toxaphene were attained in blood and fat tissues (Andrews et al., 1996). Immune testing occurred between: exposure Weeks 33−46 for immune components in blood, Weeks 44−53 for SRBC responses, and Weeks 53−63 for tetanus toxoid responses and pneumococcus responses. Blood was collected immediately prior to immunizations and at weekly intervals (for 3−5 weeks). Titers to SRBC (IgM and IgG), pneumococcus (IgG), and tetanus toxoid (IgG) were determined using ELISAs. Delayed-type dermal hypersensitivity (DTH) to dinitrochlorobenzene (DNCB) was measured during Weeks 66−70. Challenged sites were evaluated by measuring skin-fold

thickness prior to application and at 24 and 48 hours postapplication of DNCB or acetone. The sites were scored for macroscopic appearance (erythema, contour, induration, texture, and appearance of superficial layers compared to adjacent skin). Endpoint scores were combined to generate total clinical scores. The monkeys were not sacrificed after the exposure period, and no histological analyses of tissues were performed in this study.

No statistically significant exposure-related changes in feed or water consumption were observed. Although some statistically significant differences in weight gain during Weeks 24−42 were discussed, the study authors concluded that no toxaphene-related effects on body weight were observed (body weight and body-weight gain data were not provided). Weight changes in the control and exposed males were not compared because the groups differed in age. Females in the 0.8-mg/kg-day exposure group were reported to have a higher incidence of a slight nail bed prominence, edema of the eyelids, as well as a lower incidence of dry skin, but the numbers of females affected were not provided. No other clinical signs were reported. Statistical analysis found no consistent effect of exposure on hematological endpoints. The only consistent exposure-related change in serum biochemistry endpoints was a trend with time for decreasing cholesterol in exposed female monkeys. Menstrual status endpoints (e.g., menses duration) were comparable between exposed and control female monkeys.

Mean anti-SRBC (IgM) responses were significantly decreased (by >27−53% compared with control values) at several postimmunization periods in females administered 0.4 and 0.8 mg/kg-day and in males given 0.8 mg/kg-day (see Table B-3). High-dose females also had significantly decreased anti-SRBC (IgG) and antitetanus toxoid (IgG) responses at several postimmunization periods (see Table B-3). No significant differences in response to pneumococcus were detected between exposed and control females (males were not tested). Peripheral blood leukocyte populations were unaffected by exposure, with the exception of a significant decrease (−37%) in absolute CD20+ B lymphocytes in high-dose females only, compared with control values. The DTH response, mean percent NKC activity, and lymphoproliferative responses of peripheral blood leukocytes to mitogens (phytohemagglutinin and pokeweed mitogen) were comparable to control values. No exposure-related effects on cortisol levels were seen.

The results of this study indicate a LOAEL of 0.4 mg/kg-day for impaired immune responses to SRBC in female cynomolgus monkeys exposed to encapsulated technical toxaphene for up to 75 weeks. The NOAEL from this study is 0.1 mg/kg-day. At the high dose of 0.8 mg/kg-day, female monkeys also showed suppressed immune response to tetanus toxoid, and male monkeys showed decreased anti-SRBC IgM (which was the only dose level tested in males).

Chu et al. (1986) (dog)

Groups of Beagle dogs (six/sex/group) were administered technical toxaphene (FBC Chemicals, Scarborough, Ontario) via gelatin capsules (in corn oil vehicle) at nominal doses of 0, 0.2, 2.0, or 5.0 mg/kg-day for 13 weeks. An initial high dose of 10 mg/kg-day was administered during the first 2 days, but brief convulsions, salivation, and vomiting were observed in one male and two females, and some animals consumed little to no diet at this dose. Subsequently, the high dose was reduced to 5 mg/kg-day for 4 weeks, followed by erroneous administration of 2.5 mg/kg-day in Weeks 4−8. Doses of 5.0 mg/kg-day were then administered during Weeks 9−13. For this assessment, an approximate TWA dose of 4.5 mg/kg-day was

calculated for the high-dose group. Beagles, 7−8 months-of-age, were acclimated for 2 weeks prior to treatment. Capsules were prepared weekly using corn oil (vehicle) and administered daily at 8:00 AM. Animals were offered 400 g/day of standard dog food during a 1-hour feeding period in the afternoon. Fresh water was provided ad libitum. Clinical signs were monitored twice daily, food consumption was measured daily, and body weights were recorded weekly. Comprehensive serum biochemistry, comprehensive hematology, and nonfasting urinalytic (glucose, creatinine, urea nitrogen, protein, and albumin) endpoints were measured in samples collected 2 weeks before study initiation and at Weeks 5, 10, and 13 of treatment. Gross examinations were performed at necropsy, and all major tissues and organs were collected for histological examination. Tissue samples were also collected for hepatic mixed function oxidase activities (liver) and tissue residue analysis (liver and fat). Analyses were carried out in a similar manner for the rat experiment by the same researchers (described below).

No dose-related differences in body weight, gross pathological changes, or other clinical signs were reported (other than those noted when high-dose dogs received 10 mg/kg doses for 2 days). Body-weight and feed-consumption data were not provided. Increased mean relative liver weights (compared with controls; see Table B-4) were observed in high-dose males (19%) and in all treated females (13, 20, and 30% increases in low-, medium-, and high-dose groups, respectively; statistically significant at medium and high doses). Neither absolute liver weights nor other organ-weight differences were reported. Statistically significant increases in ALP (see Table B-4) were observed in high-dose males and females at Weeks 5 (99 and 107% increase, respectively) and 13 (140 and 150% increase, respectively), compared with controls. No other hematological, serum biochemistry or urinalytic endpoints were affected in the exposed groups.

Incidences for hepatic periportal eosinophilia and increased cytoplasmic density were 100% (6/6) and significantly increased in high-dose male dogs, compared with controls (1/6); eosinophilia was also 6/6 in high-dose females, but due to higher incidence in controls (2/6), the difference was not statistically significant ($p = 0.06$) (see Table B-5). Incidences for non-neoplastic lesions in the kidney were not significantly increased in exposed groups of either sex, compared with controls (see Table B-5). In exposed females, significantly increased incidences for thyroidal reduced colloid density occurred at 0.2 and 2.0 mg/kg-day, but not in the high-dose group; significantly increased incidence of reduced follicle size/follicular collapse was only found in the 2.0-mg/kg-day female group (see Table B-5). The relationship of the thyroid lesions to toxaphene exposure is uncertain due to the lack of a clear dose-response. No exposure-related increased incidences of non-neoplastic lesions were reported in other tissues. Concentrations of toxaphene residues in liver and fat samples from both sexes increased in a dose-dependent manner, and higher concentrations were found in fat than in liver samples.

The results of this study indicate a LOAEL of 0.2 mg/kg-day for a biologically significant relative liver-weight increase (≥10%) in the absence of body-weight changes in female Beagle dogs administered encapsulated technical toxaphene for 13 weeks. No NOAEL could be determined. Additional changes observed in both sexes at the high dose of 4.5 mg/kg-day were increased mean serum activity of ALP and histological liver changes (periportal eosinophilia and increased cytoplasmic density, but not cytoplasmic vacuolation).

Chu et al. (1986) (rat)

Groups of Sprague-Dawley (S-D) rats (10/sex/group) were administered technical toxaphene (FBC Chemicals, Scarborough, Ontario) via diet at concentrations of 0, 4, 20, 100, or 500 ppm for 13 weeks. The commercial test material (90% w/w solution in xylene) was vacuum distilled to remove 80% of the xylene, and then dissolved in corn oil and incorporated into food. The frequency of food preparation was not reported. Rats were acclimatized for 1 week before initiation of the study with free access to food and water. The animals were randomly divided into exposure groups. Based on body weights and food consumption, average technical toxaphene intakes were reported by the study authors to be 0, 0.35, 1.8, 8.6, and 45.9 mg/kg-day (males) and 0, 0.50, 2.6, 12.6, and 63 mg/kg-day (females). Clinical observations were made daily. Food consumption and body-weight gain were recorded weekly. At necropsy, all animals were grossly examined. Organ weights for the brain, heart, liver, spleen, and kidney were recorded, and ~32 internal organs/tissues were processed for histological examination. Blood samples were collected and analyzed for standard hematology endpoints and numerous serum chemistry endpoints (total protein, glucose, sodium, potassium, calcium, cholesterol, uric acid, inorganic phosphate, total bilirubin, ALP, AST, and lactate dehydrogenase [LDH]). Enzymatic activities of several CYP450 oxygenases were determined in liver samples (aniline hydroxylase [AH], aminopyrine demethylase [APDM], and ethoxyresorufin-*O*-deethylase [EROD]). Aspirate from femoral bone marrow was stained for cytological evaluation. Toxaphene residue concentrations in samples of liver and perirenal fat were determined.

No clinical signs of toxicity or mortality were observed. There were slight, but nonsignificant, increases in weight gain (8−16%) and food consumption (5−9%) in exposed male rats, compared with controls; however, no exposure-related patterns were seen in female body weight or food-consumption data. Mean concentrations of toxaphene in liver and fat samples were similar in the control and low-dose groups, but increased in the higher dose groups (1.8, 8.6, and 45.9 mg/kg-day [males] and 2.6, 12.6, and 63 mg/kg-day [females]). In the highest dose group, concentrations were 10.6 ± 4.9 ppm in liver and 103 ± 28 ppm in fat for females, and 7.4 ± 3.9 ppm and 57 ± 28 ppm for males. Gross examination at necropsy revealed fatty liver in single animals in the control and several exposed groups, as well as enlarged kidneys in two 45.9-mg/kg-day males, one 0.35-mg/kg-day male, and one 0.50-mg/kg-day female. Statistically significant organ-weight changes (compared with controls) were increased relative liver weights (see Table B-6) in 45.9-mg/kg-day males (18%) and 63-mg/kg-day females (32%), and increased relative kidney weights in 45.9-mg/kg-day males (23%). Liver activities for CYP450 APDM and AH were also statistically significantly increased in 45.9-mg/kg-day males (96 and 99% increased) and 63-mg/kg-day females (98 and 72% increased). Values for hematology and serum chemistry endpoints were reported to be similar between all exposed groups and controls.

Histochemical evaluations found statistically significant increased incidences of non-neoplastic changes in the liver, kidneys, and thyroid of exposed groups of both sexes, compared with controls (see Table B-7). In both sexes, liver lesions with significantly increased incidences included anisokaryosis (at ≥1.8 mg/kg-day in males and ≥0.50 mg/kg-day in females; moderate to severe in both sexes at the highest dose tested and minimal to mild in both sexes at lower doses), architectural changes described as accented zonation (at ≥8.6 mg/kg-day in males and ≥2.6 mg/kg-day in females; moderate to severe in females at the highest dose tested and minimal to mild in both sexes at lower doses), and nuclear necrosis (at 1.8 and 45.9 mg/kg-day in males and 63 mg/kg-day in females; minimal to mild in both sexes) (see Table B-7). The study

authors considered the liver changes observed at doses ≥1.8 mg/kg-day in males and ≥2.6 mg/kg-day in females to be biologically significant. Kidney lesions with significantly increased incidences included primary tubular injury described as large eosinophilic inclusions, which protruded into the tubular lumen (at ≥1.8 mg/kg-day in males and ≥12.6 mg/kg-day in females; moderate to severe in males at 45.9 mg/kg-day and minimal to mild in females at 63 mg/kg-day and in both sexes at lower doses) and focal tubular necrosis (at ≥8.6 mg/kg-day in males and ≥0.5 mg/kg-day in females; minimal to mild in both sexes) (see Table B-7). The study authors considered the renal injury in the 0.35- and 1.8-mg/kg-day males and 0.50- and 2.6-mg/kg-day females to be minimal and focal and not biologically significant. Thyroid lesions with significantly increased incidences in females included reduced follicular size, increased epithelial height, cytoplasmic vacuolation, and reduced colloid density at doses ≥0.50 mg/kg-day (see Table B-7). In males, thyroid lesions consisted of moderate to severe increased epithelial height and cytoplasmic vacuolation (all severity) at ≥8.6 mg/kg-day, and moderate to severe reduced colloid density at ≥1.8 mg/kg-day (see Table B-7). The study authors considered the moderate to severe changes in the thyroid at ≥1.8 mg/kg-day in males and 63 mg/kg-day in females to be biologically significant. No exposure-related histological changes in other organs were found. Because the liver, kidney, and thyroid were distinct target organs within this study and in other studies in which a dose-response was seen for the incidence of various pathologies, all severity grades of lesions observed in these organs were considered biologically relevant for the purpose of this PPRTV assessment.

The results of this study indicate a LOAEL of 0.50 mg/kg-day for histopathological changes in the thyroid, kidney, and liver of female S-D rats exposed to toxaphene in food for 13 weeks. No NOAEL could be determined.

Koller et al. (1983)

Groups of male S-D rats (12/group) were administered technical toxaphene at concentrations of 0, 30, or 300 ppm in their diet for 9 weeks. Based on reference body weights and food-consumption rates for male S-D rats in a subchronic-duration study (U.S. EPA, 1988b), estimated daily intakes of 2.6 and 25.8 mg/kg-day were calculated for this assessment.[4] Cesarean-derived rats (Charles River) were obtained at 2 weeks-of-age, acclimated for 1 week, and placed on exposure regimens postweaning. Specific details of animal facilities or access to feed and water were not provided. After 6 weeks of exposure, the animals were antigenically challenged with 1 mg KLH in 0.2 mL of sterile water via subcutaneous (s.c.) injection at the base of the tail. After 15 days, the animals received a second KLH challenge. Blood samples were collected via cardiac puncture on Days 8, 15 (primary response), and 21 (secondary response) following the initial KLH antigen challenge and used for measuring IgG titers by ELISAs. A separate positive control group (six rats) was given intraperitoneal (i.p.) doses of 75 mg/kg of cyclophosphamide on Days 2, 13, and 15 after antigen challenge. The study also included other groups of rats exposed to 50 or 500 ppm Aroclor 1254. At necropsy, the liver, spleen, and thymus were weighed and samples were fixed for microscopic examination along with samples of kidney, heart, lung, and the gastrointestinal (GI) tract.

[4]Dose estimates were calculated using reference values for body weight and food-consumption rate (U.S. EPA, 1988b). Reference body weight for male S-D rats in a subchronic-duration study = 0.267 kg. Reference food-consumption rate for male S-D rats in a subchronic-duration study = 0.023 kg/day.

Mean terminal body weights in exposed groups were lower than negative control values by <5%. Mean relative liver weight was increased in both exposure groups (11 and 24% increased compared with the control mean at the low and high doses, respectively) (see Table B-8). The mean relative weights of thymus and spleen in exposed animals were comparable to control values. Technical toxaphene was qualitatively described to produce less severe liver lesions than a 9-week exposure to Aroclor 1254 at the highest dose tested (which induced liver lesions described as megalocytosis of hepatocytes, accompanied by enlarged hepatocytes showing various degrees of vacuolar degeneration). Incidence data were not reported for histological findings. The histology of other organs in the exposed groups "did not appear to differ significantly from the controls." Decreased IgG titers in response to KLH challenge reached significance at the 15-day collection point in the 2.6- and 25.8-mg/kg-day groups (46 and 50% decreased, respectively, compared with negative controls). However, 6 days after a secondary KLH challenge on Day 15, KLH IgG titers were comparable between exposed groups and negative controls. Immunosuppressive effects from technical toxaphene were not as marked or prolonged as those observed with the positive control, cyclophosphamide.

The results of this study indicate that 2.6 mg/kg-day, the lowest tested exposure level, was a LOAEL for transient immunosuppressive effects and increased relative liver weight in male S-D rats exposed to technical toxaphene in the diet for 9 weeks. No NOAEL could be determined. Other liver effects (qualitatively described megalocytosis of hepatocytes) were observed at 25.8 mg/kg-day, but not at 2.6 mg/kg-day.

Allen et al. (1983)

In two immunological studies, groups of 23−26 female Swiss-Webster mice were administered technical toxaphene in their diet at concentrations of 0, 10, 100, or 200 ppm for up to 8 weeks. Toxaphene (Hercules Lot X-188825-6) dissolved in acetone was mixed into ground rat pellets. The acetone was evaporated and the dried food fed to the animals in powder form. In the first study, 3-week-old female mice (Washington State University Laboratory Animal Resources) were housed in groups of five animals/cage. Estimated daily intakes of 1.9, 19.1, and 39.2 mg/kg-day were calculated based on group averages between reported means for initial and final (8 weeks) body weights and an allometric equation for food consumption (food consumption in kg/day = 0.056 × [body weight in $kg^{0.6611}$]) described by U.S. EPA (1988b). In a second study, 36 females (3 animals/cage; presumably 12 dams/group) were exposed beginning 3 weeks prior to mating, and throughout gestation, and lactation (~9 weeks). The offspring (exposed ~6 weeks in duration from Gestation Day [GD] 0 through lactation) were placed on standard control diets at weaning and aged to 8 weeks prior to immunological testing. The numbers of offspring in each group differed between immune tests, but were clearly specified in the report. All animals were provided with free access to food and water throughout the duration of the study.

All mice were weighed weekly (but only data from the first study were reported). In both studies, DTH antibody response and phagocytosis assays were performed on subsets of 8-week-old mice from each exposure group. For the DTH assays, the mice were sensitized to mycobacteria plus 0.1 mL Freund's complete adjuvant (FCA) 29 and 20 days before testing. Testing began with i.p. injection of tritiated thymidine, followed 24 hours later by s.c. injection of purified protein derivative into the left rear footpad and saline into the right rear footpad. The animals were sacrificed 24 hours later, and radioactivity levels in the foot pads were measured. To test IgG antibody response, the mice were immunized with BSA mixed with FCA and saline

at 29 and 8 days prior to determining IgG titers (by ELISA) in serum from blood collected from the hearts of sacrificed mice. For phagocytosis assays conducted in the second study, the same animals also received i.p. injections of mineral oil 5 days before sacrifice, when peritoneal fluid was collected for macrophage analysis. Isolated macrophages were incubated in tubes containing SRBCs for 1 hour and examined microscopically. If a macrophage had engulfed two or more SRBCs, it was reported as phagocytic. Positive control animals for the DTH and antibody assays in the first study were i.p. injected with 100 mg/kg cyclophosphamide on 13 and 6 days prior to testing and on the day of testing. At necropsy, liver weights were recorded and samples of liver, kidney, spleen, heart, lungs, thymus, and GI tract were collected for microscopic examination. Statistical analysis was performed using a Student's *t*-test and χ^2 contingency methods where appropriate.

No mortalities or exposure-related clinical signs were reported in either study. In the first study, mean body weights in the exposed and control groups were comparable. Mean absolute and relative liver weights in the 19.1- and 39.2-mg/kg-day groups were increased by ≥10% compared with control means (14 and 27% higher absolute weights and 16 and 44% higher relative weights, respectively) (see Table B-9). Histological changes in the liver were described as moderate to severe, with variation in hepatocyte size (enlarged up to 2−3 times) in the 19.1- and 39.2-mg/kg-day dose groups, and some fatty infiltration in the 19.1-mg/kg-day dose group, but incidence data were not provided. No statistically significant differences in delayed hypersensitivity were found between exposed groups and negative controls; only the positive control group showed DTH suppression. IgG titers to BSA were statistically significantly lower in the 19.1- and 39.2-mg/kg-day groups than titers in the control and 1.9-mg/kg-day group (as assessed with a χ^2 contingency table). Median IgG BSA titers ($\times 10^3$) were 512 in the control and 1.9-mg/kg-day groups, 128 for the 19.1-mg/kg-day group, 64 for the 39.2-mg/kg-day group, and 32 for the positive control group.

For the second study, body-weight, organ-weight, and histology data were not provided. The DTH and BSA IgG antibody responses were statistically significantly decreased only in the 19.1-mg/kg-day group, compared with control values: a 17.2% decrease for the DTH test, and a median BSA IgG titer of 256×10^3 versus 512×10^3 for controls. All exposed groups had statistically significantly decreased phagocytosis ability, compared with controls. For control, 1.9-, 19.1-, and 39.2-mg/kg-day groups, respective mean percentage (± SD) phagocytosis values were: 75 ± 28 (n = 34 mice); 51 ± 37 (n = 28); 16 ± 13 (n = 24); and 28 ± 12 (n = 40).

The results of the first study indicate a LOAEL of 19.1 mg/kg-day and a NOAEL of 1.9 mg/kg-day for immune suppression (reduced BSA IgG titers), increased absolute and relative liver weights, and possible histologic changes in the liver (variation in hepatocyte size) in female Swiss-Webster mice fed technical toxaphene in food for 8 weeks, starting at weaning. In the second study, for similarly aged mice exposed through their dams in utero and during lactation for about 6 weeks, the lowest exposure level, 1.9 mg/kg-day, is a LOAEL for immune suppression assayed as decreased ability of macrophages to engulf SRBCs. No NOAEL could be determined from the second study.

Weathered Toxaphene

No subchronic-duration toxicity studies of weathered toxaphene in laboratory animals by oral exposure have been identified.

Toxaphene Congeners

No subchronic-duration toxicity studies of individual toxaphene congeners in laboratory animals by oral exposure have been identified.

Chronic-Duration and Carcinogenicity Studies

Technical Toxaphene

Litton Bionetics (1978)

Groups of B6C3F$_1$ mice (54/sex/group) were fed technical toxaphene in food at concentrations of 0, 7, 20, or 50 ppm for 18 months, followed by a 6-month observation period (see Table 5B). The numbers of early deaths in treated groups did not differ from controls. Available accounts of this study only report cancer findings from the histological examination of major organs of sacrificed mice (U.S. EPA, 1988a, 1985, 1980). Other data (e.g., incidence data for non-neoplastic histologic lesions) that may have been collected are not available (U.S. EPA, 1988a, 1985, 1980). Only incidence data for liver tumors were reported in available sources. Based on an assumed body weight of 0.030 kg and an animal lifetime of 735 days, U.S. EPA (U.S. EPA, 1988a, 1985, 1980) calculated the estimated doses to be 0, 0.91, 2.6, and 6.5 mg/kg-day. Liver tumor incidence data are reported in Table B-10. A statistically significant increase in the incidence of combined hepatocellular adenomas and carcinomas was found in male mice at 6.5 mg/kg-day, but no significantly elevated tumor incidences occurred in exposed female groups.

NCI (1979)

Groups of Osborne-Mendel rats (50/sex/dose group) and B6C3F$_1$ mice (50/sex/dose group) were fed technical toxaphene in the diet for 80 weeks at TWA concentrations of 556 and 1,112 ppm for male rats, 540 and 1,080 ppm for female rats, and 99 and 198 ppm for mice (both sexes). Due to clinical signs of toxicity, high and low dietary concentrations were lowered from initial concentrations in both species (twice for male rats and once for female rats and male and female mice). TWA toxaphene concentrations were calculated by NCI (1979). Estimated daily intakes of 38.9 and 77.88 mg/kg-day for male rats, 41.6 and 83.29 mg/kg-day for female rats, 17 and 34.0 mg/kg-day for male mice, and 17 and 34.2 mg/kg-day for female mice were calculated for this assessment based on reference body weights and food-consumption rates for these strains (U.S. EPA, 1988b).[5] Groups of 10 matched rats or mice/sex served as nonexposed concurrent controls. The pooled control groups contained up to 52 rats/sex or 48 mice/sex from other studies started within a 5-month period before or after the start of the technical toxaphene study. Toxaphene was dissolved in acetone and mixed into feed with 2% corn oil. The animals were acclimatized for 7 days (rats) or 13 days (mice), and at 5 weeks-of-age, were assigned to exposure groups. After 80 weeks of exposure, the exposed animals were placed on control diets and observed for an additional 28−30 weeks (rats) or 10−11 weeks (mice) prior to sacrifice.

The animals were observed twice daily for clinical signs of toxicity. The pathological evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from moribund animals and animals that survived to the end of the postexposure

[5]Dose estimates were calculated using reference values for body weight and food-consumption rate (U.S. EPA, 1988b). Reference body weights for Osborne-Mendel rats in a chronic-duration study: 0.514 kg (male) and 0.389 kg (female). Reference food-consumption rates for Osborne-Mendel rats in a chronic-duration study = 0.036 kg/day (male) and 0.030 kg/day (female). Reference body weights for B6C3F$_1$ mice in a chronic-duration study: 0.0373 kg (male) and 0.0353 kg (female). Reference food-consumption rates for B6C3F$_1$ mice in a chronic-duration study: 0.0064 kg/day (males) and 0.0061 kg/day (females).

period. The following tissues were examined microscopically (following preservation in 10% buffered formalin, embedding in paraffin, and staining with hematoxylin and eosin): skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, gallbladder (mice), pancreas, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, and brain. Data were analyzed using the one-tailed Fisher's exact test for pairwise comparison of tumor incidence data, the Cochran-Armitage test for detecting tumor incidence dose-response trends, and Kaplan-Meier procedures for mortality data.

In rats, clinical signs of toxicity (hyperactivity) were observed in high-dose males 2 weeks after study initiation; consequently, the high and low dietary concentrations were lowered. At Week 53, the majority of male and female high-dose rats developed body tremors, and concentrations were again lowered. From Weeks 52−80, other clinical signs included alopecia, diarrhea, dyspnea, pale mucous membranes, rough hair coats, dermatitis, ataxia, leg paralysis, epistaxis, hematuria, abdominal distention, and vaginal bleeding, which were noted primarily in the exposed groups (incidence data were not provided). Impaired equilibrium in one low-dose and one high-dose female was also reported. Kaplan-Meier survival curves indicated decreased survival probabilities in high-dose males after approximately 60 weeks, but the Tarone test for dose-related trend in mortality was not significant in either sex. Mean body weights of low- and high-dose females, but not males, were lower than matched controls throughout most of the study; TWA mean body weights were lower by 8 and 13%, respectively. A few non-neoplastic lesions in the liver and thyroid were observed in exposed groups; however, incidences were not statistically significantly different from controls (see Table B-11 for incidence data for non-neoplastic lesions found in liver, kidney, or thyroid of exposed rat groups), and it is unknown if these lesions are related to the observed carcinogenicity. Statistically significantly increased incidences (compared with pooled controls) were found for liver neoplastic nodules in low-dose males; thyroid follicular-cell carcinoma or adenoma in high-dose males; thyroid follicular cell adenomas in high-dose females; and pituitary chromophobe adenoma, adenoma (not otherwise specified [NOS]), or carcinoma in high-dose female rats (see Table B-12).

The study results indicate LOAELs of 77.88 (males) and 83.29 mg/kg-day (females), and NOAELs of 38.9 (males) and 41.6 mg/kg-day (females) for technical toxaphene in Osborne-Mendel rats exposed in their diet for 80 weeks based on statistically and toxicologically (≥10%) significant decreased body weight in females and clinical signs of toxicity in both sexes.

In mice, several died before exposure Week 19 in both dose groups (causes of death were not described), and the dietary concentrations were lowered. By the second year of the study abdominal distention was observed predominantly in high-dose males. Other clinical signs included alopecia, diarrhea, rough hair coats, and dyspnea (incidences were not provided). From Weeks 60−76, low-dose males were described as appearing hyperexcitable. Tarone tests for dose-related trends in mortality were statistically significant, with Kaplan-Meier survival curves showing decreased survival after about 75 weeks in high-dose males and females. The increase in late mortality may have been related to high incidence of hepatocellular carcinomas in these groups. Mean body weights were lower than controls in high-dose males throughout the study, but comparable to control values in low-dose males and low- and high-dose female mice. TWA mean body weights for high-dose males were about 6% lower than the control value. No statistically significant increased incidences of any non-neoplastic lesions were found in any of

the dose groups, compared with controls (see Table B-11 for liver, kidney, or thyroid lesions that were reported at very low incidences in exposed groups). Significantly increased incidences of liver tumors (carcinomas alone, or combined carcinomas and adenomas) were found in the low- and high-dose groups of males and females (see Table B-12).

The low dose of 17 mg/kg-day is a NOAEL in both male and female $B6C3F_1$ mice exposed to technical toxaphene in the diet for 80 weeks. Increased late mortality at the high dose of 34.0 and 34.2 mg/kg-day in male and female mice, respectively, may have been secondary to carcinogenic effects in these groups. Incidences for non-neoplastic histological lesions were not elevated in exposed groups, compared with controls, thus no LOAEL was identified.

Weathered Toxaphene

No chronic-duration toxicity or carcinogenicity oral-exposure animal studies of weathered toxaphene have been identified.

Toxaphene Congeners

No chronic-duration toxicity or carcinogenicity oral-exposure animal studies of individual toxaphene congeners have been identified.

Reproductive Toxicity Studies

Technical Toxaphene

Chu et al. (1988)

S-D rats (aged 5−6 weeks; six females and three males/group) were administered technical toxaphene at concentrations of 0, 4, 20, 100, or 500 ppm in their diet for up to 29 weeks in a one-generation reproductive toxicity study. The commercial test material (90% w/w solution in xylene) was vacuum distilled to remove 8% of the xylene, and then dissolved in corn oil and incorporated into food. The animals had free access to food and water. After 13 weeks of exposure, two F0 generation females and one F0 male rat from each dose group were cohabitated until mating occurred, allowing up to 3 weeks (time to mate was not provided). To confirm copulation, females were examined daily for the presence of sperm in vaginal smears or for vaginal plugs. Toxaphene exposure in F0 rats was maintained throughout mating, gestation, and lactation. At weaning (21 days), F1a pups were switched to the same exposure diets as their parents. At 5 weeks-of-age, the litters were randomly reduced to 15 males and 30 females/exposure group, and exposure regimes were maintained for an additional 26 weeks (F1a adults). Following a week of rest postweaning, F0 dams still on their exposure diets, were remated to a separate exposed male from the same dose group to generate the F1b litter. F1b pups, along with F0 dams and sires were sacrificed 21 days postpartum.

Exposure periods in F0 dams and sires (depending upon time of mating) ranged from ~25−29 weeks. The F1a adult groups were exposed for ~34 weeks total (3 weeks in utero, 3 weeks via lactation, and 28 weeks via diet); F1b pups were exposed for ~6 weeks (3 weeks in utero, 3 weeks lactation). Based on body-weight and feed-consumption data, average daily intakes of technical toxaphene were reported to be 0, 0.36, 1.8, 9.2, and 45 mg/kg-day (F0 males); 0, 0.36, 1.9, 8.5, and 46 mg/kg-day (F0 females); 0, 0.29, 1.4, 7.5, and 37 mg/kg-day (F1a males); and 0, 0.38, 1.9, 9.4, and 49 mg/kg-day (F1a females).

Clinical observations of all animals were made daily. Body weights and feed consumption were determined weekly for F0 and F1a adults. Body weights and survival of F1a

and F1b pups were recorded at birth and at Days 4, 7, 14, and 21. Gross examinations were done at necropsy. Organ weights for F0 and F1a adult liver, brain, heart, kidney, and spleen were recorded, and ~32 internal organs/tissues were processed for histological examination. Blood samples were collected and analyzed for standard hematology serum chemistry endpoints including ALP, AST, LDH, and serum sorbitol dehydrogenase (SDH) activity. Enzymatic activities of several CYP450 oxygenases (AH, APDM, and ER) were determined in liver samples of all adult rats and in groups of five randomly selected F1b pups/dose/sex. Differential leukocyte counts and cytological evaluation of femoral bone marrow were performed on the adult control and highest dose groups. Toxaphene residue concentrations in samples of liver and perirenal fat from F1a adults, and of liver and total body from F1b pups, were determined.

No exposure-related effects were observed with respect to clinical signs, mortality, survival indices, fertility and gestation indices, litter sizes, or postnatal F1 growth. Average weight gain over the exposure period was significantly reduced in F1a males (−10%) and females (−15%) in the high-dose group, compared with controls. Body-weight gain was not affected in F0 animals. Slight fatty infiltration of the liver was reported in 9.2- and 45-mg/kg-day F0 males, 8.5- and 46-mg/kg-day F0 females, 7.5- and 37-mg/kg-day F1a males, and 9.4- and 49-mg/kg-day F1a females. No other gross changes at necropsy were described.

Absolute and relative liver weight means were increased by ≥10% compared with control means at the highest dose in F0 males and at concentrations ≥1.9 mg/kg-day in F0 females (see Table B-13). In addition, absolute, but not relative, liver weight was increased by ≥10% (11%) at the lowest dose of 0.36 mg/kg-day in F0 females (see Table B-13). In F1a males and females, absolute and relative liver weights were clearly increased by ≥10% compared with controls at the highest dose (see Table B-13). The mean relative liver weight reported in the study for control F1a males was abnormally low (1.7% of body weight), compared with control means for F1a females (3.9%), F0 males (3.6%), and F0 females (3.7%). It is likely that this value reflects a typographical error, as the mean and SD are identical to those for absolute kidney weight reported in a neighboring column in the study table. Based on an expectation that the F1a male control relative liver weight should be in the range of ~3.6, it appears that the only relevant increase (≥10%) is in the highest dose group, consistent with the effect seen in F1a females.

Absolute and relative kidney weights were increased by ≥10% in 45-mg/kg-day F0 males and in 7.5- and 37-mg/kg-day F1a males, but not in any exposed F0 or F1a female groups (see Table B-13). The report by Chu et al. (1988) did not mention any other exposure-related changes in other organ-weight data (brain, heart, and spleen).

Toxaphene residue levels in the fat and liver of adult rats, and in the liver and the whole body of rat pups, increased in a dose-dependent manner. Levels in fat were generally higher than liver levels (7−17 and 7−106% higher in F1a adult males and females, respectively), and also higher in F1a females than F1a males (58−269% higher). Concentrations in the liver were comparable between sexes. In the high-dose groups, toxaphene residue levels in the livers of male and female F1b pups were 54 and 108% higher, respectively, than in the livers of F0 dams.

Changes in biochemical endpoints (compared with controls) included increased (28%) serum cholesterol in the 46-mg/kg-day F0 females and decreased (up to 21%) serum glucose in the F0 males exposed to ≥1.8 mg/kg-day. The study authors were uncertain about the biological

significance of these changes. Compared with controls, significant increases in hepatic APDM activity were observed in the 45-mg/kg-day F0 males (59%) and in the F1a adult females at ≥9.4 mg/kg-day (up to 45%). In F1b female pups from the 0.36- and 1.9-mg/kg-day F0 dams, APDM activity decreased significantly (−45 and −26%, respectively). The activities of other liver oxygenases were not reported. Liver protein (mg/mL homogenate) was reported for F1b pups only and, compared with controls, was elevated (62%) in F1b male pups from the 46-mg/kg-day F0 dams, and in F1b female pups from the 8.5- and 46-mg/kg-day F0 dams (40 and 88%, respectively). No other exposure-related changes in biochemical endpoints were described.

Histochemical evaluations of tissues from F0 and F1a adult rats found statistically significantly increased incidences of non-neoplastic changes in the liver, kidneys, and thyroid of exposed groups of both sexes, compared with controls (see Tables B-14 and B-15). Liver lesions with significantly increased incidences included cytoplasmic density, anisokaryosis, increased vacuolation, and increased cytoplasmic homogeneity. These lesions were found most prominently in high-dose F0 and F1a adults of both sexes, but elevated incidences of minimal to mild gradations occurred in F1a adults at doses ≥0.29 (males) and 0.38 mg/kg-day (females) (see Tables B-14 and B-15). The study authors suggested that many of these observed liver changes could be largely adaptive in nature. Similarly, in the kidney, significant increases in lesions (primary renal tubular injury in F0 males and females and F1a adult males, and anisokaryosis, pyknosis, interstitial sclerosis in F0 males) occurred primarily in the highest-dose group, with increased incidences of minimal to mild gradations of some lesions occurring in some of the lower dose groups (see Tables B-14 and B-15). Thyroid changes, graded moderate to severe, were limited to reduced colloid density and colloid inspissation in 45-mg/kg-day F0 males. Statistically significant increases in incidences of other thyroid lesions (when all severity grades are considered) were observed in many exposure groups as follows: reduced colloid density (at ≥1.8 mg/kg-day in F0 males, 1.4 mg/kg-day in F1a males, and ≥0.38 mg/kg-day in F1a females); colloid inspissation (at 0.36, 1.8, and 45 mg/kg-day in F0 males and ≥0.29 mg/kg-day in F1a males); increased epithelial height (at 46 mg/kg-day in F0 females, 0.29, 1.4, and 7.5 mg/kg-day in F1a males, and ≥0.38 mg/kg-day in F1a females); follicular collapse/angularity (at 45 mg/kg-day in F0 males, 1.9 mg/kg-day in F0 females, 1.4 and 37 mg/kg-day in F1a males, and 0.38 and 1.9 mg/kg-day in F1a females); and reduced follicle size (at ≥9.4 mg/kg-day in F1a males) (see Tables B-14 and B-15). The study authors expressed uncertainty regarding the biological significance of the changes in the thyroid. Statistically significant incidences of non-neoplastic changes in thyroid, liver, and kidney were also present in 3-week-old F1b pups exposed to the highest exposure level (see Table B-15). As with the Chu et al. (1986) rat study, all severity grades of lesions observed in this study are considered biologically relevant for the purpose of this PPRTV assessment because the liver, kidney, and thyroid are distinct target organs that exhibited a dose-response for the incidence of various pathologies.

A LOAEL of 0.29 mg/kg-day is identified for this study based on increases in histopathological lesions in the thyroid and liver of F1a adult males. No NOAEL could be determined.

The results also indicate that the highest dietary exposure level of 500 ppm (45−46 mg/kg-day in the F0 adults), was a NOAEL for combined reproductive function

endpoints measured in exposed F0 male and F0 females (fertility and gestation indices, litter sizes, and pup survival).

Kennedy et al. (1973)[6]

Groups of S-D albino rats (8 males and 16 females/group) were exposed daily to technical toxaphene in food at concentrations of 0, 25, and 100 ppm for up to 42 weeks in a multigeneration reproductive toxicity study. Technical toxaphene was mixed with 2% corn oil and added to standard rat food. Choice of exposure levels was guided by an early report of hepatic fatty degeneration and cytoplasmic vacuolation in rats fed 100 ppm technical toxaphene, but not 25 ppm, in food (Lehman, 1952). Based on reference body weights and food-consumption rates for S-D rats in a chronic-duration study (U.S. EPA, 1988b), estimated daily intakes of 0, 1.7, and 6.88 mg/kg-day (males) and 0, 2.0, and 7.99 mg/kg-day (females) were calculated for this assessment.[7] Diets were prepared fresh weekly, and the animals were allowed free access to feed. F0 animals were received as weanlings and allowed to acclimate for 1 week prior to initiation of the study at 28 days-of-age. The F0 rats were mated at 100 days-of-age (two females to one male). Males were removed upon confirmation of copulation (sperm-positive vaginal examination). The first litters (F1a) were reduced to 10 pups/litter on Day 5 and retained for 21 days. F0 dams were given 10 days of rest postweaning and were remated to generate F1b litters. At weaning, 8 males and 16 female F1b pups were selected from each group at random as parental animals for the F2 generation. This procedure was continued through three successive two-litter generations until F3b pups were born. F0 dams were sacrificed after a total of 42 weeks of exposure to technical toxaphene, whereas F1b and F2b parents were sacrificed after 39 weeks.

All parental rats were necropsied at sacrifice, and absolute and relative organ weights were determined (for liver, kidneys, spleen, gonads, heart, brain, adrenals, and thyroid). Thirty-four tissues and organs from parental rats were collected, preserved, and examined histologically. Weight gains for parental animals (F0, F1b, F2b) were determined prior to the first mating and up to time of sacrifice. Total and free serum cholesterol were measured in eight parental animals/sex/group after 39 weeks of exposure. Complete blood and platelet counts, cell indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [Hb] concentration, as well as color, saturation, and volume indices), prothrombin time, activities of serum glutamic-pyruvic transaminase (GPT = ALT) and glutamic-oxaloacetic transaminase (GOT = AST), serum ALP, fasting blood sugar, blood urea nitrogen (BUN), icterus indices, and urinalysis (glucose, albumin, and microscopic exam) were determined on three parental rats/sex/generation (control and 100-ppm dietary dose group). Reproductive endpoints were

[6]This study was conducted by Industrial Bio-Test Laboratories (IBT) and published in a peer-reviewed journal prior to the development of Good Laboratory Practices (GLP) in 1979. In its 2007 *Manual for Investigation of HPV Chemicals*, OECD (2007) noted that 618 of 867 nonacute toxicity studies conducted by IBT prior to its closing in 1978 (including subacute, subchronic-duration, carcinogenicity, reproductive toxicity/teratogenicity, genotoxicity, and neurotoxicity studies) were found to be invalid during a post hoc audit program conducted by U.S. EPA and the Canadian Health and Welfare Department. There is no information on whether the study by Kennedy et al. (1973) was audited.

[7]Dose estimates were calculated using reference values for body weight and food-consumption rate (U.S. EPA, 1988b). Reference body weights for S-D rats in a chronic-duration study: 0.523 kg (male) and 0.338 kg (female). Reference food-consumption rates for S-D rats in a chronic-duration study = 0.036 kg/day (male) and 0.027 kg/day (female).

determined for each litter, including mating index, fertility index, pregnancy index, parturition index, mean litter size, live birth index, 5-day survival index, and lactation index.

All viable and stillborn progeny were counted, examined for physical abnormalities, and records of survival/mortalities were maintained. Male and female weanling body weights were measured in all litters. Gross and microscopic pathologic studies (except for organ weights) were conducted on F3b weanlings only.

All data were reportedly analyzed by ANOVA, and Student's *t*-test was used for intergroup comparisons. However, adequate summary data for independent analysis of most endpoints (e.g., incidence data for discontinuous variables or mean, SD, and *n* for continuous variables) were not provided in the published report.

No treatment-related mortalities, clinical signs of toxicity, or effects on growth of parental rats were reportedly observed (summary data were not provided). No differences in cholesterol concentrations, hematologic endpoints, urinalytic endpoints, or other clinical chemistry findings (e.g., ALT, AST, ALP serum activities) were reportedly observed between F2 parental exposed and control groups; results for these endpoints in other parental generations (F0, F1) were not mentioned. Mean relative liver weight in exposed male groups was increased compared with controls by ≥10% in F1 males at 1.7 mg/kg-day and 2−8% in F0 and F2 males. In females, mean relative liver weights were increased compared with controls at doses of 2.0 and 7.99 mg/kg-day, respectively, as follows: 12 and 26% in the F0 groups, 9 and 0.3% in the F1 groups, and 9 and 10% in the F2 groups. Gross and microscopic examination reportedly revealed no exposure-related effects on tissues and organs, except for hepatic cytoplasmic vacuolization in 63% of all high-dose parental rats (compared with none in controls); incidence data specific to generation, sex, and exposure groups were not reported. No differences were reportedly observed between the production of F1, F2, or F3 litters compared with controls in mating index, fertility index, pregnancy index, parturition index, mean litter size, live birth index, 5-day offspring survival index, lactation index, and weanling body weights of offspring. Mean values were reported for these endpoints by exposure group and generation, but values for *n* and SD or standard error (SE) were not provided. No significant differences were reported between exposed and control groups for the number of pups delivered, number of stillborn pups, number of viable pups at birth or through lactation, or growth of offspring through lactation (summary data were not provided). The findings from gross and microscopic examination of tissues from F3b weanlings were not provided, except for a general statement that no evidence for exposure-related teratogenicity was found.

The study results indicate LOAELs of 1.7 and 2.0 mg/kg-day for F1 males and F0 females, respectively, for increased (≥10%) relative liver weight in rats fed technical toxaphene in food for 39−42 weeks. The highest exposure level, 6.88 and 7.99 mg/kg-day in males and females, respectively, is a reproductive NOAEL for the lack of effects on reproductive function in three exposed parental male generations, absence of gross abnormalities in offspring, and lack of effects on offspring survival and growth. Confidence in these determinations is compromised by reporting deficiencies in the available published report, as well as by uncertainties regarding the reliability of studies conducted by IBT.

Keplinger et al. (1970)

Groups of Swiss white mice (4 males and 14 females/group) were exposed daily to technical toxaphene in food at concentrations of 0 or 25 ppm for 120 days, in a five-generation reproductive toxicity study. Technical toxaphene (source and purity were not provided) was mixed into standard Purina laboratory chow. This study also tested several other substances (the pesticides aldrin, dieldrin, chlordane, and dichlorodiphenyltrichloroethane [DDT]), but only the toxaphene results are reported here. Mice were raised from a laboratory stock. Based on the mean reference body weights and food-consumption rates for BAF_1 and $B6C3F_1$ mice in a subchronic-duration study (U.S. EPA, 1988b), estimated daily intakes of 4.7 mg/kg-day (males) and 5.1 mg/kg-day (females) technical toxaphene have been calculated for this assessment.[8] Study details such as animal care, time of study initiation, or whether time had elapsed between the start of exposure and mating were not provided. F0 mice (120 days old) were divided into two cages for mating (two males and seven females/cage). Pregnant females were removed, housed individually, and continued on their exposure diets. After weaning, F1 litter 1 (F1a) pups were fed the same exposure diet as the mother until Postnatal Day (PND) 120, when they were sacrificed for chemical or histological analysis. F0 dams were given 7 days of rest postweaning then remated to generate a second litter (F1b). At weaning, 4 males and 14 F1b females were selected as breeders for the next-generation litters (F2a and F2b). Remaining pups and F0 parents were sacrificed for chemical or histological analysis. This breeding scheme was continued through five successive, two-litter generations until F5b pups were born. Mice from all litters were exposed in utero, through lactation, and then in feed until sacrifice at PND 120 (nonbreeders).

At sacrifice, the liver, lungs, kidneys, brain, small intestine, thymus, adrenals, spleen, stomach, and heart were fixed for microscopic examination. Organ weights were measured for brain and liver from 10 males and 10 females/group. For exposed and control animals, the number of females that delivered, total number of pups born, average litter size, survival at three time points (birth, 4 days, and 4 months), total number of animals weaned, and pup weight at weaning and at sacrifice were recorded. These data were used to determine fertility, gestation, pup viability, lactation, and pup survival indices. No specifics regarding the chemical analyses performed were provided. Statistically significant differences in indices were evaluated using two unspecified methods.

