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Provisional Peer-Reviewed Toxicity Values for

Dibenzothiophene
(CASRN 132-65-0)

U.S. EPA Office of Research and Development
Center for Public Health and Environmental Assessment

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Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
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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 (ORD) Center for Public Health and Environmental Assessment (CPHEA) website at https://ecomments.epa.gov/pprtv.

TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS AND ACRONYMS

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
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
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
CPHEA	Center for Public Health and Environmental Assessment
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
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

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR DIBENZOTHIOPHENE (CASRN 132-65-0)

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 U.S. Environmental Protection Agency (U.S. EPA) guidance on human health toxicity value derivations.

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.

Currently available PPRTV assessments can be accessed on the U.S. EPA's PPRTV website at https://www.epa.gov/pprtv. PPRTV assessments are eligible to be updated on a 5-year cycle and revised as appropriate to incorporate new data or methodologies that might impact the toxicity values or affect the characterization of the chemical's potential for causing adverse human-health effects. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA eComments Chemical Safety website at https://ecomments.epa.gov/chemicalsafety/.

QUALITY ASSURANCE

This work was conducted under the U.S. EPA Quality Assurance (QA) program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This PPRTV was written with guidance from the CPHEA Program Quality Assurance Project Plan (PQAPP), the QAPP titled *Program Quality Assurance Project Plan (PQAPP) for the Provisional Peer-Reviewed Toxicity Values (PPRTVs) and Related Assessments/Documents (L-CPAD-0032718-QP)*, and the PPRTV development contractor QAPP titled *Quality Assurance Project Plan—Preparation of Provisional Toxicity Value (PTV) Documents (L-CPAD-0031971-QP)*. As part of the QA system, a quality product review is done prior to management clearance. A Technical Systems Audit may be performed at the discretion of the QA staff.

All PPRTV assessments receive internal peer review by at least two CPHEA scientists and an independent external peer review by at least three scientific experts. The reviews focus on whether all studies have been correctly selected, interpreted, and adequately described for the purposes of deriving a provisional reference value. The reviews also cover quantitative and qualitative aspects of the provisional value development and address whether uncertainties associated with the assessment have been adequately characterized.

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 ORD CPHEA website at https://ecomments.epa.gov/pprtv.

1. INTRODUCTION

Dibenzothiophene (CASRN 132-65-0) is a solid, sulfur-containing, three-ringed, heterocyclic polycyclic aromatic hydrocarbon (PAH) derivative. It is one of the organosulfur components of petroleum and coal and is used as a chemical intermediate and as an ingredient in cosmetics and pharmaceuticals (NLM, 2021b; Blümer et al., 2011; Deutschmann et al., 2011). Dibenzothiophene is listed as an active substance in commerce on the public Toxic Substances Control Act (TSCA) inventory (U.S. EPA, 2021e) and it is registered with Europe's Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) program (ECHA, 2021).

Production and import volumes were not reported in U.S. EPA's Chemical Data Reporting (CDR) database (U.S. EPA, 2021a). No public information on industrial production or synthetic processes were located.

The empirical formula for dibenzothiophene is $C_{12}H_8S$; its structure is shown in Figure 1. Experimental and estimated physicochemical properties identified for dibenzothiophene from U.S. EPA (2021c) and NLM (2021b) are presented in Table 1. When more than one experimental value was available, an experimental average is presented. Dibenzothiophene is moderately volatile from water and moist soil surfaces based on its calculated Henry's law constant; the soil adsorption coefficient indicates that dibenzothiophene will strongly sorb to soil and sediment, however, which may limit volatilization from these surfaces. Due to strong sorption and low water solubility, the potential to leach to groundwater or undergo runoff after precipitation is low.

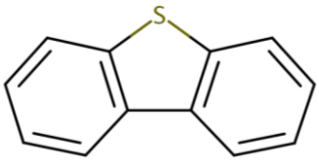


Figure 1. Dibenzothiophene (CASRN 132-65-0) Structure

Table 1. Physicochemical Properties of Dibenzothiophene (CASRN 132-65-0)

Property (unit)	Value[a]
Physical state	Solid[b]
Boiling point (°C)	333
Melting point (°C)	97.0
Density (g/cm^3)	1.23–1.25 (estimated)
Vapor pressure (mm Hg at 25°C)	0.000205 (extrapolated)[b]
pH (unitless)	NA
pKa (unitless)	NA
Solubility in water (mg/L at 25°C)	1.47 (converted from PhysProp NCCT value of 7.98×10^{-6} mol/L)
Log octanol/water partition coefficient (log K_{ow})	4.38
Henry's law constant (atm-m^3/mole at 25°C)	3.38×10^{-5} (calculated from vapor pressure/water solubility)[c]
Soil adsorption coefficient K_{oc} (units not reported)	5,273–20,535[b]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	8.10×10^{-12} [b]
Atmospheric half-life (d)	1.3 (estimated using 12-h day; 1.5×10^6 OH/cm^3)[d]
Relative vapor density (air = 1)	Not applicable for solid
Molecular weight (g/mol)	184.26
Flash point (°C)	Not applicable for solid

[a]Unless otherwise noted, values are from U.S. EPA (2021c).
[b]NLM (2021b).
[c]U.S. EPA (2012); calculated by EPI Suite™ using a vapor pressure of 0.000205 mm Hg and a water solubility of 1.47 mg/L.
[d]U.S. EPA (2012).

EPI Suite™ = Estimation Programs Interface Suite; NA = not applicable; NCCT = National Center for Computational Toxicology; PhysProp = Physical Properties Database.

A summary of available toxicity values for dibenzothiophene from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Dibenzothiophene (CASRN 132-65-0)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2021d)
HEAST	NV	NA	U.S. EPA (2011b)
DWSHA	NV	NA	U.S. EPA (2018)
ATSDR	NV	NA	ATSDR (2021)
WHO	NV	NA	WHO (2021)
CalEPA	NV	NA	CalEPA (2021, 2020)
OSHA	NV	NA	OSHA (2021a, 2021b, 2021c)
NIOSH	NV	NA	NIOSH (2018)
ACGIH	NV	NA	ACGIH (2020)
Cancer			
IRIS	NV	NA	U.S. EPA (2021d)
HEAST	NV	NA	U.S. EPA (2011b)
DWSHA	NV	NA	U.S. EPA (2018)
NTP	NV	NA	NTP (2016)
IARC (WOE)	Group 3: not classifiable as to its carcinogenicity to humans	Based on inadequate evidence for carcinogenicity in experimental animals and no available data for carcinogenicity in humans.	IARC (2013)
CalEPA	NV	NA	CalEPA (2021, 2020)
ACGIH	NV	NA	ACGIH (2020)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.
[b]Parameters: WOE = weight of evidence.

NA = not applicable; NV = not available.

Literature searches were conducted in June 2019 and updated in June 2022 for studies relevant to the derivation of provisional toxicity values for dibenzothiophene. Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE[1] (including TSCATS1), and Web of Science. The following resources were searched outside of HERO for

[1]Note that this version of TOXLINE is no longer updated (https://www.nlm.nih.gov/databases/download/toxlinesubset.html); therefore, it was not included in the literature search update from June 2022.

health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), U.S. EPA Chemical Data Access Tool (CDAT), U.S. EPA ChemView, U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), U.S. EPA TSCATS2/TSCATS8e, U.S. EPA High Production Volume (HPV), Chemicals via International Programme on Chemical Safety (IPCS) INCHEM, Japan Existing Chemical Data Base (JECDB), 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 World Health Organization (WHO).

2. REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the relevant noncancer and cancer evidence bases, respectively, for dibenzothiophene and include all repeated-dose short-term, subchronic, and chronic studies, as well as reproductive and developmental toxicity studies identified from the literature search. Principal studies used in the PPRTV assessment for derivation of provisional toxicity values are identified in bold. The phrase "statistical significance" and term "significant," used throughout the document, indicate a *p*-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for Dibenzothiophene (CASRN 132-65-0)							
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Human							
1. Oral (mg/kg-day)							
ND							
2. Inhalation (mg/m^3)							
ND							
Animal							
1. Oral (mg/kg-day)							
Short-term	**6–12 M/6–12 F, Sprague Dawley, rat, unspecified oral, 28 d** **Reported doses: 0, 3, 10, 30 mg/kg-d**	**0, 3, 10, 30**	**Increased relative liver weight in both males and females and reduced motor activity and increased prothrombin time in males at ≥10 mg/kg-d. Other effects occurring mostly at the highest dose (30 mg/kg-d): hepatocyte hypertrophy in males and females and changes in serum markers of liver function in males (reduced albumin protein fraction and A/G ratio); increased relative kidney weights and kidney lesions in males; increased APTT in males.**	**3**	**10**	JECDB (2011)	**PS, NPR**

Table 3A. Summary of Potentially Relevant Noncancer Data for Dibenzothiophene (CASRN 132-65-0)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Subchronic to Chronic	Male (number not specified), albino, rat, diet, 165 d Reported dietary concentrations: 0 (historical), 0.025, 0.05, 0.10%	0 (historical), 13, 27, 63	Increased liver weight compared with laboratory historical controls; histopathological changes in liver.	NDr	NDr	Thomas et al. (1942) (The design and reporting limitations [including the lack of a concurrent control and information on the number of test animals] prevent the determination of effect levels for this study.)	PR
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 or ≤10% life span for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% life span for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: doses are presented as ADDs (mg/kg-day) for oral noncancer effects and as HECs (in mg/m^3) for inhalation noncancer effects.
[c]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; A/G = albumin/globulin; APTT = activated partial thromboplastin time; F = female(s); HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level.

Table 3B. Summary of Potentially Relevant Cancer Data for Dibenzothiophene (CASRN 132-65-0)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Duration**	**Dosimetry**	**Critical Effects**	**Reference (comments)**	**Notes**
Human					
1. Oral (mg/kg-day)					
ND					
2. Inhalation (mg/m^3)					
ND					
Animal					
1. Oral (mg/kg-day)					
ND					
2. Inhalation (mg/m^3)					
ND					

ND = no data.

2.1. HUMAN STUDIES

2.1.1. Oral Exposures

No studies were identified.

2.1.2. Inhalation Exposures

No studies were identified.

2.2. ANIMAL STUDIES

2.2.1. Oral Exposures

The effects of oral exposure to dibenzothiophene in animals have been evaluated in short-term (JECDB, 2011) and chronic (Thomas et al., 1942) studies in rats.

Short-Term Studies

JECDB (2011)

In an OECD Test Guideline (TG) 407 study from the Japanese literature (JECDB, 2011), groups of 12, 6, 6, and 12 Crl:CD(SD) rats/sex received dibenzothiophene at doses of 0, 3, 10, or 30 mg/kg-day, respectively, by oral administration (additional details not available in English from the existing Japanese language report) for 28 days. At the end of exposure, six rats/sex/group were sacrificed; six rats/sex in the control and high-dose groups were followed for an additional 14 days untreated (recovery) prior to sacrifice. The animals were observed for clinical signs of toxicity, and body weight and food intake were measured once each week. Detailed clinical observations of the animals in cages, during handling, and in open field were performed weekly. During exposure week 4 and recovery week 2, the animals were subjected to functional observational battery (FOB), assessing reactivity (visual, touch, auditory, pain, proprioceptive), righting reflex, grip strength, and motor activity. Blood and urine were collected at the end of exposure and at the end of the recovery period. Hematology parameters included erythrocytes (red blood cells [RBCs] and reticulocyte counts, hemoglobin, hematocrit, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]), platelet counts, prothrombin time [PT], activated partial thromboplastin time [APTT], and white blood cells [WBCs; total and differential counts]). Serum chemistry was evaluated including total protein, albumin, globulins, albumin/globulin (A/G) ratio, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), total bilirubin, glucose, total cholesterol, triglycerides, blood urea nitrogen (BUN), creatinine, and electrolytes. Urinalysis parameters included pH, protein, glucose, ketone bodies, urobilinogen, bilirubin, occult blood, color, volume, and specific gravity. All animals received gross necropsy. The following organs were weighed in all animals: liver, kidney, spleen, heart, brain, pituitary, thymus, thyroid, adrenal, and reproductive organs (testis, epididymis, prostate, seminal vesicle, ovary, and uterus). Histopathology results were reported for the following organs: lung, cecum, ileum, pancreas, liver, kidney, testis, epididymis, prostate, and pituitary gland (other organs may have been examined as well).

Both male and female rats at the high dose of 30 mg/kg-day consumed less food than controls on administration day 7 (−17 and −14% relative to controls, respectively, $p \leq 0.01$) but not at other time points (14, 21, and 28 days). Male rats receiving 30 mg/kg-day exhibited lower body weights (−7%) on Days 7 and 14, but there were no statistically significant differences in body weight at Day 21 or 28 or after the recovery period, or in body-weight gains over the full treatment or recovery periods (terminal body weights changes are displayed in Table B-1).