Compared with controls, no changes in fertility, gestation, lactation, pup viability, or pup survival indices, resulting from exposure to technical toxaphene, were observed. No significant changes in brain or liver weight were noted, although data were not provided. The study authors stated that all compounds tested caused changes in the liver that included fatty metamorphosis, increased basophilic activity, or hepatic cell necrosis. The study authors also noted that these liver changes were "usually more marked in the second litter;" however, no substance-specific incidence data were reported. Damage to the kidney, lungs, and brains was also reported for most of the test substances (except for the lack of toxaphene-induced brain changes), but incidence data were not reported. Results from chemical analyses were not presented.

[8]Dose estimates were calculated using the mean reference body weight and food-consumption rate values for BAF_1 and $B6C3F_1$ mice in a subchronic-duration study (U.S. EPA, 1988b). Mean reference body weights: 0.0270 kg (male) and 0.0225 kg (female). Mean reference food-consumption rates: 0.0051 kg/day (male) and 0.0046 kg/day (female).

The study results indicate a NOAEL of 4.7 mg/kg-day (males) for the lack of effects on reproductive function endpoints in the four exposed parental generations, and lack of effects on offspring survival or growth in the animals exposed to technical toxaphene in utero, through lactation, and in feed to PND 120. The reporting of the histology findings in this study is inadequate to assess whether the single exposure level is a LOAEL for histological changes in the liver or other organs.

Weathered Toxaphene

No oral-exposure reproductive toxicity studies of weathered toxaphene in laboratory animals have been identified.

Toxaphene Congeners

No oral-exposure reproductive toxicity studies of individual toxaphene congeners in laboratory animals have been identified.

Developmental Toxicity Studies

Technical Toxaphene

Chernoff and Carver (1976)

Groups of pregnant mice (26−90/group) and rats (16−39/group) were administered technical toxaphene (Hercules, Inc.) at doses of 0, 15, 25, or 35 mg/kg-day in corn oil (vehicle) by gastric intubation, on GDs 7−16. The CD-1 mice and CD rats were obtained from the Charles River Breeding Laboratories (Wilmington, MA) and were maintained in constant temperature rooms (22−26°C) on a 12-hour light/dark cycle. Feed and water were available ad libitum. Pregnancies were confirmed by presence of sperm in the vaginal smear. Body weights measured on GD 6 were used for dose and body-weight gain calculations. Mortality and the number of pregnancies that went to term were recorded. Mice and rats were sacrificed on GDs 18 and 21, respectively. Maternal-weight gain (weight of intact animal − [weight of the removed uterus + weight measured at GD 6]), liver weight, weights of live fetuses, number of implants, and fetal mortality were recorded. At sacrifice, fetuses were grossly examined then placed in fixatives for 3−5 days for either necropsy or skeletal examination (sternal and caudal ossification centers).

In exposed rats, statistically significantly decreased incidences of pregnancies that went to term were observed at 25 and 35 mg/kg-day, and increased dam mortality occurred at 35 mg/kg-day (see Table B-16). All exposed groups showed statistically significantly decreased maternal-weight gain, ranging from 22−41% decrease below the control average (see Table B-16). Fetal body weights were decreased 5−12% across all dose groups compared with controls, but decreases were only statistically significant at the 25-mg/kg-day dose (see Table B-16). No significant differences were observed between the control and exposed groups in maternal liver to body-weight ratios, the average number of implants, or fetal mortality (see Table B-16). Exposed groups had statistically significantly lower average numbers of fetal sternal ossification centers than the control group, but the numbers of caudal ossification centers were not significantly different in exposed versus control groups, except for a lower number in the 25-mg/kg-day group. Dose-related changes were not found in the number of fetal anomalies revealed by necropsy.

In rats, the lowest dose, 15 mg/kg-day, is a maternal LOAEL for decreased average-weight gain. More severe maternal effects were noted at 25 and 35 mg/kg-day,

including decreases in the number of pregnancies brought to term and increased maternal mortality. The 15-mg/kg-day dose is also a developmental LOAEL for decreased numbers of sternal ossification centers in fetuses and biologically significant (≥5%) decreased fetal body weight. No exposure-related effects were observed on the average number of implants, fetal mortality, or the occurrence of fetal anomalies. No NOAELs can be identified.

In mice, pregnancies brought to term were not significantly different in the exposed and control groups (see Table B-16). There was a marginal increase in dam mortality at 35 mg/kg-day ($p = 0.07$). Maternal-weight gain was significantly reduced in the 25- and 35-mg/kg-day dams, and average liver weights were increased ≥23% (relative to controls) in all exposed groups (see Table B-16). Average fetal body weights and numbers of ossification centers were not significantly different between exposed and control groups. Necropsy of fetuses found encephaloceles (portions of the brain protruding from the skull) in five high-dose litters and 11 high-dose fetuses, but none in the control or other exposed groups (see Table B-16). The elevated incidence of high-dose litters with this anomaly, compared with the control incidence, did not reach statistical significance ($p = 0.07$).

In mice, the lowest dose, 15 mg/kg-day, is a maternal LOAEL for increased relative liver weight. Decreased maternal average-weight gain occurred in the 25- and 35-mg/kg-day groups, and there was a marginal increase in maternal mortality at 35 mg/kg-day. No maternal NOAEL can be identified. Due to the lack of statistical significance observed for any of the reproductive and developmental parameters, the highest dose tested (35 mg/kg-day) is identified as a reproductive and developmental NOAEL, and no LOAEL can be confidently identified. Note, however, that the incidence of litters with encephaloceles, although not statistically significant, was 5/61 (11%) at 35 mg/kg-day. Additionally, the average fetal mortality was twice that of the control value at 25 mg/kg-day, albeit with a substantial associated variance (i.e., SD) for both groups.

Chernoff and Kavlock (1983)

Groups of pregnant female CD-1 mice (25/group) were exposed daily to technical toxaphene by gavage (in 0.5 mL corn oil vehicle) at doses of 0 or 75 mg/kg-day on GDs 8−12. The source of technical toxaphene was not provided. Feed and water were available ad libitum.

Maternal-weight gain and pup survival at birth were assessed. Litters were counted and weighed on PNDs 1 and 3. Dead pups were necropsied and gross abnormalities were noted. Dams that did not give birth by GD 22 were sacrificed, and uteri were examined for the presence of implantation sites. Comprehensive examination of fetuses for visceral and skeletal variations or anomalies was not conducted.

No significant differences were found between the exposed and control groups in clinical signs, maternal mortality, or pup survival on PNDs 1 and 3. Statistically significant decreases in maternal-weight gain (mean of 4.2 g in exposed group vs. mean of 7.4 g in the control group, or a 43% decrease) and the mean weight of pups on PND 1 (mean of 1.54 g in exposed group vs. mean of 1.68 g in the control group, or an 8% decrease) were observed. No difference in pup weight between the exposed and control groups was observed on PND 3.

The results indicate that the only dose tested, 75 mg/kg-day, is a maternal LOAEL for decreased maternal-weight gain in CD-1 pregnant mice exposed by gavage to technical

toxaphene on GDs 8−12, and also a developmental LOAEL for decreased PND 1 pup body weight. No NOAEL could be determined.

Chernoff et al. (1990)

Groups of pregnant female S-D rats (~25/exposed group and ~50/control group) were administered technical toxaphene via gavage at doses 0 or 32 mg/kg-day on GDs 6−15. Technical toxaphene (purity 100%) was obtained from the U.S. EPA Chemical Repository (Research Triangle Park, NC) and mixed with 1.0 mL corn oil (vehicle). The animals were allowed free access to feed and water. Pregnancies were confirmed upon presence of sperm in a vaginal smear. The animals were monitored for weight loss, mortality, or for other overt signs of toxicity. Dams were weighed on GD 6 prior to administering the first dose and then every 2 days throughout the dosing period. A subset of animals from each group (4−6 exposed animals and 6−30 control animals) was sacrificed on GDs 8, 12, 16, and 20. Terminal body weights (on GD 20) were measured and corrected for gravid uteri weights. At each time point, thymus, spleen, and adrenal glands were removed and weighed. Developmental endpoints assessed on GD 20 included the number of pregnancies, number of litters and fetuses, and fetal survival and body weight. Half of each litter was fixed in formalin and examined for soft tissue anomalies. The remaining fetuses were cleared in potassium hydroxide (KOH) and stained for skeletal examination. The lateral and fourth ventricles as well as the renal pelvis lumina were scored on a scale of 1 (no visible space) to 4 (apparent hydrocephaly or hydronephorsis).

Decreased maternal survival was observed beginning after two exposures on GD 8 (86% survival compared with 100% in controls). By GDs 16 and 20, maternal survival dropped to ~50%, whereas 100% of control animals survived for the duration of the study. The causes of death were not explored. Body-weight gain data were presented as the difference between average body-weight gain of exposed groups and controls. At each time point examined within the exposure period (GDs 8, 12, and 16), exposed animals gained statistically significantly less weight (from study initiation to each time point) than the controls (−23.7, −48.5, and −55.2 g, respectively). No significant differences in maternal-weight gain (from study initiation) were observed at GD 20. Thymus, spleen, and adrenal organ weights in exposed dams were less than control values at scattered collection time points, but statistical significance was not consistent between time points and the reduced organ weights did not appear to be linked to exposure duration. No statistically significant differences were observed between the exposed and control groups in fetal mortality or body weight. No statistically significant differences between the control and exposed groups were found in the mean proportion of fetuses with fourth or lateral ventricle scores or left/right kidney scores >1.0. A statistically significant increase in the mean proportion of fetuses with supernumerary ribs, compared with controls, was reported. No other visceral or skeletal variations or anomalies in fetuses were reported to be induced from exposure. Litter or fetal incidence data for variations or anomalies were not specified in the available report.

The study results indicate a LOAEL of 32 mg/kg-day for increased mortality and decreased maternal-weight gain in pregnant S-D rats exposed to technical toxaphene via gavage during GDs 6−15. The single exposure level also was a developmental LOAEL for increased proportion of fetuses with supernumerary ribs, with no effects on fetal mortality and body weight or evidence for other visceral or skeletal variations or anomalies. No NOAEL could be determined.

Crowder et al. (1980)

Groups of S-D rats (three, presumably pregnant, females/group) were administered technical toxaphene (Boots-Hercules, Inc.; purity 99.9%) at doses of 0 or 6 mg/kg-day by gavage (in 0.1 mL corn oil) between GDs 7−21. F0 dams were gavaged once daily from Day 7 after introduction to males (presumed GD 7) through delivery of pups. The rats were caged in pairs until 2−3 days prior to giving birth, and then caged individually. The animals were given free access to food and water. Additional housing details were not provided. Body weight and mortalities of F1 pups (controls or exposed in utero) were recorded daily. Pups were evaluated for ontogeny of reflexes (grasp-hold reflex, righting reflex, and startle reflex) three times daily, beginning on PND 7. The ages at which the first responses occurred, and ages when 90% of the trials by the litter were positive, were recorded. Between 14−16 weeks-of-age, five male and five female F1 rats/group were chosen randomly for evaluation of learning and learning transfer abilities using maze testing. Each rat received 10 maze trials/day.

Offspring body weights and survival were reportedly similar between the exposed and control groups (data were not provided). No statistically significant differences in grasp-hold, startle reflexes, or in the mean number of days for observation of first correct righting reflex responses were observed in exposed pups, compared with controls. However, a statistically significant increase in the mean number of days for ≥90% of the trials to be positive in litters for the righting reflex was observed in the exposed group, compared with controls (18.5 days, exposed; 15.5 days, control). No statistically significant effects were found on maze learning or learning transfer, assessed between 14−16 weeks-of-age. The study authors concluded that there was no exposure-related impact on learning, and interpreted the additional time for exposed litters to master the righting reflex to be due to slight changes in motor function and behavior.

The study results indicate a developmental LOAEL of 6 mg/kg-day for delayed attainment of the righting reflex ability in offspring of female S-D rats exposed to technical toxaphene between GDs 7−21 (birth). This exposure level produced no effects on early postnatal development of grasp-hold, startle reflexes, maze learning, or learning transfer, as assessed between 14−16 weeks-of-age. No NOAEL could be determined.

Olson et al. (1980)

Groups of pregnant Holtzman albino rats (three/group) were fed diets delivering reported daily doses of 0 or 0.050 mg technical toxaphene/kg-day, 0.002 mg Toxicant A (p-42)/kg-day, or 0.002 mg Toxicant B (p-32)/kg-day from GD 5 through weaning and PND 30, in a study of neurobehavioral endpoints in the offspring that were exposed through PND 90. The animals were housed in stainless steel cages and allowed to acclimate for 5 days prior to initiation of the study. Food and water were available ad libitum. Test substances (sources and purities were not reported) were mixed into standard Purina Rat Chow; diets were prepared fresh every 1−2 weeks. Toxicant A and Toxicant B were presumably purified from technical toxaphene in the laboratory of one of the study authors (F. Matsumura), who published reports on separation techniques [Nelson and Matsumura (1975) and Matsumura et al. (1975), both cited in Olson et al. (1980)]. Sufficient quantities of Toxicant A were not available to sustain exposure past PND 40; the animals in this group were provided Toxicant B through the remainder of the study. Offspring were kept with their dams until PND 30, then housed in pairs until PND 45, at which time, the offspring were moved to individual cages for the remainder of the experiment. Offspring were kept in the same treatment groups as their mothers through PND 90, when

neurobehavioral testing was completed. All pups were tested for early development of swimming ability, and 15−16 offspring per group were administered maze tests.

Pup weights were recorded on PNDs 7, 10, 13, and 16. Between PNDs 7−17, tests of swimming ability and righting reflex were administered to all pups. A subjective scoring system from "0" through "4" was used for the swimming test: "0" indicated lack of swimming ability and "4" indicated mature swimming ability. For righting reflex, a score of "1" was assigned if the rat landed on all fours during the righting test, otherwise a score of "0" was given. Following these initial tests, 15 control animals (8 females and 7 males) and 16 exposed animals (8/sex), were randomly selected for symmetrical maze testing to evaluate motivational behavior, learning, and retention. Selected rats were first aged to PND 70; body weights were reduced to 80−85% of their recorded weight at PND 66, and weight reduction was maintained for the duration of the study. Behaviors analyzed for motivational testing included: the number of errors made before mastering a problem; the number of retraces or re-entries made into the "start" endbox; the sum of the trials necessary for the task to be mastered; and the cumulative time required to solve the problem. The animals were given 2 days of rest after completing the motivational test, then challenged with five more trials of the same problem to measure learning and retention. When behavioral tests were complete (PND 90), the animals were sacrificed. Liver, kidney, heart, lung, and brain were weighed and fixed for histological examination, along with tissues from thyroid, adrenal, stomach, small and large intestines, and bladder.

No exposure-related clinical signs or differences in offspring body weight between exposed and controlled animals were reported for technical toxaphene-, Toxicant A-, or Toxicant B-exposed groups. Histological examination revealed no significant changes in tissues for exposed groups, compared with controls. Exposed-group relative liver and kidney weights were reported comparable to controls (data were not provided). Delays in attaining the ability to swim were noted in all exposed groups on PNDs 10, 11, and 12, compared with controls, but swimming abilities in exposed offspring were comparable to controls by PNDs 13−16. Righting reflex ability between PNDs 7−17 was reported to be statistically significantly inferior to controls in technical toxaphene-exposed offspring, but not in Toxicant A- or Toxicant B-exposed offspring. However, these data were not provided and the magnitude of the apparent effect could not be evaluated. Thus, due to this incomplete reporting, the biological significance of exposure-related delays in swimming ability and righting reflex is unclear. Results from maze testing conducted between PNDs 70−90 indicated: (1) no significant differences between exposed and control groups in motivational endpoints (data not shown in the report), (2) no consistent differences between exposed and control groups in most measures of learning (see Table 1 of the study report), and (3) no consistent differences between exposed and control groups in most measures of retention (see Table 3 of the study report). The report discusses some of the possible implications of the few measures of maze learning or learning retention showing statistically significant differences among the groups, but most measures of performance were similar between exposed and control groups.

The results indicate NOAELs of 0.002 mg Toxicant A (p-42)/kg-day and 0.002 mg Toxicant B (p-32)/kg-day for the absence of clear biologically significant neurobehavioral effects, body-weight effects, or effects on tissue histology in Holtzman albino rat offspring exposed in utero, during lactation, and up to 90 days-of-age. No LOAELs can be identified. No NOAEL or LOAEL can be identified for technical toxaphene in this particular study due to incomplete reporting as described above.

Weathered Toxaphene

No oral-exposure developmental toxicity studies of weathered toxaphene in laboratory animals have been identified.

Toxaphene Congeners

The only oral developmental toxicity study of toxaphene congeners in laboratory animals identified was the study reported by Olson et al. (1980), which included tests of two individual toxaphene congeners (Toxicants A and B [p-42 and p-32]), in addition to technical toxaphene. Study methods and results for Toxicants A and B are included along with the methods and results for technical toxaphene in the study summary provided above. The results indicate NOAELs of 0.002 mg Toxicant A (p-42)/kg-day and 0.002 mg Toxicant B (p-32)/kg-day for the absence of clear biologically significant neurobehavioral effects, body-weight effects, or effects on tissue histology in Holtzman albino rat offspring exposed in utero, during lactation, and up to 90 days-of-age. No LOAELs can be identified.

Inhalation Exposures

No toxicity studies of any type have been identified for animals exposed by inhalation to technical toxaphene, weathered toxaphene, or individual toxaphene congeners.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Older Studies Identifying the Liver and Kidney as Toxicity Targets of Technical Toxaphene

A number of early animal toxicity studies reviewed by U.S. EPA (1985) and U.S. EPA (1980) reported finding liver or kidney effects following subacute or longer term repeated exposure to technical toxaphene in the diet, by gavage, or via capsules with food. However, primary reports of some of these older studies were not available for this assessment, and primary reports for others indicate inadequate designs or reporting. Effects reported in the shorter term studies included "questionable liver pathology" in male and female rats fed 50 or 200 ppm in the diet for 2−9 months (Ortega et al., 1957), "questionable liver pathology and renal tubular degeneration" in dogs given gavage doses of 4 mg/kg-day (in corn oil) for 44 or 106 days [Lackey (1949a) as cited in U.S. EPA (1980)], and no apparent adverse effects in rats fed 189 ppm in the diet for 12 weeks [Clapp et al. (1971) as cited in U.S. EPA (1980)]. Effects reported in longer duration studies included: "liver pathology" in rats fed 100 ppm in the diet, but not 25 ppm, for life [Lehman (1952a) as cited in U.S. EPA (1980)]; "liver pathology" in rats fed 25 ppm in the diet for life (Fitzhugh and Nelson, 1951); central nervous system (CNS) stimulation at concentrations of 1,000−1,600 ppm, "slight liver damage" at 100 ppm, and no effect at 25 ppm in rats fed toxaphene-containing diets for life [Hercules, Inc. updated as cited in U.S. EPA (1980)]; "moderate liver damage" at 200 ppm, "slight liver damage" at 40 ppm, and no effects at 5−20 ppm in dogs fed toxaphene-containing diets for life [Hercules, Inc. updated as cited in U.S. EPA (1980)]; "liver necrosis" in dogs fed encapsulated doses (in corn oil) of 5 mg/kg-day for 1,360 days [Hercules, Inc. updated as cited in U.S. EPA (1980)]; and no clinical or histological effects in monkeys fed 10−15 ppm in the diet for 2 years [Hercules, Inc. updated as cited in U.S. EPA (1980)].

Other reports of liver responses of unclear biological significance following oral exposure to technical toxaphene include (1) increased serum and liver activities of gamma-glutamyl transpeptidase (GGTP) in rats given single gavage doses of 110 mg/kg technical toxaphene (in mineral oil) or 16.5 mg/kg-day for 120 days (García and Mourelle, 1984)

and (2) increased (with time of exposure) mean relative liver weights and hepatic enzyme activities for androgen hydroxylases in rats of unspecified strain or sex given an oral dose of 0.24 mg/kg-day for up to 180 days (Peakall, 1976).

Genotoxicity and Mutagenicity

Results from short-term-duration tests of genotoxic, mutagenic, and clastogenic endpoints for technical toxaphene, weathered toxaphene, and several toxaphene congeners are summarized in Table 6.

Technical Toxaphene

In short-term-duration tests of technical toxaphene's mutagenicity in prokaryotes or nonmammalian eukaryotes, positive results were obtained with some species or strains (e.g., *Salmonella typhimurium* TA98 and TA100), but not in others (e.g., *S. typhimurium* TA1535 and TA1537), and mutagenic activity could be negatively affected by metabolic activation in some test strains or species (e.g., *Vibrio fischeri* M169). Technical toxaphene was mutagenic in several studies of *S. typhimurium* strains TA98 and TA100 with and without metabolic activation (see Table 6 for references), in *Escherichia coli* B/r strains WP2s and SR712 with and without activation (Houk and Demarini, 1987), in *V. fischeri* M169 without activation (but not mutagenic with activation) (Boon et al., 1998), and in *Neurospora crassa* strain H-59 (uvs-2) without metabolic activation (Brockman et al., 1983). Fractions of technical toxaphene (e.g., methanol fraction, hexane fraction, and a KOH-treatment of technical toxaphene) were also mutagenic in *S. typhimurium* TA100 without metabolic activation (Hooper et al., 1979). However, technical toxaphene was (1) not mutagenic with or without metabolic activation in *S. typhimurium* strains TA1535 and TA1537 (Mortelmans et al., 1986); (2) mutagenic without activation, but not mutagenic or equivocally mutagenic with activation, in strains TA97 and TA104 (Schrader et al., 1998); and (3) equivocally mutagenic without activation and not mutagenic with activation in strain TA102 (Schrader et al., 1998). Technical toxaphene-induced DNA damage in one assay (SOS chromotest) with *E. coli* PQ37, but not in another assay (*umu*C test) with *S. typhimurium* TA1535/pSK1002 (Bartos et al., 2005). Incubation of isolated DNA with technical toxaphene did not increase DNA breakage rates over control rates (Griffin and Hill, 1978).

Consistent evidence for genotoxic potential has not been demonstrated across a variety of in vitro and in vivo tests in mammalian species. In Chinese hamster V79 cells, technical toxaphene was mutagenic at the hypoxanthine-guanine phosphoribosyltransferase (HGPRT) locus, induced DNA strand breaks only in the presence of UV-B light, and did not markedly increase sister chromatid exchanges (SCEs) with or without metabolic activation from human HepG2 cells or induce unscheduled DNA synthesis above that induced by UV-B light (Schrader et al., 1998). Technical toxaphene increased SCEs in human lymphoid LAZ-007 with or without metabolic activation (Sobti et al., 1983) and in Chinese hamster lung (CHL) (Don) cells without metabolic activation (Steinel et al., 1990), but the responses were mostly less than twofold above control values. Technical toxaphene also induced micronuclei (MN) in primary beluga whale skin fibroblasts with or without metabolic activation (Gauthier et al., 1999) and in human HepG2 cells without metabolic activation (Wu et al., 2003). Technical toxaphene did not induce dominant lethal mutations in mice after single i.p. doses as high as 180 mg/kg or 5 days of gavage doses as high as 80 mg/kg-day (Epstein et al., 1972). Other short-term in vivo tests found no evidence for DNA damage (alkaline elution assay) in livers of rats after gavage administration of technical toxaphene doses of 12 or 36 mg/kg (Kitchin and Brown, 1994, 1989)

or increased DNA adducts in livers of mice administered seven daily gavage doses of technical toxaphene as high as 100 mg/kg-day (Hedli et al., 1998).

In summary, mutagenic activity and DNA damage from technical toxaphene has been demonstrated in some species and strains of nonmammalian prokaryotic and eukaryotic cells, but not in others. In mammalian test systems, technical toxaphene only induced HGPRT locus mutations and DNA strand breaks in cultured hamster cells also exposed to UV-B light, but did not induce SCEs in the absence of UV-B light. In other studies, technical toxaphene induced SCEs to a moderate degree in human lymphoid LAZ-007 cells and CHL cells, and induced MN in human HepG2 cells and beluga whale skin fibroblasts. In vivo tests with laboratory animals found no evidence for technical toxaphene induction of dominant lethal mutations, DNA damage, or DNA adducts. In addition to the lack of consistent evidence of the genotoxicity of technical toxaphene in various test systems, there is an absence of increased DNA breakage rates when technical toxaphene is incubated with isolated DNA samples (Griffin and Hill, 1978).

Weathered Toxaphene

Possible genotoxicity, mutagenicity, and clastogenicity of weathered toxaphene has been examined in two studies in bacteria. Weathered toxaphene samples (toxaphene residues extracted from fish, from a contaminated site, and toxaphene residues extracted from soil aged with technical toxaphene for 104 weeks) were mutagenic in *S. typhimurium* strain TA100 with and without metabolic activation, similar to unweathered samples of technical toxaphene (Young et al., 2009). In the other genotoxicity study with "weathered" toxaphene samples, DNA damage detected by the *umu*C assay in *S. typhimurium* TA1535/pSK1002 was found after exposure to technical toxaphene treated with UV light for up to 9 hours, but was not detected after exposure to nontreated technical toxaphene (Bartos et al., 2005).

Toxaphene Congeners

A few studies in bacteria have found no consistent evidence for mutagenicity of toxaphene congeners. No definitive increased mutagenic activities (compared with controls) were detected with or without metabolic activation in *S. typhimurium* TA100 exposed to p-26, p-32, p-62, or p-32 (Steinberg et al., 1998); in *S. typhimurium* TA1535, TA1537, TA1538, TA98, or TA100 exposed to heptachlorobornane-I (p-32) (Hooper et al., 1979); or in *V. fischeri* M169 exposed to p-26, p-50, p-62, or a synthetic mixture of p-32, p-26, p-50, and p-62 (Boon et al., 1998). However, in the Mutatox® assay with *V. fischeri* M169, p-32 alone induced mutations (Boon et al., 1998). Other genotoxicity studies using toxaphene congeners were not available.

Table 6. Summary of Genotoxicity and Mutagenicity Studies for Technical Toxaphene, Weathered Toxaphene, and Toxaphene Congeners

Endpoint	Test System	Doses/Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Studies in prokaryotic organisms						
Technical toxaphene						
Mutation	*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537	0, 100, 333, 1,000, 3,333, 6,666, 10,000 µg/plate	+ TA98, TA100 – TA1535, TA1537	+ TA100, TA98 – TA1535, TA1537	Plate incorporation assay (S9 activation): Precipitate was noted at ≥1,000 µg/plate. Reproducible dose-related increases were considered a positive response even if the increase was <twofold.	Mortelmans et al. (1986)
Mutation	*S. typhimurium* strains TA98 and TA100	0, 500, 1,000, 2,000, 3,000 µg/plate	+ TA98, TA100	± TA100 ND TA98	The mutagenicity of toxaphene was decreased by 50% in TA100 with the addition of S9 activation.	Hooper et al. (1979)
Mutation	*S. typhimurium* strains TA98 and TA100	0, 156.25, 312.5, 625, 1,250, 2,500, 5,000, 10,000 µg/plate	+	ND	Plate incorporation assay: induction of revertants was observed at all concentrations in TA100, but only at 10,000 µg/plate in TA98.	Steinberg et al. (1998)
Mutation	*S. typhimurium* strains TA98 and TA100	0, 156.25, 312.5, 625, 1,250, 2,500, 5,000, 10,000 µg/mL	+ TA100 – TA98	ND	Microsuspension-modified preincubation assay: 68, 110, and 190% increase in revertants was observed at 2,500, 5,000, and 10,000 µg/mL, respectively, in TA100.	Steinberg et al. (1998)
Mutation	*S. typhimurium* strains TA97, TA98, TA100, TA102, and TA104	0, 10, 100, 500, 1,000, 5,000, 10,000 µg/plate	± TA102 + TA97, TA98, TA100, TA104	+ TA100, TA98 ± TA104 – TA97, TA102	Plate incorporation assay: Induction of revertants was observed in all strains without S9 activation, and a two- to threefold increase in the number of revertants was observed in TA98 and TA100 at ≥500 µg/plate. The number of revertants was reduced by ≥50% in TA98 and TA100 with the addition of S9 metabolic activation.	Schrader et al. (1998)

Table 6. Summary of Genotoxicity and Mutagenicity Studies for Technical Toxaphene, Weathered Toxaphene, and Toxaphene Congeners

Endpoint	Test System	Doses/Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Mutation	*S. typhimurium* strain TA100	0, 100, 200, 500, 1,000 µg/plate	+	+	Ames test (S9 activation): Data expressed as number of revertants per plate (after correction for the solvent blank). Number of revertants increased with increasing TT dose.	Young et al. (2009)
Mutation (λ-prophage induction)	*Escherichia coli* B/r strains $WP2_s$ (λ) and SR712 (*trpE, uvrD*$_3$)	0, 0.10, 0.19, 0.38, 0.76, 1.52, 3.05, 6.10, 12.2 mM	+	+	Precipitate was observed at the highest dose. The minimum TT concentrations required to produce a significant positive response at the 99% CI were 1.26 and 0.13 mM, in the presence and absence of S9 activation, respectively. Prophage induction increased with increasing dose.	Houk and Demarini (1987)
Mutatox® assay	*Vibrio fischeri* M169	0.0083−4.23 mg/L	+	−	Light levels were measured at 1-hr intervals from 10−24 hr after incubation; the concentration that gave the CMR determined from the dose-response curve. LOEC = 3.15 mg/L; CMR ≥4.23 mg/L[c] Metabolic activation with S9.	Boon et al. (1998)
Mutation	*S. typhimurium* strain TA100 (ethanolic KOH treatment of toxaphene [1:1 or 1:10 molar ratio; 24 hr at 25°C])	NR	+	ND	Reversion data not reported.	Hooper et al. (1979)

Table 6. Summary of Genotoxicity and Mutagenicity Studies for Technical Toxaphene, Weathered Toxaphene, and Toxaphene Congeners

Endpoint	Test System	Doses/Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Mutation	*S. typhimurium* strain TA100 (fractionated toxaphene: methanol, hexane, and recrystallized from isopropanol)	100−3,000 µg/plate	+ Mother liquor fraction + Methanol fraction + Hexane fraction ± Recrystallized	ND	Revertants: Mother liquor = 500 rev/mg Methanol = 2,640 rev/mg Hexane = 200 rev/mg Recrystallized = 116 rev/mg	Hooper et al. (1979)
DNA damage (SOS chromotest)	*E. coli* PQ37	0, 2.5, 5.0, 10.0, 20, 40.0 mg/L	+	ND	SOS induction factor was >1.5 at TT concentrations ≥10 mg/L.	Bartos et al. (2005)
DNA damage (*umu*C test)	*S. typhimurium* strain TA1535/pSK1002	0, 2.5, 5.0, 10.0, 40.0 mg/L	−	ND	A nonsignificant, dose-dependent increase in β-galactosidase activity was observed at 2.5−40.0 mg/L.	Bartos et al. (2005)
Weathered toxaphene						
Mutation	*S. typhimurium* strain TA100 exposed to TT or a soil-weathered TT sample	0, 100, 200, 500, 1,000 µg toxaphene/plate (aged soil extract)	+	+	Revertant colonies were slightly increased with the addition of S9. The number of revertants/µg toxaphene was also plotted. Weathered and TT were similarly mutagenic. Hx-Sd and Hp-Sd represented 8.7 and 5.7%, respectively, of the total residual toxaphene in soil aged for 104 wk.	Young et al. (2009)

Table 6. Summary of Genotoxicity and Mutagenicity Studies for Technical Toxaphene, Weathered Toxaphene, and Toxaphene Congeners

Endpoint	Test System	Doses/Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Mutation	*S. typhimurium* strain TA100 exposed to toxaphene residues extracted from fish collected at a contaminated site	Approximate doses from fish tissue extract of 0, 150, 320, 380, 800, and 900 µg toxaphene/plate	+	+	The data were expressed as revertants/µg residual toxaphene. Hx-Sd and Hp-Sd represented 19.5 and 14.6% of residual toxaphene found in fish collected from a contaminated site. Weathered and TT displayed similar mutagenicity. An initial increase followed by a decrease in the number of revertants was observed with increasing concentration in the presence of S9. The number of revertants increased with increasing dose in the absence of S9.	Young et al. (2009)
DNA damage (*umu*C test)	*S. typhimurium* strain TA1535/pSK1002 exposed to irradiated TT or TT	0, 7.5, 15, 30, 60 mg/L	+	ND	Toxaphene irradiated with UV for 6 and 9 hr inhibited bacterial growth at >60 mg/L (−78.8%); after 9-hr growth inhibition was observed at 30 mg/L (−85.2%) and at 60 mg/L (−100%). *β*-Galactosidase activity was increased at 15 mg/L (9-hr irradiation) and 30 mg/L (6-hr irradiation) by 3.2- and 2.4-fold, respectively. The abundance of toxaphene congeners decreased with UV radiation time. TT without irradiation did not induce *β*-galactosidase activities beyond 1.5-fold of control values.	Bartos et al. (2005)
Toxaphene congeners						
Mutation	*S. typhimurium* strains TA98 and TA100 (p-26, p-50, p-62, and p-32)	0, 312.5, 625, 1,250, 2,500 µg/plate	−	−	Microsuspension modified Ames test (S9 activation).	Steinberg et al. (1998)

Table 6. Summary of Genotoxicity and Mutagenicity Studies for Technical Toxaphene, Weathered Toxaphene, and Toxaphene Congeners

Endpoint	Test System	Doses/Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Mutation	*S. typhimurium* strain TA100 (p-26, p-50, p-62, and p-32)	0, 156.25, 312.5, 625, 1,250, 2,500, 5,000, 10,000 µg/plate	−	−	p-26 induced an increase in the number of revertants only at 10,000 µg/plate (20%). p-50 induced increases in the number of revertants only at 156.25 and 5,000 µg/plate (29 and 15−22%, respectively). Precipitation of p-26, p-50, and p-32 was observed at 10,000 µg/plate.	Steinberg et al. (1998)
Mutation	*S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 (heptachlorobornane-I = p-32)	100−2,000 µg/plate	−	−	NA	Hooper et al. (1979)
Mutatox® assay	*V. fischeri* M169 (p-32)	9.87−1,500 µg/L	+	−	Light levels were measured at 1-hr intervals from 10−24 hr after incubation; the concentration that gave the CMR determined from the dose-response curve. LOEC = 580 µg/L; CMR = 770 µg/L[c] Metabolic activation with S9.	Boon et al. (1998)
Mutatox® assay	*V. fischeri* M169 (p-26, p-50, p-62)	9.87−1,500 µg/L	−	−	p-26, p-50, and p-62 were assayed individually with negative results without and with S9 activation.	Boon et al. (1998)
Mutatox® assay	*V. fischeri* M169 (T-4 mix)	9.87−1,500 µg/L	−	−	p-32, p-26, p-50, and p-62 were assayed as a mixture with negative results without and with S9 activation.	Boon et al. (1998)

Table 6. Summary of Genotoxicity and Mutagenicity Studies for Technical Toxaphene, Weathered Toxaphene, and Toxaphene Congeners

Endpoint	Test System	Doses/Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Studies in nonmammalian eukaryotic organisms						
Technical toxaphene						
Mutation (ad-3 forward mutation test)	*Neurospora crassa* H-12(uvs-2$^+$) and H-59(uvs-2)	Five concentrations (NR)	+ H-59(uvs-2)	ND H-59(uvs-2)	Toxaphene induced multilocus deletions (~20%) and intracistronic mutations (~40%) in H-59(uvs-2).	Brockman et al. (1983)
Studies in mammalian cells—in vitro						
Technical toxaphene						
Mutation (HGPRT)	Chinese hamster V79 cells	0, 1, 2, 3, 4, 5, 6, 7.5, 10 µg/mL	−	−	Metabolic activation with γ-irradiated human HepG2 cells.	Schrader et al. (1998)
Mutation (HGPRT)	Chinese hamster V79 cells exposed to TT and UV-B light	0.001−1.0 µg/mL	+	+	V79 cells were preincubated with TT and exposed to 5 J/m^2 UV-B light, resulting in a dose-dependent increase in HGPRT mutations, up to a twofold maximum (1 µg/mL), over cells exposed to UV-B radiation alone.	Schrader and Langlois (1999)
SCE	Chinese hamster V79 cells	0, 1, 2, 3, 4, 5, 6, 7.5, 10 µg/mL	−	−	Metabolic activation with γ-irradiated human HepG2 cells. Although small increases in SCE were observed in some exposed groups, no consistent and marked TT-induced increases in SCE were observed. Positive control groups exposed to ethylmethane-sulfonate without activation or dimethylbenz[a]anthracene with activation showed three- to fourfold increases in SCE frequencies.	Schrader et al. (1998)
Unscheduled DNA synthesis	Chinese hamster V79 cells and human HepG2 cells	NR; 0.001−1.0 µg/mL (presumably)	−	−	TT had no effect on excision repair of UV-B damage.	Schrader and Langlois (1999)

Table 6. Summary of Genotoxicity and Mutagenicity Studies for Technical Toxaphene, Weathered Toxaphene, and Toxaphene Congeners

Endpoint	Test System	Doses/Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
DNA damage and repair	Chinese hamster V79 cells	0.001−1.0 µg/mL	+	+	DNA strand breakage was increased in UV-B exposed cells when preincubated with TT in a dose-dependent manner.	Schrader and Langlois (1999)
SCE	Human lymphoid LAZ-007 cells	10^{-4}, 10^{-5}, 10^{-6} M	+	+	TT induced increased SCE frequency by 59 and 81% (−S9) and 44 and 54% (+S9) at low and high doses, respectively.	Sobti et al. (1983)
SCE	CHL (Don) cells	0, 5, 10, 15, 20 µg/mL	+	ND	Cells were incubated for 18, 22, or 26 hr in media containing TT and 10 µM BrdU, and then for an additional 2.5 hr in fresh media containing colcemid for SCE and metaphase analysis. SCEs increased significantly in both a dose- and time-dependent manner.	Steinel et al. (1990)
Mammalian cytokinesis-block MN assay	Primary beluga whale skin fibroblasts	0, 0.05, 0.5, 5, 10 µg/mL	+	+ (at 0.5 µg/mL) − (0.05, 5, and 10 µg/mL)	In the absence of S9, mean MN cell frequency significantly increased at all doses, ranging from a 1.7- to a 3.6-fold increase at 10 µg/mL. In the presence of S9, a statistically significant increase in MN cells was observed at 0.5 µg/mL, but then decreased as dose increased from 0.5−10 µg/mL.	Gauthier et al. (1999)

Table 6. Summary of Genotoxicity and Mutagenicity Studies for Technical Toxaphene, Weathered Toxaphene, and Toxaphene Congeners

Endpoint	Test System	Doses/Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
MN assay	Human HepG2 cells	0, 5, 10, 20, 40 µM	+	ND	MN frequencies increased with increasing concentration. At 20 and 40 µM increases of 64 and 105% (compared with controls) were observed. When HepG2 cells were pretreated with 5, 10, 20, or 40 µM TT then exposed to 50 µM BaP, the genotoxicity of BaP alone was increased by 34 and 56% at 10 and 20 µM; results at 40 µM were considered questionable due to significant cytotoxicity.	Wu et al. (2003)
Studies in mammals—in vivo						
Technical toxaphene						
Dominant lethal mutagenicity	Male ICR/Ha Swiss mice (7 and 9/group in the low- and high-dose groups, respectively) were administered a single i.p. injection of toxaphene. Exposed males were then mated to unexposed females for 8 wk following treatment. Females were sacrificed 13 d after the middle of their breeding period, and uteri were examined	0, 36, 180 mg/kg	−	−	2 mortalities (2 males out of 9 total) were observed at 180 mg/kg. TT did not significantly increase incidences of early fetal deaths/pregnancy or preimplantation losses over that observed in controls. Corpora lutea counts were not conducted: decreases in total implants were determined by contrasting total implants of females mated with control and treated males.	Epstein et al. (1972)

Table 6. Summary of Genotoxicity and Mutagenicity Studies for Technical Toxaphene, Weathered Toxaphene, and Toxaphene Congeners

Endpoint	Test System	Doses/Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Dominant lethal mutagenicity	Male ICR/Ha Swiss mice (7−9/group) were administered toxaphene via i.p. or gavage for 5 d. Exposed males were then mated to unexposed females for 8 wk. Females were sacrificed 13 d after the middle of their breeding period, and uteri were examined	0, 40, 80 mg/kg	−	−	TT did not significantly increase incidences of early fetal deaths/pregnancy or preimplantation losses over that observed in controls. Corpora lutea counts were not conducted: decreases in total implants were determined by contrasting total implants of females mated with control and treated males.	Epstein et al. (1972)
DNA damage	Female S-D rats (8/group) were administered 2 doses of toxaphene (in corn oil) via gavage at 21 and 4 hr before sacrifice. Livers were collected and prepared for the following assays: DNA alkaline elution, ODC, glutathione activity, CYP450, and serum ALT	0, 12 mg/kg	−	−	TT did not induce hepatic DNA damage (although ODC activity and CYP450 were increased).	Kitchin and Brown (1989)
DNA damage (alkaline elution)	90-d-old female S-D rats (8−9/group) were administered 2 doses of toxaphene (in 1:1:1 mixture of Tween 80, Triton X-100, and DMSO) via gavage at 21 and 4 hr before sacrifice	0, 12, 36 mg/kg	−	−	Endpoints assessed included ODC activity, ALT activity, and hepatic DNA damage by alkaline elution. Hepatic CYP450 content and Ames test results from other studies were included in the study report's data table.	Kitchin and Brown (1994); Kitchin et al. (1992)

Table 6. Summary of Genotoxicity and Mutagenicity Studies for Technical Toxaphene, Weathered Toxaphene, and Toxaphene Congeners

Endpoint	Test System	Doses/Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
DNA adducts (^{32}P-post labeling)	Male CD-1 mice (3−4/group) were exposed to toxaphene in corn oil by gavage for 7 consecutive d. Mice were sacrificed 24 hr after final dosing and DNA was extracted from livers	0, 10, 25, 50, 100 mg/kg	−	−	DNA adducts in liver DNA were measured using nuclease-P1 or butanol enhancements of the ^{32}P-postlabeling method. No evidence of DNA adduct formation was found in treated or control mice.	Hedli et al. (1998)
Studies in subcellular systems						
Technical toxaphene						
DNA damage	ColE1 plasmid DNA isolated from *E. coli* K-12 strain CR34 thy$^-$ B1$^-$ thr$^-$ leu$^-$	0.1 mg/mL	−	−	No increase in DNA breakage rates compared with controls was observed.	Griffin and Hill (1978)

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive; ± = weakly positive; − = negative.
[c]Boon et al. (1998) did not clearly define a positive result, but a fourfold increase in bioluminescence is often taken as a positive response with the Mutatox® assay.

ALT = alanine aminotransferase; BaP = benzo[a]pyrene; BrdU = bromodeoxyuridine; CHL = Chinese hamster lung; CI = confidence interval; CMR = calculated maximum response; CYP450 = cytochrome P450; DMSO = dimethylsulfoxide; DNA = deoxyribonucleic acid; HGPRT = hypoxanthine-guanine phosphoribosyltransferase; Hp-Sd = heptachlorobornane; Hx-Sd = hexachlorobornane; i.p. = intraperitoneal; KOH = potassium hydroxide; LOEC = lowest-observed-effect concentration; MN = micronuclei; NA = not applicable; ND = no data; NR = not reported; ODC = ornithine decarboxylase; SCE = sister chromatid exchange; S-D = Sprague-Dawley; TT = technical toxaphene; UV = ultraviolet.

Metabolism/Toxicokinetic Studies for Technical Toxaphene

Results from laboratory animal studies indicate rapid and extensive absorption of technical toxaphene by the GI tract, metabolic dechlorination of absorbed toxaphene congeners, and extensive and fairly rapid elimination of metabolites in the urine and feces [see ATSDR (2014) for a more comprehensive review of toxicokinetic data]. For example, oral administration of single doses of 20 mg/kg ^{36}Cl-labeled technical toxaphene in rats resulted in excretion of about 52.6% of the administered radioactivity within 9 days in feces (37.3%) and urine (15.3%) (Crowder and Dindal, 1974). In another study that administered single doses of 14.2 mg/kg ^{36}Cl-labeled technical toxaphene to rats, 14-day urine and feces contained 49.1 and 26.9% of the administered ^{36}Cl-radioactivity, respectively (Ohsawa et al., 1975). Considerable amounts of radioactivity in the collected excreta in these studies was in the form of chloride ions, providing evidence for extensive metabolic dechlorination of congeners in technical toxaphene. A comparison of ^{36}Cl-radioactivity eliminated in urine following Na^{36}Cl or ^{36}Cl-toxaphene administration indicated similar elimination half-lives of 2−3 days (Ohsawa et al., 1975). Following oral administration of single doses of ^{14}C-labeled technical toxaphene to rats, 14-day urine and feces contained 31.8 and 27.1% of the administered radioactivity, respectively (Ohsawa et al., 1975). Solvent fractionation analysis indicated that about 57 and 39% of urine- and feces-^{14}C radioactivity, respectively, were in the form of partially dechlorinated metabolites (Ohsawa et al., 1975).

DERIVATION OF PROVISIONAL VALUES

Tables 7 and 8 present summaries of noncancer and cancer reference values, respectively, for technical toxaphene derived in this document. For weathered toxaphene or individual toxaphene congeners, data were inadequate to derive noncancer provisional reference values, for either oral or inhalation exposure. Appendix A discusses some options for deriving screening provisional values for weathered toxaphene.

No effort was made to derive provisional cancer values for technical toxaphene because a cancer oral slope factor (OSF), inhalation unit risk (IUR), and an associated weight-of-evidence (WOE) determination for technical toxaphene is currently on the U.S. EPA IRIS website (U.S. EPA, 1988a). Data for weathered toxaphene or individual toxaphene congeners are inadequate for assessing their possible carcinogenicity.

Table 7. Summary of Noncancer Reference Values for Technical Toxaphene (CASRN 8001-35-2)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD (HED)	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Rat/M	Cytoplasmic vacuolation in the thyroid	3×10^{-4}	$BMDL_{10}$	0.0092	30	Chu et al. (1988)
Chronic p-RfD (mg/kg-d)	Rat/M	Cytoplasmic vacuolation in the thyroid	9×10^{-5}	$BMDL_{10}$	0.0092	100	Chu et al. (1988)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

$BMDL_{10}$ = 10% benchmark dose lower confidence limit; HED = human equivalent dose (in mg/kg-day); M = male(s); NDr = not determined; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; POD = point of departure; UF_C = composite uncertainty factor.