Females exhibited no significant differences in body weight. Salivation was observed in small numbers of males and females (n = 1 or 2) at the high dose; no other clinical signs were noted. Reactivity, righting reflex, and forelimb and hindlimb grip strength were not significantly affected by exposure at any dose. At the end of exposure, statistically significant decreases in motor activity counts were observed at doses of 10 and 30 mg/kg-day in male rats (−63 and −53%, respectively; see Table B-1 for more details); no significant differences were observed for females. There were no differences in motor activity between control and high-dose rats after the recovery period. No treatment-related urinalysis changes were apparent. Male rats exhibited statistically significant longer PT (23–36% at ≥10 mg/kg-day) and APTT (41% at 30 mg/kg-day; see Table B-1) relative to controls at the end of treatment, while females did not; there were no other effects on hematology at the end of treatment and none after recovery. Statistically significant clinical chemistry findings in males at the end of exposure were increased calcium (+5%), increased alpha 2u-globulin (αu-g) and β globulin protein fraction percentages (+14%), and decreased albumin protein fraction percentages (−6%) and A/G ratios (−13%) in males receiving 30 mg/kg-day dibenzothiophene (see Table B-1). Females receiving the highest dose had significantly higher total cholesterol than controls (+54%) (see Table B-1). After the recovery period, the only observed changes were significant decreases in blood glucose in males and decreases in calcium and increases in chloride and α_1 globulin protein fraction percent in females (data not shown). Although there were no significant changes in most serum hepatocellular/hepatobiliary markers (ALT, AST, ALP, GGT, and total bilirubin [data not shown]) in male and female rats, the decreases in albumin protein fraction and A/G ratio in males at 30 mg/kg-day are indicative of potential liver damage and are consistent with other liver effects observed in exposed rats (see below for more details).

Dose-related, statistically significant increases in relative liver weights occurred at ≥10 mg/kg-day in males (11–38%) and females (10–27%) (see Table B-1). Absolute liver weight was statistically significantly increased at the low dose in females (18%) and at the high dose in males and females (29–31%); however, the changes did not follow a dose-response gradient. Female rats displayed biologically significant (≥10%) increases in absolute liver weight at all doses, while male rats achieved biologically significant increases in absolute liver weight at only the low and high doses. Males, but not females, exhibited dose-related, significant increases in relative kidney weights at ≥10 mg/kg-day (+9% at 10 mg/kg-day and +12% at 30 mg/kg-day). Absolute kidney weights increased significantly in females at 3 mg/kg-day (+14%) but there was no dose-response correspondence. Gross necropsy findings at the end of the exposure period consisted of dark brown discoloration of the liver in six of six female rats at 30 mg/kg-day (no other female groups and no males exhibited this change). Histopathology findings in the liver (see Table B-2) consisted primarily of centrilobular hepatocyte hypertrophy (six of six high-dose animals of both sexes and one of six females at 10 mg/kg-day; graded as slight in all cases). One high-dose male rat had a finding of slight focal liver necrosis. These lesions were not observed in the control group. Males (six of six in the high-dose group, two of six in the mid-dose group, and one of six in the low-dose group) also exhibited hyaline droplets and eosinophilic bodies (all graded as slight) in the proximal tubular epithelium of the kidney (see Table B-2). The kidney changes, but not the liver changes, persisted until the end of the recovery period in some rats.

No-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values of 3 and 10 mg/kg-day, respectively, are identified from this study based on ≥10% increases in relative liver weights in both sexes considered biologically significant, as well as statistically significant reductions in motor activity and increased PT in males. There is some

uncertainty due to lack of a full English language report. Although ≥10% increases in absolute liver weights were observed at a dose of 3 mg/kg-day in rats, the changes in absolute liver weights did not follow a dose-response gradient. Further, the increase in relative liver weight in the mid- and high-dose groups is supported by increased incidence of hepatocyte lesions in male and female rats at ≥10 mg/kg-day (mostly hypertrophy but also possible evidence of necrosis) and significant decreases in albumin protein fraction and A/G ratio in males at 30 mg/kg-day. Biologically significant increases (≥10%) in relative kidney weights were observed in males at 30 mg/kg-day and these animals also showed evidence of kidney lesions (100% incidence of hyaline droplets and eosinophilic bodies). The administered doses of 0, 3, 10, and 30 mg/kg-day correspond to human equivalent doses (HEDs) of 0, 0.75, 2.5, and 7.4 mg/kg-day for males, and 0, 0.68, 2.2, and 6.7 mg/kg-day for females, respectively.[2]

Subchronic/Chronic Studies

Thomas et al. (1942)

In a published, peer-reviewed study, Thomas et al. (1942) administered dibenzothiophene (purity not reported) in the diet of male albino rats (source and number not reported) aged 25–28 days with an average body weight of 48 g at the beginning of the study. The animals received 0.25, 0.50, or 1.00% dibenzothiophene in the diet for the first 4 days of the dosing period (number of animals per dose group not reported). Because of low food intakes and decreases in body weight, the doses were decreased to 0.025, 0.050, or 0.100% dibenzothiophene for the remainder of the 165-day dosing period. Adjusted daily doses (ADDs) are estimated to be 13, 27, and 63 mg/kg-day, respectively, based on total dibenzothiophene consumption reported by the study authors and time-weighted average (TWA) body weights obtained by digitizing the growth curves provided by the study authors. Animals were housed five to a cage; other details regarding animal husbandry were not provided. Appearance and behavior were recorded by the study authors "throughout the duration of the study." Food and water were provided ad libitum; animals and food cups were weighed twice a week for the duration of the study. Experimental data for each exposure group were compared with data for age- or body-weight-matched historical control animals; the type of historical control used for each endpoint is listed below with the results for that endpoint.

At study termination, animals were sacrificed, and histopathological examinations were performed. The study authors noted that they used a necropsy technique previously described by Wilson et al. (1938); the spleen, liver, adrenal glands, kidneys, testes, ovaries, and heart were weighed under this necropsy protocol. Histopathological sections of the liver, spleen, adrenal gland, heart, bladder, intestine, lung, testis, and stomach were prepared from five animals in each exposure group and stained with hematoxylin and eosin (Thomas et al., 1942). Frozen sections of the livers from three animals in the high-dose group and all animals in the low-dose group were stained with Sudan IV. Blood was collected on Days 107 and 157 from the tails of five high-dose animals and analyzed for hemoglobin and for erythrocyte, reticulocyte, and total and differential WBC counts. Although the study authors indicated statistical significance of their findings, no information was provided regarding their statistical methods. This study was performed prior to

[2]Administered doses were converted to HEDs by multiplying by dosimetric adjustment factors (DAFs) of 0.250, 0.248, and 0.247 for low-, mid-, and high-dose males and 0.226, 0.223, and 0.222 for low-, mid-, and high-dose females 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. Study-specific TWA animal body weights of 0.272, 0.264, and 0.259 kg for low-, mid-, and high-dose males, and 0.182, 0.174, and 0.171 kg for low-, mid-, and high-dose females were used. For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).

the adoption of Good Laboratory Practice (GLP), and little information regarding the laboratory procedures was provided. The study authors also reported a second experiment examining the presence of dibenzothiophene metabolites in the urine of rabbits (see Table 4B in Section 2.3.2).

No deaths or clinical signs of toxicity were reported during the study. Body weights throughout the course of the study were presented graphically, and mean terminal body weights were provided in numerical form for each exposure group (see Table B-3). A dose-dependent decrease in body weight was observed; however, the study authors attributed this to reduced food consumption and did not consider it a direct effect of dibenzothiophene. For the evaluation of organ weights, animals dosed with dibenzothiophene were compared with laboratory historical controls matched according to body weight. As a result, the differences from the control group approximate a change in relative (to body weight) organ weight. The only significant effects on organ weight observed were in the liver and spleen. Although statistical significance for weight changes in both the liver and spleen were noted by the study authors, neither an indication of the dose at which significance occurred nor any levels of significance were reported. Data for these organs are presented in Table B-3. Liver weights increased (7–115%) in a dose-dependent manner, with changes >10% occurring at ≥27 mg/kg-day. Spleen weights decreased (29–57%) in a dose-dependent manner. The decreased spleen weight may be related to the decreased food consumption, as spleen weight has been shown to decrease disproportionately to body weight when food consumption is decreased (Peters and Boyd, 1966). Gross examination revealed that the livers in the mid- and high-dose animals were large and presented a yellowish, fatty appearance. Spleens appeared normal except for a reduction in their sizes upon gross examination. Liver and kidney histopathological lesions were reported by the study authors; however, incidence was not reported, and no control group was examined. Histopathology of livers from the high-dose animals revealed extensive fatty metamorphosis of the hepatic cells, abnormal fat accumulation, and irregular vacuolation of the parenchymal cells extending throughout the lobules. Livers from high-dose animals also had some cells with indistinct borders where it appeared that adjacent cells had fused. Other liver cells had a rim of homogenous, deeply stained cytoplasm surrounding groups of vacuoles. Similar changes, but less severe, were observed in the mid-dose group. The liver effects observed in the low-dose group were described as “still less severe” than those observed at the mid-dose. There was no evidence of fibrosis or necrosis, and the Kupffer cells were unchanged. Kidneys of all exposed animals had slight-to-moderate, light brown, granular pigmentation in the epithelial cells of the proximal convoluted tubules, but there was no evidence of cell destruction. Histopathological abnormalities in other organs, including the spleen, were not observed. Hematological effects were compared to age-matched controls. There were no hematological effects observed based on the blood analyses of the high-dose animals when compared with age-matched laboratory historical controls. In addition, the study authors noted that similar blood counts were seen in previously published hematological data from untreated animals and in animals treated with the closely related compound, diphenylene oxide.

The outstanding limitations in the study design and data reporting, primarily the lack of a concurrent control group or reporting on the number of test animals, prevent further interpretation of the results or the determination of NOAEL and LOAEL values. The

administered doses of 0, 13, 27, and 63 mg/kg-day correspond to HEDs of 0, 2.9, 5.9, and 13 mg/kg-day, respectively.[3]

Reproductive/Developmental Studies

No studies were identified.

2.2.2. Inhalation Exposures

No studies were identified.

2.3. OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

2.3.1. Genotoxicity

The available genotoxicity data for dibenzothiophene are limited and primarily indicate a lack of genotoxic activity. Dibenzothiophene was negative for mutagenicity in the Ames test involving *Salmonella typhimurium* strains at doses up to 5,000 µg/plate (JECDB, 2010a; Madill et al., 1999; Mcfall et al., 1984; Pelroy et al., 1983; Dickson and Adams, 1980), with or without metabolic activation. A positive result was reported for mutation in the photoluminescent bacterium, *Vibrio fisheri*, in the Mutatox test (without activation), although the study authors noted that a positive response in this assay can occur without deoxyribonucleic acid (DNA) damage (Madill et al., 1999). Studies in mammalian cells were negative for mutation in Chinese hamster ovary (CHO) cells at doses up to 100 µg/mL (Rasmussen et al., 1991) and chromosomal aberrations (CAs) in Chinese hamster lung fibroblast (CHL) cells at doses up to 116 µg/mL for 24 hours with S9 or up to 1,850 µg/L for 6 hours without activation (JECDB, 2010b). A study in cultured rainbow trout liver RTL-W1 cells reported induction of micronucleus formation by dibenzothiophene, with an EC_{25} (the concentration causing 25% of the maximum effect level of the standard, 4-nitroquinoline oxide) of 10.8 mg/mL (3.2 mg/L after correction for estimated losses due to volatilization, sorption, etc.) (Brinkmann et al., 2014). This is of uncertain relevance to mammals, however, Amat et al. (2004) observed weak DNA adduct formation at cytotoxic concentrations in HepG2 human hepatocellular carcinoma cells exposed to ≥50 µM dibenzothiophene. These studies are further described in Table 4A.

[3]Administered doses were converted to HEDs by multiplying by DAFs of 0.225, 0.219, and 0.208 for low-, mid-, and high-dose rats 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. Study-specific estimated average animal body weights of 0.179, 0.161, and 0.130 kg for low-, mid-, and high-dose rats were used. For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).

Table 4A. Summary of Dibenzothiophene (CASRN 132-65-0) Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested[a]**	**Results Without Activation[b]**	**Results With Activation[b]**	**Comments**	**Reference**
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	Ames assay using *Salmonella typhimurium* strain TA98 treated with 10–100 µg dibenzothiophene per plate dissolved in DMSO and incubated at 37°C for 48 h with Aroclor 1254-induced rat-liver S9 homogenate activation (S9 concentrations of 4, 10, or 20%)	100 µg/plate	ND	–	Not mutagenic at any dose; S9 volume did not affect activity.	Mcfall et al. (1984)
	Ames assay using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 treated with an unreported quantity of dibenzothiophene dissolved in DMSO with Aroclor 1254-induced rat-liver S9 homogenate activation	NR	ND	–	Not mutagenic; mutagenicity results presented as revertant ratio (number of revertants per plate/number of spontaneous revertants); dibenzothiophene reportedly had "no mutagenic response" with an average revertant ratio <2.0.	Dickson and Adams (1980)
	Ames assay using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 treated with 2–500 µg dibenzothiophene per plate dissolved in DMSO with and without Aroclor 1254-induced rat-liver S9 homogenate activation	500 µg/plate	–	–	Not mutagenic at any dose.	Pelroy et al. (1983)