Table 8. Summary of Cancer Reference Values for Technical Toxaphene (CASRN 8001-35-2)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	An OSF value is available on IRIS (U.S. EPA, 1988a)[a]			
p-IUR $(mg/m^3)^{-1}$	An IUR value is available on IRIS (U.S. EPA, 1988a)[a]			

[a]Value based on increased incidence of hepatocellular tumors in mice and thyroid tumors in rats following oral exposure.

IRIS = Integrated Risk Information System; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of a Subchronic Provisional Reference Dose

The rat study designed to evaluate reproductive toxicity by Chu et al. (1988) is selected as the principal study for deriving the subchronic provisional reference dose (p-RfD) for technical toxaphene, with rationale provided below. The critical effect is cytoplasmic vacuolation (all severity grades) in the thyroid of F0 male S-D rats following 25−29 weeks of dietary exposure. The study report was published in a peer-reviewed journal. The study is adequate with regard to design (e.g., inclusion of controls and several exposure levels) and performance pertaining to examination of potential toxicity endpoints, and presentation of materials, methods, and results. Details of the study are provided in the "Review of Potentially Relevant Data" section. No pertinent toxicity data were identified for laboratory animals repeatedly exposed orally to weathered toxaphene or toxaphene congeners.

Convulsions (presumably from effects on the nervous system) are the most common effect reported in acute poisoning case reports. A limited number of epidemiological studies have examined possible associations between occupational exposure to technical toxaphene and noncancer diseases. In U.S. male pesticide applicators, self-reported hypothyroidism was associated with "ever-use" of 50 specific insecticides (including technical toxaphene) (Goldner et al., 2013), but no statistically significantly elevated ORs were found for amyotrophic lateral sclerosis and "ever-use" of any of the subject pesticides, including technical toxaphene (Kamel et al., 2012). Additionally, a statistically significant exposure-response trend in association with rheumatoid arthritis was observed for lifetime days of toxaphene use (Meyer et al., 2017).

Results from several short-term- and subchronic-duration oral toxicity studies, as well as two oral reproductive toxicity studies and a number of oral developmental toxicity studies, identify the liver, kidney, thyroid, and immune system (including spleen and thymus) as sensitive noncancer toxicity targets of repeated exposure to technical toxaphene. LOAELs in Table 5A for systemic effects induced by oral exposure to technical toxaphene range from 0.2−4.5 mg/kg-day for increased liver weight and liver, kidney, and thyroid lesions in 13-week dietary studies in rats and dogs (Chu et al., 1986) and a single-generation reproductive toxicity study in rats (Chu et al., 1988) to 7.3 mg/kg-day for increased absolute and relative liver weight (≥10%) (14-day dietary study), or 60.3 mg/kg-day for increased absolute and relative liver weight (≥10%), serum ALT activities, hepatic cell proliferation rates, and liver MDA concentrations in mice (28-day dietary study) (Wang et al., 2015).

Immune system noncancer effects from oral exposure to technical toxaphene are examined in multiple species, and several LOAELs were identified (see Table 5A). In cynomolgus monkeys, a LOAEL of 1 mg/kg-day was identified for decreased IgG and IgM responses to SRBCs, as well as changed proportions of lymphocytes in females administered technical toxaphene in gelatin capsules for 52 weeks (Arnold et al., 2001; Bryce et al., 2001; Tryphonas et al., 2000), as well as LOAELs of 0.4 mg/kg-day in females and 0.8 mg/kg-day in males for decreased IgM responses to SRBCs in a 75-week study of cynomolgus monkeys administered encapsulated technical toxaphene (Arnold et al., 2001; Tryphonas et al., 2001). Additionally, a LOAEL of 2.6 mg/kg-day was identified for transient decreased IgG responses to keyhole limpet hemocyanin (KLH) in male rats fed dietary technical toxaphene for 9 weeks (Koller et al., 1983), and a LOAEL of 19.1 mg/kg-day was identified for decreased IgG response to bovine serum albumin (BSA) in mice fed dietary technical toxaphene for 8 weeks (Allen et al., 1983).

NOAELs in Table 5A for reproductive toxicity from oral exposures of laboratory animals to technical toxaphene are higher than the lowest LOAELs for liver, kidney, thyroid, or immune system effects. The reproductive NOAELs are: 45 (males) and 46 mg/kg-day (females) in a one-generation rat study (Chu et al., 1988); 6.88 (males) and 7.99 mg/kg-day (females) in a multiple-generation rat study (Kennedy et al., 1973); and 4.7 (males) and 5.1 mg/kg-day (females) in a multiple-generation mouse study (Keplinger et al., 1970).

LOAELs in Table 5A for developmental effects from oral gestational exposure of laboratory animals to technical toxaphene also are higher than the lowest LOAELs for liver, kidney, thyroid, or immune system effects. Developmental LOAELs for technical toxaphene

(given by gavage, unless otherwise noted) in rats are as follows: 15 mg/kg-day for decreased number of sternal, but not caudal, ossification centers in fetuses exposed on GDs 7−16 (Chernoff and Carver, 1976); 32 mg/kg-day for increased proportion of fetuses with supernumerary ribs in fetuses exposed on GDs 6−15 (Chernoff et al., 1990); and 6 mg/kg-day for delayed attainment of righting reflex in offspring exposed on GDs 7−21 (Crowder et al., 1980). Developmental LOAELs identified in mice included: 75 mg/kg-day for decreased body weight on PND 1, but not on PND 3, in pups of mice exposed on GDs 8−12 (Chernoff and Kavlock, 1983), and 1.9 mg/kg-day for suppression of SRBC phagocytosis by macrophages (one of three evaluated immune responses) in offspring of mice exposed to dietary technical toxaphene for 3 weeks before mating and continuing throughout gestation and lactation (Allen et al., 1983).

Justification

Looking at the laboratory animal oral toxicity database as a whole, degenerative changes to the liver and kidney are relatively consistent findings across a range of technical toxaphene exposure levels tested (see Table 5A). In the 28-day rat study by Wang et al. (2015), the effects on the liver endpoints evaluated (e.g., relative liver weight, hepatocyte cell proliferation rates, serum ALT) were mostly confined to the highest exposure group evaluated, 60.3 mg/kg-day (human equivalent dose [HED] = 8.51 mg/kg-day), which reportedly produced no histological evidence for liver regenerative hyperplasia or hepatocyte necrosis. No changes in any of these endpoints occurred in rats exposed to 5.9 mg/kg-day (HED = 0.85 mg/kg-day) (Wang et al., 2015). Increased relative liver weight was biologically significant (≥10% increase), but not statistically significant in female Beagle dogs at 0.2 mg/kg-day (HED = 0.1 mg/kg-day), the lowest dose tested. With respect to technical toxaphene-induced kidney toxicity, although the Chu et al. (1986) and Chu et al. (1988) studies identified kidney lesions in rats that were primarily minimal to mild in severity at the lowest doses tested, no histological changes in the kidney were observed following subchronic exposure in other studies of rats (Koller et al., 1983) and mice (Allen et al., 1983).

Identification of immune suppression as a health hazard from repeated oral exposure to technical toxaphene comes from several reports on experiments conducted in cynomolgus monkeys that exhibited decreased immunoglobulin responses to SRBC, as well as spleen and thymus effects, at low doses (0.4 mg/kg-day; HED = 0.2 mg/kg-day) (Arnold et al., 2001; Bryce et al., 2001; Tryphonas et al., 2000). This is supported by observations of decreased ability of macrophages to engulf SRBCs in 8-week postweaning offspring of Swiss-Webster mice exposed to dietary technical toxaphene (1.6 mg/kg-day) 3 weeks before mating, and throughout gestation and lactation and decreased IgG response to BSA in adult male Swiss-Webster mice exposed to 19.1 mg/kg-day dietary toxaphene for 8 weeks (Allen et al., 1983), and transiently decreased IgG responses to KLH in male S-D rats exposed to technical toxaphene dietary doses of 2.6 and 25.8 mg/kg-day (Koller et al., 1983).

There is ample evidence suggesting that thyroid toxicity is a relevant and sensitive response following exposure to technical toxaphene. In a study of U.S. male pesticide applicators and "ever-use" of 50 specific insecticides, technical toxaphene was associated with increased ORs of self-reported hypothyroid disease, showing an association at low exposure (based on intensity-weighted cumulative days of use), but not high exposure (Goldner et al.,

2013). When 11 moderately correlated pairs of pesticides were analyzed by logistic regression models in this study, the association between technical toxaphene and hypothyroidism remained statistically significant, and associations with the other pesticides and hypothyroid disease were reduced. Evidence from animal studies is coherent with the human study indicating effects in the thyroid. In animal studies, increased incidences of a variety of histopathologic lesions were observed in the thyroid of both male and female rats across different life stages (i.e., in adult F0 and F1 animals) following subchronic and chronic dietary exposure to low doses (HEDs = 0.10−0.47 mg/kg-day) of technical toxaphene (Chu et al., 1988; Chu et al., 1986). Additionally, increased incidences of thyroid histopathology as well as increased TSH serum levels were observed in a short-term-duration (28-day) gavage study in rats, albeit at a significantly higher dose (HED = ~19 mg/kg-day) (Waritz et al., 1996). Finally, the NCI (1979) chronic-duration study found elevated incidences of thyroid tumors in technical toxaphene exposed rats, although no elevated incidences of non-neoplastic lesions were observed in any tissue in the exposed groups (NCI, 1979).

To provide a common basis for comparing potential points of departure (PODs) and critical effects for a subchronic p-RfD for technical toxaphene (i.e., comparing benchmark dose [BMD] and benchmark dose lower confidence limits [BMDLs] among the most sensitive endpoints), data sets from studies in Table 5A with multiple exposure levels for liver, kidney, thyroid, and immune effects were selected for BMD analysis. In addition, three liver-endpoint data sets were selected from the most recent repeated-dose oral toxicity study in mice for comparison purposes [Wang et al. (2015); relative liver weight, serum ALT, and liver cell proliferation rates]. Details regarding modeling procedures and detailed BMD modeling results are presented in Appendix C. For BMD modeling of several of the selected data sets for liver, kidney, and thyroid lesions observed in rat studies by Chu et al. (1988) and Chu et al. (1986), the sum of incidences of minimal-to-mild and moderate-to-severe severity grades were statistically significantly increased at the lowest dose tested. However, many of these data sets were difficult to model primarily because the responses at the lowest exposure levels for each of these data sets were considered far in excess of the benchmark response (BMR), or had near maximal responses, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD. Thus, the resultant BMDs and BMDLs for several endpoints were considered unreliable, and LOAELs or NOAELs were selected as PODs for many of the Chu et al. (1986) and Chu et al. (1988) rat data sets to compare with potential PODs from the other selected data sets.

Table 9 summarizes the BMD modeling results for endpoints associated with each of the aforementioned sensitive toxicity targets following exposure to technical toxaphene to identify potential PODs (expressed as HEDs) for the derivation of the subchronic p-RfD.

Table 9. Candidate Principal Studies and PODs for the Derivation of the Subchronic p-RfD

Endpoint/Reference	NOAEL (HED)[a] (mg/kg-d)	LOAEL (HED)[a] (mg/kg-d)	BMDL (HED)[a] (mg/kg-d)	Selected POD (HED) (mg/kg-d)	Comments
Immune Effects					
Decreased mean primary anti-SRBC IgM response in female cynomolgus monkeys (1-wk postimmunization), 75 wk (Tryphonas et al., 2001)[b]	0.05	0.2	0.02	0.02 ($BMDL_{1SD}$)	NA
Kidney Effects					
Primary tubular injury (all severity grades) in the kidney of male S-D rats, 13 wk (Chu et al., 1986)[c]	0.090	0.46	0.020	0.020 ($BMDL_{10}$)	NA
Tubular necrosis (all severity grades) in the kidney of male S-D rats, 13 wk (Chu et al., 1986)[c]	0.090	0.46	0.045	0.045 ($BMDL_{10}$)	NA
Tubular necrosis (only minimal to mild observed) in the kidney of female S-D rats, 13 wk (Chu et al., 1986)[c]	NDr	0.11	0.0012	0.11 (LOAEL)	Model fit obtained after dropping 2 high doses, but not considered reliable due to lack of data point near the BMR (see Appendix C)
Primary tubular injury (all severity grades) in the kidney of F0 male S-D rats, 25−29 wk (Chu et al., 1988)[d]	NDr	0.10	DUB	0.10 (LOAEL)	No models provided adequate fit to data; lacks dose-response
Primary tubular injury (all severity grades) in the kidney of F0 female S-D rats, 25−29 wk (Chu et al., 1988)[d]	0.083	0.44	0.088	0.088 ($BMDL_{10}$)	NA
Thyroid Effects					
Reduced colloid density (moderate to severe) in the thyroid of male S-D rats, 13 wk (Chu et al., 1986)[c]	0.090	0.46	0.013	0.013 ($BMDL_{10}$)	NA
Reduced colloid density (all severity grades) in the thyroid of female S-D rats, 13 wk (Chu et al., 1986)[c]	NDr	0.11	0.00051	0.11 (LOAEL)	Model fit obtained, but not considered reliable (see Appendix C)

Table 9. Candidate Principal Studies and PODs for the Derivation of the Subchronic p-RfD

Endpoint/Reference	NOAEL (HED)[a] (mg/kg-d)	LOAEL (HED)[a] (mg/kg-d)	BMDL (HED)[a] (mg/kg-d)	Selected POD (HED) (mg/kg-d)	Comments
Reduced colloid density (all severity grades) in the thyroid of F1a female S-D rats, 34 wk (Chu et al., 1988)[d]	NDr	0.089	0.0075	0.089 (LOAEL)	Model fit obtained after dropping high dose, but not considered reliable (see Appendix C)
Colloid inspissation (all severity grades) in the thyroid of F0 male S-D rats, 25−29 wk (Chu et al., 1988)[d]	NDr	0.10	0.0050	0.10 (LOAEL)	Model fit obtained after dropping 2 high doses, but not considered reliable (see Appendix C)
Colloid inspissation (all severity grades) in the thyroid of F1a male S-D rats, 34 wk (Chu et al., 1988)[d]	NDr	0.078	0.0089	0.078 (LOAEL)	Model fit obtained after dropping high dose, but not considered reliable (see Appendix C)
Reduced follicular size (all severity grades) in the thyroid of female S-D rats, 13 wk (Chu et al., 1986)[c]	NDr	0.11	0.0052	0.11 (LOAEL)	Model fit obtained, but not considered reliable (see Appendix C)
Follicle collapse/angularity (minimal to mild observed) in the thyroid of F1a male S-D rats, 34 wk (Chu et al., 1988)[d]	0.078	0.37	0.014	0.014 ($BMDL_{10}$)	Model fit obtained after dropping 2 high doses
Increased epithelial height (all severity grades) in the thyroid of female S-D rats, 13 wk (Chu et al., 1986)[c]	NDr	0.11	0.00014	0.11 (LOAEL)	Model fit obtained, but not considered reliable (see Appendix C)
Cytoplasmic vacuolation (all severity grades) in the thyroid of female S-D rats, 13 wk (Chu et al., 1986)[c]	NDr	0.11	DUB	0.11 (LOAEL)	No models provided adequate fit to data
Cytoplasmic vacuolation (all severity grades) in the thyroid of F0 male S-D rats, 25−29 wk (Chu et al., 1988)[d]	**0.10**	**0.47**	**0.0092**	**0.0092 ($BMDL_{10}$)**	**Model fit obtained after dropping 2 high doses**

Table 9. Candidate Principal Studies and PODs for the Derivation of the Subchronic p-RfD

Endpoint/Reference	NOAEL (HED)[a] (mg/kg-d)	LOAEL (HED)[a] (mg/kg-d)	BMDL (HED)[a] (mg/kg-d)	Selected POD (HED) (mg/kg-d)	Comments
Cytoplasmic vacuolation (all severity grades) in the thyroid of F0 female S-D rats, 25−29 wk (Chu et al., 1988)[d]	0.44	1.9	0.037	0.037 ($BMDL_{10}$)	Model fit obtained after dropping high dose, but considered a borderline case for passing visual inspection of the model fit
Cytoplasmic vacuolation (only minimal to mild observed) in the thyroid of F1a female S-D rats, 34 wk (Chu et al., 1988)[d]	NDr	0.089	0.0059	0.089 (LOAEL)	Model fit obtained after dropping high dose, but not considered reliable (see Appendix C)
Liver Effects					
Increased relative liver weight (≥10%) in female Beagle dogs, 13 wk (Chu et al., 1986)[c]	NDr	0.1	DUB	0.1 (LOAEL)	No models provided adequate fit to data
Increased absolute liver weight (≥10%) in F0 female S-D rats, 25−29 wk (Chu et al., 1988)[d]	NDr	0.083	0.028	0.028 ($BMDL_{10}$)	Model fit obtained after dropping high dose
Increased relative liver weight (≥10%) in male $B6C3F_1$ mice; 28 d (Wang et al., 2015)	0.1	0.85	DUB	0.1 (NOAEL)	The fit of the nonconstant variance model provided only a marginal fit (variance $p = 0.09$)
Increased BrdU labeling index in liver of male $B6C3F_1$ mice; 28 d (Wang et al., 2015)	0.1	0.85	DUB	0.1 (NOAEL)	No models provided adequate fit to data
Accented zonation (all severity grades) in the liver of female S-D rats, 13 wk (Chu et al., 1986)[c]	0.11	0.58	0.024	0.11 (NOAEL)	Model fit obtained, but not considered reliable (see Appendix C)
Anisokaryosis (all severity grades) in the liver of male S-D rats, 13 wk (Chu et al., 1986)[c]	0.09	0.46	0.0090	0.09 (NOAEL)	Model fit obtained, but not considered reliable (see Appendix C)
Anisokaryosis (all severity grades) in the liver of female S-D rats, 13 wk (Chu et al., 1986)[c]	NDr	0.11	0.0030	0.11 (LOAEL)	Model fit obtained, but not considered reliable (see Appendix C)

Table 9. Candidate Principal Studies and PODs for the Derivation of the Subchronic p-RfD

Endpoint/Reference	NOAEL (HED)[a] (mg/kg-d)	LOAEL (HED)[a] (mg/kg-d)	BMDL (HED)[a] (mg/kg-d)	Selected POD (HED) (mg/kg-d)	Comments
Anisokaryosis (all severity grades) in the liver of F0 female S-D rats, 25−29 wk (Chu et al., 1988)[d]	NDr	0.083	0.0072	0.083 (LOAEL)	Model fit obtained after dropping 2 high doses, but not considered reliable (see Appendix C)
Cytoplasmic homogeneity (all severity grades) in the liver of F1a male S-D rats, 34 wk (Chu et al., 1988)[d]	NDr	0.078	0.0039	0.078 (LOAEL)	Model fit obtained after dropping 2 high doses, but not considered reliable (see Appendix C)

[a]Following U.S. EPA (2011b) guidance, animal doses from candidate principal studies were converted to HEDs through the application of a DAF. DAFs for each dose are calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$), where BW_a = animal body weight and BW_h = human body weight. For all DAF calculations, a reference human body weight (BW_h) of 70 kg (U.S. EPA, 1988b) was used.
[b]DAFs were calculated using study-specific body weight (BW_a) data for female cynomolgus monkeys at the initiation of treatment with technical toxaphene.
[c]For the rat portion of the study, DAFs were calculated using body weights (BW_a) estimated from study-specific initial weight and weight-gain data for female S-D rats. For the dog portion of the study, DAFs were calculated using reference body weights (BW_a) for female Beagle dogs following subchronic exposure (U.S. EPA, 1988b).
[d]DAFs were calculated using body weights (BW_a) estimated from study-specific initial weight and weight-gain data for male and female S-D rats.
[e]DAFs were calculated using the mean of study-specific initial and terminal body weights (BW_a) of male $B6C3F_1$ mice.

BMD = benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; BMR = benchmark response; BrdU = bromodeoxyuridine; BW = body weight; DAF = dosimetric adjustment factor; DUB = data unsuitable for BMD modeling (see Appendix C for details); HED = human equivalent dose; IgM = immunoglobulin M; LOAEL = lowest-observed-adverse-effect level; NA = not applicable; NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; S-D = Sprague-Dawley; SD = standard deviation; SRBC = sheep red blood cell.

In *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information, without a complete physiologically based toxicokinetic model. In the absence of chemical-specific models or data to inform the derivation of human equivalent oral exposures, U.S. EPA endorses $BW^{3/4}$ as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an oral reference dose (RfD) under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite, but not for portal-of-entry effects. A validated human physiologically based pharmacokinetic (PBPK) model for technical toxaphene is not available for use in extrapolating doses from animals to humans. In addition, effects in the liver, kidney, thyroid, and immune system are not portal-of-entry effects. Therefore, scaling by $BW^{3/4}$ is relevant for deriving HED for this effect.

From the identified sensitive targets of technical toxaphene toxicity, the thyroid exhibits consistency and coherence in the evidence across species (including humans), sexes, life stages, and endpoints. The three lowest potential PODs (HEDs) providing reliable, adequate model fits are all for thyroid endpoints from subchronic- and chronic-duration studies in S-D rats and include: (1) a 10% BMDL ($BMDL_{10}$) of 0.0092 mg/kg-day for cytoplasmic vacuolation (all severity grades) in the thyroid of F0 males following 25−29 weeks of dietary exposure (Chu et al., 1988), (2) a $BMDL_{10}$ of 0.013 mg/kg-day for reduced colloid density (moderate to severe) in the thyroid of males following 13 weeks of dietary exposure (Chu et al., 1986), and (3) a $BMDL_{10}$ of 0.014 mg/kg-day for follicle collapse/angularity (only minimal to mild observed) in the thyroid of F1a males following 34 weeks of dietary exposure (Chu et al., 1988). In the subchronic-duration (13-week) rat study by (Chu et al., 1986), moderate to severe reduced colloid density appears to be the most sensitive effect. When all severity grades are considered, however, a high control incidence in males precluded BMD modeling and subsequent identification of a reliable POD. With respect to thyroid effects following chronic exposure, cytoplasmic vacuolation and reduced colloid density are comparably sensitive in F0 males [Chu et al. (1988); see Table B-14]. Therefore, when considering all the BMDL estimates presented in Table 9, 0.0092 mg/kg-day for cytoplasmic vacuolation (all severity grades) in the thyroid of F0 males following 25−29 weeks of dietary exposure is considered the most reliable and the most sensitive (see Appendix C).

Chu et al. (1988) is, therefore, chosen as the principal study, and cytoplasmic vacuolation (all severity grades) in the thyroid of F0 male S-D rats following 25−29 weeks of dietary exposure is the critical effect, with a $BMDL_{10}$ (HED) of 0.0092 mg/kg-day as the POD. As noted in Table 9, this $BMDL_{10}$ was estimated after dropping the two highest doses, which resulted in a significant improvement of the model fit to the low-dose range. Although this $BMDL_{10}$ is approximately 10-fold lower than the identified NOAEL of 0.10 mg/kg-day for this endpoint, there is a 30% (3/10) response at the NOAEL. Thus, due to the animal sample size examined at 0.10 mg/kg-day, the estimated $BMDL_{10}$ is considered an appropriate POD for this endpoint. Based on all of the laboratory animal oral toxicity data, this POD is expected to be protective against all thyroid effects (regardless of severity), as well as any potential liver, kidney, and immune effects observed in other studies and across other species (including those

effects for which only LOAELs could be identified) following subchronic or chronic exposure to technical toxaphene.

The subchronic p-RfD for technical toxaphene is derived as follows:

Subchronic p-RfD = $BMDL_{10}$ (HED) ÷ UF_C
for Technical Toxaphene = 0.0092 mg/kg-day ÷ 30
= **3×10^{-4} mg/kg-day**

Table 10 summarizes the uncertainty factors for the subchronic p-RfD for technical toxaphene.

Table 10. Uncertainty Factors for the Subchronic p-RfD for Technical Toxaphene

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following technical toxaphene exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	1	A UF_D of 1 is applied because the oral exposure database contains numerous short-term- and subchronic-duration toxicity studies of laboratory animals, a one-generation reproductive toxicity study of rats (Chu et al., 1988), multiple-generation reproductive toxicity studies in rats (Kennedy et al., 1973) and mice (Keplinger et al., 1970), and several developmental toxicity studies in rats (Chernoff et al., 1990; Crowder et al., 1980; Olson et al., 1980; Chernoff and Carver, 1976) and mice (Allen et al., 1983; Chernoff and Kavlock, 1983; Chernoff and Carver, 1976). Analysis of the database indicates that the effects on reproductive function and early development in rats and mice occurred at higher exposure levels than the lowest exposure levels resulting in thyroid, liver, kidney, or immune effects (see Table 5A).
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of technical toxaphene in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because the principal study is greater than subchronic duration (25−29 wk).
UF_C	30	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Confidence in the subchronic p-RfD for technical toxaphene is high as explained in Table 11.

Table 11. Confidence Descriptors for the Subchronic p-RfD for Technical Toxaphene

Confidence Categories	Designation	Discussion
Confidence in study	H	Confidence in the principal study is high because the study was published in a peer-reviewed journal and is of quality study design and performance with regard to examining potential toxicity endpoints and in presenting materials, methods, and results. The number of dose groups (4 plus control for males and females) and group sizes (10−13 males, 10−17 females examined histologically) were adequate, thus allowing reliable evaluation of the endpoints investigated and identification of treatment-related changes in relation to dose. Details of the study are provided in the "Review of Potentially Relevant Data" section.
Confidence in database	H	There is high confidence in the oral toxicity database because there are numerous short-term and subchronic-duration toxicity studies, including studies in monkeys, dogs, and rodents, and several reproductive and developmental toxicity studies.
Confidence in subchronic p-RfD[a]	H	Overall confidence in the subchronic p-RfD is high.

[a]The overall confidence cannot be greater than the lowest entry in the table (high).

H = high; p-RfD = provisional reference dose.

Derivation of a Chronic Provisional Reference Dose

The subchronic p-RfD based on cytoplasmic vacuolation (all severity grades) in the thyroid of F0 male S-D rats following 25−29 weeks of dietary exposure (Chu et al., 1988) is selected as the basis of the chronic p-RfD for technical toxaphene.

Justification

In the only available chronic-duration animal toxicity bioassay that exposed animals for a longer duration than the Chu et al. (1988) study and also provided comprehensive examinations of tissues for non-neoplastic lesions, NCI (1979) did not find significantly elevated incidences of non-neoplastic lesions (including identified sensitive targets of thyroid, liver, and kidney) in rats or mice exposed for 80 weeks to average daily doses of technical toxaphene as high as 83.29 and 34.2 mg/kg-day, respectively. However, with respect to thyroid toxicity, it is important to note that the NCI (1979) study tested a different rat strain (Osborne-Mendel) than did either the subchronic- or chronic-duration studies by Chu and colleagues (which tested S-D rats). Nevertheless, there was a 3−12% response (albeit not statistically significant) in noncancer thyroid lesions in males and females, and there was a significant increase in thyroid tumors in both sexes, further establishing the thyroid as a target of technical toxaphene following chronic exposure. Furthermore, the Chu et al. (1988) and NCI (1979) chronic-duration studies did not examine endpoints of immune suppression, which is also a sensitive noncancer effect identified in the oral database for technical toxaphene. Thus, in the absence of chronic-duration data on immune effects, application of an additional database uncertainty factor (UF_D) is warranted to account for uncertainty in identifying potentially more sensitive immune effects following chronic exposure.

The chronic p-RfD for technical toxaphene, based on the $BMDL_{10}$ (HED) of 0.0092 mg/kg-day for cytoplasmic vacuolation (all severity grades) in the thyroid of F0 male S-D rats following 25−29 weeks of dietary exposure (Chu et al., 1988), is derived as follows:

Chronic p-RfD	=	$BMDL_{10}$ (HED) ÷ UF_C
for Technical Toxaphene	=	0.0092 mg/kg-day ÷ 100
	=	**9×10^{-5} mg/kg-day**

Table 12 summarizes the uncertainty factors for the chronic p-RfD for technical toxaphene.

Table 12. Uncertainty Factors for the Chronic p-RfD for Technical Toxaphene

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following TT exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	3	A UF_D of 3 is applied because the oral exposure database contains numerous short-term- and subchronic-duration toxicity studies of laboratory animals, 2 chronic-duration toxicity studies of rats and mice that included comprehensive histological examination of most tissues, a one-generation reproductive toxicity study of rats (Chu et al., 1988), multiple-generation reproductive toxicity studies in rats (Kennedy et al., 1973) and mice (Keplinger et al., 1970), and several developmental toxicity studies in rats (Chernoff et al., 1990; Crowder et al., 1980; Olson et al., 1980; Chernoff and Carver, 1976) and mice (Allen et al., 1983; Chernoff and Kavlock, 1983; Chernoff and Carver, 1976). Analysis of the database indicates that the effects on reproductive function and early development in rats and mice occurred at higher exposure levels than the lowest exposure levels resulting in thyroid, liver, kidney, or immune effects (see Table 5A). However, an additional uncertainty factor is warranted to account for uncertainty in identifying potentially more sensitive immune effects following chronic exposure.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of TT in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because the principal study is of chronic duration (25−29 wk).
UF_C	100	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; TT = technical toxaphene; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Confidence in the chronic p-RfD for technical toxaphene is medium as explained in Table 13.

Table 13. Confidence Descriptors for the Chronic p-RfD for Technical Toxaphene

Confidence Categories	Designation	Discussion
Confidence in study	H	Confidence in the principal study is high because the study was published in a peer-reviewed journal, and is of quality study design and performance with regard to examining potential toxicity endpoints and in presenting materials, methods, and results. The number of dose groups (4 plus control for males and females) and group sizes (10−13 males, 10−17 females examined histologically) were adequate, thus allowing reliable evaluation of the endpoints investigated and identification of treatment related changes in relation to dose. Details of the study are provided in the "Review of Potentially Relevant Data" section.
Confidence in database	M	Confidence in the oral toxicity database is medium because there are numerous short-term- and subchronic-duration toxicity studies, as well as chronic-duration toxicity studies, and several reproductive and developmental toxicity studies, but no dose-response data for immune suppression endpoints (a sensitive target identified in subchronic-duration studies) following chronic exposure.
Confidence in chronic p-RfD[a]	M	Overall confidence in the chronic p-RfD is medium.

[a]The overall confidence cannot be greater than the lowest entry in the table (medium).

H = high; M = medium; p-RfD = provisional reference dose.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of a Subchronic Provisional Reference Concentration

Appropriate data to derive a subchronic provisional reference concentration (p-RfC) for technical toxaphene, weathered toxaphene, or individual toxaphene congeners has not been identified.

Derivation of a Chronic Provisional Reference Concentration

Appropriate data to derive a chronic p-RfC for technical toxaphene, weathered toxaphene, or individual toxaphene congeners has not been identified.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR AND POTENCY VALUES

A cancer OSF of 1.1 $(mg/kg\text{-}day)^{-1}$ and IUR of 3.2×10^{-4} $(\mu g/m^3)^{-1}$ for technical toxaphene is currently listed on IRIS (U.S. EPA, 1988a), along with a cancer WOE classification of Group B2 based on sufficient evidence of carcinogenicity in laboratory animals (hepatocellular tumors in mice and thyroid tumors in rats) and no studies in humans at the time of the cancer assessment. The slope factor was based on incidence data for hepatocellular carcinomas and neoplastic nodules in male $B6C3F_1$ mice in the bioassay conducted by Litton Bionetics (1978), using a linearized multistage modeling procedure.

APPENDIX A. SCREENING PROVISIONAL VALUES

For the reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, toxicity data for weathered toxaphene or individual toxaphene congeners are inadequate to derive noncancer provisional toxicity values or assess the carcinogenicity of these substances. However, information is available for this chemical, which although insufficient to support deriving 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 main 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 deriving 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 Heath Risk Technical Support Center.

OVERVIEW OF AVAILABLE TOXICITY DATA ON WEATHERED TOXAPHENE AND TOXAPHENE CONGENERS

The chemical composition of weathered toxaphene mixtures can vary widely depending on time in the environment and environmental conditions. Known differences in composition between technical toxaphene and various types of weathered toxaphene could potentially lead to qualitative or quantitative differences in toxicity. Comparative toxicity studies of technical toxaphene and weathered toxaphene samples are rare, so the degree to which weathered toxaphene samples may differ in toxicity from technical toxaphene is uncertain. Toxaphene residues purified from lake trout samples were reportedly similar to technical toxaphene in toxicity to mosquito larvae (Gooch and Matsumura, 1987). However, a weathered toxaphene sample extracted from the livers of cod (cod liver extract [CLE]) exposed to technical toxaphene was eightfold more potent than ultraviolet (UV)-weathered technical toxaphene or technical toxaphene in an in vitro assay of gap junctional intercellular communication (GJIC) in mouse Hepa1c1c7 cells (Besselink et al., 2008). In a recent in vitro study examining GJIC inhibition in $B6C3F_1$ mouse hepatocyte cultures, toxaphene congeners and congener mixtures exhibited comparable or lower potency as that observed for technical toxaphene Kerger et al. (2018). A synthetic mixture of chlorinated camphenes with very low amounts of congeners in the hepta- to nona-chlorinated range was 1.3- and 2.3-fold more potent in producing lethal and nonlethal malformations, respectively, in zebrafish embryos than a synthetic mixture with a compositional profile similar to technical toxaphene, which had high amounts of congeners in the hepta- to nona-chlorinated range (Kapp et al., 2006). A more detailed overview of the limited toxicity data on samples of weathered toxaphene and toxaphene congeners, as well as considerations for deriving screening provisional toxicity values for oral exposure to these compounds, follows.

Only one in vivo study, described in several reports (Besselink et al., 2008; Besselink et al., 2000; EU, 2000), has been identified that has any relevance to deriving a screening provisional reference dose (p-RfD) for weathered toxaphene. In a two-stage liver tumor initiation/promotion study involving subcutaneous (s.c.) injection, the effects of technical toxaphene, UV-weathered toxaphene (i.e., UV-irradiated technical toxaphene), and biologically weathered toxaphene (a liver extract from cod fish fed technical toxaphene) were examined. Groups of partially hepatectomized female Sprague-Dawley (S-D) rats obtained from

Møllegaard Breeding Centre in Copenhagen, Denmark were administered the technical and weathered toxaphene samples once weekly by s.c. injection for 20 weeks after a single intraperitoneal (i.p.) injection of a tumor-initiating dose of *N*-nitrosodiethylamine (NDEA) (Besselink et al., 2008). To generate the CLE, cod were given toxaphene-enriched feed (containing 30 ppm technical toxaphene) in their diet for 63 days, followed by a 14-day postdosing period with untreated feed to permit appropriate metabolism. Approximately 30 kg of liver enriched in toxaphene residues was harvested from 300 cod for preparing a biologically weathered toxaphene extract. The rat treatment groups were tested in two experimental scenarios with rats receiving four different doses. Doses administered to rats via s.c. injection in Experiment 1 (a comparison of technical toxaphene with UV-weathered toxaphene) were: 0 (corn oil control; $n = 14$), 0.62, 2, 6, or 18 mg technical toxaphene/kg body weight per week ($n = 10$), and 0.3, 0.89, 2.67, or 8 mg UV-weathered toxaphene/kg body weight per week ($n = 10$). Doses in Experiment 2 (a comparison of technical toxaphene with CLE) were: 0 (corn oil control; $n = 14$), 18 mg technical toxaphene/kg body weight per week ($n = 10$), and 0.46, 1.39, 4.17, or 12.5 mg CLE/kg body weight per week ($n = 10$). Both experiments also included a positive control group that was administered 2,3,7,8-tetrachlorodibenzodioxin (TCDD) (1 µg/kg body-weight injection per week; $n = 10$). One week after the last dosing, the animals were weighed, blood was collected, and the livers removed and weighed after sacrifice. For each treatment group, three endpoints evaluating the occurrence of altered liver foci positive for glutathione-S-transferase-P (number of foci per cm^2 of liver, mean foci area [mm^2], and area fraction of liver with foci) were used as measures of liver tumor promotion activity. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity were also measured.

The CLE sample had a markedly different compositional profile of toxaphene congeners than the technical toxaphene fed to the cod. Compared with technical toxaphene, the CLE sample had decreased relative percentages of octa- and nona-chlorinated congeners like p-26, p-32, p-50, and p-62, and increased relative percentages of unidentified lower chlorinated congeners. The summed concentration of p-26, p-50, and p-62 (dubbed ∑3PC, approximate fractional composition of 1:2:2) accounted for <1% of total toxaphene in CLE, which is significantly lower than the mean ∑3PC percentages of 22.45% in other examples of biologically measured toxaphene, specifically 29 tissue biotic samples from several northern latitude species of fish (e.g., trout, salmon, and burbot) and aquatic mammals (narwhal, beluga whale, walrus), and 4.47% in >50 aquatic tissue samples from a U.S. Superfund site in Georgia (including blue crab, red and black drum, croaker, mullet, sea trout, shrimp, spot, yellowtail, and whiting) [see Simon and Manning (2006) for references of these monitoring studies]. The approximate fractional composition of p-26, p-50, and p-62 in the UV-weathered toxaphene test substance was 1:1:2.

Mean values for relative liver weight were statistically significantly increased, compared with controls, in TCDD-treated positive control groups in both experiments. Means for body-weight gain, relative liver weight, and relative thymus weight were not significantly different between vehicle control groups and groups exposed to technical toxaphene, UV-weathered toxaphene, or CLE. No changes in ALT or AST activity were observed in groups exposed to technical toxaphene, UV-weathered toxaphene, or CLE. TCDD, however, caused an increase in AST activity. Mean values for tumor-promotion endpoints in the positive control groups were statistically significantly increased (about two- to fourfold depending on the endpoint), compared with vehicle controls, but no statistically significant increases in

tumor-promotion endpoints were found in any groups exposed to the toxaphene mixtures, compared with controls. A statistically significantly lower value for the number of foci per cm^2 liver was found in the highest CLE-treated dose group, compared with controls. The other measures of altered foci were also lower in the highest CLE-treated dose group than in the control group, but the differences were not statistically significant. Besselink et al. (2008) discussed the hypothesis that this may have been caused by an apoptotic effect leading to enhanced liver cell death rates at the highest dose. The highest doses used in this study for technical toxaphene, UV-weathered toxaphene, and CLE are s.c., subchronic no-observed-adverse-effect levels (NOAELs) for liver tumor promotion activity.

Besselink et al. (2008) also collected data on in vitro inhibition of GJIC in cultured mouse Hepa1c1c7 cells. Twenty percent effective concentration (EC_{20}) values in the in vitro test of inhibition of intercellular communication indicated the following potency order: CLE (0.24 µg/mL) > UV-weathered = technical toxaphene (1.9 µg/mL) (albeit CLE was 77,000 times less potent than the positive control, TCDD). The GJIC results indicate that CLE may be about eightfold more potent than technical toxaphene or UV-weathered toxaphene, at least for this particular in vitro endpoint. In a recent study that also examined the effects of toxaphene on GJIC in vitro, Kerger et al. (2018) treated hepatocytes isolated and cultured from male and female $B6C3F_1$ mice with increasing concentrations of technical toxaphene, individual toxaphene congeners (p-26, p-50, and p-62), Hx-Sed, and two congener mixtures (Mixture 1 = p-26, p-50, and p-62 [2:1:1 fractional composition], and Mixture 2 = p-26, p-50, p-62, and Hx-Sed [2:1:1:1 fractional composition]) for 3 or 24 hours. Phenobarbital was used as a positive control. The study authors state that compared to untreated control cells, the lowest concentration of technical toxaphene that produced a significant change in GJIC inhibition (dubbed the lowest significant effect level [LSEL]) was generally comparable to that observed for the congeners and mixtures. The LSEL for Hp-Sed was three- to fivefold higher than for technical toxaphene, while all other treatment groups were within twofold. The male hepatocyte responses for p-26, Hx-Sed, and Mixture 1 were not significantly different than untreated controls at any concentration tested. After modeling selected in vitro dose-response data, the predicted EC_{20} values for technical toxaphene, toxaphene congeners, and toxaphene mixtures exhibited the following potency order: p-50 (2.74 µg/mL) > technical toxaphene (3.50 µg/mL) > Hx-Sed (4.06 µg/mL) > p-62 (4.15 µg/mL) > p-26 (7.93 µg/mL) > Hp-Sed (25.1 µg/mL) > Mixture 2 (31.9 µg/mL) > Mixture 1 (32.1 µg/mL). The EC_{20} value for technical toxaphene was within twofold of the EC_{20} values for technical toxaphene and UV-weathered toxaphene observed by Besselink et al. (2008) in Hepa1c1c7 cells. Additionally, Kerger et al. (2018) suggest that an interaction index of <1, 1, or >1 indicates possible antagonism, additivity, or synergy, respectively, of components in the congener mixtures measured at the EC_{20}, and the interaction index of the two congener mixtures was approximately half that expected based on pure additive responses at the EC_{20}, in contrast to the apparent synergistic response suggested by the CLE in vitro GJIC data (Besselink et al., 2008). Taken together, the results of the Besselink et al. (2008) and Kerger et al. (2018) in vitro studies indicate that relative toxic properties of technical toxaphene, toxaphene congeners, congener mixtures, or weathered toxaphene can be dependent on endpoint or test systems, as well as specific substances tested.

The literature search also identified studies of cultured cells (human breast cancer cell model) (Stelzer and Chan, 1999), cultured rat embryos (Calciu et al., 2002; Calciu et al., 1997), zebrafish embryos (Kapp et al., 2006), mosquito larvae (Gooch and Matsumura, 1987), juvenile rats (Olson et al., 1980), and mice (Turner et al., 1977) comparatively exposed to individual

toxaphene congeners, toxaphene mixtures, or "weathered" toxaphene mixtures (see Table A-1). Overall, the available information on the toxicity of individual toxaphene congeners is too sparse to propose a component-based approach (such as the toxic equivalency factor approach for dioxins and dioxin-like compounds, or the relative potency factor approach for nonsubstituted polycyclic aromatic hydrocarbons [PAHs]) for assessing health risks from mixtures of toxaphene congeners, but the available information indicates that individual congeners may differ in toxic properties. In addition, the results from the most recent of these studies (Kapp et al., 2006) indicate that mixtures enriched in low-chlorinated congeners (penta- and hexa-chlorinated congeners) may be more toxic to zebrafish embryos than toxaphene mixtures, like technical toxaphene, that are more enriched in congeners with ≥7 chlorines.

Table A-1. Studies Featuring Comparative Testing of Toxaphene Congeners and Mixtures

Study Description	Reference
Intraperitoneal LD_{50} values for TT were equivalent in mice with or without a PB pretreatment (42 and 47 mg/kg), whereas LD_{50} values for "Toxicant B" (2,2,5-endo,6-exo,8,9,10-heptachlorobornane, or p-32) were higher in mice without pretreatment (75 mg/kg, less toxic) and lower with pretreatment (9.5 mg/kg, more toxic). Among 5 other tested octachloro-derivatives of Toxicant B, PB pretreatment did not influence LD_{50} values to the same degree as Toxicant B values, but 2 compounds were less toxic than TT ("3-exo-B": >100 mg/kg ± PB; 10-Cl-B: >100 mg/kg − PB, 48 mg/kg + PB) and the other 3 were more toxic ("5-exo-B": 24 and 28 mg/kg; 8-Cl-B [57%] + 9-Cl-B [43%]: 3.3 and 3.1 mg/kg; 10-Cl-B: 2.5 and 1.9 mg/kg).	Turner et al. (1977)
Neurobehavioral tests were conducted in offspring of groups of pregnant Holtzman albino rats exposed to control diets, a diet delivering 50 µg/kg-d TT, a diet delivering 2 µg/kg-d "Toxicant A" (p-42a or p-42b), or a diet delivering 2 µg/kg-d "Toxicant B" (p-32). Dietary exposure started on GD 5 and lasted until the offspring were 90 d old. The results indicate apparent NOAELs of 0.002 mg Toxicant A (p-42)/kg-d and 0.002 mg Toxicant B (p-32)/kg-d for the absence of clear biologically significant neurobehavioral effects, body-weight effects, or effects on tissue histology in Holtzman albino rat offspring. No LOAELs were identified. Neither a NOAEL nor a LOAEL could be identified for TT due to incomplete reporting.	Olson et al. (1980)[a]
A 48-hr zebrafish (*Danio rerio*) embryo test for lethal malformations and nonlethal malformations was conducted with 2 synthetic mixtures of chlorinated camphenes: 1 enriched in higher-chlorinated congeners (hepta- to nona-chlorinated components) and showing a GC/electron capture negative ion mass spectrometry multiple ion chromatogram similar to TT, and 1 enriched in lower-chlorinated congeners with very small amounts of chlorinated components in the hepta- to nona-chlorination range. The respective 48-hr EC_{50} values for lethal and nonlethal malformations were 15.3 and 5.6 mg/L for the lower chlorination mixture and 20.6 and 13.4 mg/L for the higher chlorination mixture. The results suggest that mixtures containing enhanced amounts of lower chlorinated congeners resulting from environmental weathering (i.e., dechlorination) may be more potent in this test system than TT.	Kapp et al. (2006)
Numerous morphological endpoints were assessed in explanted rat embryos following a 48-hr exposure to TT, p-26, or p-50, each at 0, 0.1, 1, or 5 µg/mL (Calciu et al., 1997). Yolk sac diameters, head length, and crown rump length were measured after exposure, and 16 morphological features were scored on a numerical ranking from 0−5. Total morphological score, crown-rump length, and head length were decreased by exposure to TT, p-26, and p-50 to similar degrees at most of the tested concentrations, indicating equivalent potencies of the test materials on these endpoints. All 3 test substances also increased the incidence of embryos with neural tube malformations at most tested concentrations. However, p-26 and p-50 decreased scores for otic development to a greater degree than TT. Based on results from exposure to a 50:50 mixture of p-26 and p-50, Calciu et al. (1997) proposed synergistic effects on certain endpoints. These claims, however, cannot be substantiated by the study design and analytical procedure employed. The effects of TT, p-26, and p-50 on morphological endpoints were also examined in explanted rat embryos under normal and hyperglycemic conditions (Calciu et al., 2002). In the absence of hyperglycemia, results were similar to those reported in the earlier study. Tested hyperglycemic conditions alone caused decreased crown-rump length, head length, and total morphological score, but did not produce malformations. Exposure to TT or p-26 under the highest hyperglycemic conditions increased the incidence of neural tube malformations, compared with responses in the absence of hyperglycemia, whereas hyperglycemia appeared to decrease the effects of p-50 on this endpoint.	Calciu et al. (2002); Calciu et al. (1997)

Table A-1. Studies Featuring Comparative Testing of Toxaphene Congeners and Mixtures

Study Description	Reference
TT, congener T2 (p-26), and congener T12 (p-50) each displayed estrogenic activities (proliferative effects in MCF7-E3 human breast cancer cells) at a similar concentration (10 µM), but the response to TT was greater than responses to either of the congeners.	Stelzer and Chan (1999)
Static 24-hr acute bioassays with mosquito larvae indicated that toxaphene mixtures purified from lake trout samples from 2 U.S. lakes were similar in toxicity to TT. The fish residue test materials showed a gas chromatogram profile of similar complexity to TT, but a slightly lower combined concentration of "Toxicant A" (p-42a, p-42b) and "Toxicant B" (p-32) than TT.	Gooch and Matsumura (1987)

[a]A more complete description of this study was presented in the main body of this report.