Table 4A. Summary of Dibenzothiophene (CASRN 132-65-0) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested[a]	Results Without Activation[b]	Results With Activation[b]	Comments	Reference
	Ames assay (preincubation modified plate incorporation test) using *S. typhimurium* strains TA98 and TA100 treated with unspecified three-log dose dilutions of dibenzothiophene in DMSO with or without S9 activation; control experiments conducted with DMSO as negative control and BaP and 4-nitroquinoline-*N*-oxide as positive controls	NR	–	–	Not mutagenic at any dose.	Madill et al. (1999)
	Ames assay using S. *typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2*uvr*A treated with dibenzothiophene in DMSO at 78.1–5,000 µg/plate with or without S9 activation; negative and positive controls included	5,000 µg/plate	–	–	Not mutagenic at any dose. Precipitation and growth inhibition were seen in all strains at the higher dose levels tested (1,250–5,000 µg/plate).	JECDB (2010a)
Mutation	Mutatox assay in which photoluminescent bacterium *Vibrio fisheri* were incubated with 0.01–5 µg/tube dibenzothiophene in methanol for 45 min with or without S9 activation; control experiments conducted with methanol as negative control and BaP and phenol as positive controls	0.38 µg/tube	+	–	In absence of activation, positive response (twofold increase in light output vs. negative control) in 5 of 10 tubes in dilution series, with 0.38 µg/tube dibenzothiophene being the lowest effective dose. In presence of activation, negative at all doses up to 5 µg/tube. Positive response in this assay can occur without DNA damage (e.g., phenol, the positive control, is nongenotoxic and noncarcinogenic).	Madill et al. (1999)
Genotoxicity studies in nonmammalian eukaryotic cells—in vitro						
Micronucleus formation	Micronucleus assay conducted in rainbow trout liver RTL-W1 cells using 0.3–41 mg/L dibenzothiophene	10.8 mg/L (EC_{25})	+	ND	EC_{25} = 10.8 mg/L for micronucleus induction (3.2 mg/L after correction for estimated losses due to volatilization, sorption, etc.).	Brinkmann et al. (2014)

Table 4A. Summary of Dibenzothiophene (CASRN 132-65-0) Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested[a]**	**Results Without Activation[b]**	**Results With Activation[b]**	**Comments**	**Reference**
Genotoxicity studies in mammalian cells—in vitro						
Mutation	Chinese hamster ovary (CHO-K1BH4) cells treated with 1–100 µg/mL dibenzothiophene with Ham's F12 medium, activated with 4% Aroclor-induced rat-liver S9 solution and incubated for 5 h; control experiments conducted with DMSO as the control and methyl methane sulfonate as a positive control	100 µg/mL	ND	–	Not mutagenic at any dose.	Rasmussen et al. (1991)
CAs	Cultured Chinese hamster lung fibroblast CHL/IU cells incubated with dibenzothiophene at 7.23−116 µg/mL for 6–24 h (without S9) or 57.8−1,850 µg/mL for 6 h (with S9)	1,850 µg/mL	–	–	No effect on structural or numerical aberrations at any dose. Toxicity was observed at the higher doses in the tests without S9 (86.9–116 µg/mL) but not in the tests with S9.	JECDB (2010b)
DNA adduct formation	Cultured HepG2 human hepatocellular carcinoma cells incubated with 0.25–150 µM dibenzothiophene (dissolved in methanol) for 24 or 48 h; control experiments conducted with culture medium alone as negative control and BaP in DMSO as positive control.	50 µM	±	ND	Weak DNA adduct formation at cytotoxic concentrations.	Amat et al. (2004)

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive; ± = weakly positive; – = negative.

BaP = benzo[*a*]pyrene; CA = chromosomal aberration; DMSO = dimethylsulfoxide; DNA = deoxyribonucleic acid; EC_{25} = the concentration causing 25% of the maximum effect level of the standard, 4-nitroquinoline oxide; ND = no data.

2.3.2. Metabolism/Toxicokinetic and Supporting Animal Studies

Additional studies investigating the metabolism of dibenzothiophene in rats (Jacob et al., 1991; Vignier et al., 1985), elimination of dibenzothiophene in the urine of rabbits (Thomas et al., 1942), acute toxicity of dibenzothiophene in mice (Leighton, 1989), and toxicity of dibenzothiophene by weekly injection in rats (Silva et al., 2015), as well as in vitro studies of effects of dibenzothiophene on aggregation of platelets (Chaudhury et al., 1988) and viability of differentiated SK-N-SH human neuroblastoma cells (Sarma et al., 2017) are also available. See Table 4B for details of these studies.

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	Reference
Supporting Animal Studies				
Short-term	CD-1 mice treated via gavage. Pilot range-finding studies: 4 mice/sex/dose, single dose of 0–3,250 mg/kg or four consecutive daily doses of 0–325 mg/kg; necropsy performed 24 h after last dose; blood taken from hearts of mice and examined for hematological effects; liver, kidney, spleen, heart, lungs, thymus, and duodenum examined at necropsy. LD_{50} Experiment 1: 12 male mice/dose, 12 vehicle controls, 8 untreated controls; single doses of 0, 260, 374, 540, 777, 1,118, or 1,609 mg/kg; LD_{50} determined at 7 d; surviving mice sacrificed on day 14 for histology of liver, lung, heart, and thymus. LD_{50} Experiment 2: 12 mice/treatment group, 5 preinduced vehicle controls; MFO pretreatment (one i.p. injection of 3-methylcholanthrene [80 mg/kg] followed by daily i.p. injections of phenobarbital [50 mg/kg] in sterile saline for 3 d) followed 24 h later by single doses of 0, 215, 265, 325, 400, 492, 605, or 744 mg/kg.	Pilot range finding studies: No treatment-related hematological changes seen; no treatment-related histological lesions seen in the kidney, duodenum, spleen, or heart; liver lesions included centrilobular or periacinar degeneration and necrosis. LD_{50} experiments: All mortality occurred within 72 h of treatment and was increased in groups with prior induction of MFO; animals were sluggish; gross lesions in mice found dead included pulmonary congestion and edema, mild to moderate hydrothorax, intestinal hemorrhage, and mottled livers; all MFO-induced mice had mild fibrinous peritonitis; histological lesions included severe centrilobular hepatic necrosis across doses in both experiments, necrosis of lymphocytes in thymic cortices at ≥540 mg/kg in Experiment 1 and ≥265 mg/kg in Experiment 2, and degenerative changes in the walls of small arteries in the lung in five mice dosed with 265–492 mg/kg (Experiment 2).	Without induction: acute LD_{50} of 470 mg/kg; with prior induction of MFO, acute LD_{50} of 335 mg/kg; preinduction of MFO potentiated the toxicity of dibenzothiophene.	Leighton (1989)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	Reference
Injection	Male Wistar rats were given weekly i.p. injections of saline (n = 5), soy oil (n = 5) or 30 mg/kg dibenzothiophene in soy oil (n = 15) for 10 wk and were examined after a latency period of 14 wk for hematology (RBC, hematocrit, WBC total and differential), serum chemistry (amylase, ALT, AST), organ weights (liver and spleen), histology (liver, spleen, lungs, and intestines), immunohistochemistry (using anti-CEA and anti-CD44 antibodies) and proteomic analysis. Body weights were recorded weekly.	There were no treatment-related effects on body weight, hematology, serum chemistry, or organ weights. Histopathological examination showed effects only in the intestines, including increased incidence of cellular atypia in the mucosa and submucosa, mucosa inflammation, necrosis, and hyperplasia of lymphoid nodules in both the large and small intestines. Counts of cells positive for antibody labelling were increased threefold (either CEA or CD44), suggesting the presence of preneoplasia. Proteomic analysis identified 23 proteins showing altered levels (≥1.5-fold change versus controls) in the small intestine, with functions including heat-shock response; cytoskeleton organization; antioxidant activity; cell signaling; carbohydrate, lipid and nucleotide metabolism; and protein folding.	Dibenzothiophene produced dysplastic lesions in the large and small intestines of male rats treated weekly by injection of 30 mg/kg in soy oil for 10 wk and examined at 24 wk.	Silva et al. (2015)
Metabolism/toxicokinetic				
Metabolism/ Toxicokinetic	Male Wistar rat (number not specified), treated with daily i.p. injections of 40 mg/kg dibenzothiophene for 3 d, 3-methylcholanthrene for 3 d, 500 mg/kg Aroclor 1254 for 5 d, or twice daily i.p. injections of 40 mg/kg phenobarbital for 4 d, then starved for 24 h after final injection; liver microsomes isolated; in vitro oxidation assay performed using dibenzothiophene (0.02−0.50 mM) and rat liver microsomal suspension (10 μL).	Dibenzothiophene metabolic pathway determined to be S-oxidation with metabolites of dibenzothiophene-5-oxide (primary) and dibenzothiophene-5-dioxide (secondary); Aroclor 1254, 3-methylcholanthrene, and phenobarbital increased rate of formation of sulfoxide, but dibenzothiophene pretreatment had no effect; carbon monoxide inhibited sulfoxidation.	Dibenzothiophene metabolite, dibenzothiophene-5-oxide, was further oxidized to dibenzothiophene-5-dioxide; CYP450 monooxygenases most likely involved in the metabolism.	Vignier et al. (1985)

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**Reference**
	Male Wistar rat (number not specified), treated with i.p. injections of 40 mg 5,6-benzoflavone/kg for 3 d, 200 mg Aroclor/kg once, or 80 mg phenobarbital/kg in 0.9% NaCl over 3 d and sacrificed 24 h after last dose; microsomes from four animals per group were incubated with 50 µmol/L dibenzothiophene for 20 min at 37°C and analyzed; solvent-only controls.	Metabolic products were sulfoxide (main product) and sulfone; no pretreatments affected sulfoxide formation, but pretreatments with phenobarbital and Aroclor increased sulfone formation.	Dibenzothiophene metabolites (using rat microsomes) were sulfoxide and sulfone, controlled by different enzymes; only the one responsible for sulfone formation can be induced by CYP450 inducers such as phenobarbital.	Jacob et al. (1991)
	One rabbit (sex and strain not specified) given an emulsion of 2 g dibenzothiophene in water administered via stomach tube; urine collected (time not specified) and analyzed.	Main excretion product was mono-hydroxy-diphenylene sulfone.	Dibenzothiophene oxidized to mono-hydroxy-diphenylene sulfone in the rabbit.	Thomas et al. (1942)
Mode of action/mechanistic				
In vitro	Aggregation of platelets from blood collected from male Sprague Dawley rats was measured photometrically after incubation for 2 min with 1, 3, or 5 µL of dibenzothiophene in DMSO or DMSO alone. Tests were also conducted with addition of thrombin or ADP to stimulate platelet aggregation, mobilization of internal calcium stores within platelets, and uptake of extracellular calcium by platelets.	Platelet aggregation was significantly reduced in a dose-related manner by dibenzothiophene relative to controls. Dibenzothiophene also reduced aggregation stimulated by thrombin or ADP and reduced extracellular calcium uptake by platelets.	Dibenzothiophene may inhibit platelet aggregation by bringing about alterations in the platelet plasma membrane.	Chaudhury et al. (1988)
	Differentiated SK-N-SH human neuroblastoma cells were cultured for 24 h with 5–100 µM dibenzothiophene and assessed for viability and production of ROS relative to unexposed controls.	Neuroblastoma cell viability was reduced relative to controls at all test concentration, with LC_{10} = 5.07 µM and LC_{20} = 47.26 µM. Significant increases in ROS were seen at ≥10 µM.	Dibenzothiophene induces neuronal cell damage by a mechanism that involves generation of oxidative stress.	Sarma et al. (2017)

ADP = adenosine diphosphate; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CYP450 = cytochrome P450; DMSO = dimethyl sulfoxide; i.p. = intraperitoneal; MFO = mixed function oxidase; NaCl = sodium chloride; RBC = red blood cell; ROS = reactive oxygen species; WBC = white blood cell.

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF ORAL REFERENCE DOSES

The database of repeat-dose oral studies for dibenzothiophene is limited to a non-peer-reviewed, 28-day study in Japanese with only tables and figures in English (JECDB, 2011) and a peer-reviewed, 165-day study from 1942 that relied on historical laboratory control groups instead of a concurrent control (Thomas et al., 1942). Due to the shortcomings of these studies, reference doses (RfDs) cannot be confidently derived here. However, the studies provide sufficient data to develop a screening subchronic provisional reference dose (p-RfD) value (see Appendix A).

3.2. DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No subchronic or chronic provisional reference concentration (p-RfC) can be derived because no inhalation studies on exposure to dibenzothiophene were identified.

The feasibility of using an analogue approach was attempted for the derivation of screening-level p-RfC values via read-across but no candidate analogues with inhalation toxicity values were identified (see Appendix A).

3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

Table 5 presents a summary of the noncancer provisional references values.

Table 5. Summary of Noncancer Risk Estimates for Dibenzothiophene (CASRN 132-65-0)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED/HEC)	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d) (see Appendix A)	Rat/F	Increased hepatocyte hypertrophy	3×10^{-3}	$BMDL_{10}$	1.04	300	JECDB (2011)
Chronic p-RfD (mg/kg-d)	NDr						
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

BMD = benchmark dose; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); HEC = human equivalent concentration; HED = human equivalent dose; NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UFC = composite uncertainty factor.