EC_{50} = median effective concentration; GC = gas chromatograph; GD = gestation day; LD_{50} = median lethal dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PB = phenobarbital; TT = technical toxaphene.

Applicability of Computational Toxicology Methods to Fill Data Gaps for Weathered Toxaphene and Toxaphene Congeners

In light of the limited data available for weathered toxaphene mixtures and individual toxaphene congeners, U.S. EPA considered that computational toxicology methods, specifically quantitative structure activity relationships (QSARs), might be used to fill gaps in the database for these materials. U.S. EPA's Estimation Program Interfact Suite™ (EPISuite™) (U.S. EPA, 2012c), the Organisation for Economic Co-operation and Development (OECD) QSAR toolbox (OECD, 2017), and the VEGA (Benfenati et al., 2013) models, all publically available computerized QSAR models, were investigated.

U.S. EPA's EPISuite™ programs are based on a fragment contribution (additive) method, which allows complex structure to be estimated based on smaller building blocks, such as a carbon-chorine group. Fragment methods tend to overestimate a value as a fragment increases in frequency. For example, EPISuite™ produces a log K_{ow} estimate for the Cl-8 congener (CASRN 142534-71-2; T2) of 5.69, in good agreement with the experimental value of 5.52. However, the Cl-9 congener (CASRN 154159-06-5; 2,2,5,5,8,9,9,10,10-nonachlorobornane) results in an estimated value of 7.72, which is not in good agreement with its experimental value of 5.96. The fragment method does not account for differences in positional, spatial, or electronic (e.g., dipole) relationships. Thus, all congeners with seven chlorines return the same K_{ow} value, all of those with eight chlorines return another value, and all with nine yet another, and so on. Although this method provides reasonable results (except for the higher congeners), it does not provide any information to discriminate between the various congeners possessing the same degree of chlorination.

The other models that were evaluated also employ fragment-based techniques; however, they are alert based and not group-contribution based. In other words, they may trigger an alert if a single structural alert is identified. Thus, if the model issues an alert for a carbon-chlorine bond, it may issue the same alert whether six, seven, or eight chlorines are identified. This happens when the model is trained on only a few compounds that are analogs to the compounds being evaluated, which is the case for the toxaphene congeners. The chemical space they occupy is not well represented in the model-building exercises, so the models are expected to give results with a high degree of uncertainty. This is consistent with the results provided by the VEGA models. Using the Cl-8 congener and the Cl-9 congener, as above, VEGA provided estimates for 10 models associated with human health endpoints (mutagenicity, cancer, reproductive and developmental toxicity, and skin sensitization). The Cl-8 and Cl-9 congeners showed the exact same results for all 10 models. Moreover, 7 of the 10 models reported the results as "not reliable" or missing critical aspects. Similar results were provided by the OECD QSAR toolbox, which listed the same alerts for both the Cl-8 and Cl-9 congeners for the cancer/genotoxicity ([poly] halogen and aliphatic halogen) and mutagenicity (halogen) endpoints, for example.

Based on this initial exercise, U.S. EPA concluded that (1) the chemical space associated with the toxaphene congeners is not sufficiently represented in the training sets to provide a basis for meaningful or reliable predictions of congener toxicity based on structure and (2) the techniques do not discriminate between the toxicity of Cl-8 and Cl-9 congeners, and are unlikely to do so for any congeners having the same degree of chlorination. As a result of this exercise, QSAR approaches to predict toxicity of toxaphene congeners and mixtures were not pursued further.

Considerations of Alternative Approaches to Deriving Screening Subchronic and Chronic p-RfDs for Weathered Toxaphene Mixtures

Approaches to deriving screening subchronic and chronic p-RfDs for weathered toxaphene mixtures were considered, based on the available data. In one approach, the 10% benchmark dose lower confidence limit human equivalent dose ($BMDL_{10}$ [HED]) of 0.0092 mg/kg-day for cytoplasmic vacuolation (all severity grades) in the thyroid of F0 male S-D rats following 25−29 weeks of dietary exposure (Chu et al., 1988) is used as the point of departure (POD), and a screening p-RfD for weathered toxaphene mixtures is therefore derived as follows:

Screening Subchronic p-RfD	=	$BMDL_{10}$ (HED) ÷ UF_C
for Weathered Toxaphene	=	0.0092 mg/kg-day ÷ 300
based on Technical Toxaphene	=	**3×10^{-5} mg/kg-day**

Table A-2 summarizes the uncertainty factors for this screening subchronic p-RfD for weathered toxaphene mixtures.

Table A-2. Uncertainty Factors for a Screening Subchronic p-RfD for Weathered Toxaphene Mixtures Based on Cytoplasmic Vacuolation (All Severity Grades) in the Thyroid of F0 Male S-D Rats Following 25−29 Weeks of Dietary Exposure

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following TT exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	10	A UF_D of 10 is applied because of the limited available data comparing the toxicity of TT and samples of weathered toxaphene. Given the wide range in relative potencies of weathered toxaphene samples and TT in the limited number of available comparisons, a UF_D of 10 is applied to protect against the possibility that any specific type or sample of weathered toxaphene may be more toxic than technical toxaphene.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of TT in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because the principal study is greater than subchronic duration (25−29 wk).
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; S-D = Sprague-Dawley; TT = technical toxaphene; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

The $BMDL_{10}$ (HED) of 0.0092 mg/kg-day for cytoplasmic vacuolation (all severity grades) in the thyroid of F0 male S-D rats following 25−29 weeks of dietary exposure (Chu et al., 1988), used as the POD for the screening subchronic p-RfD for weathered toxaphene mixtures, is also used as the POD for the screening chronic p-RfD with the same composite uncertainty factor (UF_C) as follows:

Screening Chronic p-RfD	=	$BMDL_{10}$ (HED) ÷ UF_C
for Weathered Toxaphene	=	0.0092 mg/kg-day ÷ 300
based on Technical Toxaphene	=	**3×10^{-5} mg/kg-day**

Other approaches have been proposed in the literature for deriving an oral reference dose (RfD) for weathered toxaphene using the data provided in Besselink et al. (2008). Besselink et al. (2008) described an approach to deriving p-RfDs using a daily-dose-adjustment of the 12.5 mg CLE/kg-week rat NOAEL noted above (12.5 mg CLE/kg-week × 1 week/7 days = 1.79 mg/kg-day). In a similar approach, Simon and Manning (2006) proposed the mass (or concentration) of p-26 (B8-1413), p-50 (B9-1679), and p-62 (B9-1025) as the dose metric for the CLE test substance in the Besselink et al. (2008) study. These congeners were selected by Simon and Manning (2006) to represent weathered toxaphene for deriving an RfD based on analyses of toxaphene congeners in human serum and breast milk samples. Samples were collected in five studies and show that >90% of the total congeners detected was the sum of only three, p-26, p-50, and p-62 (∑3PC). This suggests that humans are only exposed to these three congeners due to rapid metabolic disposition and elimination of other congeners.

Comparatively, the Besselink et al. (2008) dosimetric approach based on total dose of weathered toxaphene is more straightforward, involves fewer assumptions, and is better supported by the data than the Simon and Manning (2006) approach, as detailed below:

1. *The central assumption of the* Simon and Manning (2006) *approach that humans are primarily exposed to the ∑3PC persistent congeners detected in human serum and breast milk samples is highly uncertain*. This is because the central assumption is based only on detected levels in serum or breast milk samples [examination of toxaphene residues in other human tissues was not conducted in the five studies cited by Simon and Manning (2006)], and the analytical techniques employed may not have been designed to detect lower chlorinated toxaphene congeners with five or six chlorines per molecule. There are no data to directly support the idea of rapid metabolic disposition and elimination of other congeners in humans. There are, however, data suggesting the opposite (i.e., a shift away from highly chlorinated to lesser-chlorinated congeners) by biological weathering in fish (Besselink et al., 2008).

2. *The ∑3PC content of the CLE test substance represented a very low percentage of its total toxaphene mass and does not account for other toxaphene congeners in the CLE sample that may be toxic*. Simon and Manning (2006) estimated from chromatograms presented in the Besselink et al. (2008) study report that the ∑3PC percent content in the CLE test substance was only between 0.2−0.3%. The chromatogram of the CLE sample shows a complex profile of toxaphene congeners that is decidedly different from the technical toxaphene fed to the cod, with enrichment of peaks in the lower chlorination range of the chromatogram (Besselink et al., 2008). There is evidence that toxaphene mixtures enriched in congeners with <7 chlorines per molecule can be more toxic than

mixtures enriched in congeners with ≥7 chlorines, including p-26, p-50, and p-62 (Kapp et al., 2006). Not including these lower-chlorinated toxaphene congeners in deriving a toxicity value for weathered toxaphene mixtures may miss a considerable toxic fraction of whatever specific mixture of weathered toxaphene is being considered. This possibility would lead to an underestimation of hazard potential or risk if the exposure assessment were only based on measurements of ∑3PC content in environmental media (e.g., fish as food, sediments, water) and the weathered toxaphene mixture to which the target population was exposed was enriched in other toxic congeners, including those with <7 chlorines.

The screening p-RfDs derived above using the Chu et al. (1988) study on technical toxaphene are based on a dose metric of milligrams total toxaphene residues per kilogram body weight per day. Applying the screening p-RfDs for weathered toxaphene to estimate health risks would require chemical analyses for total toxaphene residues detected in environmental samples to estimate daily intakes in exposed populations. Confidence is low in this derivation due to the uncertainties discussed above and follow from the small amount of data comparing relative toxicities of technical toxaphene with weathered toxaphene mixtures or among weathered toxaphene mixtures of differing chemical composition. However, there is greater confidence in the derivation based on technical toxaphene than a derivation based on the CLE study because there is greater confidence in the POD used in the former. The POD for technical toxaphene was derived from a high-quality study that administered technical toxaphene via the oral route and established a lowest-observed-adverse-effect level (LOAEL) and a NOAEL for a sensitive critical effect (histopathological thyroid lesions) supported by related findings in other animal and human studies, as well as a comprehensive evaluation of other endpoints in the database as a whole. In contrast, the POD for CLE was derived from a single study in rats that administered CLE via a s.c. injection route (which imparts inherent uncertainty when extrapolating to an oral dose), evaluated a single, less sensitive endpoint (liver tumor promotion), and failed to find any effect supported in the toxicological database for technical toxaphene. Taken together, derivation of a CLE-based screening p-RfD is precluded.

APPENDIX B. DATA TABLES

Table B-1. Liver Endpoints in Male Mice Fed Technical Toxaphene in Diet for 14 Days[a]

Parameter[b]	Dose Group (mg/kg-d [ppm in food])					
	0	**1.8 (10 ppm)**	**7.3 (40 ppm)**	**15 (80 ppm)**	**29.6 (160 ppm)**	**60.1 (320 ppm)**
Range-Finding 14-D Study ($B6C3F_1$)						
Relative liver weight (% BW) (n = 12)	4.81 ± 0.18	4.78 ± 0.25 (−0.6%)	5.32 ± 0.26 (+11%)	6.05 ± 0.37* (+26%)	6.55 ± 0.32* (+36%)	7.43 ± 0.59* (+54%)
Absolute liver weight (g) (n = 12)	1.51 ± 0.08	1.51 ± 0.06 (0%)	1.72 ± 0.21 (+14%)	1.77 ± 0.17* (+17%)	1.96 ± 0.14* (+30%)	2.05 ± 0.15* (+36%)
Serum ALT (IU/L) (n = 3−5)	30.8 ± 6.13	29.3 ± 4.11 (−5%)	37.0 ± 8.49 (+20%)	34.7 ± 5.69 (+13%)	40.5 ± 2.12 (+32%)	52.0 ± 9.9* (+69%)
BrdU labeling index in liver (%)[c] (n = 5)	1.2 ± 0.0	1.0 ± 0.2 (−17%)	3.3 ± 0.7 (+175%)	6.3 ± 0.6 (+425%)	11.1 ± 0.9* (+825%)	17.6 ± 3.6* (+1,370%)
CAR Knockout 14-D Study (C57BL/6 and $CAR^{-/-}$)						
Paramater[b]	**Dose Group (mg/kg-d [ppm in food])**					
	0	**(10 ppm)**	**(40 ppm)**	**(80 ppm)**	**(160 ppm)**	**60.4 (320 ppm)**
Absolute liver weight: Wild-type (C57BL/6) mice	1.54 ± 0.04	NT	NT	NT	NT	1.96 ± 0.14* (+27%)
Absolute liver weight: $CAR^{-/-}$ mice	1.65 ± 0.23	NT	NT	NT	NT	1.57 ± 0.45 (−5%)
Relative liver weight: Wild-type (C57BL/6) mice	5.80 ± 0.21	NT	NT	NT	NT	9.09 ± 0.45* (+57%)
Relative liver weight: $CAR^{-/-}$ mice	5.91 ± 0.26	NT	NT	NT	NT	6.35 ± 0.9 (+7%)

[a]Wang et al. (2015).
[b]Values denote mean ± SD (% change from control) or SE as indicated, except where noted.
[c]Values denote mean ± SE (% change from control) digitally extracted from graphically presented data using GrabIt! software.
*Statistically significantly different from control at $p < 0.05$ using one-way ANOVA with Dunnett's post hoc test as reported in the study.

ALT = alanine aminotransferase; ANOVA = analysis of variance; BrdU = bromodeoxyuridine; BW = body weight; CAR = constitutive androstane receptor; NT = not tested; SD = standard deviation; SE = standard error.

Table B-2. Liver Endpoints in Male B6C3F$_1$ Mice Fed Technical Toxaphene in Diet for up to 28 Days[a, b]

Time point	Dose Group (mg/kg-d [ppm in food])			
	0	**0.6 (3 ppm)**	**5.9 (32 ppm)**	**60.3 (320 ppm)**
	Relative Liver Weight (g; *n* = 12)			
D 7	4.95 ± 0.31	5.28 ± 0.39 (+7%)	5.36 ± 0.73 (+8%)	7.46 ± 0.53* (+51%)
D 14	5.25 ± 0.33	5.36 ± 0.36 (+2%)	5.57 ± 0.33 (+6%)	7.94 ± 0.56* (+51%)
D 28	5.28 ± 0.27	5.27 ± 0.24 (−0.2%)	5.58 ± 0.16 (+6%)	8.37 ± 0.64* (+59%)
	Absolute Liver Weight (% BW; *n* = 12)			
D 7	1.31 ± 0.10	1.40 ± 0.13 (+7%)	1.39 ± 0.28 (+6%)	1.93 ± 0.21* (+47%)
D 14	1.49 ± 0.13	1.46 ± 0.12 (−2%)	1.59 ± 0.12 (+7%)	2.07 ± 0.23* (+40%)
D 28	1.57 ± 0.10	1.60 ± 0.12 (+2%)	1.72 ± 0.11 (+10%)[c]	2.34 ± 0.26* (+49%)
	Serum ALT (IU/L; *n* = 12)			
D 7	38.67 ± 18.85	25.92 ± 4.12 (−33%)	41.33 ± 17.1 (+7%)	66.58 ± 14.89* (+72%)
D 14	39.25 ± 17.03	32.08 ± 10.74 (−18%)	33.73 ± 6.48 (−14%)	77.83 ± 37.46* (+98%)
D 28	59.83 ± 37.82	34.55 ± 6.80 (−42%)	43.36 ± 7.20 (−28%)	100.67 ± 38.36* (+68%)
	BrdU Labeling Index in Liver (%; *n* = 5)[d]			
D 7	0.9 ± 0.3	0.9 ± 0.3 (0%)	3.3 ± 1.7 (+267%)	10.7 ± 2.4* (+1,089%)
D 14	1.2 ± 0.6	1.5 ± 0.3 (+25%)	2.4 ± 0.3 (+100%)	12.5 ± 4.3* (+942%)
D 28	0.9 ± 0.2	1 ± 0.7 (+11%)	1.7 ± 0.7 (+89%)	3.9 ± 1.7* (+333%)
	MDA Concentration in Liver (nmol/mg protein; *n* = 7)[d]			
D 7	9.6 ± 0.8	9.9 ± 0.5 (+3%)	10.7 ± 0.4 (+12%)	12.2 ± 1.1* (+27%)
D 14	9.6 ± 0.8	9.3 ± 0.5 (−3%)	9.5 ± 1.2 (−1%)	12.8 ± 0.6* (+33%)
D 28	8.6 ± 0.7	8.7 ± 0.7 (+1%)	9.5 ± 0.5 (+11%)	11.6 ± 0.4* (+35%)

[a]Wang et al. (2015).
[b]Values denote mean ± SD (% change from control) except where noted.
[c]Increase was only 9.6% and not deemed to be biologically significant (i.e., ≥10%).
[d]Values denote mean ± SE digitally extracted from graphically presented data using GrabIt! software.
*Statistically significantly different from control at $p < 0.05$ using one-way ANOVA with Dunnett's post hoc test as reported in the study.

ALT = alanine aminotransferase; ANOVA = analysis of variance; BrdU = bromodeoxyuridine; BW = body weight; MDA = malondialdehyde; SD = standard deviation; SE = standard error.

Table B-3. Anti-SRBC Response (IgM and IgG) and Antitetanus Toxoid Response (IgG) in Cynomolgus Monkeys Exposed to Encapsulated Technical Toxaphene for up to 75 Weeks[a, b]

Response	Weeks Postimmunization	Dose Group (mg/kg-d)			
		0	0.1	0.4	0.8
		Mean Log^2 Titers ± SE (% change)[c]			
		Females (n = 10/group)			
Anti-SRBC primary response (IgM)	1	7.1 ± 0.35	6.4 ± 0.54 (−9.9)	5.2 ± 0.79* (−26.8)	3.7 ± 0.83* (−47.9)
	2	6.4 ± 0.31	5.2 ± 0.73 (−18.8)	4.6 ± 0.78 (−28.1)	3 ± 0.88* (−53.1)
	3	5.3 ± 0.34	4.5 ± 0.64 (−15.1)	3.8 ± 0.85 (−28.3)	3 ± 0.75* (−43.4)
	4	4.9 ± 0.41	4 ± 0.61 (−18.4)	3.2 ± 0.63* (−34.7)	2.8 ± 0.61* (−42.9)
Anti-SRBC secondary response[d] (IgM)	5	6.1 ± 0.43	4.6 ± 0.62 (−24.6)	4.4 ± 0.48* (−27.9)	4.1 ± 0.69* (−32.8)
	6	4.7 ± 0.34	3.8 ± 0.42 (−19.1)	4.4 ± 0.52 (−6.4)	3.8 ± 0.57 (−19.1)
	7	4.3 ± 0.21	3.3 ± 0.47 (−23.3)	2.8 ± 0.55* (−34.9)	3.1 ± 0.46* (−27.9)
	8	3.9 ± 0.28	2.8 ± 0.53 (−28.2)	2.6 ± 0.64 (−33.3)	2.3 ± 0.58* (−41)
Anti-SRBC (IgG)	1	6 ± 1.12	3.5 ± 0.75 (−41.7)	4.5 ± 1.13 (−25)	3.3 ± 0.87 (−45)
	2	7.3 ± 1	5.6 ± 1.01 (−23.3)	5.5 ± 1.19 (−24.7)	3.6 ± 0.91* (−50.7)
	3	7.4 ± 0.9	5.4 ± 1.07 (−27)	5.2 ± 1.17 (−29.7)	4.2 ± 0.84* (−43.2)
Antitetanus toxoid (IgG)	Preimmune	−1.54 ± 0.13	−1.41 ± 0.11 (−8.4)	−1.62 ± 0.12 (+5.2)	−1.54 ± 0.17 (0)
	1	−1.03 ± 0.13	−0.89 ± 0.08 (−13.6)	−1.04 ± 0.1 (+1)	−1.21 ± 0.17 (+17.5)
	2	0.75 ± 0.1	0.81 ± 0.06 (+8)	0.84 ± 0.04 (+12)	0.45 ± 0.08* (−40)
	3	1.01 ± 0.07	1.05 ± 0.07 (+4)	1.1 ± 0.07 (+8.9)	0.68 ± 0.08* (−32.7)
	4	1.11 ± 0.07	1.16 ± 0.06 (+4.5)	1.21 ± 0.07 (+9)	0.84 ± 0.09* (−24.3)
	5	0.85 ± 0.08	0.89 ± 0.05 (+4.7)	0.95 ± 0.07 (+11.8)	0.87 ± 0.08 (+2.4)
Anti-SRBC primary response (IgM)		Males (n = 5, controls; n = 4, 0.8 mg/kg-d)			
	1	9 ± 0.32	ND	ND	6.5 ± 0.29* (−27.8)
	2	8 ± 0.32	ND	ND	5.25 ± 0.63* (−34.4)
	3	7.4 ± 0.4	ND	ND	4.75 ± 0.85* (−35.8)

[a]Tryphonas et al. (2001).
[b]Immune testing occurred between exposure Weeks 33−46 for levels of immune components in blood, Weeks 44−53 for SRBC responses, Weeks 53−63 for tetanus toxoid responses, and Weeks 66−70 for pneumococcus responses. No exposure-related effects on blood immune components or antipneumoccocus responses were found.
[c]% change = ([exposure mean − control mean] ÷ control mean) × 100.
[d]Secondary response (Weeks 5−8) indicates responses following a second exposure to SRBC antigen administered during Week 4.
*Statistically significantly different from control value ($p < 0.05$ with Bonferroni adjustment) as determined by study authors.

IgG = immunoglobulin G; IgM = immunoglobulin M; ND = no data; SE = standard error; SRBC = sheep red blood cell.

Table B-4. Relative Liver Weight and Serum ALP in Beagle Dogs Administered Technical Toxaphene in Gelatin Capsules (Corn Oil Vehicle) for 13 Weeks[a]

	Dose Group (mg/kg-d)			
	0	**0.2**	**2.0**	**4.5**
Parameter[b]	**Males**			
Relative liver weight (% BW)	3.7 ± 0.54	3.6 ± 0.46 (−3%)	3.6 ± 0.21 (−3%)	4.4 ± 0.45* (+19%)
Serum ALP (13 wk) (mIU/mL)	70 ± 26	73 ± 49[c] (+4%)	94 ± 47 (+34%)	168 ± 66* (+140%)
Parameter[b]	**Females**			
Relative liver weight (% BW)	3.0 ± 0.6	3.4 ± 0.4 (+13%)	3.6 ± 0.31* (+20%)	3.9 ± 0.46* (+30%)
Serum ALP (13 wk) (mIU/mL)	74 ± 22	153 ± 80[c] (+107%)	145 ± 95[c] (+96%)	185 ± 68*[c] (+150%)

[a]Chu et al. (1986).
[b]Values denote mean ± SD (% change from control) (n = 6 unless noted).
[c]n = 5.
*Significantly different from controls ($p \leq 0.05$) using one-way ANOVA with Dunnett's post hoc test as reported in the study.

ALP = alkaline phosphatase; ANOVA = analysis of variance; BW = body weight; SD = standard deviation.

Table B-5. Incidences of Non-neoplastic Lesions in Beagle Dogs Administered Technical Toxaphene in Gelatin Capsules (Corn Oil Vehicle) for 13 Weeks[a]

Lesion[b]	Dose Group (mg/kg-d)			
	0	0.2	2.0	4.5
	Males			
Liver:				
Accented zonation	2/6 (33)	2/6 (33)	1/6 (17)	3/6 (50)
Periportal eosinophilia	1/6 (17)	3/6 (50)	4/6 (67)	6/6* (100)
Cytoplasmic vacuolation	0/6 (0)	0/6 (0)	2/6 (33)	2/6 (33)
Increased cytoplasmic density	1/6 (17)	3/6 (50)	3/6 (50)	6/6* (100)
Kidney:				
Glomerular adhesions	1/6 (17)	3/6 (50)	2/6 (33)	4/6 (67)
Thyroid:				
Reduced follicle size/follicular collapse	0/6 (0)	0/6 (0)	1/6 (17)	3/6 (50)
Increased epithelial height	0/6 (0)	1/6 (17)	3/6 (50)	2/6 (33)
Reduced colloid density	0/6 (0)	1/6 (17)	1/6 (17)	2/6 (33)
Lesion	**Females**			
Liver:				
Accented zonation	1/6 (17)	2/6 (33)	3/6 (50)	4/6 (67)
Periportal eosinophilia	2/6 (33)	1/6 (17)	4/6 (67)	6/6 (100)
Cytoplasmic vacuolation	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)
Increased cytoplasmic density	2/6 (33)	1/6 (17)	4/6 (67)	5/6 (83)
Kidney:				
Glomerular adhesions	0/6 (0)	1/6 (0)	3/6 (50)	1/6 (17)
Thyroid:				
Reduced follicle size/follicular collapse	0/6 (0)	4/6 (67)	5/6* (83)	3/6 (50)
Increased epithelial height	0/6 (0)	4/6 (67)	4/6 (67)	2/6 (33)
Reduced colloid density	0/6 (0)	5/6 (83)*	5/6* (83)	2/6 (33)

[a]Chu et al. (1986).
[b]Values denote number of animals showing changes/total number of animals examined (% in parentheses).
*Statistically significantly different from control at $p < 0.05$, as calculated for this review (Fisher's exact test, two-tailed).

Table B-6. Relative Liver Weight in S-D Rats Fed Technical Toxaphene in Food for 13 Weeks[a]

	Dose Group (mg/kg-d [ppm in food])				
	Males				
Parameter[b]	0	0.35 (4 ppm)	1.8 (20 ppm)	8.6 (100 ppm)	45.9 (500 ppm)
Relative liver weight (% BW)	3.8 ± 0.27	3.7 ± 0.29 (−3%)	3.9 ± 0.29 (+3%)	3.9 ± 0.18 (+3%)	4.5 ± 0.58* (+18%)
	Females				
Parameter[b]	0	0.5 (4 ppm)	2.6 (20 ppm)	12.6 (100 ppm)	63 (500 ppm)
Relative liver weight (% BW)	3.4 ± 0.32	3.6 ± 0.31 (+6%)	3.7 ± 0.22 (+9%)	3.7 ± 0.36 (+9%)	4.5 ± 0.20*[c] (+32%)

[a]Chu et al. (1986).
[b]Values denote mean ± SD (% change from control) (n = 9 or 10).
[c]SD is reported in the study as 20; this is assumed to be typographical error.
*Significantly different from controls at $p < 0.5$ using one-way ANOVA with Dunnett's post hoc test as reported in the study.

ANOVA = analysis of variance; BW = body weight; S-D = Sprague-Dawley; SD = standard deviation.

Table B-7. Incidences of Non-neoplastic Lesions in S-D Rats Fed Technical Toxaphene in Food for 13 Weeks[a]

	Dose Group (mg/kg-d [ppm in food])				
	Males				
Lesion[b]	0	0.35 (4 ppm)	1.8 (20 ppm)	8.6 (100 ppm)	45.9 (500 ppm)
Liver:					
Accented zonation					
Minimal to mild	0/10 (0)	1/10 (10)	3/10 (30)	5/10* (50)	6/10* (60)
Moderate to severe	0/10 (0)	0/10 (0)	1/10 (10)	0/10 (0)	4/10 (40)
All severity	0/10 (0)	1/10 (10)	4/10 (40)	5/10† (50)	10/10† (100)
Anisokaryosis					
Minimal to mild	2/10 (20)	4/10 (40)	7/10 (70)	9/10* (90)	3/10 (30)
Moderate to severe	0/10 (0)	0/10 (0)	1/10 (0)	0/10 (0)	7/10* (70)
All severity	2/10 (20)	4/10 (40)	8/10† (80)	9/10† (90)	10/10† (100)
Nuclear necrosis					
Minimal to mild	0/10 (0)	0/10 (0)	5/10* (50)	2/10 (20)	9/10* (90)
Moderate to severe	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
All severity	0/10 (0)	0/10 (0)	5/10† (50)	2/10 (20)	9/10† (90)
Kidney:					
Tubular injury-primary					
Minimal to mild	0/10 (0)	2/10 (20)	8/10* (80)	8/10* (80)	1/10 (10)
Moderate to severe	1/10 (10)	2/10 (20)	2/10 (20)	2/10 (20)	9/10* (90)
All severity	1/10 (0)	4/10 (40)	10/10† (100)	10/10† (100)	10/10† (100)
Tubular necrosis					
Minimal to mild	0/10 (0)	0/10 (0)	4/10 (40)	7/10* (70)	9/10* (90)
Moderate to severe	0/10 (0)	0/10 (0)	1/10 (10)	0/10 (0)	1/10 (10)
All severity	0/10 (0)	0/10 (0)	5/10† (50)	7/10† (70)	10/10† (100)

Table B-7. Incidences of Non-neoplastic Lesions in S-D Rats Fed Technical Toxaphene in Food for 13 Weeks[a]

	Dose Group (mg/kg-d [ppm in food])				
Thyroid:					
Reduced follicular size					
Minimal to mild	4/10 (40)	2/10 (20)	5/10 (50)	6/9 (67)	3/9 (33)
Moderate to severe	0/10 (0)	0/10 (0)	1/10 (10)	1/9 (11)	2/9 (22)
All severity	4/10 (40)	2/10 (20)	6/10 (60)	7/18 (39)	5/9 (56)
Increased epithelial height					
Minimal to mild	5/10 (50)	7/10 (70)	3/10 (30)	0/9 (0)	0/9 (0)
Moderate to severe	2/10 (20)	3/10 (30)	7/10 (70)	9/9* (100)	9/9* (100)
All severity	7/10 (70)	10/10 (100)	10/10 (100)	9/9 (100)	9/9 (100)
Cytoplasmic vacuolation					
Minimal to mild	1/10 (10)	2/10 (20)	2/10 (20)	5/9 (56)	5/9 (56)
Moderate to severe	1/10 (10)	1/10 (10)	2/10 (20)	4/9 (44)	2/9 (22)
All severity	2/10 (20)	3/10 (30)	4/10 (40)	9/9† (100)	7/9† (78)
Reduced colloid density					
Minimal to mild	6/10 (60)	7/10 (70)	3/10 (30)	1/9 (11)	0/9 (0)
Moderate to severe	1/10 (10)	3/10 (30)	7/10* (70)	8/9* (89)	9/9* (100)
All severity	7/10 (70)	10/10 (100)	10/10 (100)	9/9 (100)	9/9 (100)
	Females				
Lesion[b]	**0**	**0.5 (4 ppm)**	**2.6 (20 ppm)**	**12.6 (100 ppm)**	**63 (500 ppm)**
Liver:					
Accented zonation					
Minimal to mild	0/10 (0)	4/10 (40)	5/10 (50)	7/10* (70)	3/10 (30)
Moderate to severe	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	7/10* (70)
All severity	0/10 (0)	4/10 (4)	5/10† (50)	7/10† (70)	10/10† (100)
Anisokaryosis					
Minimal to mild	0/10 (0)	6/10* (60)	9/10* (90)	9/10* (90)	3/10 (30)
Moderate to severe	0/10 (0)	0/10 (0)	0/10 (0)	1/10 (10)	7/10* (70)
All severity	0/10 (0)	6/10† (60)	9/10† (90)	10/10† (100)	10/10† (100)
Nuclear necrosis					
Minimal to mild	0/10 (0)	0/10 (0)	3/10 (30)	3/10 (30)	7/10* (70)
Moderate to severe	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
All severity	0/10 (0)	0/10 (0)	3/10 (30)	3/10 (30)	7/10† (70)
Kidney:					
Tubular injury-primary					
Minimal to mild	0/10 (0)	2/10 (20)	1/10 (10)	6/10* (60)	10/10* (100)
Moderate to severe	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
All severity	0/10 (0)	2/10 (20)	1/10 (10)	6/10† (60)	10/10† (100)
Tubular necrosis					
Minimal to mild	0/10 (0)	8/10* (80)	9/10* (90)	8/10* (80)	8/10* (80)
Moderate to severe	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
All severity	0/10 (0)	8/10† (80)	9/10† (90)	8/10† (80)	8/10† (80)

Table B-7. Incidences of Non-neoplastic Lesions in S-D Rats Fed Technical Toxaphene in Food for 13 Weeks[a]

	Dose Group (mg/kg-d [ppm in food])				
Thyroid:					
Reduced follicular size					
Minimal to mild	0/10 (0)	5/10* (50)	5/10* (50)	7/10* (70)	5/10* (50)
Moderate to severe	0/10 (0)	1/10 (10)	3/10 (30)	2/10 (20)	5/10* (50)
All severity	0/10 (0)	6/10† (60)	8/10† (80)	9/10† (90)	10/10† (100)
Increased epithelial height					
Minimal to mild	0/10 (0)	6/10* (60)	10/10* (100)	9/10* (90)	8/10* (80)
Moderate to severe	0/10 (0)	3/10 (30)	0/10 (0)	1/10 (10)	2/10 (20)
All severity	0/10 (0)	9/10† (90)	10/10† (100)	10/10† (100)	10/10† (100)
Cytoplasmic vacuolation					
Minimal to mild	0/10 (0)	8/10* (80)	8/10* (80)	8/10* (80)	3/10 (30)
Moderate to severe	0/10 (0)	2/10 (20)	0/10 (0)	1/10 (10)	7/10* (70)
All severity	0/10 (0)	10/10† (100)	8/10† (80)	9/10† (90)	10/10† (100)
Reduced colloid density					
Minimal to mild	0/10 (0)	9/10* (90)	9/10* (90)	10/10* (100)	3/10 (30)
Moderate to severe	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	7/10* (70)
All severity	0/10 (0)	9/10† (90)	9/10† (90)	10/10† (100)	10/10† (100)

[a]Chu et al. (1986).
[b]Number of animals with lesion/number of animals examined microscopically (corresponding %).
*Statistically significantly ($p < 0.05$) different from control within the same severity group, as calculated for this review (Fisher's exact test, two-tailed).
†Statistically significantly ($p < 0.05$) different from control; total number of lesions (minimal to mild + moderate to severe) compared with the total number of lesions in the control, as calculated for this review (Fisher's exact test, two-tailed).

S-D = Sprague-Dawley.

Table B-8. Relative Liver Weight in Male S-D Rats Fed Technical Toxaphene in Diet for 9 Weeks[a]

Parameter[b]	Dose Group (mg/kg-d [ppm in food])		
	0	**2.6 (30 ppm)**	**25.8 (300 ppm)**
Relative liver weight (% BW)	4.5 ± 0.1	5.0 ± 0.1 (+11%)	5.6 ± 0.1* (+24%)

[a]Koller et al. (1983).
[b]Values denote mean ± SE (% change from control).
*Significantly different from controls ($p < 0.0001$) using ANOVA and least square means as reported in the study.

ANOVA = analysis of variance; BW = body weight; S-D = Sprague-Dawley; SE = standard error.

Table B-9. Liver-Weight Changes in Female Swiss-Webster Mice Fed Technical Toxaphene in Diet for 8 Weeks[a]

Parameter[b]	Dose Group (mg/kg-d [ppm in food])			
	0	1.9 (10 ppm)	19.1 (100 ppm)	39.2 (200 ppm)
Absolute liver weight (g)	1.76	1.78 (+1%)	2.01 (+14%)	2.24 (+27%)
Relative liver weight (g/g BW)	0.062	0.061 (−2%)	0.072* (+16%)	0.089* (+44%)

[a]Allen et al. (1983).
[b]Presented as mean (% change from control) (n = 23−26).
*Statistically significantly different from control at $p < 0.5$ based on t-test as reported in the study.

BW = body weight.

Table B-10. Incidence Data for Liver Tumors in B6C3F$_1$ Mice Fed Technical Toxaphene in Diet for 18 Months[a, b]

Tumor Type	Dose Group (mg/kg-d [ppm in food])			
	0	0.91 (7 ppm)	2.6 (20 ppm)	6.5 (50 ppm)
Males				
Early deaths				
Hepatocellular adenomas	0/9	0/7	0/8	0/5
Hepatocellular carcinomas	2/9	2/7	2/8	1/5
Terminal sacrifice				
Hepatocellular adenomas	3/44	0/47	2/45	11/46
Hepatocellular carcinomas	5/44	9/47	10/45	11/46
Total for livers with hepatocellular tumors	10/53**	10/54	12/53	18/51*
Females				
Early deaths				
Hepatocellular adenomas	0/7	0/7	0/9	0/7
Hepatocellular carcinomas	0/7	0/7	0/9	0/7
Terminal sacrifice				
Hepatocellular adenomas	1/46	1/46	1/43	3/45
Hepatocellular carcinomas	1/46	1/46	3/43	2/45
Total for livers with hepatocellular tumors	2/53	2/53	4/52	6/52

[a]Litton Bionetics (1978) as reported by U.S. EPA (1980).
[b]Mice were fed technical toxaphene in food for 18 months, followed by a 6-month observation period. Reported incidence data are for mice with tumors at the terminal sacrifice and for mice that died earlier.
*Significantly different from control by Fisher's exact test as reported by U.S. EPA (1980).
**Significant trend by Cochran-Armitage trend test as reported by U.S. EPA (1980).

Table B-11. Incidence of Non-neoplastic Lesions in Osborne-Mendel Rats and B6C3F$_1$ Mice Fed Technical Toxaphene in the Diet for 80 Weeks[a]

	Dose Group (mg/kg-d [TWA concentration in food, ppm])		
	Male Rats		
Lesion[b]	**0**	**38.9 (556 ppm)**	**77.88 (1,112 ppm)**
Liver			
Degeneration, ballooning	0/9 (0)	1/44 (2)	1/45 (2)
Necrosis, focal	0/9 (0)	0/44 (0)	1/45 (2)
Fatty metamorphosis	0/9 (0)	2/44 (5)	4/45 (9)
Kidney			
Multiple cysts	0/9 (0)	1/45 (2)	0/45 (0)
Chronic inflammation	4/9 (44)	9/45 (20)	20/45 (44)
Cystic degeneration	0/9 (0)	1/45 (2)	0/45 (0)
Thyroid			
Follicular cyst	0/7 (0)	2/41 (5)	1/35 (3)
C-cell hyperplasia	0/7 (0)	2/41 (5)	1/35 (3)
Follicular hyperplasia	0/7 (0)	3/41 (7)	3/35 (9)
	Female Rats		
Lesion[b]	**0**	**41.6 (540 ppm)**	**83.29 (1,080 ppm)**
Liver			
Fatty metamorphosis	1/10 (1)	2/42 (5)	2/40 (5)
Basophilic cytoplasmic change	0/10 (0)	0/42 (2)	1/40 (3)
Kidney			
Chronic inflammation	1/8 (13)	8/49 (16)	2/48 (4)
Thyroid			
Follicular cyst	0/6 (0)	0/43 (0)	2/42 (5)
C-cell hyperplasia	0/6 (0)	4/43 (9)	2/42 (5)
Follicular hyperplasia	0/6 (0)	5/43 (12)	3/42 (7)
	Female Mice		
Lesion[b]	**0**	**17 (99 ppm)**	**34.2 (198 ppm)**
Liver			
Chronic inflammation	0/9 (0)	1/49 (2)	0/49 (0)
Fatty metamorphosis	0/9 (0)	0/49 (0)	1/49 (2)
Thyroid			
Follicular hyperplasia	0/7 (0)	0/45 (0)	1/38 (3)

[a]NCI (1979).
[b]Values denote number of animals showing lesion/total number of animals examined (% in parentheses). No statistically significantly increased incidences of any non-neoplastic lesions were found in exposed groups, compared with controls. Incidence data in table are for lesions in liver, kidney, or thyroid with nonzero incidences in exposed groups.

TWA = time-weighted average.

Table B-12. Statistically Significant Incidence Data for Tumors in Osborne-Mendel Rats and B6C3F$_1$ Mice Fed Technical Toxaphene in Diet for 80 Weeks[a, b, c]

Tumor Type	Dose Group (mg/kg-d [ppm in food])			
Male Rats				
	Matched Control	Pooled Control	38.9 (556 ppm)	77.88 (1,112 ppm)
Liver				
Neoplastic nodules	1/9	1/52	6/44**	4/45
Thyroid				
Follicular-cell carcinoma or adenoma	1/7	2/44	7/41	9/35**
Female Rats				
	Matched Control	Pooled Control	41.6 (540 ppm)	83.29 (1,080 ppm)
Pituitary				
Chromophobe adenoma, adenoma (NOS), or carcinoma	3/8***	17/51***	15/41	23/39**
Thyroid				
Follicular cell adenoma	0/6***	1/46***	1/43	7/42**
Male Mice				
	Matched Control	Pooled Control	17 (99 ppm)	34.0 (198 ppm)
Liver				
Hepatocellular carcinoma	0/10***	4/48***	34/49*/**	45/46*/**
Hepatocellular carcinoma or adenoma	2/10***	7/48***	40/49*/**	45/46*/**
Female Mice				
	Matched Control	Pooled Control	17 (99 ppm)	34.2 (198 ppm)
Liver				
Hepatocellular carcinoma	0/9***	0/48***	5/49*/**	34/49*/**
Hepatocellular carcinoma or adenoma	0/9***	0/48***	18/49*/**	40/49*/**

[a]NCI (1979).
[b]Only data for significantly increased incidences or increased dose trends are reported in this table.
[c]Rats were fed technical toxaphene in food for 80 weeks. Groups of 10 matched rats/sex served as nonexposed concurrent controls and up to 52 control rats/sex or 48 control mice/sex were pooled from other studies started within a 5-month period of the start of the toxaphene study.
*Significantly different from matched control by Fisher's exact test as reported by NCI (1979).
**Significantly different from pooled control by Fisher's exact test as reported by NCI (1979).
***Significant trend by Cochran-Armitage trend test as reported by NCI (1979).

NOS = not otherwise specified.

Table B-13. Body-, Liver-, and Kidney-Weight Changes in S-D Rats Fed Technical Toxaphene in Diet for up to 34 Weeks[a, b]

	Dose Group (mg/kg-d [ppm in diet])				
	F0 Males				
Parameter[c]	0	0.36 (4 ppm)	1.8 (20 ppm)	9.2 (100 ppm)	45 (500 ppm)
Body-weight gain (g)	529 ± 66	551 ± 71 (+4%)	480 ± 58 (−9%)	528 ± 74 (−0.2%)	520 ± 41 (−2%)
Absolute liver weight (g)	21.6 ± 2.9	22.8 ± 4.4 (+6%)	20.1 ± 2.6 (−7%)	21.2 ± 3.6 (−2%)	25.5 ± 3* (+18%)
Relative liver weight (% BW)	3.6 ± 0.47	3.6 ± 0.52 (0%)	3.6 ± 0.42 (0%)	3.5 ± 0.57 (−3%)	4.2 ± 0.4*[d] (+17%)
Absolute kidney weight (g)	1.7 ± 0.15	1.9 ± 0.21 (+12%)	1.7 ± 0.19 (0%)	1.8 ± 0.16 (+6%)	2 ± 0.22* (+18%)
Relative kidney weight (% BW)	0.28 ± 0.03	0.29 ± 0.03 (+4%)	0.31 ± 0.04 (+11%)	0.3 ± 0.03 (+7%)	0.33 ± 0.03* (+18%)
	F0 Females				
Parameter[c]	0	0.36 (4 ppm)	1.9 (20 ppm)	8.5 (100 ppm)	46 (500 ppm)
Body-weight gain (g)	237 ± 32	249 ± 54 (+5%)	240 ± 35 (+1%)	235 ± 34 (−0.8%)	239 ± 35 (+0.8%)
Absolute liver weight (g)	11.6 ± 2	12.9 ± 2 (+11%)	13.8 ± 3.3* (+19%)	13.6 ± 2.7* (+17%)	16.6 ± 3.2* (+43%)
Relative liver weight (% BW)	3.7 ± 0.48	4 ± 0.57 (+8%)	4.4 ± 0.92* (+19%)	4.4 ± 0.59* (+19%)	5.3 ± 0.84* (+43%)
Absolute kidney weight (g)	1.1 ± 0.09	1.1 ± 0.09 (0%)	1.2 ± 0.14 (+9%)	1.2 ± 0.18 (+9%)	1.1 ± 0.09 (0%)
Relative kidney weight (% BW)	0.36 ± 0.03	0.36 ± 0.04 (0%)	0.38 ± 0.03 (+6%)	0.37 ± 0.04 (+3%)	0.37 ± 0.03 (+3%)
	F1a Adult Males				
Parameter[c]	0	0.29 (4 ppm)	1.4 (20 ppm)	7.5 (100 ppm)	37 (500 ppm)
Body-weight gain (g)	526 ± 53	500 ± 57 (−5%)	507 ± 43 (−4%)	544 ± 64 (+3%)	471 ± 68* (−11%)
Absolute liver weight (g)	20 ± 2.5	22 ± 3.1 (+10%)	21 ± 4.1 (+5%)	21 ± 2.4 (+5%)	24 ± 3.6* (+20%)
Relative liver weight (% BW)[e]	1.7 ± 0.19	3.6 ± 0.49 (+112%)	3.4 ± 0.62 (+100%)	3.4 ± 0.31 (+100%)	4.2 ± 0.38* (+147%)
Absolute kidney weight (g)	1.7 ± 0.19	1.8 ± 0.23 (+6%)	1.8 ± 0.15 (+6%)	2.0 ± 0.2* (+18%)	2.0 ± 0.33* (+18%)
Relative kidney weight (% BW)	0.28 ± 0.02	0.3 ± 0.04 (+7%)	0.3 ± 0.02 (+7%)	0.31 ± 0.02 (+11%)	0.34 ± 0.05* (+21%)

Table B-13. Body-, Liver-, and Kidney-Weight Changes in S-D Rats Fed Technical Toxaphene in Diet for up to 34 Weeks[a, b]

	Dose Group (mg/kg-d [ppm in diet])				
	F1a Adult Females				
Parameter[c]	0	0.38 (4 ppm)	1.9 (20 ppm)	9.4 (100 ppm)	49 (500 ppm)
Body-weight gain (g)	254 ± 61	240 ± 29 (−6%)	245 ± 32 (−4%)	246 ± 42 (−3%)	216 ± 26* (−15%)
Absolute liver weight (g)	12 ± 1.7	13.7 ± 1.9 (+14%)	12.8 ± 1.6 (+7%)	13 ± 2.2 (+8%)	15.7 ± 2.2* (+31%)
Relative liver weight (% BW)	3.9 ± 0.93	4.1 ± 0.47 (+5%)	3.9 ± 0.43 (0%)	4.1 ± 0.54 (+5%)	5.2 ± 0.76* (+33%)
Absolute kidney weight (g)	1.1 ± 0.18	1.2 ± 0.11 (+9%)	1.1 ± 0.14 (0%)	1.2 ± 0.16 (+9%)	1.1 ± 0.12 (0%)
Relative kidney weight (% BW)	0.35 ± 0.08	0.36 ± 0.04 (+3%)	0.35 ± 0.04 (0%)	0.38 ± 0.05 (+9%)	0.36 ± 0.04 (+3%)

[a]Chu et al. (1988).
[b]F0 rats were exposed to toxaphene between 25−29 weeks depending upon length of mating time, which was described as "up to 3 weeks" and GD 0. F1 rats were exposed for a total of 34 weeks (3 weeks in utero, 3 weeks via lactation, followed by 28 weeks via diet).
[c]Data reported as mean ± SD (% change from control).
[d]Study reports SD as 4.0; this is assumed to be a typographical error.
[e]The control relative liver weight for F1a male rats was unusually low, compared with control means for F1a females (3.9), F0 males (3.6), and F0 females (3.7). It is likely that this reflects a typographical error (note that the values are the same as the control absolute kidney weight reported in a neighboring column in the study) and that the calculated percent change values are erroneous.
*Statistically significantly different from control at $p \leq 0.05$, using one-way ANOVA with Duncan's multiple range test, as reported in the study.