3.4. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No human or animal data were located on the carcinogenicity of dibenzothiophene by oral or inhalation exposure. One available injection study observed dysplastic lesions in the intestines of rats treated for 10 weeks, suggesting that dibenzothiophene may have some carcinogenic potential (Silva et al., 2015). Genotoxicity studies were largely negative, including

multiple Ames tests for mutation in bacteria and assays for mutation and CAs in mammalian cells (JECDB, 2010a, b; Madill et al., 1999; Rasmussen et al., 1991; Mcfall et al., 1984; Pelroy et al., 1983; Dickson and Adams, 1980). Under the U.S. EPA Cancer Guidelines (U.S. EPA, 2005), there is "*Inadequate Information to Assess Carcinogenic Potential*" of dibenzothiophene by oral or inhalation exposure (see Table 6).

Table 6. Cancer WOE Descriptor for Dibenzothiophene (CASRN 132-65-0)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	No human carcinogenicity data are available.
"Likely to Be Carcinogenic to Humans"	NS	NA	No adequate animal cancer bioassays or human cancer data are available.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	No adequate animal cancer bioassays or human cancer data are available.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**Selected due to the lack of adequate data on carcinogenicity. One injection study provided limited evidence of carcinogenic potential.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available.

NA = not applicable; NS = not selected; WOE = weight-of-evidence.

3.5. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES

The absence of suitable data precludes the development of cancer risk estimates for dibenzothiophene (see Table 7).

Table 7. Summary of Cancer Risk Estimates for Dibenzothiophene (CASRN 132-65-0)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

APPENDIX A. SCREENING PROVISIONAL VALUES

Due to the lack of evidence described in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional toxicity values for dibenzothiophene. However, some information is available for this chemical, which although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Center for Public Health and Environmental Assessment (CPHEA) 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 provisional reference values 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 could be 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 CPHEA.

A screening subchronic provisional reference doses (p-RfD) was derived for dibenzothiophene as described in the section below. For inhalation, an alternative analogue approach was evaluated (see APPLICATION OF AN ALTERNATIVE ANALOGUE APPROACH (METHODS) below), but suitable analogues were not identified and a screening value was not derived.

DERIVATION OF SCREENING PROVISIONAL REFERENCE DOSES

As discussed in the main body of the report, the available repeat-dose oral studies for dibenzothiophene include only JECDB (2011) and Thomas et al. (1942), both of which have limitations precluding their use in deriving provisional toxicity values. In order to account for the uncertainty associated with basing a toxicity assessment on these studies, the assessment is considered a screening-level assessment.

The 28-day oral exposure study by JECDB (2011) is limited by unpublished status, lack of peer review, and use of Japanese language with only tables and figures in English. There was enough material presented in English, however, to ascertain that the study appeared to be adequately designed and conducted, and to provide dose-response information on a wide range of endpoints suitable for use in quantitative toxicity assessment, including body weight, food consumption, clinical observations, functional observational battery (FOB), hematology, serum chemistry, urinalysis, and selected organ weight and histopathology (see study summary in Section 2.2.1 for more details). Liver effects were a sensitive target for dibenzothiophene in the JECDB (2011) study. Dose-related and biologically significant (≥10%) increases in relative liver weight were reported in both male and female rats at ≥10 mg/kg-day and were a primary basis for the study reported no-observed-adverse-effect level (NOAEL)/lowest-observed-adverse-effect level (LOAEL) values (NOAEL = 3 mg/kg-day and LOAEL = 10 mg/kg-day). The relative liver weight changes were accompanied by increased incidence of hepatocyte hypertrophy in both sexes at ≥10 mg/kg-day (1/6 females at 10 mg/kg-day and 6/6 males and females at 30 mg/kg-day) and possible evidence of structural degeneration (slight necrosis in 1/6 animals) and changes in serum markers of liver damage (decreased albumin protein fraction and albumin/globulin [A/G] ratio]) in males at 30 mg/kg-day. Although increases (≥10%) in absolute liver weights were observed in rats at ≥3 mg/kg-day, the changes at the lowest dose

were not supported by corroborative evidence of liver toxicity and overall pattern of effects lacked a dose-response relationship (see Table B-1). The findings across organ weight, histopathology, and clinical chemistry measures provide coherent evidence of liver toxicity after short-term oral exposure to dibenzothiophene.

Other treatment-related effects observed at the JECDB (2011) study LOAEL of 10 mg/kg-day included significant reductions in motor activity, although there was no corroborative evidence from other FOB assays evaluating reactivity (visual, touch, auditory, pain, proprioceptive), righting reflex, or grip strength. Additionally, significant increases in prothrombin time (PT) were reported in males at ≥10 mg/kg-day, accompanied by significant increases in activated partial thromboplastin time (APTT) at 30 mg/kg-day in these animals. Prolonged clotting times (i.e., increased PT and APTT) are consistent with findings of dibenzothiophene-induced platelet aggregation in vitro (Chaudhury et al., 1988), and decreased motor activity is consistent with findings of decreased viability of differentiated SK-N-SH human neuroblastoma cells with in vitro dibenzothiophene exposure (Sarma et al., 2017). However, there is limited in vivo evidence to determine the biological significance of the changes in motor activity and prolonged clotting times in males.

Male rats in the JECDB (2011) study exhibited biologically significant increases (≥10%) in relative kidney weights at 30 mg/kg-day. Dose-related increases in the incidence of hyaline droplets and eosinophilic bodies in the proximal tubular epithelium of the kidney (one of six, two of six, and six of six animals at 3, 10, and 30 mg/kg-day, respectively) also occurred in males. Accumulation of hyaline droplets (also described as cytoplasmic eosinophilic bodies containing protein) are commonly associated with alpha 2u-globulin (α2u-g)-mediated nephropathy (Hard et al., 1999), a male rat-specific nephropathy not considered relevant to humans. According to (U.S. EPA, 1991), three criteria are required for evaluating the relevance of kidney lesions in males based on possible involvement of α2u-g: (1) observation of an increase in number and size of hyaline droplets only in male kidneys; (2) identification of the protein contained in the hyaline droplets as α2u-g; and (3) observation of additional events in the pathological sequence of lesions associated with α2u-g disease (i.e., single cell necrosis, exfoliation of epithelial cells into tubular lumen, and granular casts). The evidence for dibenzothiophene is limited to increases in hyaline droplets occurring only in male rats in the 28-day JECDB (2011) study. Given that the study is in Japanese, it is unclear whether the study authors performed any specialized staining for detection of α2u-g and no additional observations were made regarding other events in the pathological sequence of the development of α2u-g disease. Further, there is no supporting evidence for α2u-g-, including the 165-day study by Thomas et al. (1942). Thomas et al. (1942) reported slight-to-moderate, light brown, granular pigmentation in the epithelial cells of the proximal convoluted tubules of male rats (with no evidence of cell destruction) but no other details were provided; therefore, the toxicological significance of the findings is unknown. The limitations in the database for dibenzothiophene prevent further interpretation of the relevance of the male rat kidney lesions in the JECDB (2011) study. Given the uncertainty and lack of information for further evaluation, these kidney lesions in male rats (hyaline droplets and eosinophilc bodies) were not further considered for dose-response analysis.