ANOVA = analysis of variance; BW = body weight; GD = gestation day; S-D = Sprague-Dawley; SD = standard deviation.

Table B-14. Incidences of Non-neoplastic Lesions in Parental S-D Rats Fed Technical Toxaphene for 25−29 Weeks[a, b]

	Dose Group (mg/kg-d [ppm in diet])				
	F0 Males				
Lesion[c]	0	0.36 (4 ppm)	1.8 (20 ppm)	9.2 (100 ppm)	45 (500 ppm)
Thyroid:					
Follicle collapse/angularity					
Minimal to mild	0/12 (0)	1/10 (10)	3/10 (30)	3/11 (27)	6/13* (46)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	0/11 (0)	0/13 (0)
All severity	0/12 (0)	1/10 (10)	3/10 (30)	3/11 (27)	6/13† (46)
Cytoplasmic vacuolation					
Minimal to mild	0/12 (0)	3/10 (30)	8/10* (80)	6/11* (55)	12/13* (92)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	1/11 (9)	0/13 (0)
All severity	0/12 (0)	3/10 (30)	8/10† (80)	7/11† (64)	12/13† (92)
Reduced colloid density					
Minimal to mild	5/12 (42)	8/10 (0)	10/10* (100)	9/11* (82)	3/13 (23)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	2/11 (18)	9/13* (69)
All severity	5/12 (42)	8/10 (80)	10/10† (100)	11/11† (100)	12/13† (92)
Colloid inspissation					
Minimal to mild	0/12 (0)	4/10* (40)	8/10* (80)	4/11 (36)	5/13* (38)
Moderate to severe	0/12 (0)	1/10 (1)	0/10 (0)	0/11 (0)	7/13* (54)
All severity	0/12 (0)	5/10† (50)	8/10† (80)	4/11 (36)	12/13† (92)
Liver:					
Increased cytoplasmic density					
Minimal to mild	0/12 (0)	4/10* (40)	2/10 (20)	2/11 (18)	12/13* (92)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
All severity	1/12 (0)	4/10† (40)	2/10 (20)	2/11 (18)	12/13† (92)
Increased cytoplasmic homogeneity					
Minimal to mild	0/12 (0)	0/10 (0)	0/10 (0)	1/11 (9)	8/13* (62)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	0/11 (0)	4/13 (31)
All severity	0/12 (0)	0/10 (0)	0/10 (0)	1/11 (9)	12/13† (92)
Anisokaryosis					
Minimal to mild	2/12 (17)	2/10 (20)	4/10 (40)	3/11 (27)	11/13* (85)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	0/11 (0)	0/13 (0)
All severity	2/12 (17)	2/10 (20)	4/10 (40)	3/11 (27)	11/13† (85)
Kidney:					
Primary tubular injury					
Minimal to mild	0/12 (0)	4/10* (40)	5/10* (50)	3/11 (27)	11/13* (85)
Moderate to severe	0/12 (0)	3/10 (30)	0/10 (0)	0/11 (0)	2/13 (15)
All severity	0/12 (0)	7/10† (70)	5/10† (50)	3/11 (27)	13/13† (100)
Anisokaryosis					
Minimal to mild	1/12 (8)	2/10 (20)	5/10* (50)	0/11 (0)	5/13 (38)
Moderate to severe	0/12 (0)	1/10 (10)	0/10 (0)	1/11 (9)	1/13 (8)
All severity	1/12 (8)	3/10 (30)	5/10† (50)	1/11 (9)	6/13† (46)
Pyknosis					
Minimal to mild	0/12 (0)	2/10 (20)	2/10 (20)	1/11 (9)	5/13* (38)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	0/11 (0)	0/13 (0)
All severity	0/12 (0)	2/10 (20)	2/10 (20)	1/11 (9)	5/13† (38)
Interstitial sclerosis					
Minimal to mild	0/12 (0)	2/10 (20)	3/10 (30)	2/11 (18)	5/13* (38)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	0/11 (0)	1/13 (8)
All severity	0/12 (0)	2/10 (20)	3/10 (30)	2/11 (18)	6/13† (46)

Table B-14. Incidences of Non-neoplastic Lesions in Parental S-D Rats Fed Technical Toxaphene for 25−29 Weeks[a, b]

Lesion	Dose Group (mg/kg-d [ppm in diet])				
	F0 Females				
	0	0.36 (4 ppm)	1.9 (20 ppm)	8.5 (100 ppm)	46 (500 ppm)
Thyroid:					
Follicle collapse/angularity					
Minimal to mild	5/17 (29)	6/10 (60)	8/10* (80)	7/10 (70)	9/17 (65)
Moderate to severe	0/17 (0)	1/10 (10)	0/10 (0)	0/10 (0)	1/17 (12)
All severity	5/17 (29)	7/10 (70)	8/10† (80)	7/10 (70)	10/17 (59)
Increased epithelial height					
Minimal to mild	12/17 (71)	10/10 (100)	10/10 (100)	7/10 (70)	17/17* (100)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	3/10 (30)	0/17 (0)
All severity	12/17 (71)	10/10 (100)	10/10 (100)	10/10 (100)	17/17† (100)
Cytoplasmic vacuolation					
Minimal to mild	2/17 (12)	4/10 (40)	4/10 (40)	6/10* (60)	9/17* (53)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	1/10 (10)	0/17 (0)
All severity	2/17 (12)	4/10 (40)	4/10 (40)	7/10† (70)	9/17† (53)
Liver:					
Increased cytoplasmic vacuolation					
Minimal to mild	1/17 (6)	0/10 (0)	0/10 (0)	0/10 (0)	9/17* (53)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/17 (0)
All severity	1/17 (6)	0/10 (0)	0/10 (0)	0/10 (0)	9/17† (53)
Increased cytoplasmic density					
Minimal to mild	10/17 (59)	5/10 (50)	6/10 (60)	7/10 (70)	9/17 (53)
Moderate to severe	0/17 (0)	0/10 (0)	2/10 (2)	1/10 (10)	8/17* (47)
All severity	10/17 (59)	5/10 (50)	8/10 (80)	8/10 (80)	17/17† (100)
Increased cytoplasmic homogeneity					
Minimal to mild	0/17 (0)	0/10 (0)	0/10 (0)	0/10 (0)	12/17* (71)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	0/10 (0)	5/17 (18)
All severity	0/17 (0)	0/10 (0)	0/10 (0)	0/10 (0)	17/17† (100)
Anisokaryosis					
Minimal to mild	4/17 (24)	8/10* (80)	10/10* (100)	7/10* (70)	14/17* (82)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	0/10 (0)	3/17 (18)
All severity	4/17 (24)	8/10† (80)	10/10† (100)	7/10† (70)	17/17† (100)
Kidney:					
Primary tubular injury					
Minimal to mild	0/17 (0)	0/10 (0)	5/10* (50)	6/10* (60)	17/17* (100)
Moderate to severe	0/17 (0)	1/10 (10)	0/10 (0)	0/10 (0)	0/17 (0)
All severity	0/17 (0)	1/10 (10)	5/10† (50)	6/10† (60)	17/17† (100)

[a]Chu et al. (1988).
[b]F0 rats were exposed to toxaphene between 25−29 weeks depending upon length of mating time, which was described as "up to 3 weeks" and GD 0.
[c]Number of animals with lesion/number of animals examined microscopically (corresponding %).
*Statistically significantly different from control at $p < 0.05$, compared with control (within the same severity group), as calculated for this review (Fisher's exact test).
†Statistically significantly different from control at $p < 0.05$, total number of lesions (minimal to mild + moderate to severe) compared with the total number of lesions in the control, as calculated for this review (Fisher's exact test).

GD = gestation day; S-D = Sprague-Dawley.

Table B-15. Incidences of Non-neoplastic Lesions in F1 S-D Rats Fed Technical Toxaphene in Diet for 34 Weeks[a, b]

	Dose Group (mg/kg-d [ppm in diet])				
	F1a Adult Males				
Lesion[c]	0	0.29 (4 ppm)	1.4 (20 ppm)	7.5 (100 ppm)	37 (500 ppm)
Thyroid:					
Reduction of follicle size					
Minimal to mild	3/12 (25)	5/10 (50)	5/10 (50)	4/10 (40)	5/13 (38)
Moderate to severe	0/12 (0)	1/10 (10)	1/10 (10)	5/10* (50)	4/13 (31)
All severity	3/12 (25)	6/10 (60)	6/10 (60)	9/10† (90)	9/13† (69)
Follicle collapse/angularity					
Minimal to mild	0/12 (0)	3/10 (30)	5/10* (50)	3/10 (30)	5/13* (38)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
All severity	0/12 (0)	3/10 (30)	5/10† (50)	3/10 (30)	5/13† (38)
Increased epithelial height					
Minimal to mild	5/12 (42)	9/10* (90)	10/10* (100)	8/10 (80)	9/13 (69)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	2/10 (20)	1/13 (8)
All severity	5/12 (42)	9/10† (90)	10/10† (100)	10/10† (100)	10/13 (77)
Reduced colloid density					
Minimal to mild	6/12 (50)	8/10 (80)	10/10* (100)	6/10 (60)	7/13 (54)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	3/10 (30)	3/13 (23)
All severity	6/12 (50)	8/10 (80)	10/10† (100)	9/10 (90)	10/13 (77)
Colloid inspissation					
Minimal to mild	1/12 (8)	1/10 (10)	3/10 (30)	5/10* (50)	6/13* (46)
Moderate to severe	0/12 (0)	4/10* (40)	3/10 (30)	4/10* (40)	2/13 (15)
All severity	1/12 (8)	5/10† (50)	6/10† (60)	9/10† (90)	8/13† (62)
Liver:					
Increased cytoplasmic vacuolation					
Minimal to mild	3/12 (25)	9/10* (90)	7/10 (70)	10/10* (100)	7/13 (54)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	0/10 (0)	3/13 (23)
All severity	3/12 (25)	9/10† (90)	7/10 (70)	10/10† (100)	10/13† (77)
Increased cytoplasmic density					
Minimal to mild	0/12 (0)	3/10 (30)	3/10 (30)	4/10 (40)	9/13* (69)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	0/10 (0)	1/13 (8)
All severity	0/12 (0)	3/10 (30)	3/10 (30)	4/10 (40)	10/13† (77)
Increased cytoplasmic homogeneity					
Minimal to mild	0/12 (0)	6/10* (60)	7/10* (70)	4/10* (40)	4/13* (31)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	0/10 (0)	6/13* (46)
All severity	0/12 (0)	6/10† (60)	7/10† (70)	4/10† (40)	10/13† (77)
Anisokaryosis					
Minimal to mild	0/12 (0)	1/10 (10)	6/10* (60)	3/10 (30)	6/13* (46)
Moderate to severe	0/12 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
All severity	0/12 (0)	0/10 (0)	6/10† (60)	3/10 (30)	6/13† (46)
Kidney:					
Primary tubular injury					
Minimal to mild	3/12 (25)	4/10 (40)	5/10 (50)	5/10 (50)	9/13* (69)
Moderate to severe	0/12 (0)	1/10 (10)	1/10 (10)	0/10 (0)	1/13 (8)
All severity	3/12 (25)	5/10 (50)	6/10 (60)	5/10 (50)	10/13† (77)

Table B-15. Incidences of Non-neoplastic Lesions in F1 S-D Rats Fed Technical Toxaphene in Diet for 34 Weeks[a, b]

	Dose Group (mg/kg-d [ppm in diet])				
	F1a Adult Females				
Lesion[c]	0	0.38 (4 ppm)	1.9 (20 ppm)	9.4 (100 ppm)	49 (500 ppm)
Thyroid:					
Reduction of follicle size					
Minimal to mild	1/17 (6)	3/10 (30)	3/10 (30)	6/10* (60)	5/17 (29)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	1/10 (10)	2/17 (12)
All severity	1/17 (6)	3/10 (30)	3/10 (30)	7/10† (70)	7/17† (41)
Follicle collapse/angularity					
Minimal to mild	0/17 (0)	3/10* (30)	7/10* (70)	2/10 (20)	4/17 (24)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/17 (0)
All severity	0/17 (0)	3/10† (30)	7/10† (70)	2/10 (20)	4/17 (24)
Increased epithelial height					
Minimal to mild	1/17 (6)	9/10* (90)	9/10* (90)	9/10* (90)	7/17* (41)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	0/10 (0)	2/17 (12)
All severity	1/17 (6)	9/10† (90)	9/10† (90)	9/10† (90)	9/17† (53)
Cytoplasmic vacuolation					
Minimal to mild	1/17 (6)	5/10* (50)	8/10* (80)	9/10* (90)	6/17 (35)
Moderate to severe	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
All severity	1/17 (6)	5/10† (50)	8/10† (80)	9/10† (90)	6/17 (35)
Reduced colloid density					
Minimal to mild	1/17 (6)	4/10* (40)	8/10* (80)	9/10* (90)	8/17* (47)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	0/10 (0)	1/17 (6)
All severity	1/17 (6)	4/10† (40)	8/10† (80)	9/10† (90)	9/17† (53)
Colloid inspissation					
Minimal to mild	0/17 (0)	2/10 (20)	2/10 (20)	8/10* (80)	3/17 (18)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	0/10 (0)	1/17 (6)
All severity	0/17 (0)	2/10 (20)	2/10 (20)	8/10† (80)	4/17 (24)
Papillary proliferation					
Minimal to mild	0/17 (0)	2/10 (20)	2/10 (20)	8/10* (80)	3/17 (18)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	0/10 (0)	1/17 (6)
All severity	0/17 (0)	2/10 (20)	2/10 (20)	8/10† (80)	4/17 (24)
Liver:					
Increased cytoplasmic density					
Minimal to mild	1/17 (6)	7/10* (70)	7/10* (70)	8/10* (80)	8/17* (47)
Moderate to severe	0/17 (0)	1/10 (10)	0/10 (0)	0/10 (0)	2/17 (12)
All severity	1/17 (6)	8/10† (80)	7/10† (70)	8/10† (80)	10/17† (59)
Increased cytoplasmic homogeneity					
Minimal to mild	0/17 (0)	0/10 (0)	0/10 (0)	3/10* (30)	9/17* (53)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	0/10 (0)	1/17 (6)
All severity	0/17 (0)	0/10 (0)	0/10 (0)	3/10† (30)	10/17† (59)
Anisokaryosis					
Minimal to mild	0/17 (0)	4/10* (40)	3/10* (30)	4/10* (40)	7/17*† (41)
Moderate to severe	0/17 (0)	0/10 (0)	0/10 (0)	0/10 (0)	2/17 (12)
All severity	0/17 (0)	4/10† (40)	3/10† (30)	4/10† (40)	9/17† (53)

Table B-15. Incidences of Non-neoplastic Lesions in F1 S-D Rats Fed Technical Toxaphene in Diet for 34 Weeks[a, b]

	Dose Group (mg/kg-d [ppm in diet])					
	F1b Male Pups		F1b Female Pups		Total F1b Pups	
Lesion[c]	0	46[d] (500 ppm)	0	46[d] (500 ppm)	0	46[d] (500 ppm)
Thyroid:						
Reduction in follicle size						
Minimal to mild	0/5 (0)	2/5 (40)	0/4 (0)	3/5 (60)	0/9 (0)	5/10* (50)
Moderate to severe	0/5 (0)	0/5 (0)	0/4 (0)	0/5 (0)	0/9 (0)	0/10 (0)
All severity	0/5 (0)	2/5 (0)	0/4 (0)	3/5 (60)	0/9 (0)	5/10† (50)
Increased epithelial height						
Minimal to mild	0/5 (0)	3/5 (60)	1/5 (20)	3/5 (60)	1/10 (10)	6/10* (60)
Moderate to severe	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/10 (0)	0/10 (0)
All severity	0/5 (0)	3/5 (60)	1/5 (20)	3/5 (60)	1/10 (10)	6/10† (60)
Liver:						
Accentuated zonation						
Minimal to mild	0/5 (0)	4/5* (80)	0/5 (0)	5/5* (100)	0/10 (0)	9/10* (90)
Moderate to severe	0/5 (0)	1/5 (20)	0/5 (0)	0/5 (0)	0/10 (0)	1/10 (10)
All severity	0/5 (0)	5/5† (100)	0/5 (0)	5/5† (100)	0/10 (0)	10/10† (100)
Increased portal density						
Minimal to mild	0/5 (0)	5/5* (100)	0/5 (0)	5/5* (100)	0/10 (0)	10/10* (100)
Moderate to severe	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/10 (0)	0/10 (0)
All severity	0/5 (0)	5/5† (100)	0/5 (0)	5/5† (100)	0/10 (0)	10/10† (100)
Kidney:						
Anisokaryosis						
Minimal to mild	2/5 (40)	2/5 (40)	0/5 (0)	5/5* (100)	2/10 (20)	7/10 (70)
Moderate to severe	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/10 (0)	0/10 (0)
All severity	2/5 (40)	2/5 (40)	0/5 (0)	5/5† (100)	2/10 (0)	7/10 (70)

[a]Chu et al. (1988).
[b]Adult F1 rats were exposed for a total of 34 weeks (3 weeks in utero, 3 weeks via lactation, followed by 28 weeks via diet).
[c]Number of animals with lesion/number of animals examined microscopically (corresponding %).
[d]F1 pup dose based on that administered to F0 dams.
*Statistically significantly different from control at $p < 0.05$, compared with control (within the same severity group), as calculated for this review (Fisher's exact test).
†Statistically significantly different from control at $p < 0.05$, total number of lesions (minimal to mild + moderate to severe) compared with the total number of lesions in the control, as calculated for this review (Fisher's exact test).

S-D = Sprague-Dawley.

Table B-16. Developmental Effects in Rats and Mice Exposed to Technical Toxaphene in Corn Oil by Gastric Intubation during GDs 7−16[a]

Reproductive Parameters[b]	Exposure Group (mg/kg-d)			
	0	15	25	35
	CD Stock Charles River Rats			
Conception				
Pregnancies brought to term[c]	29/33 (88%)	31/39 (79%)	25/39* (64%)	4/16* (25%)
Mortality (dams)	0/33 (0%)	2/39 (5%)	3/39 (8%)	5/16* (31%)
Maternal observations				
Average-weight gain (g)	110 ± 23	86 ± 19* (−22%)	80 ± 26* (−27%)	65 ± 40* (−41%)
Average liver/body weight (%)	4.9 ± 0.4	5.2 ± 0.5 (+6%)	5.0 ± 0.03 (+2%)	4.6 ± 0.8 (−6%)
Fetal observations				
Average implants	9.3 ± 2.7	9.5 ± 1.9 (+2%)	10.6 ± 2.5 (+14%)	9.5 ± 1.9 (+2%)
Average mortality	10.7 ± 9.8	7.6 ± 6.6 (−29%)	10.7 ± 18.1 (0%)	8.5 ± 6 (−21%)
Average body weight (g)	4.19 ± 0.32	3.99 ± 0.39 (−5%)	3.71 ± 0.32* (−12%)	3.8 ± 0.78 (−9%)
Average number of sternal ossification centers	5.4 ± 0.06	5.1 ± 0.6* (−6)	4.9 ± 0.6* (−9%)	5.1 ± 0.5 (−6%)[d]
Average number of caudal ossification centers	4.6 ± 0.6	4.5 ± 0.6 (−2%)	4 ± 0.6* (−13%)	4.4 ± 1.1 (−4%)
Reproductive Parameters[b]	**CD-1 Stock Charles River Mice**			
Conception				
Pregnancies brought to term[c]	45/75 (60%)	16/26 (62%)	32/45 (71%)	61/90 (68%)
Mortality (dams)	1/75 (1%)	0/26 (0%)	0/45 (0%)	7/90 (8%)[e]
Maternal observations				
Average-weight gain (g)	5.9 ± 2.5	4.6 ± 1.7 (−22%)	4.6 ± 1.6* (−22%)	3.5 ± 2.1* (−41%)
Average liver/body weight (%)	6.5 ± 0.6	8.0 ± 0.9* (+23%)	8.1 ± 0.6* (+25%)	8.6 ± 0.7* (+32%)
Fetal observations				
Average implants	11.4 ± 2.3	12.1 ± 1.7 (+6%)	12.3 ± 2 (+8%)	12.6 ± 1.2 (+11%)
Average mortality (%)	8.3 ± 8.3	12.6 ± 13.4	16.6 ± 14.2	10.2 ± 10
Average body weight (g)	1.13 ± 0.27	1.19 ± 0.24 (+5%)	1.2 ± 0.22 (+6%)	1.17 ± 0.21 (+4%)
Average number of sternal ossification centers	6.0 ± 0.2	5.6 ± 0.1 (−7%)	5.9 ± 0.3 (−2%)	5.8 ± 0.6 (−3%)
Average number of caudal ossification centers	6.4 ± 2.3	5.7 ± 2.2 (−11%)	6.2 ± 2.3 (−3%)	6.3 ± 2.7 (−2%)
Incidence of litters with encephaloceles (number of fetuses)	0/45 (0)	0/16 (0)	0/32 (0)	5/61[e] (11)

[a]Chernoff and Carver (1976).
[b]Presented as mean ± SD (% change), except for incidence data.
[c]Number full term pregnancies/number inseminated (%).
[d]Available copy of this report did not have an asterisk for this group, but given the statistical significance of the means and SD of the other groups, this was likely significantly different from control.
[e]Fisher's exact test indicated a marginal ($p = 0.07$) increase compared with control incidence.
*Statistically significantly different from control at $p < 0.05$, using the Mann-Whitney "U" test for continuous variables as reported by Chernoff and Carver (1976) or a two-tailed Fisher's exact test for incidence data for this assessment.

GD = gestation day; SD = standard deviation.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

SELECTION OF DATA SETS FOR BMD MODELING

Based on the review of the available laboratory animal toxicity studies, the liver, kidney, thyroid, and immune system are sensitive noncancer toxicity targets of technical toxaphene. To provide a common basis for comparing potential points of departure (PODs) and critical effects for a subchronic provisional reference dose (p-RfD) for technical toxaphene (i.e., comparing benchmark dose [BMD] and benchmark dose lower confidence limits [BMDLs] among the most sensitive endpoints), data sets from available studies with multiple exposure levels for each of these sensitive toxicity targets were selected for BMD analysis (see Table 4A and the "Derivation of Provisional Values" section in the main body of this report).

MODELING PROCEDURE FOR DICHOTOMOUS DATA

The BMD modeling of dichotomous (quantal) data was conducted with U.S. EPA's Benchmark Dose Software (BMDS, Version 2.5). For these data, all of the dichotomous models (i.e., Gamma, Multistage, Logistic, Log-Logistic, Probit, Log-Probit, and Weibull) available within the software were fit using recommended parameter constraints and a benchmark response (BMR) of 10% extra risk [as outlined in the *Benchmark Dose Technical Guidance*; U.S. EPA (2012b)]. For all technical toxaphene-induced dichotomous effects modeled, a BMR other than 10% is not supported by the statistical and biological characteristics of the data sets (i.e., there are no developmental/fetal effects or epidemiological effects). Adequacy of model fit was judged based on the goodness-of-fit *p*-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. Among all models providing adequate fit, the lowest BMDL was selected if the BMDL estimates from different models varied ≥threefold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) was selected as the best BMDL estimate for this data set.

In addition, in the absence of a mechanistic understanding of the biological response to a toxic agent, data from exposures much higher than the study's lowest-observed-adverse-effect level (LOAEL) do not provide reliable information regarding the shape of the response at low doses. Such exposures, however, can have a strong effect on the shape of the fitted model in the low-dose region of the dose-response curve. Thus, if the lack of fit is due to characteristics of the dose-response data for high doses, then the *Benchmark Dose Technical Guidance* document allows for data to be adjusted by eliminating the high-dose group (U.S. EPA, 2012b). Because the focus of BMD analysis is on the low-dose regions of the response curve, elimination of the high-dose group(s) is deemed reasonable.

MODELING PROCEDURE FOR CONTINUOUS DATA

The BMD modeling of continuous data was conducted with U.S. EPA's BMDS (Versions 2.5 and 2.6). For these data, all continuous models available within the software were fit using recommended parameter constraints and a standard BMR of 1 standard deviation (SD) relative risk unless a biologically determined BMR was available, as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b). An adequate fit was judged based on the goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made on whether the variance across dose groups was homogeneous. If a constant/homogeneous variance model was deemed appropriate based on the

statistical test provided by BMDS (i.e., Test 2), the final BMD results were estimated from a constant/homogeneous variance model. If the test for homogeneity of 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/nonhomogeneous variance. If this nonconstant/nonhomogeneous variance model did not adequately fit the data (i.e., Test 3; $p < 0.1$), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL was selected if the BMDL estimates from different models varied ≥threefold; otherwise, the BMDL from the model with the lowest AIC was selected as the best BMDL estimate for this data set.

As described above for dichotomous data, if none of the models fit and lack of fit is due to characteristics of the dose-response data for high doses, then the *Benchmark Dose Technical Guidance* document allows for data to be adjusted by eliminating the high-dose group(s) (U.S. EPA, 2012b). Because the focus of BMD analysis is on the low-dose regions of the response curve, elimination of the high-dose group(s) is deemed reasonable.

BMD MODELING TO IDENTIFY POTENTIAL PODS FOR THE DERIVATION OF A SUBCHRONIC PROVISIONAL REFERENCE DOSE

Decreased Mean Primary Anti-SRBC IgM Response in Female Cynomolgus Monkeys Administered Technical Toxaphene in Oral Capsules for 75 Weeks (Tryphonas et al., 2001)

The procedure outlined above was applied to the data for decreased mean primary anti sheep red blood cell (SRBC) immunoglobulin M (IgM) response (measured 1 week postimmunization) in female cynomolgus monkeys administered technical toxaphene via oral capsule for 75 weeks (Tryphonas et al., 2001) (see Table C-1). Table C-2 summarizes the BMD modeling results. The constant variance model did not fit the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, all models except the Hill model provided adequate fit to the means. The Power and Polynomial 2- and 3-degree models converged onto the Linear model. BMDLs for models providing adequate fit were not sufficiently close (differed by ≥threefold), so the model with the lowest BMDL was selected (Exponential Model 4; the Exponential Model 5 converged onto the Exponential Model 4). Thus, the $BMDL_{1SD}$ of 0.02 mg/kg-day from this model is selected for this endpoint (see Figure C-1 and the BMD text output for details).

Table C-1. Mean Primary Anti-SRBC IgM Response in Female Cynomolgus Monkeys Administered Technical Toxaphene Orally in Capsules for 75 Weeks (Measured 1 Week Postimmunization)[a]

	HED (mg/kg-d)			
	0	**0.05**	**0.2**	**0.4**
Sample size	10	10	10	10
Mean	7.1	6.4	5.2	3.7
SEM	0.35	0.54	0.79	0.83
SD[b]	1.11	1.71	2.5	2.62

[a]Tryphonas et al. (2001).
[b]Calculated using U.S. EPA BMDS (Version 2.5).

BMDS = Benchmark Dose Software; HED = human equivalent dose; IgM = immunoglobulin M; SD = standard deviation; SEM = standard error of the mean; SRBC = sheep red blood cell.

Table C-2. BMD Model Predictions for Decreased Anti-SRBC Primary Response (IgM) in Female Cynomolgus Monkeys Administered Technical Toxaphene Orally in Capsules for 75 Weeks (Measured 1 Week Postimmunization)

Model	Variance *p*-Value[a]	Means *p*-Value[a]	AIC	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)
Nonconstant variance					
Exponential (model 2)[b]	0.48	0.61	96.66	0.13425	0.07516
Exponential (model 3)[b]	0.48	0.61	96.66	0.13425	0.07516
Exponential (model 4)[b, c]	**0.48**	**0.93**	**97.68**	**0.07426**	**0.02438**
Exponential (model 5)[b]	0.48	0.93	97.68	0.07426	0.02438
Hill	0.48	NA[d]	99.68	0.07145	0.02043
Linear[d]	0.48	0.41	97.45	0.17225	0.10993
Polynomial (2-degree)[e]	0.48	0.41	97.45	0.17225	0.10993
Polynomial (3-degree)[e]	0.48	0.41	97.45	0.17225	0.10993
Power[b]	0.48	0.41	97.45	0.17225	0.10993

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Selected model.
[d]Degrees of freedom for Test 4 [means *p*-value] are ≤0; the χ^2 test for fit is not valid.
[e]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; IgM = immunoglobulin M; NA = not applicable; SD = standard deviation; SRBC = sheep red blood cell.

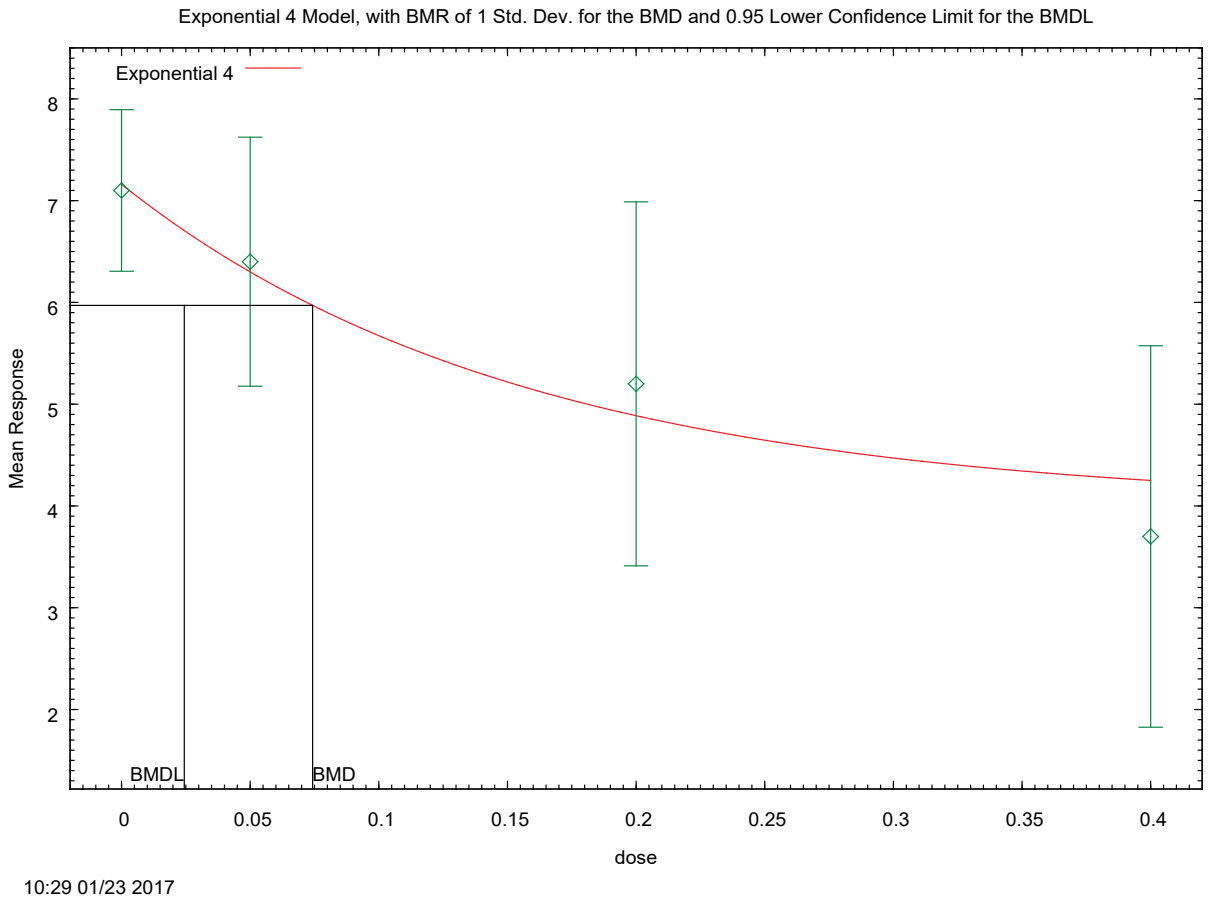

Figure C-1. Exponential Model 4 for Anti-SRBC Primary Response (IgM) in Female Cynomolgus Monkeys Administered Technical Toxaphene Orally in Capsules for 75 Weeks (Measured 1 Week Postimmunization) (Tryphonas et al., 2001)

Text Output for Figure C-1:

```
================================================================
        Exponential Model. (Version: 1.10;  Date: 01/12/2015)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/exp_Tryphonas_2001_IgM_monkey_1wk_HEDs_Exp-Mod
elVariance-BMR1Std-Down.(d)
        Gnuplot Plotting File:
                                          Mon Jan 23 10:29:08 2017
 ================================================================

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

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
```

```
      sign = -1 for decreasing trend.

   Model 2 is nested within Models 3 and 4.
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
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 = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 4	
lnalpha	5.31043	
rho	-2.39187	
a	7.455	
b	7.05264	
c	0.472677	
d	1	Specified

Parameter Estimates

Variable	Model 4	Std. Err.
lnalpha	6.80044	5.58486e-121
rho	-3.27847	1.828
a	7.16005	0.348381
b	6.36769	5.37507
c	0.559175	0.173055

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.1	1.11
0.05	10	6.4	1.71
0.2	10	5.2	2.5
0.4	10	3.7	2.62

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.16	1.189	-0.1597
0.05	6.299	1.467	0.2169
0.2	4.887	2.224	0.445
0.4	4.251	2.796	-0.6232

Other models for which likelihoods are 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 + log(mean(i)) * rho)

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

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-47.14702	5	104.294
A2	-43.09597	8	102.1919
A3	-43.83786	6	99.67571
R	-54.27915	2	112.5583
4	-43.84127	5	97.68254

Additive constant for all log-likelihoods = -36.76. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	22.37	6	0.001039
Test 2	8.102	3	0.04395
Test 3	1.484	2	0.4762
Test 6a	0.006824	1	0.9342

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 6a is greater than .1. Model 4 seems

```
  to adequately describe the data.

Benchmark Dose Computations:
  Specified Effect = 1.000000
         Risk Type = Estimated standard deviations from control
  Confidence Level = 0.950000
               BMD =    0.0742627
              BMDL =    0.0243837
```

Increased Incidence of Primary Tubular Injury (All Severity Grades) in the Kidney of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

The procedure outlined above was applied to the data for increased incidence of primary tubular injury (all severity grades) in the kidney of male Sprague-Dawley (S-D) rats administered technical toxaphene in the diet for 13 weeks (Chu et al., 1986) (see Table C-3). Table C-4 summarizes the BMD modeling results. All models provided adequate fit to the full data set. BMDLs were considered to be sufficiently close (differed by <threefold), so the model with the lowest AIC was selected (Probit). Thus, the $BMDL_{10}$ of 0.020 mg/kg-day from this model is selected for this endpoint (see Figure C-2).

Table C-3. Incidence of Primary Tubular Injury (All Severity Grades) in the Kidney of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks[a]

	HED (mg/kg-d)				
	0	**0.090**	**0.46**	**2.2**	**11.8**
Sample size	10	10	10	10	10
Incidence	1	4	10	10	10

[a]Chu et al. (1986).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-4. BMD Modeling Results for Incidence of Primary Tubular Injury (All Severity Grades) in the Kidney of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	1	25.96	0.06448	0.00989
Logistic	0.9998	23.98	0.03731	0.02100
LogLogistic[c]	1	25.96	0.07902	0.01903
LogProbit[c]	1	25.96	0.07164	0.01977
Multistage (1-degree)[d]	0.8291	25.24	0.01541	0.00841
Multistage (2-degree)[d]	0.9993	25.96	0.04100	0.00988
Multistage (3-degree)[d]	0.9999	25.96	0.04586	0.00988
Multistage (4-degree)[d]	0.9881	27.96	0.04586	0.00988
Probit[e]	**1**	**23.96**	**0.03530**	**0.01994**
Weibull[b]	1	25.96	0.04897	0.00989

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

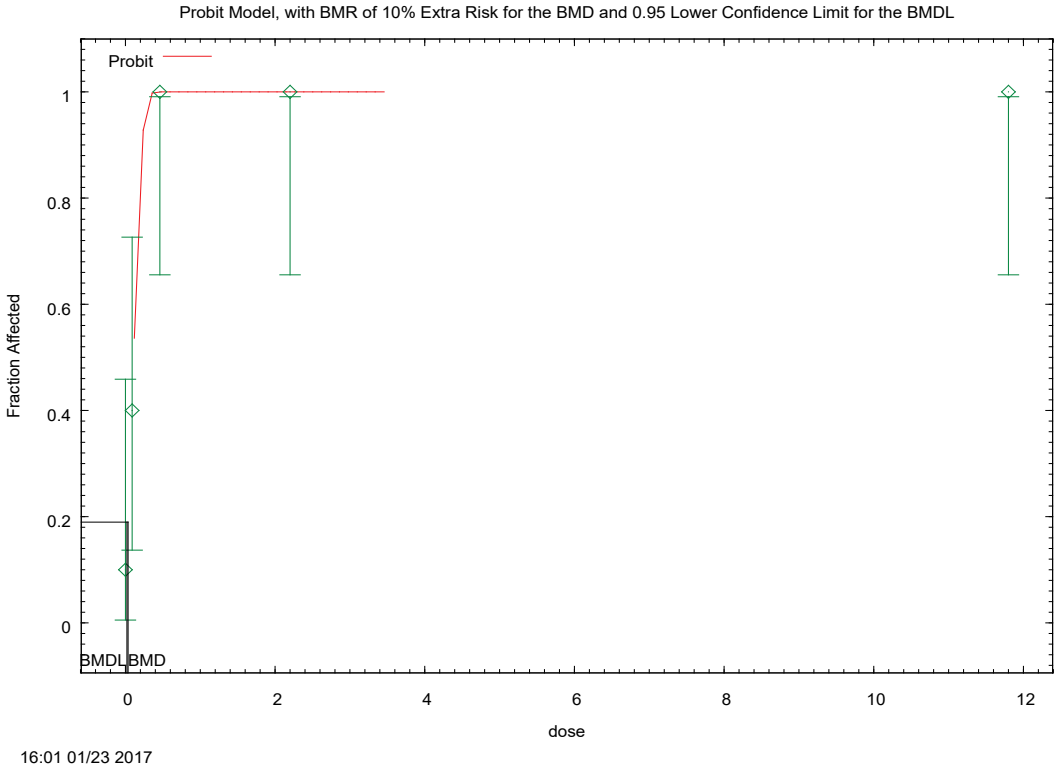

Figure C-2. Probit Model for Increased Incidence of Primary Tubular Injury (All Severity Grades) in the Kidney of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

Text output for Figure C-2:

```
================================================================================
        Probit Model. (Version: 3.3;  Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/pro_Chu_1986_prim_tub_inj_male_rats_HEDs_Pro-B
MR10.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/pro_Chu_1986_prim_tub_inj_male_rats_HEDs_Pro-B
MR10.plt
                                          Mon Feb 13 08:44:16 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = CumNorm(Intercept+Slope*Dose),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is not restricted
```

```
   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial (and Specified) Parameter Values
                     background =            0   Specified
                      intercept =     0.440208
                          slope =     0.151431


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept        slope

 intercept            1         -0.8

     slope         -0.8            1


                                Parameter Estimates

                                                                  95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
      intercept         -1.28325
0.533694            -2.32927            -0.23723
          slope          11.4563          7.29794            -2.84743
25.76


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -9.98095         5
   Fitted model        -9.98129         2   0.000688441      3              1
  Reduced model        -30.5432         1       41.1245      4         <.0001

           AIC:         23.9626


                               Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size          Residual
  ----------------------------------------------------------------------
    0.0000     0.0997         0.997     1.000      10.000          0.003
    0.0900     0.4004         4.004     4.000      10.000         -0.003
    0.4600     1.0000        10.000    10.000      10.000          0.018
    2.2000     1.0000        10.000    10.000      10.000          0.000
   11.8000     1.0000        10.000    10.000      10.000          0.000

 Chi^2 = 0.00      d.f. = 3        P-value = 1.0000
```

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0352965

            BMDL =      0.0199366
```

Increased Incidence of Tubular Necrosis (All Severity Grades) in the Kidney of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

The procedure outlined above was applied to the data for increased incidence of tubular necrosis (all severity grades) in the kidney of male S-D rats administered technical toxaphene in the diet for 13 weeks (Chu et al., 1986) (see Table C-5). Table C-6 summarizes the BMD modeling results. All models except the Logistic and Probit models provided adequate fit to the full data set. BMDLs for models providing adequate fit were not sufficiently close (differed by ≥threefold; i.e., LogLogistic vs. LogProbit), so the model with the lowest BMDL was selected (LogLogistic). Thus, the $BMDL_{10}$ of 0.045 mg/kg-day from this model is selected for this endpoint (see Figure C-3).

Table C-5. Incidence of Tubular Necrosis (All Severity Grades) in the Kidney of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks[a]

	HED (mg/kg-d)				
	0	**0.090**	**0.46**	**2.2**	**11.8**
Sample size	10	10	10	10	10
Incidence	0	0	5	7	10

[a]Chu et al. (1986).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-6. BMD Modeling Results for Incidence of Tubular Necrosis (All Severity Grades) in the Kidney of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.4677	31.99	0.14578	0.09087
Logistic	0.0363	39.86	0.46924	0.29560
LogLogistic[c, d]	**0.448**	**33.43**	**0.13829**	**0.04492**
LogProbit[c]	0.4188	31.66	0.21139	0.13219
Multistage (1-degree)[e]	0.4677	31.99	0.14578	0.09087
Multistage (2-degree)[e]	0.4677	31.99	0.14578	0.09087
Multistage (3-degree)[e]	0.4677	31.99	0.14578	0.09087
Multistage (4-degree)[e]	0.312	33.99	0.14586	0.09087
Probit	0.0376	39.54	0.44182	0.29375
Weibull[b]	0.4677	31.99	0.14578	0.09087

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Selected model.
[e]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

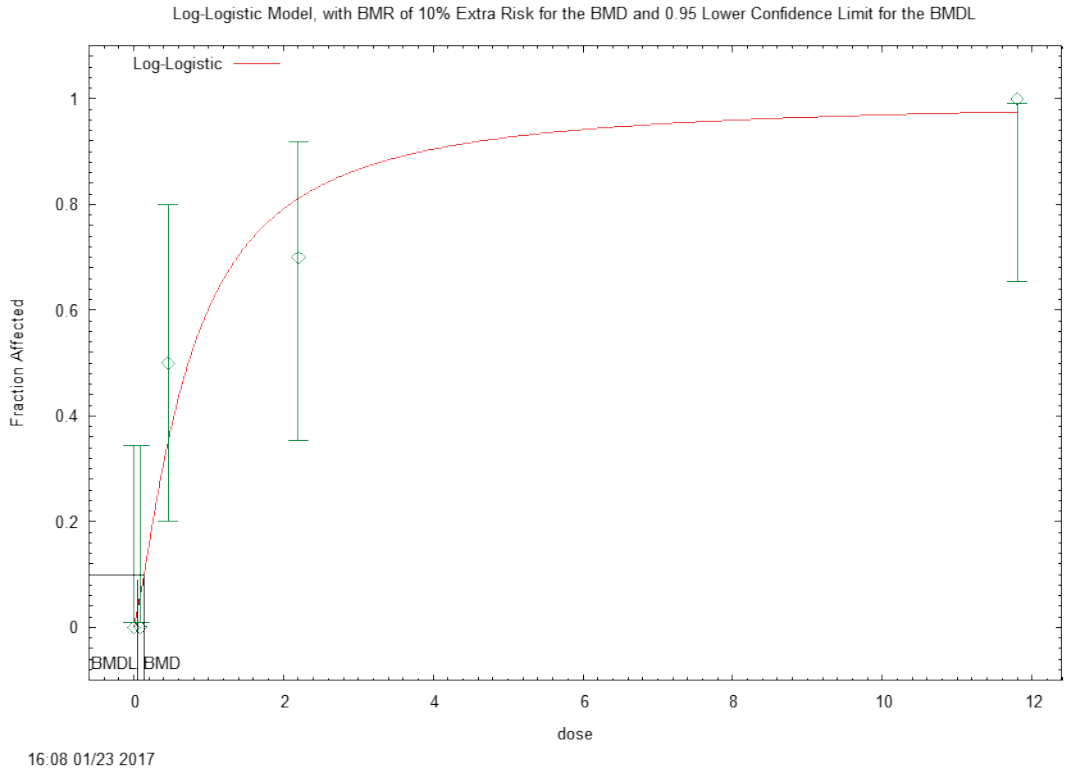

Figure C-3. LogLogistic Model for Increased Incidence of Tubular Necrosis (All Severity Grades) in the Kidney of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

Text output for Figure C-3:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_kid_tublr_necro_male_rats_HEDs_Ln
l-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_kid_tublr_necro_male_rats_HEDs_Ln
l-BMR10-Restrict.plt
                                          Mon Feb 13 08:47:32 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
```

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0
intercept = 0.190526
slope = 1.18187

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	0.23
slope	0.23	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	0.421479	0.47931	-0.517951	1.36091
slope	1.32363	0.388565	0.562058	2.08521

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-13.0401	5			
Fitted model	-14.7155	2	3.35087	3	0.3406
Reduced model	-34.2965	1	42.5128	4	<.0001

AIC: 33.4311

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	10.000	0.000
0.0900	0.0592	0.592	0.000	10.000	-0.793

```
    0.4600      0.3529          3.529      5.000       10.000         0.973
    2.2000      0.8123          8.123      7.000       10.000        -0.910
   11.8000      0.9756          9.756     10.000       10.000         0.500

 Chi^2 = 2.65       d.f. = 3         P-value = 0.4480


    Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =       Extra risk

Confidence level =           0.95

             BMD =        0.138287

            BMDL =       0.0449213
```

Increased Incidence of Minimal to Mild Tubular Necrosis (the Only Severity Grade Observed) in the Kidney of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

The procedure outlined above was applied to the data for increased incidence of minimal to mild tubular necrosis in the kidney of female S-D rats administered technical toxaphene in the diet for 13 weeks (Chu et al., 1986) (see Table C-7). Table C-8 summarizes the BMD modeling results. None of the models provided adequate fit to the full data set or the data set with the highest dose dropped. With the two highest doses dropped, only the LogLogistic model provided adequate fit to the data. Thus, a $BMDL_{10}$ of 0.0012 mg/kg-day was calculated for this endpoint (see Figure C-4). However, the modeling results for this endpoint are not considered reliable because all response levels were considered in excess of the BMR, near maximal responses, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMDL (U.S. EPA, 2012b).

Table C-7. Incidence of Minimal to Mild Tubular Necrosis (the Only Severity Grade Observed) in the Kidney of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks[a]

	HED (mg/kg-d)				
	0	**0.11**	**0.58**	**2.81**	**14**
Sample size	10	10	10	10	10
Incidence	0	8	9	8	8

[a]Chu et al. (1986).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-8. BMD Modeling Results for Incidence of Minimal to Mild Tubular Necrosis (the Only Severity Grade Observed) in the Kidney of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.0001	65.73	1.39491	0.53105
Logistic	0.0001	65.95	1.85515	0.81228
LogLogistic[c]	0	55.93	0.01208	0.00523
LogProbit[c]	0.0001	66.58	3.08714	0.83424
Multistage (1-degree)[d]	0.0001	65.73	1.39491	0.53105
Multistage (2-degree)[d]	0.0001	65.73	1.39491	0.53105
Multistage (3-degree)[d]	0.0001	65.73	1.39491	0.53105
Multistage (4-degree)[d]	0.0001	65.73	1.39491	0.53105
Probit	0.0001	65.99	1.99065	0.95831
Weibull[b]	0.0001	65.73	1.39492	0.53105
Highest dose dropped				
Gamma[b]	0.0002	51.76	0.16283	0.07286
Logistic	0.0002	52.79	0.29340	0.15043
LogLogistic[c]	0.0016	35.42	0.00733	0.00283
LogProbit[c]	0	52.83	0.19165	0.02691
Multistage (1-degree)[d]	0.0002	51.76	0.16283	0.07286
Multistage (2-degree)[d]	0.0002	51.76	0.16283	0.07286
Multistage (3-degree)[d]	0.0002	51.76	0.16283	0.07286
Probit	0.0002	52.93	0.32306	0.18394
Weibull[b]	0.0002	51.76	0.16283	0.07286
Two highest doses dropped				
Gamma[b]	0.0239	23.45	0.01453	0.00881
Logistic	0.0019	32.64	0.04609	0.02502
LogLogistic[c, e]	**0.8038**	**18.89**	**0.00392**	**0.00117**
LogProbit[c]	0.0939	21.23	0.01949	0.01035
Multistage (1-degree)[d]	0.0239	23.45	0.01453	0.00881
Multistage (2-degree)[d]	0.0239	23.45	0.01453	0.00881
Probit	0.0018	33.05	0.05261	0.03316
Weibull[b]	0.0239	23.45	0.01453	0.00881

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

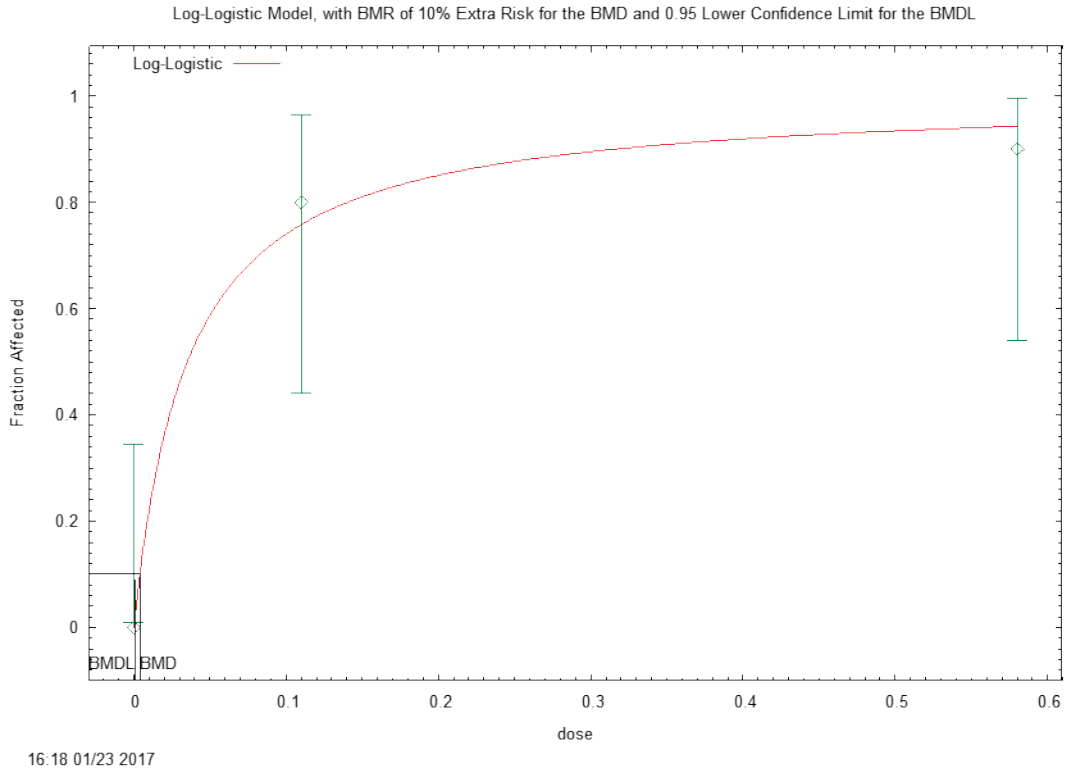

Figure C-4. LogLogistic Model for Incidence of Minimal to Mild Tubular Necrosis (the Only Severity Grade Observed) in the Kidney of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Two Highest Doses Dropped) (Chu et al., 1986)

Text output for Figure C-4:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_kid_tublr_necro_female_rats_2hdd_
HEDs_Lnl-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_kid_tublr_necro_female_rats_2hdd_
HEDs_Lnl-BMR10-Restrict.plt
                                          Mon Feb 13 08:49:29 2017
 ================================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 3
   Total number of records with missing values = 0
```

```
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =            0
                      intercept =      3.09701
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept

 intercept            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept           3.3452         0.648458             2.07425
4.61616
          slope                1              NA

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


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -8.25485         3
   Fitted model        -8.44636         1      0.383009      2          0.8257
  Reduced model         -20.527         1       24.5442      2         <.0001

           AIC:         18.8927


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size          Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      10.000          0.000
    0.1100     0.7573         7.573     8.000      10.000          0.315
    0.5800     0.9427         9.427     9.000      10.000         -0.581

 Chi^2 = 0.44      d.f. = 2        P-value = 0.8038
```

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =     0.00391702

            BMDL =     0.00116777
```

Increased Incidence of Primary Tubular Injury (All Severity Grades) in the Kidney of F0 Male S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks (Chu et al., 1988)

The procedure outlined above was applied to the data for increased incidence of primary tubular injury (all severity grades) in the kidney of F0 male S-D rats exposed to technical toxaphene for 25−29 weeks (Chu et al., 1988) (see Table C-9). Table C-10 summarizes the BMD modeling results. None of the models provided an adequate fit using the full dose range. The data were not modeled with the highest dose dropped due to the lack of a statistically significant increase in lesion incidence at the next lowest dose and the lack of a positive dose-response trend in the remaining data. Thus, these data are not amenable to BMD modeling.

Table C-9. Incidence of Primary Tubular Injury (All Severity Grades) in the Kidney of F0 Male S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks[a]

	HED (mg/kg-d)				
	0	**0.10**	**0.47**	**2.4**	**12**
Sample size	12	10	10	11	13
Incidence	0	7	5	3	13

[a]Chu et al. (1988).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-10. BMD Modeling Results for Incidence of Primary Tubular Injury (All Severity Grades) in the Kidney of F0 Male S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.0043	59.62	4.07226	1.34026
Logistic	0.0009	62.39	0.88597	0.51514
LogLogistic[c]	0.0043	59.62	4.54597	1.62888
LogProbit[c]	0.0014	61.62	5.87284	NDr
Multistage (1-degree)[d]	0.0005	64.18	0.52257	0.27666
Multistage (2-degree)[d]	0.0022	60.92	1.93718	0.49432
Multistage (3-degree)[d]	0.0037	59.92	3.13691	0.55112
Multistage (4-degree)[d]	0.0042	59.69	4.11211	0.54808
Probit	0.0011	61.98	0.89367	0.52579
Weibull[b]	0.0014	61.62	7.59794	1.11709

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose confidence limit; NDr = not determined; S-D = Sprague-Dawley.

Increased Incidence of Primary Tubular Injury (All Severity Grades) in the Kidney of F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks (Chu et al., 1988)

The procedure outlined above was applied to the data for increased incidence of primary tubular injury (all severity grades) in the kidney of F0 female S-D rats exposed to technical toxaphene for 25−29 weeks (Chu et al., 1988) (see Table C-11). Table C-12 summarizes the BMD modeling results. All models except the Logistic, LogProbit, and Probit models provided adequate fit to the full data set. BMDLs for models providing adequate fit were considered to be sufficiently close (differed by <threefold), so the model with the lowest AIC (shared by the Gamma, Multistage [1−3 degrees], and Weibull models) was selected. Thus, the $BMDL_{10}$ of 0.088 mg/kg-day from the Multistage (1-degree) model is selected for this endpoint because the first three polynomial model runs (1-, 2-, and 3-degree) result in a final 1-degree model fit (see Figure C-5).

Table C-11. Incidence of Primary Tubular Injury (All Severity Grades) in the Kidney of F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks[a]

	HED (mg/kg-d)				
	0	**0.083**	**0.44**	**1.9**	**11**
Sample size	17	10	10	10	17
Incidence	0	1	5	6	17

[a]Chu et al. (1988).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-12. BMD Modeling Results for Incidence of Primary Tubular Injury (All Severity Grades) in the Kidney of F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.3998	39.44	0.14019	0.08841
Logistic	0.0427	46.83	0.46504	0.29996
LogLogistic[c]	0.4386	41.09	0.08126	0.03541
LogProbit[c]	0.0975	43.85	0.22203	0.12513
Multistage (1-degree)[d, e]	**0.3998**	**39.44**	**0.14019**	**0.08841**
Multistage (2-degree)[d]	0.3998	39.44	0.14019	0.08841
Multistage (3-degree)[d]	0.3998	39.44	0.14019	0.08841
Multistage (4-degree)[d]	0.2564	41.44	0.14049	0.08843
Probit	0.0464	46.51	0.43295	0.29068
Weibull[b]	0.3998	39.44	0.14019	0.08841

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

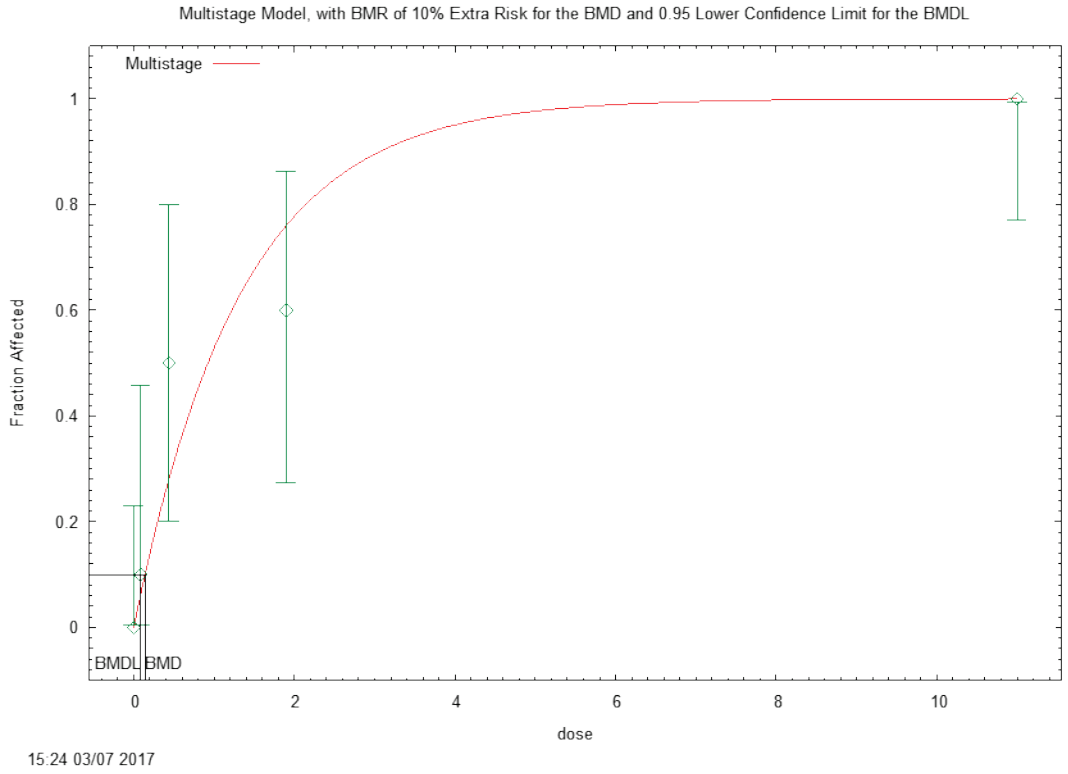

Figure C-5. Multistage (1-degree) Model for Increased Incidence of Primary Tubular Injury (All Severity Grades) in the Kidney of F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25–29 Weeks (Chu et al., 1988)

Text output for Figure C-5:

```
================================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/mst_Chu_1988_prim_tub_inj_F0_female_rats_HEDs_
Mst1-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/mst_Chu_1988_prim_tub_inj_F0_female_rats_HEDs_
Mst1-BMR10-Restrict.plt
                                          Tue Mar 07 16:00:05 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are not restricted


   Dependent variable = Effect
   Independent variable = Dose
```

```
 Total number of observations = 5
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =           0
                        Beta(1) = 9.36682e+018


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1



                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
        Beta(1)         0.751553         0.223282            0.313928
1.18918

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



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -16.9124         5
   Fitted model        -18.7185         1       3.61219      4           0.461
  Reduced model        -44.0798         1       54.3347      4         <.0001

           AIC:          39.437


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      17.000        0.000
    0.0830     0.0605         0.605     1.000      10.000        0.524
    0.4400     0.2816         2.816     5.000      10.000        1.536
```

```
    1.9000      0.7602          7.602      6.000       10.000        -1.187
   11.0000      0.9997         16.996     17.000       17.000         0.066

 Chi^2 = 4.05       d.f. = 4         P-value = 0.3998


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        0.14019

            BMDL =      0.0884148

            BMDU =       0.253985

Taken together, (0.0884148, 0.253985) is a 90     % two-sided confidence
interval for the BMD
```

Increased Incidence of Moderate to Severe Reduced Colloid Density in the Thyroid of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

The procedure outlined above was applied to the data for increased incidence of moderate to severe reduced colloid density in the thyroid of male S-D rats administered technical toxaphene in the diet for 13 weeks (Chu et al., 1986) (see Table C-13). Table C-14 summarizes the BMD modeling results. All models provided adequate fit to the full data set. BMDLs for models providing adequate fit were not sufficiently close (differed by ≥threefold), so the model with the lowest BMDL was selected (LogLogistic). Thus, the $BMDL_{10}$ of 0.013 mg/kg-day from this model is selected for this endpoint (see Figure C-6).

Table C-13. Incidence of Moderate to Severe Reduced Colloid Density in the Thyroid of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks[a]

	HED (mg/kg-d)				
	0	**0.090**	**0.46**	**2.2**	**11.8**
Sample size	10	10	10	9	9
Incidence	1	3	7	8	9

[a]Chu et al. (1986).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-14. BMD Modeling Results for Incidence of Moderate to Severe Reduced Colloid Density in the Thyroid of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.5108	43.29	0.07792	0.04310
Logistic	0.2182	45.92	0.19529	0.11066
LogLogistic[c, d]	**0.8764**	**43.59**	**0.03751**	**0.01258**
LogProbit[c]	0.5115	43.05	0.11010	0.05486
Multistage (1-degree)[e]	0.5108	43.29	0.07792	0.04310
Multistage (2-degree)[e]	0.5108	43.29	0.07792	0.04310
Multistage (3-degree)[e]	0.5108	43.29	0.07792	0.04310
Multistage (4-degree)[e]	0.5108	43.29	0.07792	0.04310
Probit	0.2039	46.14	0.21292	0.13632
Weibull[b]	0.5108	43.29	0.07792	0.04310

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Selected model.
[e]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

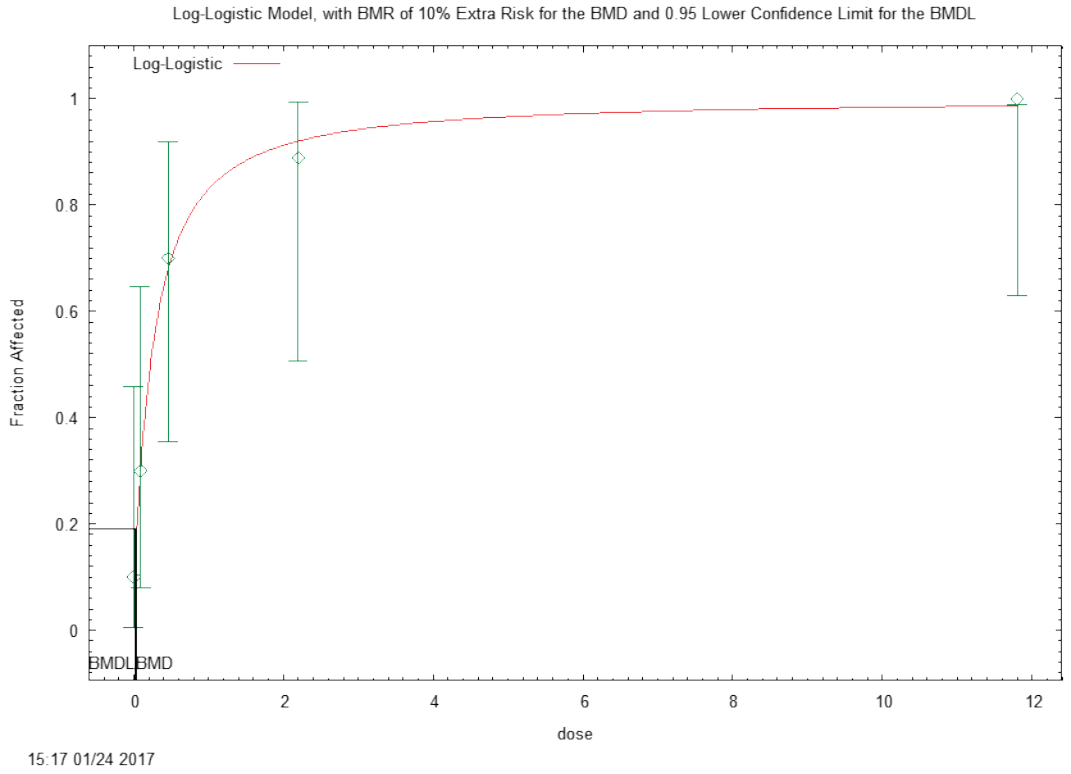

Figure C-6. LogLogistic Model for Increased Incidence of Moderate to Severe Reduced Colloid Density in the Thyroid of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

Text output for Figure C-6:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_red_coll_dens_male_rats_HEDs_Lnl-
BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_red_coll_dens_male_rats_HEDs_Lnl-
BMR10-Restrict.plt
                                          Mon Feb 13 08:51:24 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
```

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.1
intercept = 0.813584
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.23	0.23
intercept	-0.23	1	0.51
slope	0.23	0.51	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0997053	0.0936352	-0.0838163	0.283227
intercept	1.4565	0.648766	0.18494	2.72806
slope	1.11286	0.422936	0.283917	1.94179

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-18.6076	5			
Fitted model	-18.7931	3	0.371014	2	0.8307
Reduced model	-32.6013	1	27.9873	4	<.0001

AIC: 43.5862

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0997	0.997	1.000	10.000	0.003
0.0900	0.3044	3.044	3.000	10.000	-0.030
0.4600	0.6794	6.794	7.000	10.000	0.140
2.2000	0.9205	8.284	8.000	9.000	-0.350
11.8000	0.9867	8.881	9.000	9.000	0.348

Chi^2 = 0.26 d.f. = 2 P-value = 0.8764

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0375081

            BMDL =      0.0125836
```

Increased Incidence of Reduced Colloid Density (All Severity Scores) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

The procedure outlined above was applied to the data for increased incidence of reduced colloid density (all severity scores) in the thyroid of female S-D rats administered technical toxaphene in the diet for 13 weeks (Chu et al., 1986) (see Table C-15). Table C-16 summarizes the BMD modeling results. Only the LogLogistic model provided an adequate fit using the full dose range. Thus, the $BMDL_{10}$ of 0.00051 mg/kg-day from this model is selected for this endpoint (see Figure C-7). However, the modeling results for this endpoint are not considered reliable because all response levels were far in excess of the BMR and at or near maximal response at all doses tested, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD (U.S. EPA, 2012b).

Table C-15. Incidence of Reduced Colloid Density (All Severity Scores) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks[a]

	HED (mg/kg-d)				
	0	**0.11**	**0.58**	**2.81**	**14**
Sample size	10	10	10	10	10
Incidence	0	9	9	10	10

[a]Chu et al. (1986).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-16. BMD Modeling Results for Incidence of Reduced Colloid Density (All Severity Scores) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.0047	22.83	0.01252	0.00761
Logistic	0.0054	32.75	0.04007	0.02119
LogLogistic[c, d]	**0.8**	**16.33**	**0.00228**	**0.00051**
LogProbit[c]	0.0393	19.39	0.01530	0.00763
Multistage (1-degree)[e]	0.0047	22.83	0.01252	0.00761
Multistage (2-degree)[e]	0.0047	22.83	0.01252	0.00761
Multistage (3-degree)[e]	0.0047	22.83	0.01252	0.00761
Multistage (4-degree)[e]	0.0047	22.83	0.01252	0.00761
Probit	0.0058	33.36	0.04831	0.03022
Weibull[b]	0.0047	22.83	0.01252	0.00761

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Selected model.
[e]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

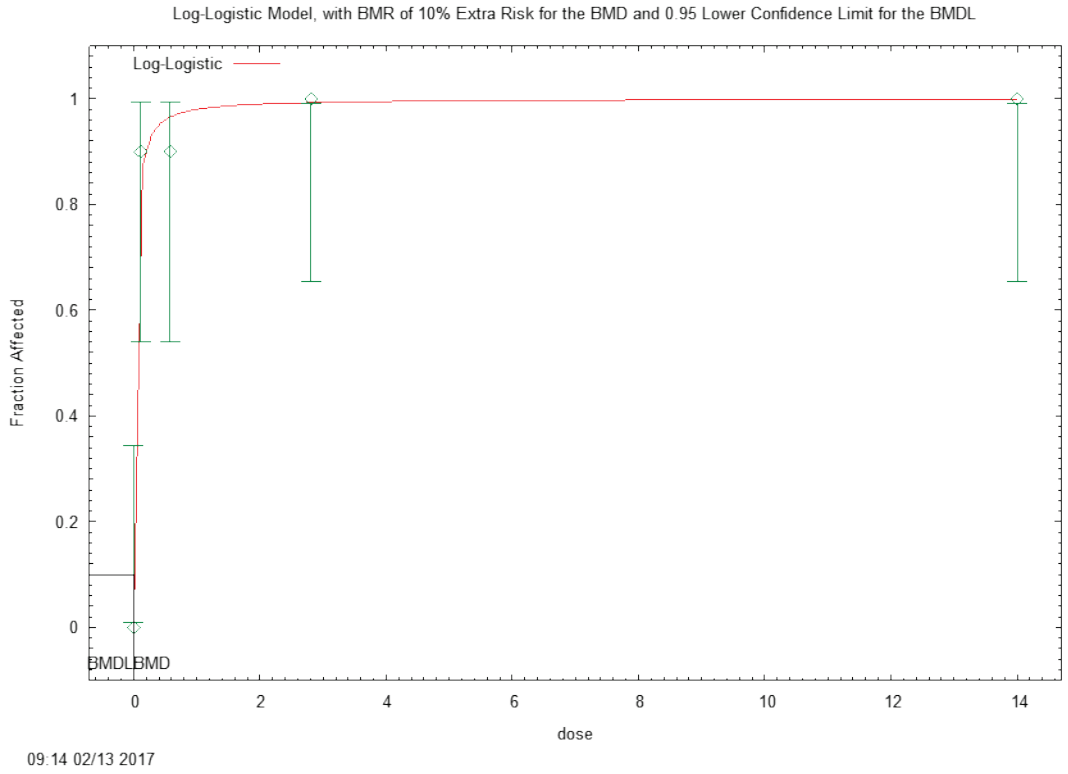

Figure C-7. LogLogistic Model for Increased Incidence of Reduced Colloid Density (All Severity Grades) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

Text output for Figure C-7:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_red_coll_dens_female_rats_HEDs_Ln
l-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_red_coll_dens_female_rats_HEDs_Ln
l-BMR10-Restrict.plt
                                          Mon Feb 13 08:57:48 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
```

```
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =            0
                      intercept =      1.03449
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept

 intercept            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept          3.88693        0.757911             2.40146
5.37241
          slope                1              NA

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


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -6.50166         5
   Fitted model        -7.16625         1       1.32919      4          0.8564
  Reduced model         -27.554         1       42.1047      4         <.0001

           AIC:         16.3325


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      10.000        0.000
    0.1100     0.8429         8.429     9.000      10.000        0.497
    0.5800     0.9658         9.658     9.000      10.000       -1.147
    2.8100     0.9928         9.928    10.000      10.000        0.270
   14.0000     0.9985         9.985    10.000      10.000        0.121
```

```
 Chi^2 = 1.65      d.f. = 4        P-value = 0.8000

   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =     0.00227868

            BMDL =    0.000511344
```

Increased Incidence of Reduced Colloid Density (All Severity Grades) in the Thyroid of F1a Female S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks (Chu et al., 1988)

The procedure outlined above was applied to the data for increased incidence of reduced colloid density (all severity grades) in the thyroid of F1a female S-D rats exposed to toxaphene for 34 weeks (Chu et al., 1988) (see Table C-17). Table C-18 summarizes the BMD modeling results. None of the models provided an adequate fit using the full dose range. However, after dropping the highest dose, the LogLogistic model provided an adequate fit to the data and a $BMDL_{10}$ of 0.0075 mg/kg-day (see Figure C-8). However, the modeling results for this endpoint are not considered reliable because all response levels were considered in excess of the BMR, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD (U.S. EPA, 2012b).

Table C-17. Incidence of Reduced Colloid Density (All Severity Grades) in the Thyroid of F1a Female S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks[a]

	HED (mg/kg-d)				
	0	**0.089**	**0.44**	**2.2**	**11**
Sample size	17	10	10	10	17
Incidence	1	4	8	9	9

[a]Chu et al. (1988).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-18. BMD Modeling Results for Incidence of Reduced Colloid Density (All Severity Grades) in the Thyroid of F1a Female S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0	94.66	116,506	0.93269
Logistic	0	91.63	4.11944	1.70852
LogLogistic[c]	0	91.04	1.64893	0.247744
LogProbit[c]	0	92.41	8.70036	2.54749
Multistage (1-degree)[d]	0	91.44	3.09326	1.07897
Multistage (2-degree)[d]	0	91.44	3.09327	1.07897
Multistage (3-degree)[d]	0	91.44	3.09327	1.07897
Multistage (4-degree)[d]	0	91.44	3.09326	1.07897
Probit	0	91.63	4.12581	1.7431
Weibull[b]	0	91.44	3.09326	1.07897
Highest dose dropped				
Gamma[b]	0.0159	47.16	0.05652	0.03286
Logistic	0.0062	52.59	0.17106	0.09569
LogLogistic[c, e]	**0.8344**	**41.90**	**0.01705**	**0.00753**
LogProbit[c]	0.0091	45.76	0.06226	0.03488
Multistage (1-degree)[d]	0.0159	47.16	0.05652	0.03286
Multistage (2-degree)[d]	0.0159	47.16	0.05652	0.03286
Multistage (3-degree)[d]	0.0159	47.16	0.05652	0.03286
Probit	0.006	53.07	0.19812	0.12902
Weibull[b]	0.0159	47.16	0.05652	0.03286

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

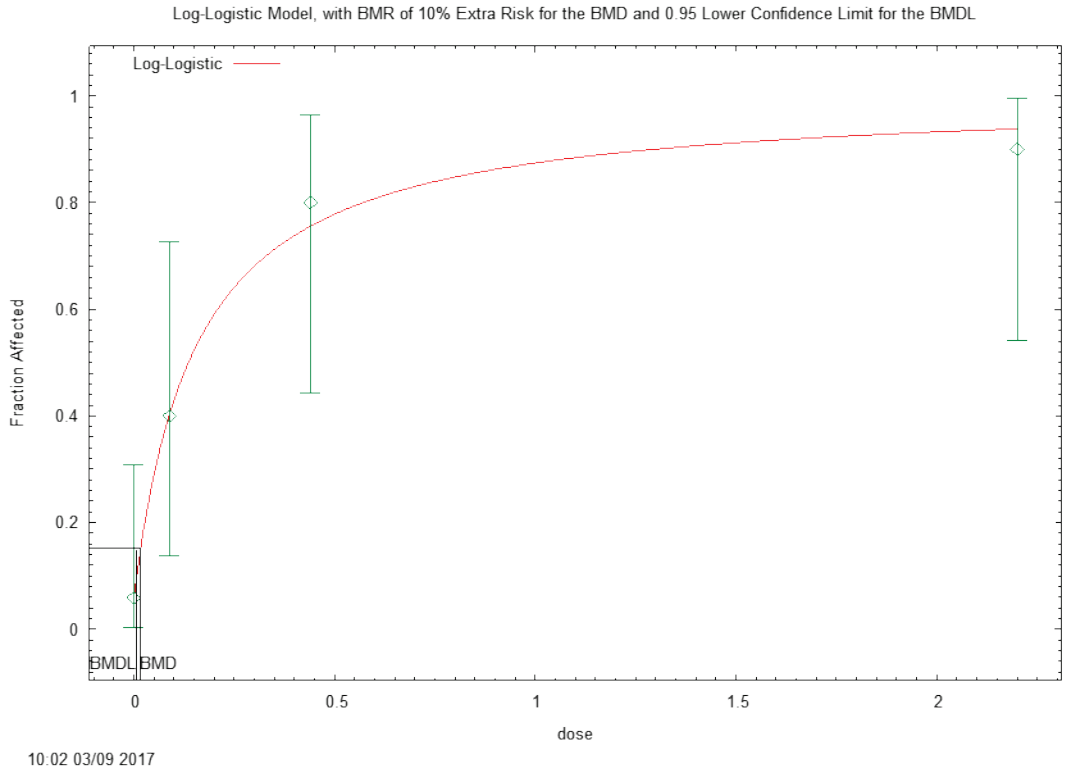

Figure C-8. LogLogistic Model for Increased Incidence of Reduced Colloid Density (All Severity Grades) in the Thyroid of F1a Female S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks (Highest Dose Dropped) (Chu et al., 1988)

Text output for Figure C-8:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_red_coll_dens_F1a_female_rats_hig
h_drop_HEDs_Lnl-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_red_coll_dens_F1a_female_rats_hig
h_drop_HEDs_Lnl-BMR10-Restrict.plt
                                              Thu Mar 09 10:02:15 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
```

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.0588235
intercept = 1.62914
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

	background	intercept
background	1	-0.24
intercept	-0.24	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0590057	0.0570236	-0.0527585	0.17077
intercept	1.87423	0.495527	0.903011	2.84544
slope	1	NA		

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-18.7882	4			
Fitted model	-18.9519	2	0.327528	2	0.8489
Reduced model	-32.4821	1	27.3879	3	<.0001

AIC: 41.9039

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0590	1.003	1.000	17.000	-0.003
0.0890	0.4044	4.044	4.000	10.000	-0.028

```
    0.4400      0.7567          7.567      8.000       10.000         0.319
    2.2000      0.9386          9.386      9.000       10.000        -0.509

 Chi^2 = 0.36      d.f. = 2        P-value = 0.8344


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.0170526

            BMDL =      0.00752682
```

Increased Incidence of Colloid Inspissation (All Severity Grades) in the Thyroid of F0 Male S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks (Chu et al., 1988)

The procedure outlined above was applied to the data for increased incidence of colloid inspissation (all severity grades) in the thyroid of F0 male S-D rats exposed to technical toxaphene for 25−29 weeks (Chu et al., 1988) (see Table C-19). Table C-20 summarizes the BMD modeling results. None of the models provided adequate fit to the full data set or the data set with the highest dose dropped. With the two highest doses dropped, all models except the Logistic and Probit models provided adequate fit to the data. BMDLs for models providing adequate fit were not sufficiently close (differed by ≥threefold), so the model with the lowest BMDL was selected (LogLogistic). Thus, the $BMDL_{10}$ of 0.0050 mg/kg-day from this model is selected for this endpoint (see Figure C-9). However, the modeling results for this endpoint are not considered reliable because all response levels were considered in excess of the BMR, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD (U.S. EPA, 2012b).

Table C-19. Incidence of Colloid Inspissation (All Severity Grades) in the Thyroid of F0 Male S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks[a]

	HED (mg/kg-d)				
	0	**0.10**	**0.47**	**2.4**	**12**
Sample size	12	10	10	11	13
Incidence	0	5	8	4	12

[a]Chu et al. (1988).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-20. BMD Modeling Results for Incidence of Colloid Inspissation (All Severity Grades) in the Kidney of F0 Male S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.0011	68.97	0.65277	0.34507
Logistic	0.0013	68.82	1.10538	0.66674
LogLogistic[c]	0.0007	69.28	0.25946	0.03458
LogProbit[c]	0.0005	70.76	8.07759	0.81332
Multistage (1-degree)[d]	0.0011	68.97	0.65277	0.34507
Multistage (2-degree)[d]	0.0004	70.79	1.27909	0.35179
Multistage (3-degree)[d]	0.0005	70.63	1.57717	0.35849
Multistage (4-degree)[d]	0.0005	70.59	1.62614	0.36007
Probit	0.0014	68.77	1.15310	0.75534
Weibull[b]	0.0011	68.97	0.65277	0.34507
Highest dose dropped				
Gamma[b]	0.0005	61.53	1.63456	0.27679
Logistic	0.0005	61.58	2.23688	0.48130
LogLogistic[c]	0.0005	61.46	1.04941	0.03266
LogProbit[c]	0.0005	61.71	94.47660	0.78750
Multistage (1-degree)[d]	0.0005	61.53	1.63458	0.27679
Multistage (2-degree)[d]	0.0005	61.53	1.63457	0.27679
Multistage (3-degree)[d]	0.0005	61.53	1.63457	0.27679
Probit	0.0005	61.57	2.20102	0.47730
Weibull[b]	0.0005	61.53	1.63459	0.27679
Two highest doses dropped				
Gamma[b]	0.4974	27.16	0.02386	0.01474
Logistic	0.0254	34.34	0.07512	0.04526
LogLogistic[c, e]	**0.9874**	**25.90**	**0.01182**	**0.00502**
LogProbit[c]	0.4656	27.20	0.03715	0.02209
Multistage (1-degree)[d]	0.4974	27.16	0.02386	0.01474
Multistage (2-degree)[d]	0.4974	27.16	0.02386	0.01474
Probit	0.0255	34.18	0.07327	0.04761
Weibull[b]	0.4974	27.16	0.02386	0.01474

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

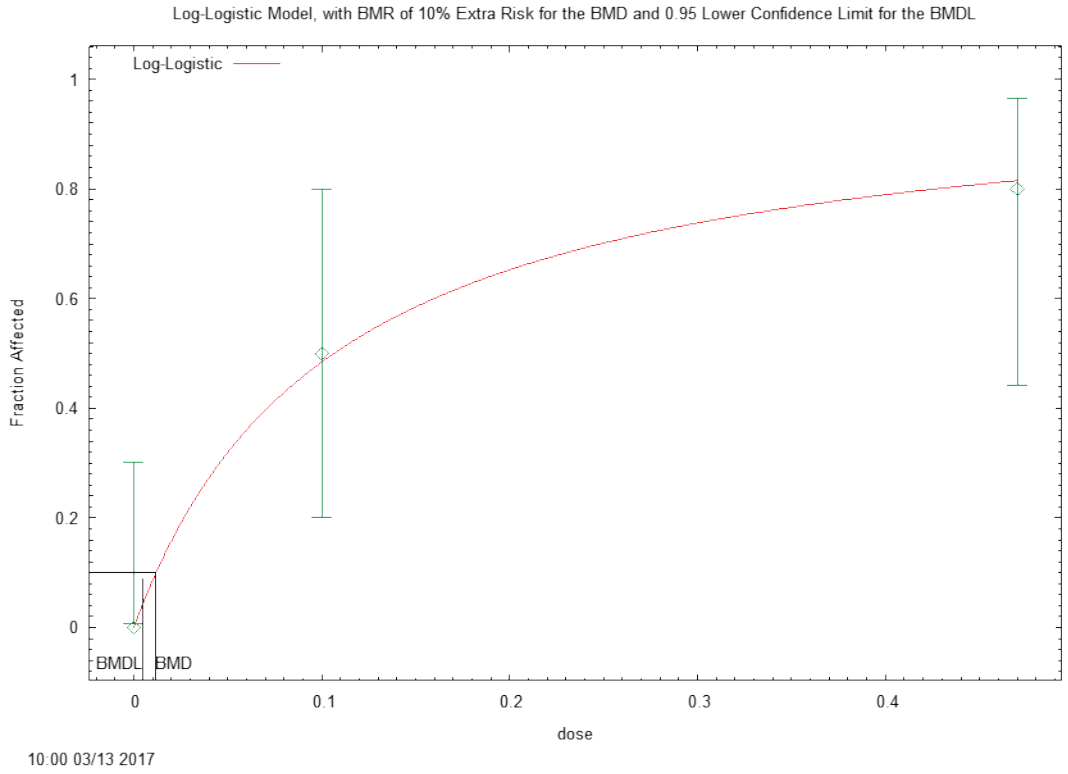

Figure C-9. LogLogistic Model for Increased Incidence of Colloid Inspissation (All Severity Grades) in the Thyroid of F0 Male S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks (Two Highest Doses Dropped) (Chu et al., 1988)

Text output for Figure C-9:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_coll_insip_F0_male_rats_2_high_dr
op_HEDs_Lnl-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_coll_insip_F0_male_rats_2_high_dr
op_HEDs_Lnl-BMR10-Restrict.plt
                                          Mon Mar 13 10:00:53 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 3
   Total number of records with missing values = 0
```

```
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =            0
                     intercept =      2.21355
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept

 intercept            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept          2.24079         0.499839             1.26113
3.22046
          slope                1              NA

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


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -11.9355         3
   Fitted model          -11.948         1     0.0250626      2          0.9875
  Reduced model         -21.6149         1       19.3587      2         <.0001

           AIC:          25.8961


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size          Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      12.000          0.000
    0.1000     0.4846         4.846     5.000      10.000          0.098
    0.4700     0.8154         8.154     8.000      10.000         -0.126

 Chi^2 = 0.03      d.f. = 2        P-value = 0.9874
```

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0118193

            BMDL =     0.00502303
```

Increased Incidence of Colloid Inspissation (All Severity Grades) in the Thyroid of F1a Male S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks (Chu et al., 1988)

The procedure outlined above was applied to the data for increased incidence of colloid inspissation in the thyroid of F1a male S-D rats exposed to technical toxaphene for 34 weeks (Chu et al., 1988) (see Table C-21). Table C-22 summarizes the BMD modeling results. None of the models provided adequate fit to the full data set. With the highest dose dropped, all models except the Logistic, LogProbit, and Probit models provided adequate fit to the data. BMDLs for models providing adequate fit were not sufficiently close (differed by ≥threefold), so the model with the lowest BMDL was selected (LogLogistic). Thus, the $BMDL_{10}$ of 0.0089 mg/kg-day from this model is selected for this endpoint (see Figure C-10). However, the modeling results for this endpoint are not considered reliable because all response levels were considered in excess of the BMR, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD (U.S. EPA, 2012b).

Table C-21. Incidence of Colloid Inspissation (All Severity Grades) in the Thyroid of F1a Male S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks[a]

	HED (mg/kg-d)				
	0	**0.078**	**0.37**	**2.0**	**10**
Sample size	12	10	10	10	13
Incidence	1	5	6	9	8

[a]Chu et al. (1988).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-22. BMD Modeling Results for Incidence of Colloid Inspissation (All Severity Grades) in the Thyroid of F1a Male S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.0028	78.43	2.42668	1.11047
Logistic	0.0034	77.16	0.51957	0.07874
LogLogistic[c]	0.0019	79.33	4.41833	1.28977
LogProbit[c]	0.0032	78.13	1.72534	0.66792
Multistage (1-degree)[d]	0.0032	78.13	1.72533	0.66792
Multistage (2-degree)[d]	0.0032	78.13	1.72532	0.66792
Multistage (3-degree)[d]	0.0032	78.13	1.72534	0.66792
Multistage (4-degree)[d]	0.0028	78.44	2.46806	1.17402
Probit	0.0032	78.13	1.72534	0.66792
Weibull[b]	0.0028	78.43	2.42668	1.11047
Highest dose dropped				
Gamma[b]	0.1411	48.68	0.07776	0.04044
Logistic	0.0815	50.37	0.17895	0.10154
LogLogistic[c, e]	**0.5095**	**46.00**	**0.02129**	**0.00885**
LogProbit[c]	0.0911	49.52	0.12050	0.04922
Multistage (1-degree)[d]	0.1411	48.68	0.07776	0.04044
Multistage (2-degree)[d]	0.1411	48.68	0.07776	0.04044
Multistage (3-degree)[d]	0.1411	48.68	0.07776	0.04044
Probit	0.0773	50.50	0.19227	0.12282
Weibull[b]	0.1411	48.68	0.07776	0.04044

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

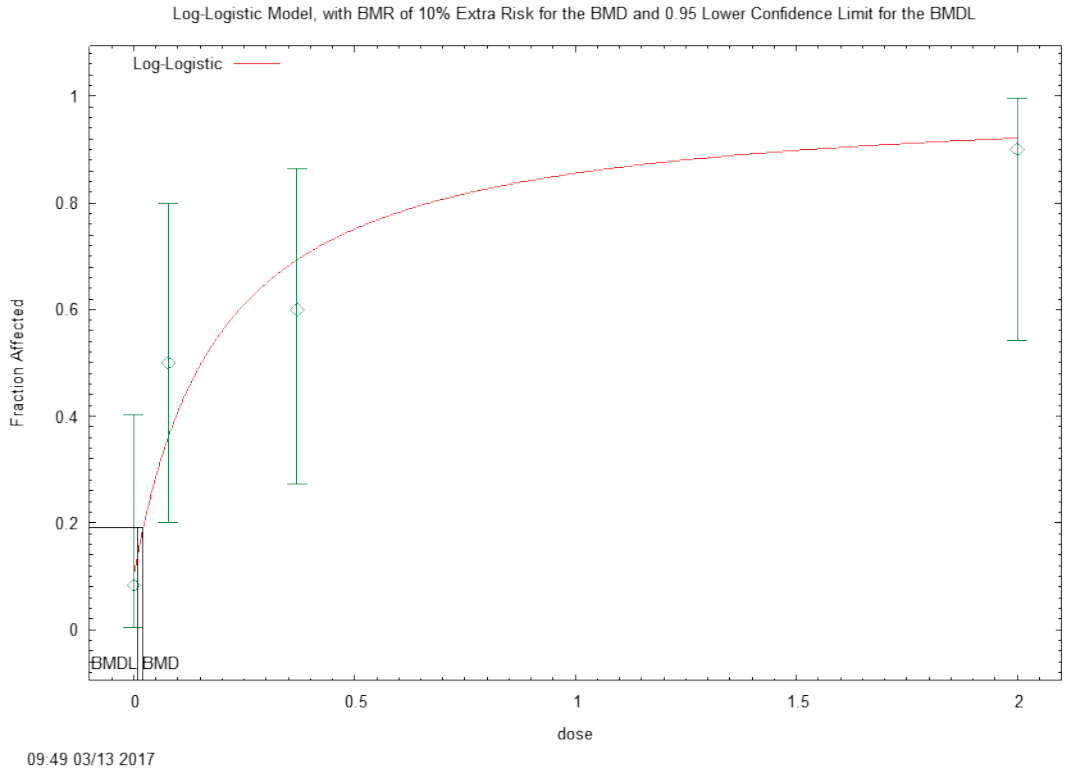

Figure C-10. LogLogistic Model for Increased Incidence of Colloid Inspissation (All Severity Grades) in the Thyroid of F1a Male S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks (Highest Dose Dropped) (Chu et al., 1988)

Text output for Figure C-10:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_coll_insip_F1a_male_rats_high_dro
p_HEDs_Lnl-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_coll_insip_F1a_male_rats_high_dro
p_HEDs_Lnl-BMR10-Restrict.plt
                                          Mon Mar 13 09:49:21 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
```

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.0833333
intercept = 1.39858
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

	background	intercept
background	1	-0.49
intercept	-0.49	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.102335	0.0959071	-0.0856397	0.290309
intercept	1.6521	0.577555	0.520111	2.78408
slope	1	NA		

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-20.3545	4			
Fitted model	-21.0022	2	1.29543	2	0.5232
Reduced model	-29.1122	1	17.5155	3	0.0005536

AIC: 46.0043

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1023	1.228	1.000	12.000	-0.217
0.0780	0.3620	3.620	5.000	10.000	0.908

```
    0.3700      0.6937          6.937      6.000       10.000        -0.643
    2.0000      0.9215          9.215      9.000       10.000        -0.253

 Chi^2 = 1.35      d.f. = 2        P-value = 0.5095


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0212942

            BMDL =     0.00884992
```

Increased Incidence of Reduced Follicular Size (All Severity Grades) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

The procedure outlined above was applied to the data for increased incidence of reduced follicular size in the thyroid of female S-D rats administered technical toxaphene in the diet for 13 weeks (Chu et al., 1986) (see Table C-23). Table C-24 summarizes the BMD modeling results. Only the LogLogistic model provided adequate fit to the data. Thus, a $BMDL_{10}$ of 0.0052 mg/kg-day was calculated for this endpoint (see Figure C-11). However, the modeling results for this endpoint are not considered reliable because all response levels were considered in excess of the BMR, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD (U.S. EPA, 2012b).

Table C-23. Incidence of Reduced Follicular Size (All Severity Grades) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks[a]

	HED (mg/kg-d)				
	0	**0.11**	**0.58**	**2.81**	**14**
Sample size	10	10	10	10	10
Incidence	0	6	8	9	10

[a]Chu et al. (1986).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-24. BMD Modeling Results for Incidence of Reduced Follicular Size (All Severity Grades) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.011	45.12	0.07840	0.03885
Logistic	0.0136	48.02	0.20145	0.10942
LogLogistic[c, d]	**0.7933**	**33.39**	**0.01208**	**0.00523**
LogProbit[c]	0	41.17	0.04871	0.02988
Multistage (1-degree)[e]	0.011	45.12	0.07840	0.03885
Multistage (2-degree)[e]	0.011	45.12	0.07840	0.03885
Multistage (3-degree)[e]	0.011	45.12	0.07840	0.03885
Multistage (4-degree)[e]	0.011	45.12	0.07840	0.03885
Probit	0.0127	48.39	0.23405	0.14672
Weibull[b]	0.011	45.12	0.07840	0.03885

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Selected model.
[e]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

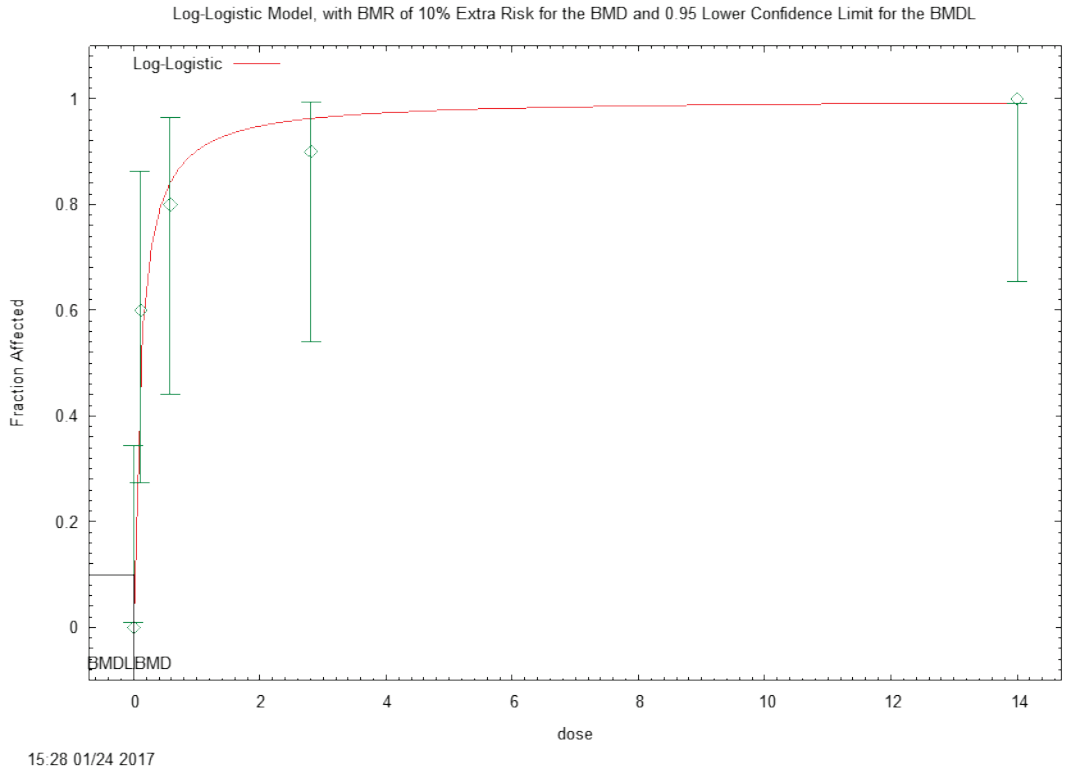

Figure C-11. LogLogistic Model for Increased Incidence of Reduced Follicular Size (All Severity Grades) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

Text output for Figure C-11:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_red_foll_size_female_rats_HEDs_Ln
l-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_red_foll_size_female_rats_HEDs_Ln
l-BMR10-Restrict.plt
                                          Mon Feb 13 08:52:41 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
```

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0
intercept = 0.741985
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept
intercept	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	2.21871	0.484232	1.26964	3.16779
slope	1	NA		

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-14.985	5			
Fitted model	-15.6956	1	1.42133	4	0.8405
Reduced model	-32.0518	1	34.1336	4	<.0001

AIC: 33.3913

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	10.000	0.000
0.1100	0.5029	5.029	6.000	10.000	0.614
0.5800	0.8421	8.421	8.000	10.000	-0.365
2.8100	0.9627	9.627	9.000	10.000	-1.048
14.0000	0.9923	9.923	10.000	10.000	0.279

```
 Chi^2 = 1.69      d.f. = 4        P-value = 0.7933

   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0120832

            BMDL =     0.00523198
```

Increased Incidence of Minimal to Mild Follicle Collapse/Angularity (the Only Severity Grade Observed) in the Thyroid of F1a Male S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks (Chu et al., 1988)

The procedure outlined above was applied to the data for increased incidence of minimal to mild follicle collapse/angularity in the thyroid of F1a male S-D rats exposed to technical toxaphene for 34 weeks (Chu et al., 1988) (see Table C-25). Table C-26 summarizes the BMD modeling results. None of the models provided adequate fit to the full data set or the data set with the highest dose dropped. With the two highest doses dropped, all models except the Logistic and Probit models provided adequate fit to the data. BMDLs were considered to be sufficiently close (differed by <threefold) for the models that fit, so the model with the lowest AIC was selected (LogLogistic). Thus, the $BMDL_{10}$ of 0.014 mg/kg-day from this model is selected for this endpoint (see Figure C-12).

Table C-25. Incidence of Minimal to Mild Follicle Collapse/Angularity (the Only Severity Grade Observed) in the Thyroid of F1a Male S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks[a]

	HED (mg/kg-d)				
	0	**0.078**	**0.37**	**2.0**	**10**
Sample size	12	10	10	10	13
Incidence	0	3	5	3	5

[a]Chu et al. (1988).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-26. BMD Modeling Results for Incidence of Minimal to Mild Follicle Collapse/Angularity (the Only Severity Grade Observed) in the Thyroid of F1a Male S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.0223	72.33	5.5×10^{13}	NDr
Logistic	0.0626	69.44	5.48264	2.32130
LogLogistic[c]	0.0619	69.36	4.15669	0.96097
LogProbit[c]	0.0615	69.61	7.18951	2.82028
Multistage (1-degree)[d]	0.0621	69.39	4.62114	1.42397
Multistage (2-degree)[d]	0.0621	69.39	4.62109	1.42397
Multistage (3-degree)[d]	0.0621	69.39	4.62111	1.42397
Multistage (4-degree)[d]	0.0621	69.39	4.62114	1.42397
Probit	0.0625	69.43	5.39480	2.24996
Weibull[b]	0.0621	69.39	4.62119	1.42397
Highest dose dropped				
Gamma[b]	0.0252	51.63	0.89025	0.23451
Logistic	0.0256	51.79	1.31883	0.48338
LogLogistic[c]	0.0249	51.50	0.62700	0.08991
LogProbit[c]	0.0255	52.30	44.40930	0.56758
Multistage (1-degree)[d]	0.0252	51.63	0.89025	0.23451
Multistage (2-degree)[d]	0.0252	51.63	0.89025	0.23451
Multistage (3-degree)[d]	0.0252	51.63	0.89025	0.23451
Probit	0.0255	51.78	1.27588	0.46317
Weibull[b]	0.0252	51.63	0.89025	0.23451
Two highest doses dropped				
Gamma[b]	0.4735	29.41	0.04343	0.02518
Logistic	0.0797	34.01	0.11959	0.07392
LogLogistic[c, e]	**0.7476**	**28.64**	**0.03016**	**0.01360**
LogProbit[c]	0.1584	31.21	0.06410	0.03927
Multistage (1-degree)[d]	0.4735	29.41	0.04343	0.02518
Multistage (2-degree)[d]	0.4735	29.41	0.04343	0.02518
Probit	0.0831	33.85	0.11075	0.07017
Weibull[b]	0.4735	29.41	0.04343	0.02518

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

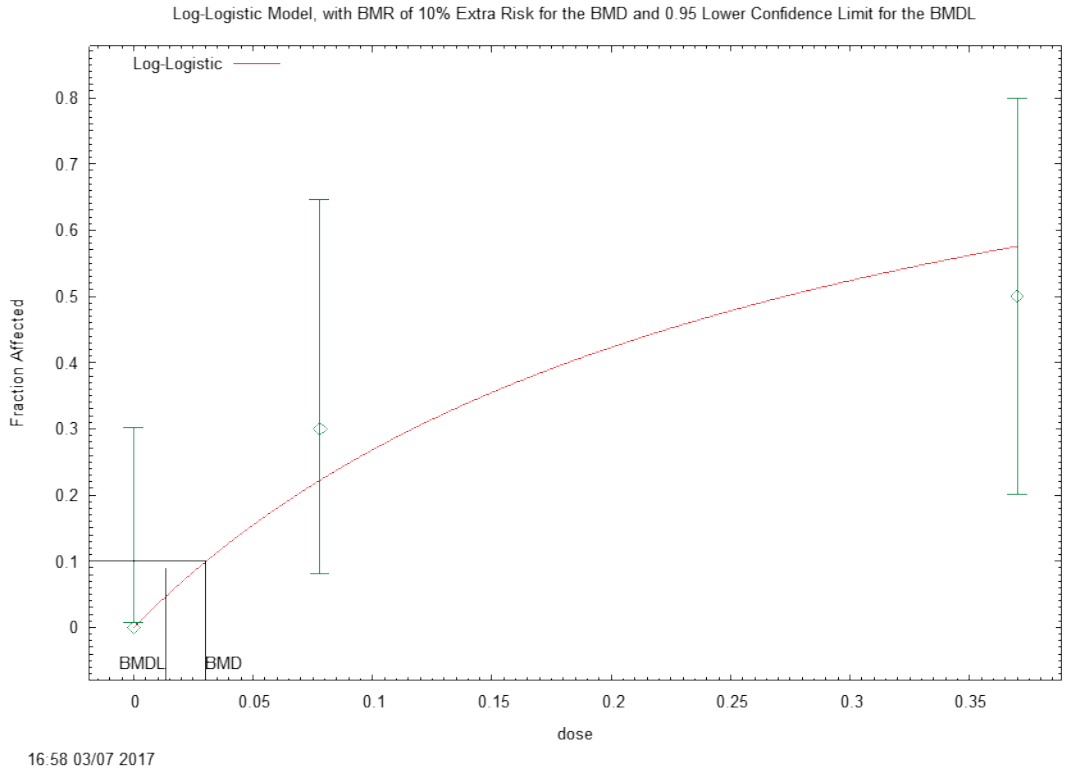

Figure C-12. LogLogistic Model for Increased Incidence of Minimal to Mild Follicle Collapse/Angularity (the Only Severity Grade Observed) in the Thyroid of F1a Male S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks (Two Highest Doses Dropped) (Chu et al., 1988)

Text output for Figure C-12:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_foll_collap_ang_F1a_male_rats_2_h
igh_drop_HEDs_Lnl-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_foll_collap_ang_F1a_male_rats_2_h
igh_drop_HEDs_Lnl-BMR10-Restrict.plt
                                                Wed Mar 08 08:46:54 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
   Total number of observations = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =            0
                     intercept =      1.31015
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept

 intercept            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept          1.30391         0.48942            0.344669
2.26316
          slope                1              NA

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


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -13.0401         3
   Fitted model        -13.3179         1      0.555651      2          0.7574
  Reduced model        -17.9947         1       9.90922      2        0.007051

           AIC:         28.6359


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size          Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      12.000          0.000
    0.0780     0.2232         2.232     3.000      10.000          0.583
    0.3700     0.5768         5.768     5.000      10.000         -0.492
```

```
 Chi^2 = 0.58      d.f. = 2        P-value = 0.7476

   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.030163

            BMDL =      0.0136007
```

Increased Incidence of Increased Epithelial Height (All Severity Scores) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

The procedure outlined above was applied to the data for increased incidence of increased epithelial height (all severity scores) in the thyroid of female S-D rats administered technical toxaphene in the diet for 13 weeks (Chu et al., 1986) (see Table C-27). Table C-28 summarizes the BMD modeling results. All of the models provided an adequate fit using the full dose range. BMDLs for models providing adequate fit were not sufficiently close (differed by ≥threefold), so the model with the lowest BMDL was selected (LogLogistic). Thus, the $BMDL_{10}$ of 0.00014 mg/kg-day from this model is selected for this endpoint (see Figure C-13). However, the modeling results for this endpoint are not considered reliable because all response levels were in excess of the BMR and at maximal response at all but the lowest dose tested, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD (U.S. EPA, 2012b).

Table C-27. Incidence of Increased Epithelial Height (All Severity Scores) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks[a]

	HED (mg/kg-d)				
	0	**0.11**	**0.58**	**2.81**	**14**
Sample size	10	10	10	10	10
Incidence	0	9	10	10	10

[a]Chu et al. (1986).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-28. BMD Modeling Results for Incidence of Increased Epithelial Height (All Severity Scores) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	1	10.50	0.01089	0.00257
Logistic	0.9556	11.09	0.03301	0.01377
LogLogistic[c, d]	**1**	**10.50**	**0.07218**	**0.00014**
LogProbit[c]	1	10.50	0.09035	NDr
Multistage (1-degree)[e]	1	8.50	0.00503	0.00257
Multistage (2-degree)[e]	1	10.50	0.00505	0.00258
Multistage (3-degree)[e]	1	12.50	0.00505	0.00258
Multistage (4-degree)[e]	0.9947	14.50	0.00505	0.00258
Probit	1	10.50	0.05945	0.01470
Weibull[b]	1	10.50	0.00503	0.00257

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Selected model.
[e]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; NDr = not determined; S-D = Sprague-Dawley.

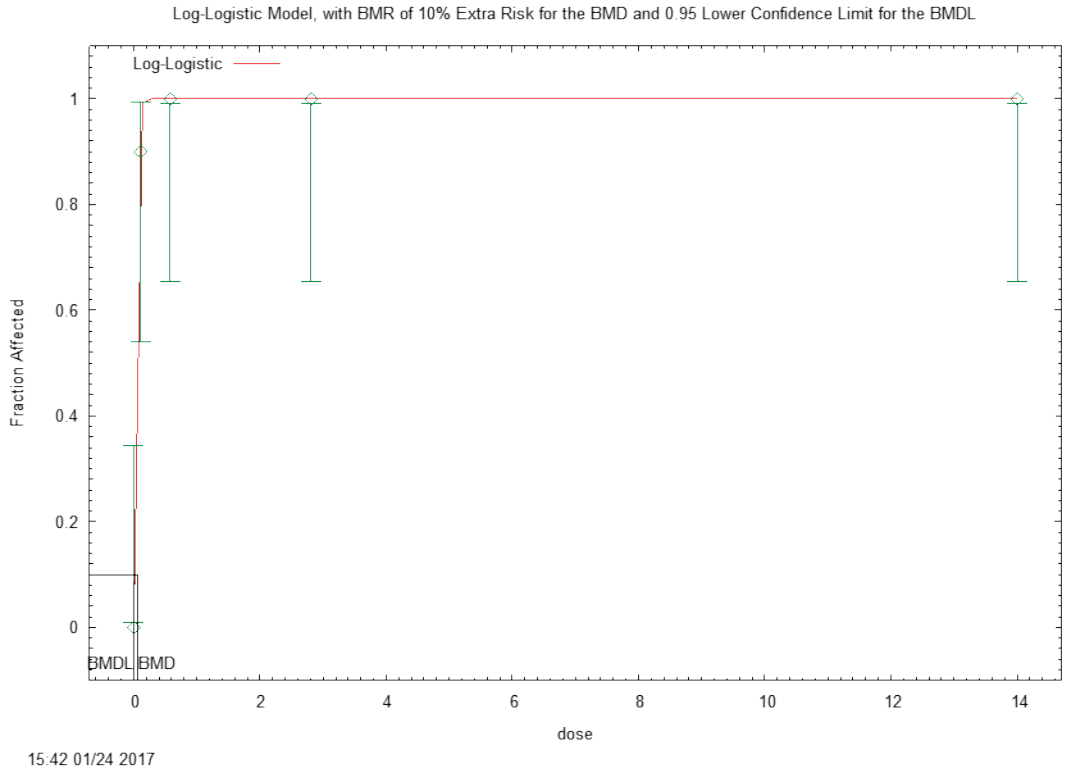

Figure C-13. LogLogistic Model for Increased Incidence of Increased Epithelial Height (All Severity Grades) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

Text output for Figure C-13:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_incr_epith_ht_female_rats_HEDs_Ln
l-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_incr_epith_ht_female_rats_HEDs_Ln
l-BMR10-Restrict.plt
                                          Mon Feb 13 08:54:11 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
```

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0
intercept = 1.15959
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	1
slope	1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	25.2192	4221.51	-8248.78	8299.22
slope	10.4301	1912.54	-3738.08	3758.94

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-3.25083	5			
Fitted model	-3.25083	2	6.5451e-008	3	1
Reduced model	-26.3454	1	46.1891	4	<.0001

AIC: 10.5017

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	10.000	0.000
0.1100	0.9000	9.000	9.000	10.000	-0.000

```
    0.5800      1.0000         10.000     10.000       10.000         0.000
    2.8100      1.0000         10.000     10.000       10.000         0.000
   14.0000      1.0000         10.000     10.000       10.000         0.000

 Chi^2 = 0.00      d.f. = 3        P-value = 1.0000


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0721794

            BMDL =    0.000141103
```

Increased Incidence of Cytoplasmic Vacuolation (All Severity Scores) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

The procedure outlined above was applied to the data for increased incidence of cytoplasmic vacuolation (all severity scores) in the thyroid of female S-D rats administered technical toxaphene in the diet for 13 weeks (Chu et al., 1986) (see Table C-29). Table C-30 summarizes the BMD modeling results. None of the models provided an adequate fit using the full dose range. The data were not modeled with doses dropped due to a plateau of incidence data at the lowest and highest doses tested. Thus, these data are not amenable to BMD modeling.

Table C-29. Incidence of Cytoplasmic Vacuolation (All Severity Scores) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks[a]

	HED (mg/kg-d)				
	0	**0.11**	**0.58**	**2.81**	**14**
Sample size	10	10	10	10	10
Incidence	0	10	8	9	10

[a]Chu et al. (1986).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-30. BMD Modeling Results for Incidence of Cytoplasmic Vacuolation (All Severity Scores) in the Thyroid of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.0002	47.53	0.10944	0.04730
Logistic	0.0001	48.55	0.19616	0.09697
LogLogistic[c]	0	43.51	0.02725	0.01594
LogProbit[c]	0.0002	47.53	0.10944	0.04730
Multistage (1-degree)[d]	0.0002	47.53	0.10944	0.04730
Multistage (2-degree)[d]	0.0002	47.53	0.10944	0.04730
Multistage (3-degree)[d]	0.0002	47.53	0.10944	0.04730
Multistage (4-degree)[d]	0.0001	48.79	0.23013	0.13185
Probit	0.0002	47.53	0.10944	0.04730
Weibull[b]	0.0002	47.53	0.10944	0.04730

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

Increased Incidence of Cytoplasmic Vacuolation (All Severity Grades) in the Thyroid of F0 Male S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks (Chu et al., 1988)

The procedure outlined above was applied to the data for increased incidence of cytoplasmic vacuolation (all severity grades) in the thyroid of F0 male S-D rats exposed to technical toxaphene for 25−29 weeks (Chu et al., 1988) (see Table C-31). Table C-32 summarizes the BMD modeling results. None of the models provided adequate fit to the full data set or the data set with the highest dose dropped. With the two highest doses dropped, all models provided adequate fit to the data. BMDLs for models providing adequate fit were not sufficiently close (differed by ≥threefold), so the model with the lowest BMDL was selected (LogLogistic). Thus, the $BMDL_{10}$ of 0.0092 mg/kg-day from this model is selected for this endpoint (see Figure C-14).

Table C-31. Incidence of Cytoplasmic Vacuolation (All Severity Grades) in the Thyroid of F0 Male S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks[a]

	HED (mg/kg-d)				
	0	**0.10**	**0.47**	**2.4**	**12**
Sample size	12	10	10	11	13
Incidence	0	3	8	7	12

[a]Chu et al. (1988).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-32. BMD Modeling Results for Incidence of Cytoplasmic Vacuolation (All Severity Grades) in the Thyroid of F0 Male S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.0033	64.24	0.41622	0.21982
Logistic	0.0021	66.22	0.90629	0.52714
LogLogistic[c]	0.0629	53.06	0.04016	0.02005
LogProbit[c]	0.0016	65.75	0.63562	0.22562
Multistage (1-degree)[d]	0.0033	64.24	0.41620	0.21982
Multistage (2-degree)[d]	0.0033	64.24	0.41621	0.21982
Multistage (3-degree)[d]	0.0033	64.24	0.41620	0.21982
Multistage (4-degree)[d]	0.0033	64.24	0.41620	0.21982
Probit	0.002	66.45	1.01220	0.66379
Weibull[b]	0.0033	64.24	0.41620	0.21982
Highest dose dropped				
Gamma[b]	0.002	54.73	0.17615	0.09134
Logistic	0.0013	57.00	0.43085	0.25783
LogLogistic[c]	0.0396	45.21	0.03580	0.01745
LogProbit[c]	0.0004	56.72	0.23870	0.10203
Multistage (1-degree)[d]	0.002	54.73	0.17615	0.09134
Multistage (2-degree)[d]	0.002	54.73	0.17615	0.09134
Multistage (3-degree)[d]	0.002	54.73	0.17615	0.09134
Probit	0.0013	56.96	0.42618	0.26827
Weibull[b]	0.002	54.73	0.17615	0.09134
Two highest doses dropped				
Gamma[b]	0.9983	24.23	0.03038	0.01832
Logistic	0.1339	29.31	0.10075	0.05946
LogLogistic[c, e]	**1**	**26.23**	**0.03925**	**0.00915**

Table C-32. BMD Modeling Results for Incidence of Cytoplasmic Vacuolation (All Severity Grades) in the Thyroid of F0 Male S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
LogProbit[d]	0.9565	24.31	0.05096	0.03045
Multistage (1-degree)[d]	0.9983	24.23	0.03038	0.01832
Multistage (2-degree)[d]	0.9983	24.23	0.03038	0.01832
Probit	0.1442	29.07	0.09463	0.05930
Weibull[b]	0.9983	24.23	0.03038	0.01832

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

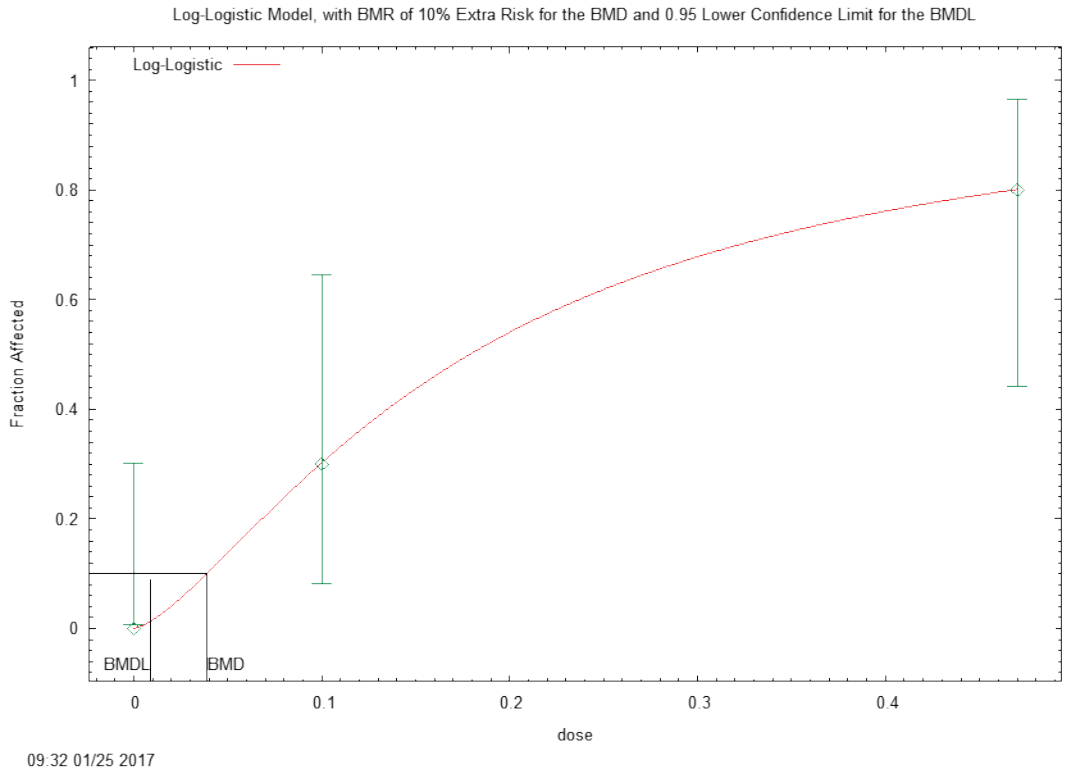

Figure C-14. LogLogistic Model for Increased Incidence of Cytoplasmic Vacuolation (All Severity Grades) in the Thyroid of F0 Male S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks (Two Highest Doses Dropped) (Chu et al., 1988)

Text output for Figure C-14:

```
================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_thy_cyt_vac_F0_male_rats_2_high_d
rop_HEDs_Lnl-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_thy_cyt_vac_F0_male_rats_2_high_d
rop_HEDs_Lnl-BMR10-Restrict.plt
                                            Mon Feb 13 09:24:54 2017
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =            0
                     intercept =      2.47602
                         slope =       1.4433


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept        slope

 intercept            1         0.91

     slope         0.91            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
```

```
      intercept          2.47602          1.22351           0.0779842
4.87405
          slope           1.4433         0.678086            0.114273
2.77232

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

 Warning: Likelihood for the fitted model larger than the Likelihood for the full
model.


                      Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -11.1127         3
   Fitted model         -11.1127         2 -3.55271e-015      1                  -1
  Reduced model         -20.5917         1       18.9581      2         <.0001

           AIC:          26.2253


                                Goodness  of  Fit
                                                                      Scaled
    Dose      Est._Prob.     Expected    Observed     Size          Residual
  ----------------------------------------------------------------------------
    0.0000      0.0000          0.000      0.000      12.000          0.000
    0.1000      0.3000          3.000      3.000      10.000          0.000
    0.4700      0.8000          8.000      8.000      10.000          0.000

 Chi^2 = 0.00      d.f. = 1        P-value = 1.0000


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0392465

            BMDL =     0.00914841
```

Increased Incidence of Cytoplasmic Vacuolation (All Severity Grades) in the Thyroid of F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks (Chu et al., 1988)

The procedure outlined above was applied to the data for increased incidence of cytoplasmic vacuolation (all severity grades) in the thyroid of F0 female S-D rats exposed to technical toxaphene for 25−29 weeks (Chu et al., 1988) (see Table C-33). Table C-34 summarizes the BMD modeling results. None of the models provided adequate fit to the full data set. With the highest dose dropped, all models provided adequate fit to the data. BMDLs for models providing adequate fit were not sufficiently close (differed by ≥threefold), so the model with the lowest BMDL was selected (LogLogistic). Although the $BMDL_{10}$ of 0.037 mg/kg-day from this model is selected for this endpoint (see Figure C-15), it is considered a borderline case for passing visual inspection of the model fit.

Table C-33. Incidence of Cytoplasmic Vacuolation (All Severity Grades) in the Thyroid of F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks[a]

	HED (mg/kg-d)				
	0	**0.083**	**0.44**	**1.9**	**11**
Sample size	17	10	10	10	17
Incidence	2	4	4	7	9

[a]Chu et al. (1988).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-34. BMD Modeling Results for Incidence of Cytoplasmic Vacuolation (All Severity Grades) in the Thyroid of F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.0052	92.46	1.3×10^{14}	NDr
Logistic	0.0357	88.06	3.37599	1.78465
LogLogistic[c]	0.0463	87.36	1.54574	0.42723
LogProbit[c]	0.0252	88.84	5.17203	2.17277
Multistage (1-degree)[d]	0.0399	87.76	2.42250	1.04272
Multistage (2-degree)[d]	0.0399	87.76	2.42250	1.04272
Multistage (3-degree)[d]	0.0399	87.76	2.42250	1.04272
Multistage (4-degree)[d]	0.0399	87.76	2.42250	1.04272
Probit	0.0359	88.05	3.33414	1.78355
Weibull[b]	0.0399	87.76	2.42255	1.04272
Highest dose dropped				
Gamma[b]	0.324	57.64	0.18336	0.09471
Logistic	0.2603	58.22	0.34526	0.21333
LogLogistic[c, e]	**0.3954**	**57.19**	**0.10299**	**0.03668**
LogProbit[d]	0.2238	58.46	0.35276	0.17064
Multistage (1-degree)[d]	0.324	57.64	0.18336	0.09471
Multistage (2-degree)[d]	0.324	57.64	0.18336	0.09471
Multistage (3-degree)[d]	0.324	57.64	0.18336	0.09471
Probit	0.2629	58.19	0.33560	0.21653
Weibull[b]	0.324	57.64	0.18336	0.09471

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; NDr = not determined; S-D = Sprague-Dawley.

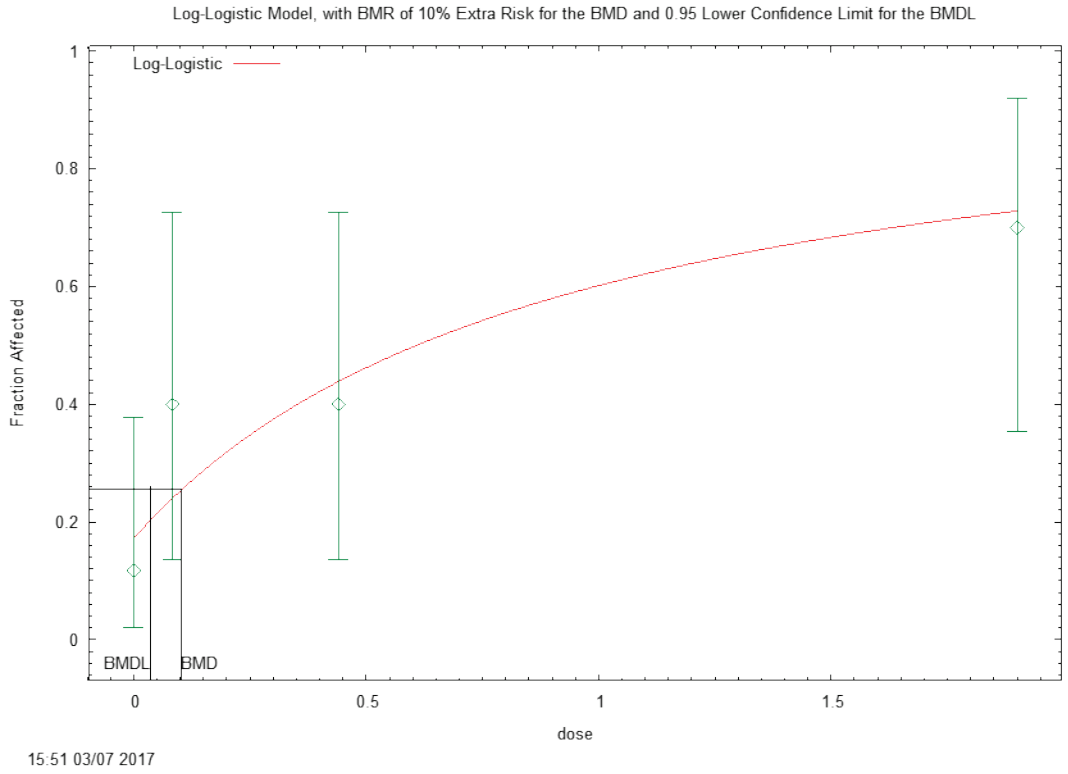

Figure C-15. LogLogistic Model for Increased Incidence of Cytoplasmic Vacuolation (All Severity Grades) in the Thyroid of F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks (Highest Dose Dropped) (Chu et al., 1988)

Text output for Figure C-15:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_thy_cyt_vac_F0_female_rats_high_d
rop_HEDs_Lnl-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_thy_cyt_vac_F0_female_rats_high_d
rop_HEDs_Lnl-BMR10-Restrict.plt
                                          Tue Mar 07 16:17:01 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
```

```
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =     0.117647
                     intercept =     0.140388
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

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

             background    intercept

background            1        -0.55

 intercept        -0.55            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background         0.172143        0.0888777         -0.00205448
0.34634
      intercept        0.0758934         0.693144            -1.28264
1.43443
          slope                1               NA

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


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -25.7265         4
   Fitted model        -26.5956         2        1.7382      2          0.4193
  Reduced model        -30.7564         1       10.0599      3         0.01806

           AIC:         57.1911


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size          Residual
  ----------------------------------------------------------------------
    0.0000     0.1721         2.926     2.000      17.000         -0.595
    0.0830     0.2402         2.402     4.000      10.000          1.183
```

```
    0.4400      0.4386          4.386      4.000       10.000        -0.246
    1.9000      0.7286          7.286      7.000       10.000        -0.203

 Chi^2 = 1.86       d.f. = 2         P-value = 0.3954


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =       Extra risk

Confidence level =            0.95

             BMD =        0.102991

            BMDL =       0.0366766
```

Increased Incidence of Minimal to Mild Cytoplasmic Vacuolation (the Only Severity Grade Observed) in the Thyroid of F1a Female S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks (Chu et al., 1988)

The procedure outlined above was applied to the data for increased incidence of minimal to mild cytoplasmic vacuolation in the thyroid of F1a female S-D rats exposed to toxaphene for 34 weeks (Chu et al., 1988) (see Table C-35). Table C-36 summarizes the BMD modeling results. None of the models provided an adequate fit using the full dose range. However, after dropping the highest dose, the LogLogistic model provided an adequate fit to the data. Thus, a $BMDL_{10}$ of 0.0059 mg/kg-day was calculated for this data set (see Figure C-16). However, the modeling results for this endpoint are not considered reliable because all response levels were considered in excess of the BMR, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD (U.S. EPA, 2012b).

Table C-35. Incidence of Minimal to Mild Cytoplasmic Vacuolation (the Only Severity Grade Observed) in the Thyroid of F1a Female S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks[a]

	HED (mg/kg-d)				
	0	**0.089**	**0.44**	**2.2**	**11**
Sample size	17	10	10	10	17
Incidence	1	5	8	9	6

[a]Chu et al. (1988).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-36. BMD Modeling Results for Incidence of Minimal to Mild Cytoplasmic Vacuolation (the Only Severity Grade Observed) in the Thyroid of F1a Female S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0	94.16	2.1×10^{13}	NDr
Logistic	0	92.16	1,100	3.46836
LogLogistic[c]	0	92.16	4.0×10^{6}	2.09089
LogProbit[c]	0	92.16	392.557	6.09914
Multistage (1-degree)[d]	0	91.97	NDr	NDr
Multistage (2-degree)[d]	0.0001	90.16	NDr	NDr
Multistage (3-degree)[d]	0.0001	90.16	NDr	NDr
Multistage (4-degree)[d]	0.0001	90.16	NDr	NDr
Probit	0	92.16	1,100	3.46537
Weibull[b]	0	92.16	1,100	NDr
Highest dose dropped				
Gamma[b]	0.0052	49.22	0.05563	0.03152
Logistic	0.0041	54.11	0.16463	0.09128
LogLogistic[c, e]	**0.7355**	**42.48**	**0.01379**	**0.00593**
LogProbit[d]	0.0007	47.76	0.05450	0.03032
Multistage (1-degree)[d]	0.0052	49.22	0.05563	0.03152
Multistage (2-degree)[d]	0.0052	49.22	0.05563	0.03152
Multistage (3-degree)[d]	0.0052	49.22	0.05563	0.03152
Probit	0.004	54.59	0.19185	0.12402
Weibull[b]	0.0052	49.22	0.05563	0.03152

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; NDr = not determined; S-D = Sprague-Dawley.

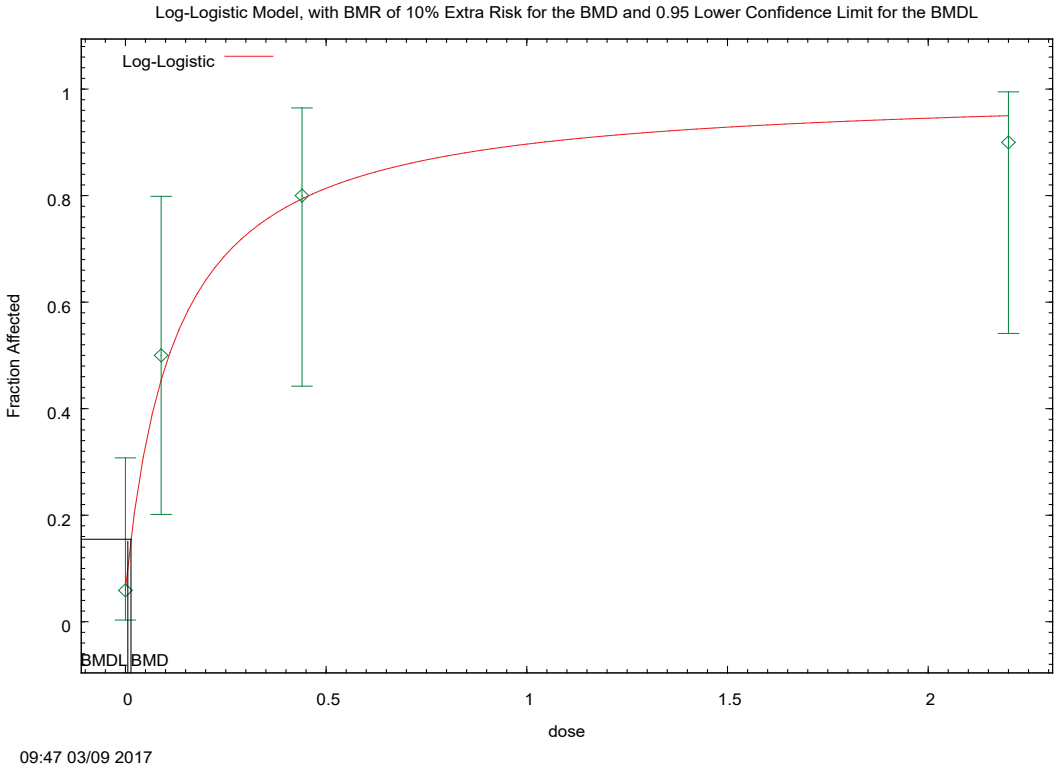

Figure C-16. LogLogistic Model for Increased Incidence of Minimal to Mild Cytoplasmic Vacuolation (the Only Severity Grade Observed) in the Thyroid of F1a Female S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks (Highest Dose Dropped) (Chu et al., 1988)

Text output for Figure C-16:

```
=================================================================
         Logistic Model. (Version: 2.14; Date: 2/28/2013)
         Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_thy_cyt_vac_F1a_female_rats_high_
drop_HEDs_Lnl-BMR10-Restrict.(d)
         Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_thy_cyt_vac_F1a_female_rats_high_
drop_HEDs_Lnl-BMR10-Restrict.plt
                                                Thu Mar 09 09:47:06 2017
 =================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0588235
                     intercept =      1.65075
                         slope =             1


           Asymptotic Correlation Matrix of Parameter Estimates

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

             background    intercept

background            1        -0.24

 intercept        -0.24            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background        0.0609484        0.0589907          -0.0546712
0.176568
      intercept          2.08662         0.507257             1.09242
3.08083
          slope                1               NA

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


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -18.9895         4
   Fitted model        -19.2407         2      0.502347      2          0.7779
  Reduced model        -32.5673         1       27.1555      3         <.0001

           AIC:         42.4814


                                  Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size          Residual
  ---------------------------------------------------------------------------
```

```
    0.0000     0.0609         1.036     1.000      17.000       -0.037
    0.0890     0.4531         4.531     5.000      10.000        0.298
    0.4400     0.7934         7.934     8.000      10.000        0.052
    2.2000     0.9499         9.499     9.000      10.000       -0.722

 Chi^2 = 0.61      d.f. = 2        P-value = 0.7355


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.0137895

            BMDL =      0.00593414
```

Increased Relative Liver Weight in Female Beagle Dogs Administered Technical Toxaphene in Gelatin Capsules for 13 Weeks (Chu et al., 1986)

The procedure outlined above was applied to the data for increased relative liver weight in female Beagle dogs administered technical toxaphene in gelatin capsules for 13 weeks (Chu et al., 1986) (see Table C-37). Table C-38 summarizes the BMD modeling results. The constant variance model provided adequate fit to the data, and all models provided adequate fit to means. However, all models besides the Hill model failed visual inspection of the model fit. While the Hill model provided an adequate model fit, the BMD was more than an order of magnitude higher than the corresponding BMDL. Thus, none of the modeling results for this endpoint are considered reliable.

Table C-37. Relative Liver Weights of Female Beagle Dogs Administered Technical Toxaphene in Gelatin Capsules for 13 Weeks[a]

	HED (mg/kg-d)			
	0	**0.1**	**0.82**	**1.8**
Sample size	6	6	6	6
Mean	3.0	3.4	3.6	3.9
SD	0.60	0.40	0.31	0.46

[a]Chu et al. (1986).

HED = human equivalent dose; SD = standard deviation.

Table C-38. BMD Model Predictions for Relative Liver Weight in Female Beagle Dogs Administered Technical Toxaphene by Gelatin Capsule for 13 Weeks[a]

Model	Variance *p*-Value[b]	Mean *p*-Value[b]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Constant variance					
Exponential (model 2)[c]	0.44	0.29	−9.71	0.82698	0.55252
Exponential (model 3)[c]	0.44	0.29	−9.71	0.82698	0.55252
Exponential (model 4)[c]	0.44	0.19	−8.47	0.36171	0.00076
Exponential (model 5)[c]	0.44	0.19	−8.47	0.36171	0.00115
Hill[c]	0.44	0.31	−9.16	0.07882	0.00322
Linear[d]	0.44	0.31	−9.84	0.76956	0.48722
Polynomial (2-degree)[d]	0.44	0.31	−9.84	0.76956	0.48722
Polynomial (3-degree)[d]	0.44	0.31	−9.84	0.76956	0.48722
Power[c]	0.44	0.31	−9.84	0.76956	0.48722

[a]Chu et al. (1986).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
[d]Power restricted to ≥1.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit.

Increased Absolute Liver Weight in F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks (Chu et al., 1988)

The procedure outlined above was applied to the data for increased absolute liver weight in F0 female S-D rats administered technical toxaphene in the diet for 25−29 weeks (Chu et al., 1988) (see Table C-39). Table C-40 summarizes the BMD modeling results. The constant variance model did not fit the variance data, but the nonconstant variance model did. With the nonconstant variance model applied using the full dose range, none of the models provided adequate fit to the means. However, after dropping the highest dose, the Exponential Model 4 provided an adequate fit to the data. Thus, a $BMDL_{10}$ of 0.028 mg/kg-day was calculated for this data set (see Figure C-17).

Table C-39 Absolute Liver Weight in F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks[a]

	HED (mg/kg-d)				
	0	**0.083**	**0.44**	**1.9**	**11**
Sample size	23	20	20	17	18
Mean	11.6	12.9	13.8	13.6	16.6
SD	2.0	2.0	3.3	2.7	3.2

[a]Chu et al. (1988).

HED = human equivalent dose; S-D = Sprague-Dawley; SD = standard deviation.

Table C-40. BMD Model Predictions for Absolute Liver Weight in F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks[a]

Model	Variance *p*-Value[b]	Mean *p*-Value[b]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Constant variance					
Exponential (model 2)[c]	0.05	0.07	298.07	3.87089	3.02370
Exponential (model 3)[c]	0.05	0.07	298.07	3.87089	3.02370
Exponential (model 4)[c]	0.05	0.06	298.82	1.45755	0.52458
Exponential (model 5)[c]	0.05	0.06	298.82	1.45755	0.52458
Hill[c]	0.05	0.06	298.65	1.22112	0.17175
Linear[d]	0.05	0.08	297.88	3.49605	2.62151
Polynomial (2-degree)[d]	0.05	0.08	297.88	3.49605	2.62151
Polynomial (3-degree)[d]	0.05	0.08	297.88	3.49605	2.62151
Power[c]	0.05	0.08	297.88	3.49605	2.62151
Nonconstant variance					
Exponential (model 2)[c]	0.38	0.01	298.79	3.83243	2.91741
Exponential (model 3)[c]	0.38	0.01	298.79	3.83243	2.91741
Exponential (model 4)[c]	0.38	0.01	298.76	1.04659	0.03477
Exponential (model 5)[c]	0.38	0.01	298.76	1.04659	0.03477
Hill[c]	0.38	0.05	295.06	0.12875	0.04087
Linear[d]	0.38	0.01	298.54	3.44816	2.50604
Polynomial (2-degree)[d]	0.38	0.01	298.54	3.44816	2.50604
Polynomial (3-degree)[d]	0.38	0.01	298.54	3.44816	2.50604
Power[c]	0.38	0.01	298.54	3.44816	2.50604

Table C-40. BMD Model Predictions for Absolute Liver Weight in F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks[a]

Model	Variance *p*-Value[b]	Mean *p*-Value[b]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Nonconstant variance (highest dose dropped)					
Exponential (model 2)[c]	0.43	0.003	238.52	1.64649	0.84705
Exponential (model 3)[c]	0.43	0.003	238.52	1.64649	0.84705
Exponential (model 4)[c, e]	**0.43**	**0.41**	**229.44**	**0.09870**	**0.02834**
Exponential (model 5)[c]	0.43	NA[f]	231.27	0.09592	0.02994
Hill[c]	0.43	NA[f]	231.27	0.08661	0.01660
Linear[d]	0.43	0.003	238.37	1.56086	0.76143
Polynomial (2-degree)[d]	0.43	0.003	238.37	1.56086	0.76143
Polynomial (3-degree)[d]	0.43	0.003	238.37	1.56086	0.76143
Power[c]	0.43	0.003	238.37	1.56086	0.76143

[a]Chu et al. (1988).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
[d]Power restricted to ≥1.
[e]Selected model.
[f]Degrees of freedom for Test 4 [means *p*-value] are ≤0; the χ^2 test for fit is not valid.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; NA = not applicable; S-D = Sprague-Dawley.

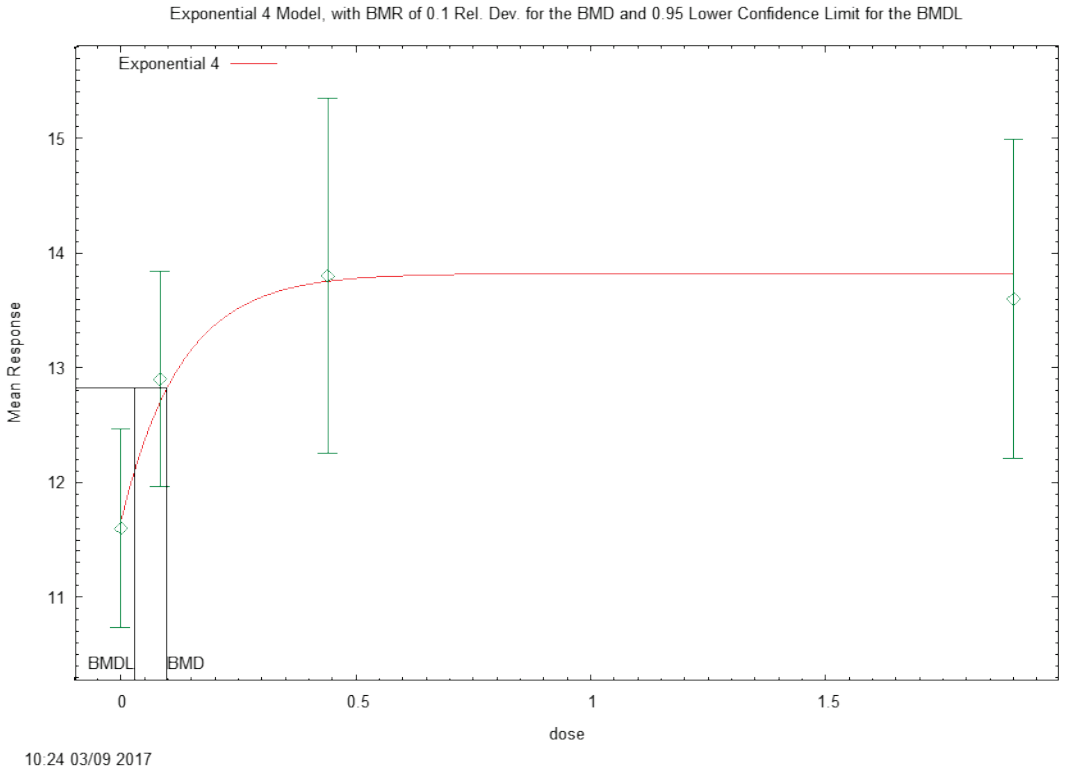

Figure C-17. Exponential Model 4 for Increased Absolute Liver Weight in F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks (Chu et al., 1986)

Text output for Figure C-17:

```
================================================================================
        Exponential Model. (Version: 1.10;  Date: 01/12/2015)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/exp_Chu_1988_abs_liv_F0_females_high_drop
_HEDs_Exp-ModelVariance-BMR10-Up.(d)
        Gnuplot Plotting File:
                                                  Thu Mar 09 10:24:03 2017
 ================================================================================

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

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
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 = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 4	
lnalpha	-11.1217	
rho	5.0409	
a	11.02	
b	0.881981	
c	1.31488	
d	1	Specified

Parameter Estimates

Variable	Model 4	Std. Err.
lnalpha	-11.4297	6.55605
rho	5.1557	2.56976
a	11.6628	0.384103
b	7.87633	4.8735
c	1.18504	0.0572076

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	23	11.6	2
0.083	20	12.9	2
0.44	20	13.8	3.3
1.9	17	13.6	2.7

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	11.66	1.854	-0.1624
0.083	12.7	2.309	0.3903
0.44	13.75	2.836	0.07337
1.9	13.82	2.872	-0.3171

```
Other models for which likelihoods are 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 + log(mean(i)) * rho)

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

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-112.2946	5	234.5893
A2	-108.5167	8	233.0334
A3	-109.3695	6	230.739
R	-117.1847	2	238.3694
4	-109.7213	5	229.4426

Additive constant for all log-likelihoods = -73.52. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	17.34	6	0.008125
Test 2	7.556	3	0.05614
Test 3	1.706	2	0.4262
Test 6a	0.7036	1	0.4016

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 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 0.100000

```
        Risk Type = Relative deviation
Confidence Level = 0.950000
              BMD =    0.0987043
             BMDL =    0.0283373
```

Increased Relative Liver Weight in Male B6C3F$_1$ Mice Administered Technical Toxaphene in the Diet for 28 Days (Wang et al., 2015)

The procedure outlined above was applied to the data for increased relative liver weight in male B6C3F$_1$ mice administered technical toxaphene in the diet for 28 days (Wang et al., 2015) (see Table C-41). Table C-42 summarizes the BMD modeling results. The constant variance model did not fit the variance data. With the nonconstant variance model applied, all models provided only a marginal fit to the data (variance $p = 0.09$). Thus, these data are not amenable to BMD modeling.

Table C-41. Relative Liver Weight in Male B6C3F$_1$ Mice Administered Technical Toxaphene in the Diet for 28 Days[a]

	HED (mg/kg-d)			
	0	**0.1**	**0.85**	**8.51**
Sample size	12	12	12	12
Mean	5.3	5.3	5.6	8.4
SD	0.27	0.24	0.16	0.64

[a]Wang et al. (2015).

HED = human equivalent dose; SD = standard deviation.

Table C-42. BMD Model Predictions for Increased Relative Liver Weight in Male B6C3F$_1$ Mice Administered Technical Toxaphene in the Diet for 28 Days

Model	Variance *p*-Value[a]	Mean *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Constant variance					
Exponential (model 2)[b]	<0.0001	0.86	−43.76	1.8	1.7
Exponential (model 3)[b]	<0.0001	0.86	−43.76	1.8	1.7
Exponential (model 4)[b]	<0.0001	0.80	−42.00	1.4	0.81
Exponential (model 5)[b]	<0.0001	NA[c]	−40.06	0.97	0.85
Hill[c]	<0.0001	NA[c]	−40.06	0.88	0.85
Linear[d]	<0.0001	0.97	−44.00	1.4	1.3
Polynomial (2-degree)[d]	<0.0001	0.97	−44.00	1.4	1.3
Polynomial (3-degree)[d]	<0.0001	0.97	−44.00	1.4	1.3
Power[b]	<0.0001	0.97	−44.00	1.4	1.3
Nonconstant variance					
Exponential (model 2)[b]	0.09	0.80	−63.27	1.8	1.6
Exponential (model 3)[b]	0.09	0.80	−63.27	1.8	1.6
Exponential (model 4)[b]	0.09	0.61	−61.47	1.4	1.0
Exponential (model 5)[b]	0.09	NA	−59.72	0.94	0.86
Hill[b]	0.09	NA	89.06	NDr	NDr
Linear[d]	0.09	0.88	−63.47	1.4	1.3
Polynomial (2-degree)[d]	0.09	0.65	−61.51	1.5	1.3
Polynomial (3-degree)[d]	0.09	0.65	−61.51	1.5	1.3
Power[b]	0.09	0.66	−61.53	1.5	1.3

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Degrees of freedom for Test 4 [means *p*-value] are ≤0; the χ^2 test for fit is not valid.
[d]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; NA = not applicable; NDr = not determined.

Increased Mean Bromodeoxyuridine Labeling Index in the Liver of Male B6C3F$_1$ Mice Administered Technical Toxaphene in the Diet for 28 Days (Wang et al., 2015)

The procedure outlined above was applied to the data for increased mean bromodeoxyuridine (BrdU) labeling index in the liver of male B6C3F$_1$ mice administered technical toxaphene in the diet for 28 days (Wang et al., 2015) (see Table C-43). Table C-44 summarizes the BMD modeling results. The constant variance model did not fit the variance data. With a nonconstant variance model applied, the modeled variance fit the data; however, none of the models provided an adequate fit to the means. The high dose was not dropped because findings at the mid dose were not statistically significant. Thus, these data are not amenable to BMD modeling.

Table C-43. Mean BrdU Labeling Index in the Liver of Male B6C3F$_1$ Mice Administered Technical Toxaphene in the Diet for 28 Days[a]

	HED (mg/kg-d)			
	0	**0.1**	**0.85**	**8.51**
Sample size	5	5	5	5
Mean	0.9	1	1.7	3.9
SEM	0.2	0.7	0.7	1.7
SD[b]	0.4	1.6	1.6	3.8

[a]Wang et al. (2015).
[b]Calculated using U.S. EPA BMDS (Version 2.5).

BMDS = Benchmark Dose Software; BrdU = bromodeoxyuridine; HED = human equivalent dose; SD = standard deviation; SEM = standard error of the mean.

Table C-44. BMD Model Predictions for Mean BrdU Labeling Index in the Liver of Male B6C3F$_1$ Mice Administered Technical Toxaphene in the Diet for 28 Days

Model	Variance *p*-Value[a]	Mean *p*-Value[a]	AIC	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)
Constant variance					
Exponential (model 2)[b]	0.0004	0.85	53.76	7.0	5.4
Exponential (model 3)[b]	0.0004	0.85	53.76	7.0	5.4
Exponential (model 4)[b]	0.0004	1.00	55.44	2.9	0.46
Exponential (model 5)[b]	0.0004	NA[c]	57.44	2.8	0.46
Hill[b]	0.0004	NA[c]	57.44	3.1	0.30
Linear[d]	0.0004	0.90	53.64	6.0	3.6
Polynomial (2-degree)[d]	0.0004	0.90	53.64	6.0	3.6
Polynomial (3-degree)[d]	0.0004	0.90	53.64	6.0	3.6
Power[b]	0.0004	0.90	53.64	6.0	3.6
Nonconstant variance					
Exponential (model 2)[b]	0.42	0.03	45.71	4.7	3.0
Exponential (model 3)[b]	0.42	0.03	45.71	4.7	3.0
Exponential (model 4)[b]	0.42	0.02	45.93	0.83	0.002
Exponential (model 5)[b]	0.42	0.02	45.93	0.83	0.004
Hill[b]	0.42	0.06	44.34	0.05	NDr
Linear[d]	0.42	0.05	44.98	2.8	1.2
Polynomial (2-degree)[d]	0.42	0.05	44.98	2.8	1.2
Polynomial (3-degree)[d]	0.42	0.05	44.98	2.8	1.2
Power[b]	0.42	0.05	44.98	2.8	1.2

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Degrees of freedom for Test 4 [means *p*-value] are ≤0; the χ^2 test for fit is not valid.
[d]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; BrdU = bromodeoxyuridine; NA = not applicable; NDr = not determined; SD = standard deviation.

Increased Incidence of Accented Zonation (All Severity Scores) in the Liver of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

The procedure outlined above was applied to the data for increased incidence of accented zonation (all severity grades) in the liver of female S-D rats exposed to toxaphene for 13 weeks (Chu et al., 1986) (see Table C-45). Table C-46 summarizes the BMD modeling results. All models except the LogProbit, and Multistage 3- and 4-degree models provided adequate fit to the full data set. BMDLs for models providing adequate fit were not sufficiently close (differed by ≥threefold), so the model with the lowest BMDL was selected (LogLogistic). Thus, the $BMDL_{10}$ of 0.024 mg/kg-day from this model is selected for this endpoint (see Figure C-18). However, the modeling results for this endpoint are not considered reliable because all response levels were

considered far in excess of the BMR, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD (U.S. EPA, 2012b).

Table C-45. Incidence of Accented Zonation (All Severity Scores) in the Liver of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks[a]

	HED (mg/kg-d)				
	0	**0.11**	**0.58**	**2.81**	**14**
Sample size	10	10	10	10	10
Incidence	0	4	5	7	10

[a]Chu et al. (1986).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-46. BMD Modeling Results for Incidence of Accented Zonation (All Severity Scores) in the Liver of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.1689	50.13	0.22549	0.11690
Logistic	0.1429	51.28	0.48347	0.29377
LogLogistic[c, d]	**0.2561**	**46.26**	**0.04914**	**0.02418**
LogProbit[c]	0.0357	54.87	1.90772	0.16655
Multistage (1-degree)[e]	0.1689	50.13	0.22549	0.11690
Multistage (2-degree)[e]	0.1689	50.13	0.22549	0.11690
Multistage (3-degree)[e]	0.0808	52.13	0.22731	0.11692
Multistage (4-degree)[e]	0.0818	52.12	0.22945	0.11708
Probit	0.1433	51.24	0.47437	0.30331
Weibull[b]	0.1689	50.13	0.22549	0.11690

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Selected model.
[e]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

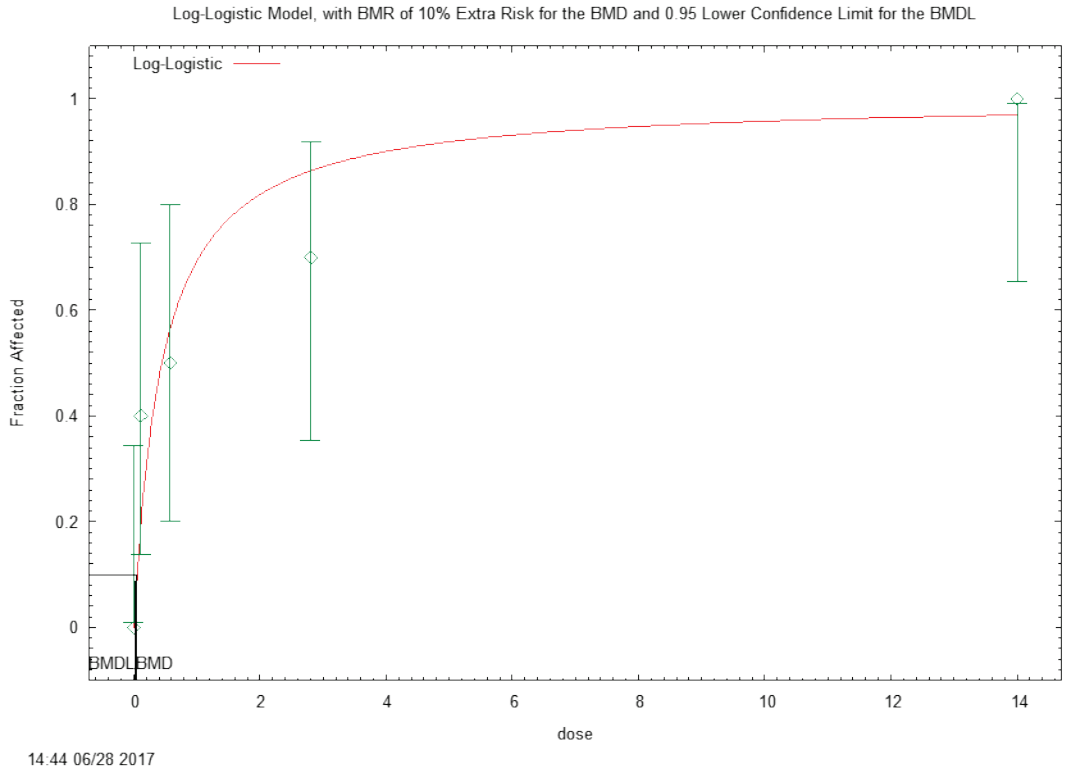

Figure C-18. LogLogistic Model for Increased Incidence of Accented Zonation (All Severity Scores) in the Liver of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

Text output for Figure C-18:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_liv_acc_zon_female_rats_HEDs_Lnl-
BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_liv_acc_zon_female_rats_HEDs_Lnl-
BMR10-Restrict.plt
                                          Thu Aug 17 08:50:16 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
```

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0
intercept = 0.11496
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept
intercept	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	0.815959	0.42557	-0.018143	1.65006
slope	1	NA		

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-19.7702	5			
Fitted model	-22.1298	1	4.71905	4	0.3174
Reduced model	-34.6173	1	29.6942	4	<.0001

AIC: 46.2595

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	10.000	0.000
0.1100	0.1992	1.992	4.000	10.000	1.590
0.5800	0.5674	5.674	5.000	10.000	-0.430
2.8100	0.8640	8.640	7.000	10.000	-1.513
14.0000	0.9694	9.694	10.000	10.000	0.562

```
 Chi^2 = 5.32      d.f. = 4        P-value = 0.2561


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.049135

            BMDL =      0.0241785
```

Increased Incidence of Anisokaryosis (All Severity Scores) in the Liver of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

The procedure outlined above was applied to the data for increased incidence of anisokaryosis (all severity grades) in the liver of male S-D rats exposed to toxaphene for 13 weeks (Chu et al., 1986) (see Table C-47). Table C-48 summarizes the BMD modeling results. All models provided adequate fit to the full data set. BMDLs for models providing adequate fit were not sufficiently close (differed by ≥threefold), so the model with the lowest BMDL was selected (LogLogistic). Thus, the $BMDL_{10}$ of 0.009 mg/kg-day from this model is selected for this endpoint (see Figure C-19). However, the modeling results for this endpoint are not considered reliable because all response levels were considered far in excess of the BMR, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD (U.S. EPA, 2012b).

Table C-47. Incidence of Anisokaryosis (All Severity Scores) in the Liver of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks[a]

	HED (mg/kg-d)				
	0	**0.090**	**0.46**	**2.2**	**11.8**
Sample size	10	10	10	10	10
Incidence	2	4	8	9	10

[a]Chu et al. (1986).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-48. BMD Modeling Results for Incidence of Anisokaryosis (All Severity Scores) in the Liver of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.3988	46.76	0.07856	0.04089
Logistic	0.2301	48.52	0.16410	0.08985
LogLogistic[c, d]	**0.7753**	**46.56**	**0.02767**	**0.00904**
LogProbit[c]	0.3857	46.21	0.10154	0.04679
Multistage (1-degree)[e]	0.3988	46.76	0.07856	0.04089
Multistage (2-degree)[e]	0.3988	46.76	0.07856	0.04089
Multistage (3-degree)[e]	0.3988	46.76	0.07856	0.04089
Multistage (4-degree)[e]	0.3988	46.76	0.07856	0.04089
Probit	0.2112	48.82	0.18718	0.11709
Weibull[b]	0.3988	46.76	0.07856	0.04089

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Selected model.
[e]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

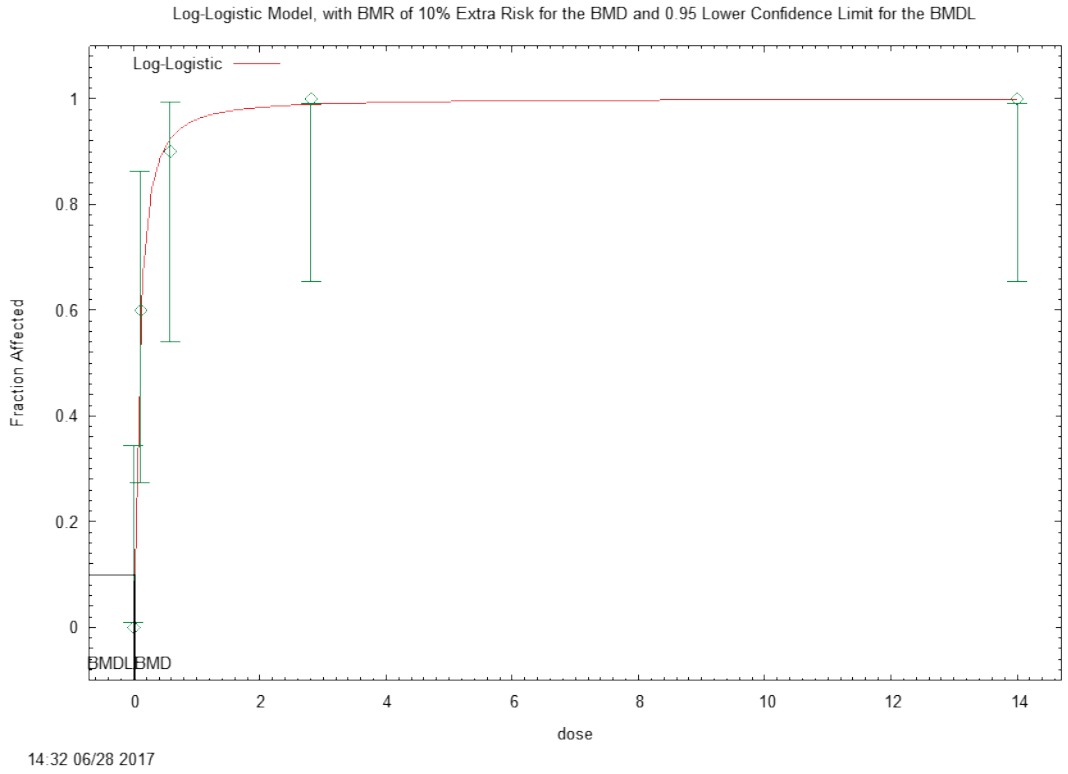

Figure C-19. LogLogistic Model for Increased Incidence of Anisokaryosis (All Severity Scores) in the Liver of Male S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

Text output for Figure C-19:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_liv_aniso_male_rats_HEDs_Lnl-BMR1
0-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_liv_aniso_male_rats_HEDs_Lnl-BMR1
0-Restrict.plt
                                          Thu Jun 29 13:25:35 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
```

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.2
intercept = 0.913084
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.3	0.22
intercept	-0.3	1	0.5
slope	0.22	0.5	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.19553	0.122016	-0.0436177	0.434678
intercept	1.65094	0.718885	0.241955	3.05993
slope	1.07272	0.440654	0.209054	1.93638

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-19.989	5			
Fitted model	-20.2804	3	0.582793	2	0.7472
Reduced model	-32.0518	1	24.1256	4	<.0001

AIC: 46.5608

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1955	1.955	2.000	10.000	0.036
0.0900	0.4228	4.228	4.000	10.000	-0.146
0.4600	0.7537	7.537	8.000	10.000	0.340
2.2000	0.9388	9.388	9.000	10.000	-0.512
11.8000	0.9892	9.892	10.000	10.000	0.330

Chi^2 = 0.51 d.f. = 2 P-value = 0.7753

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0276729

            BMDL =     0.00904366
```

Increased Incidence of Anisokaryosis (All Severity Scores) in the Liver of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

The procedure outlined above was applied to the data for increased incidence of anisokaryosis (all severity grades) in the liver of female S-D rats exposed to toxaphene for 13 weeks (Chu et al., 1986) (see Table C-49). Table C-50 summarizes the BMD modeling results. All models provided adequate fit to the full data set. BMDLs for models providing adequate fit were not sufficiently close (differed by ≥threefold), so the model with the lowest BMDL was selected (LogLogistic). Thus, the $BMDL_{10}$ of 0.003 mg/kg-day from this model is selected for this endpoint (see Figure C-20). However, the modeling results for this endpoint are not considered reliable because all response levels were considered far in excess of the BMR, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD (U.S. EPA, 2012b).

Table C-49. Incidence of Anisokaryosis (All Severity Scores) in the Liver of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks[a]

	HED (mg/kg-d)				
	0	**0.11**	**0.58**	**2.81**	**14**
Sample size	10	10	10	10	10
Incidence	0	6	9	10	10

[a]Chu et al. (1986).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-50. BMD Modeling Results for Incidence of Anisokaryosis (All Severity Scores) in the Liver of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.7844	23.45	0.01918	0.01157
Logistic	0.1402	31.15	0.06062	0.03405
LogLogistic[c, d]	**0.9758**	**24.28**	**0.01530**	**0.00295**
LogProbit[c]	0.9035	22.80	0.02891	0.01635
Multistage (1-degree)[e]	0.7844	23.45	0.01918	0.01157
Multistage (2-degree)[e]	0.7844	23.45	0.01918	0.01157
Multistage (3-degree)[e]	0.7841	23.45	0.01917	0.01157
Multistage (4-degree)[e]	0.7844	23.45	0.01918	0.01157
Probit	0.1317	31.26	0.06381	0.04034
Weibull[b]	0.7844	23.45	0.01918	0.01157

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Selected model.
[e]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

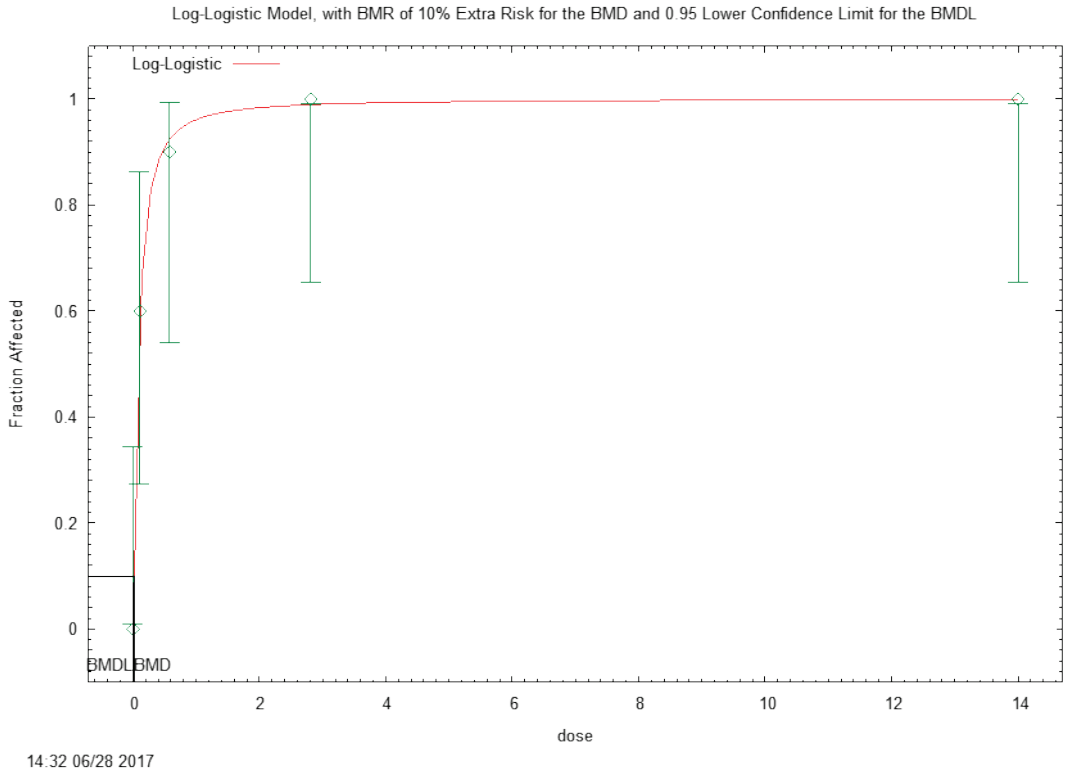

Figure C-20. LogLogistic Model for Increased Incidence of Anisokaryosis (All Severity Scores) in the Liver of Female S-D Rats Administered Technical Toxaphene in the Diet for 13 Weeks (Chu et al., 1986)

Text output for Figure C-20:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_liv_aniso_female_rats_HEDs_Lnl-BM
R10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1986_liv_aniso_female_rats_HEDs_Lnl-BM
R10-Restrict.plt
                                                Thu Jun 29 13:42:27 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
```

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0
intercept = 1.16344
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	0.89
slope	0.89	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	3.20789	1.20848	0.839309	5.57647
slope	1.29317	0.622291	0.0735049	2.51284

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-9.98095	5			
Fitted model	-10.1422	2	0.322451	3	0.9558
Reduced model	-30.5432	1	41.1245	4	<.0001

AIC: 24.2843

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	10.000	0.000
0.1100	0.5875	5.875	6.000	10.000	0.081

```
    0.5800      0.9244          9.244      9.000       10.000       -0.292
    2.8100      0.9895          9.895     10.000       10.000        0.326
   14.0000      0.9987          9.987     10.000       10.000        0.115

 Chi^2 = 0.21      d.f. = 3        P-value = 0.9758


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.0153027

            BMDL =      0.00294711
```

Increased Incidence of Anisokaryosis (All Severity Grades) in the Liver of F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25–29 Weeks (Chu et al., 1988)

The procedure outlined above was applied to the data for increased incidence of anisokaryosis (all severity grades) in the liver of female F0 S-D rats exposed to technical toxaphene for 25–29 weeks (Chu et al., 1988) (see Table C-51). Table C-52 summarizes the BMD modeling results. None of the models provided adequate fit to the full data set or the data set with the highest dose dropped. With the two highest doses dropped, only the Logistic, Multistage 1-degree, and Probit models provided adequate fit to the data. For these three models, BMDLs were considered to be sufficiently close (differed by <threefold). Of the models providing adequate fit, the Logistic and Probit models had the same lowest AIC, so the model with the lowest BMDL was selected (Logistic). Thus, the $BMDL_{10}$ of 0.0072 mg/kg-day from this model is selected for this endpoint (see Figure C-21). However, the modeling results for this endpoint are not considered reliable because all response levels were considered far in excess of the BMR, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD (U.S. EPA, 2012b).

Table C-51. Incidence of Primary Anisokaryosis (All Severity Grades) in the Liver of F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25–29 Weeks[a]

	HED (mg/kg-d)				
	0	**0.083**	**0.44**	**1.9**	**11**
Sample size	17	10	10	10	17
Incidence	4	8	10	7	17

[a]Chu et al. (1988).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-52. BMD Modeling Results for Incidence of Anisokaryosis (All Severity Grades) in the Liver of F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.0014	64.00	0.17918	0.07492
Logistic	0.0012	64.52	0.28285	0.13244
LogLogistic[c]	0	57.95	0.00956	0.00309
LogProbit[c]	0.0005	65.72	0.28642	0.07827
Multistage (1-degree)[d]	0.0014	64.00	0.17919	0.07492
Multistage (2-degree)[d]	0.0014	64.00	0.17919	0.07492
Multistage (3-degree)[d]	0.0004	66.00	0.18248	0.07495
Multistage (4-degree)[d]	0.0004	65.98	0.18653	0.07511
Probit	0.0012	64.57	0.31339	0.15386
Weibull[b]	0.0014	64.00	0.17919	0.07492
Highest dose dropped				
Gamma[b]	0.0004	63.97	0.18708	0.07521
Logistic	0.0004	64.50	0.29265	0.13279
LogLogistic[c]	0	57.75	0.01002	0.00318
LogProbit[c]	0.0002	65.53	0.37082	0.08156
Multistage (1-degree)[d]	0.0004	63.97	0.18708	0.07521
Multistage (2-degree)[d]	0.0004	63.97	0.18708	0.07521
Multistage (3-degree)[d]	0.0004	63.97	0.18708	0.07521
Probit	0.0003	64.57	0.31405	0.15387
Weibull[b]	0.0004	63.97	0.18708	0.07521
Two highest doses dropped				
Gamma[b]	NA	34.56	0.02677	0.00322
Logistic[e]	**0.9949**	**32.56**	**0.01252**	**0.00715**
LogLogistic[c]	NA	34.56	0.06050	0.00071
LogProbit[d]	NA	34.56	0.04308	0.00514
Multistage (1-degree)[d]	0.937	32.57	0.00646	0.00322
Multistage (2-degree)[d]	NA	36.56	0.03273	0.00322
Probit	1	32.56	0.01225	0.00759
Weibull[b]	NA	34.56	0.01513	0.00322

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; NA = not applicable; S-D = Sprague-Dawley.

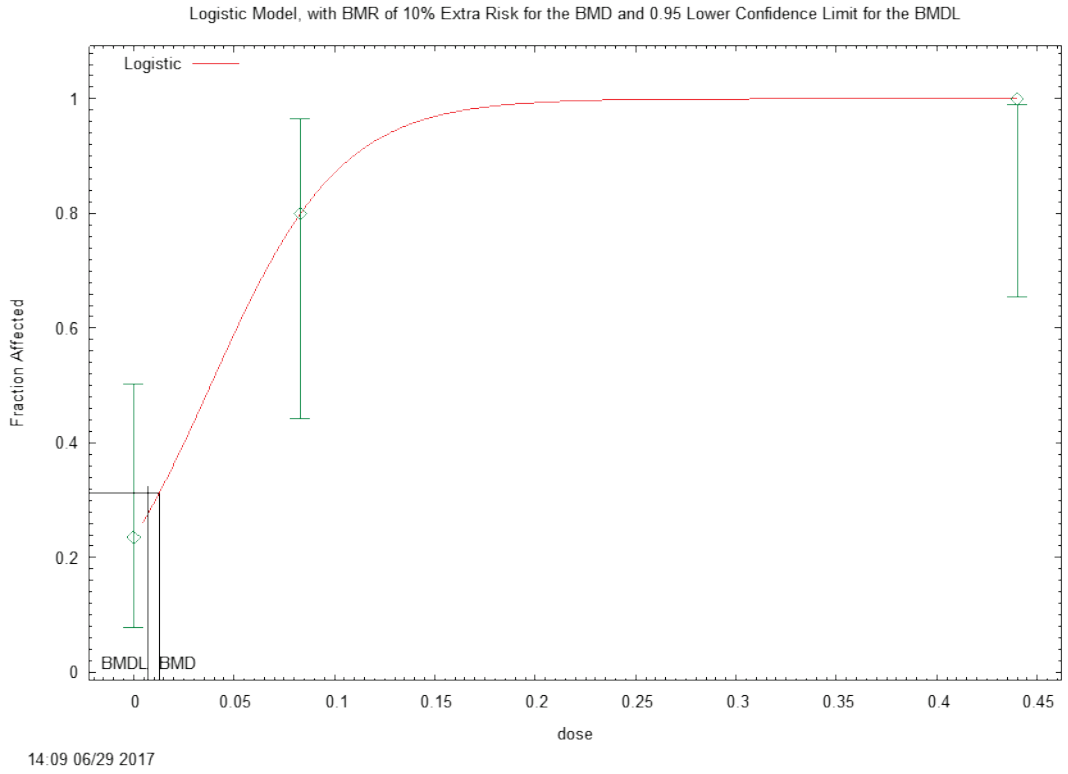

Figure C-21. Logistic Model for Increased Incidence of Anisokaryosis (All Severity Grades) in the Liver of F0 Female S-D Rats Exposed to Technical Toxaphene in the Diet for 25−29 Weeks (Two Highest Doses Dropped) (Chu et al., 1988)

Text output for Figure C-21:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/log_Chu_1988_liv_aniso_F0_female_rats_2_high_d
rop_HEDs_Log-BMR10.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/log_Chu_1988_liv_aniso_F0_female_rats_2_high_d
rop_HEDs_Log-BMR10.plt
                                          Thu Jun 29 15:31:24 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = 1/[1+EXP(-intercept-slope*dose)]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 500
```

Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
background = 0 Specified
intercept = -0.36056
slope = 8.12881

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	-0.59
slope	-0.59	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-1.17871	0.571708	-2.29924	-0.0581829
slope	30.9053	11.7498	7.87617	53.9345

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-14.2791	3			
Fitted model	-14.2792	2	8.08097e-005	1	0.9928
Reduced model	-24.9803	1	21.4023	2	<.0001

AIC: 32.5583

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2353	4.000	4.000	17.000	0.000
0.0830	0.8000	8.000	8.000	10.000	-0.000
0.4400	1.0000	10.000	10.000	10.000	0.006

Chi^2 = 0.00 d.f. = 1 P-value = 0.9949

Benchmark Dose Computation

Specified effect = 0.1

```
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0125152

            BMDL =     0.00714717
```

Increased Incidence of Cytoplasmic Homogeneity (All Severity Grades) in the Liver of F1a Male S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks (Chu et al., 1988)

The procedure outlined above was applied to the data for increased incidence of cytoplasmic homogeneity in the liver of F1a male S-D rats exposed to technical toxaphene for 34 weeks (Chu et al., 1988) (see Table C-53). Table C-54 summarizes the BMD modeling results. None of the models provided adequate fit to the full data set or the data set with the highest dose dropped. With the two highest doses dropped, only the LogLogistic model provided adequate fit to the data. Thus, the $BMDL_{10}$ of 0.0039 mg/kg-day from this model is selected for this endpoint (see Figure C-22). However, the modeling results for this endpoint are not considered reliable because all response levels were considered far in excess of the BMR, leaving no data to inform the shape of the dose-response curve in the low-dose region and requiring extrapolation far below the observable range in order to estimate the BMD (U.S. EPA, 2012b).

Table C-53. Incidence of Cytoplasmic Homogeneity (All Severity Grades) in the Liver of F1a Male S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks[a]

	HED (mg/kg-d)				
	0	**0.078**	**0.37**	**2.0**	**10**
Sample size	12	10	10	10	13
Incidence	0	6	7	4	10

[a]Chu et al. (1988).

HED = human equivalent dose; S-D = Sprague-Dawley.

Table C-54. BMD Modeling Results for Incidence of Cytoplasmic Homogeneity (All Severity Grades) in the Liver of F1a Male S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks

Model	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0.0038	74.49	1.05512	0.51671
Logistic	0.0039	74.54	1.51357	0.88846
LogLogistic[c]	0.0036	74.42	0.63692	0.17157
LogProbit[c]	0.0039	74.74	9.16632	1.00947
Multistage (1-degree)[d]	0.0038	74.49	1.05512	0.51671
Multistage (2-degree)[d]	0.0038	74.49	1.05512	0.51671
Multistage (3-degree)[d]	0.0012	76.49	1.06583	0.51671
Multistage (4-degree)[d]	0.0012	76.49	1.11203	0.51675
Probit	0.0039	74.53	1.53015	0.94297
Weibull[b]	0.0038	74.49	1.05512	0.51671
Highest dose dropped				
Gamma[b]	0.0012	60.44	1.12349	0.21385
Logistic	0.0012	60.49	1.47578	0.36399
LogLogistic[c]	0.0012	60.37	0.76576	0.04289
LogProbit[c]	0.0013	60.69	56.62090	0.55837
Multistage (1-degree)[d]	0.0012	60.44	1.12347	0.21385
Multistage (2-degree)[d]	0.0012	60.44	1.12347	0.21385
Multistage (3-degree)[d]	0.0012	60.44	1.12347	0.21385
Probit	0.0012	60.49	1.45752	0.36315
Weibull[b]	0.0012	60.44	1.12353	0.21385
Two highest doses dropped				
Gamma[b]	0.0795	32.17	0.02067	0.01298
Logistic	0.006	39.08	0.06406	0.03927
LogLogistic[e]	**0.4858**	**29.01**	**0.00925**	**0.00393**
LogProbit[d]	0.0505	32.49	0.02995	0.01812
Multistage (1-degree)[d]	0.0795	32.17	0.02067	0.01298
Multistage (2-degree)[d]	0.0795	32.17	0.02067	0.01298
Probit	0.006	38.96	0.06229	0.04069
Weibull[b]	0.0795	32.17	0.02067	0.01298

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; S-D = Sprague-Dawley.

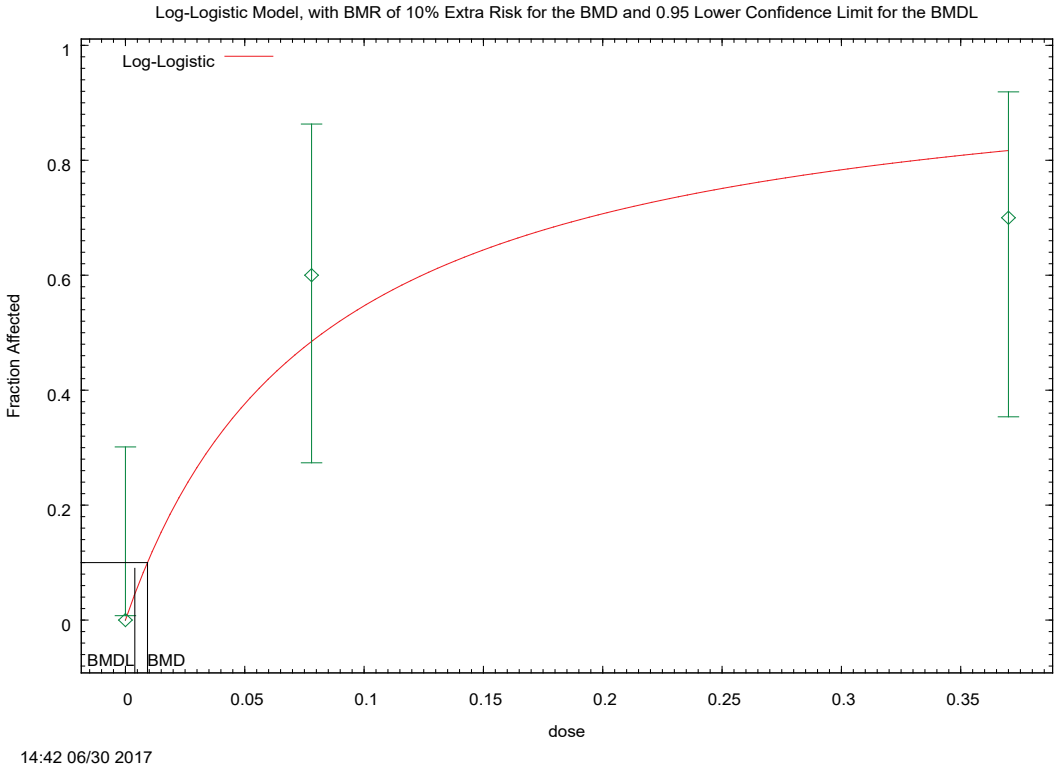

Figure C-22. LogLogistic Model for Increased Incidence of Cytoplasmic Homogeneity (All Severity Grades) in the Liver of F1a Male S-D Rats Exposed to Technical Toxaphene in the Diet for 34 Weeks (Two Highest Doses Dropped) (Chu et al., 1988)

Text output for Figure C-22:

```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_liv_cyto_homog_F1a_male_rats_2_hi
gh_drop_HEDs_Lnl-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/swesselk/Desktop/BMDS2601/Data/lnl_Chu_1988_liv_cyto_homog_F1a_male_rats_2_hi
gh_drop_HEDs_Lnl-BMR10-Restrict.plt
                                          Fri Jun 30 14:42:15 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 3
   Total number of records with missing values = 0
```

```
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =            0
                     intercept =      2.33798
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept

 intercept            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept          2.48579        0.500198             1.50542
3.46616
          slope                1              NA

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


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -12.8388         3
   Fitted model         -13.5063         1       1.33505      2           0.513
  Reduced model         -21.6149         1       17.5522      2       0.0001544

           AIC:          29.0126


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      12.000        0.000
    0.0780     0.4837         4.837     6.000      10.000        0.736
    0.3700     0.8163         8.163     7.000      10.000       -0.950

 Chi^2 = 1.44      d.f. = 2        P-value = 0.4858
```

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0092511

            BMDL =     0.00392959
```

APPENDIX D. REFERENCES

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