The 165-day dietary exposure study in rats by Thomas et al. (1942) had outstanding limitations such as the lack of a concurrent control group, instead making inferences based on historical control groups. Other limitations included the use of males only, lack of reporting on the number of test animals per group, and incomplete data reporting for histopathological outcomes. The major study findings were increases in liver weight that reached 35% at 27 mg/kg-day and 115% at 63 mg/kg-day (over body-weight-matched laboratory historical controls). Histopathological lesions in the liver (i.e., fat accumulation, irregular vacuolation of the parenchymal cells [hepatocytes] throughout the lobules, and indications that adjacent cells had fused) were also observed at all doses; however, incidence of lesions was not provided, and severity was described as much less in the low- and mid-dose groups (13 and 27 mg/kg-day) compared to the high-dose group (63 mg/kg-day). Although the study limitations add considerable uncertainty to the interpretation of the findings or the determination of NOAEL/LOAEL values, these observations are consistent with the liver effects in the JECDB (2011) study, providing supportive evidence of dibenzothiophene-induced liver toxicity.

Overall, the increases in relative liver weight and liver lesions (primarily hypertrophy) and decreases in serum markers of liver function (albumin protein fraction and A/G ratio) provide coherent evidence of liver effects in rats at ≥10 mg/kg-day after 28-day exposure (JECDB, 2011). Although the relevance of male kidney lesions reported in the JECDB (2011) study is unclear, the changes in relative kidney weights in males at 30 mg/kg-day were considered biologically significant (≥10%). Therefore, both the liver effects and relative kidney weight changes from this study were considered further for the derivation of screening p-RfDs. Other treatment-related effects (decreased motor activity, increased PT and APTT and increased hyaline droplets in males) in the JECDB (2011) study were not advanced for dose-response analysis due to the limitations in the database for dibenzothiophene, which prevent further determination of the toxicological significance of the findings.

Derivation of Screening Subchronic Provisional Reference Dose

Data for liver effects in male and female rats and increased relative kidney weights in male rats from the JECDB (2011) study were modeled using the U.S. Environmental Protection Agency (U.S. EPA) Benchmark Dose Software (BMDS, Version 3.2). Despite the non-peer-reviewed status and lack of full English language report, the study used an adequate design (28-day rat study), included multiple doses and a comprehensive array of toxicity endpoints, and identified sensitive health effects that are suitable for the derivation of the screening subchronic p-RfD (JECDB, 2011). For liver effects, dose-related increases in relative liver weight in males and females at ≥10 mg/kg-day were modeled as continuous data using a benchmark response (BMR) of 10% relative deviation (RD) because a 10% change in liver weight is considered a minimally biologically significant response in adult animals. Hepatocyte hypertrophy was modeled in females as dichotomous data, applying a standard BMR of 10% extra risk (ER). Hepatocyte hypertrophy in males was not modeled given that the effects were only observed in the high-dose group. Although the decreases in some serum markers of liver function (albumin protein fraction and A/G ratio) in male rats provide supporting evidence for dibenzothiophene-induced liver effects, these endpoints were not considered for dose-response assessment since more sensitive and relevant markers of liver toxicity were available (i.e., relative liver weight and hepatocyte hypertrophy). Increased relative kidney weight in males were modeled as continuous data using a BMR of 10%, which is considered biologically significant. Human equivalent doses (HEDs) in mg/kg-day were used as the dose metric for BMD analysis.

Table A-1 shows the data for liver and kidney endpoints that were considered for dose-response assessment and Table A-2 summarizes the BMD modeling results and provides candidate points of departure (PODs) for the derivation of the screening subchronic p-RfD. Details of model fit for each data set are presented in Appendix C. Candidate PODs that could not be evaluated via BMD analysis (i.e., hepatocyte hypertrophy in males) are presented as NOAEL/LOAEL values.

Table A-1. Data for Sensitive Endpoints in Male and Female Sprague Dawley Rats After Oral Treatment with Dibenzothiophene for 28 Days[a]

Endpoint	ADD [HED] in mg/kg-d[b]			
	0	3 [0.68 female, 0.75 male]	10 [2.2 female, 2.5 male]	30 [6.7 female, 7.4 male]
Increased relative liver weight in males[c]	3.233 ± 0.247	3.512 ± 0.271 (+9%)	3.578 ± 0.153* (+11%)	4.465 ± 0.208** (+38%)
Increased relative liver weight in females[c]	3.123 ± 0.170	3.355 ± 0.145 (+7%)	3.450 ± 0.299* (+10%)	3.970 ± 0.187** (+27%)
Increased hepatocyte hypertrophy in males[d]	0/6 (0%)	0/6 (0%)	0/6 (0%)	6/6 (100%)
Increased hepatocyte hypertrophy in females[d]	0/6 (0%)	0/6 (0%)	1/6 (17%)	6/6 (100%)
Increased relative kidney weight in males[c]	0.732 ± 0.040	0.735 ± 0.023 (+0%)	0.798 ± 0.052* (+9%)	0.823 ± 0.031** (+12%)

[a]JECDB (2011).
[b]ADDs were converted into HEDs (HED = ADD × DAF) using DAFs of 0.250, 0.248, and 0.247 for low-, mid-, and high-dose males and 0.226, 0.223, and 0.222 for low-, mid-, and high-dose females 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. Study-specific TWA animal body weights of 0.272, 0.264, and 0.259 kg for low-, mid-, and high-dose males, and 0.182, 0.174, and 0.171 kg for low-, mid-, and high-dose females were used. For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).
[c]Data are means ± SD; n = 6 for all data points; value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data are number of animals showing changes/ total number of animals examined (% incidence).
*Significantly different from control ($p < 0.05$) by Dunnett's test as reported by the study authors.
**Significantly different from control ($p < 0.01$) by Dunnett's test as reported by the study authors.

ADD = adjusted daily dose; DAF = dosimetric adjustment factor; HED = human equivalent dose; SD = standard deviation; TWA = time-weighted average.

Table A-2. Comparison of Candidate POD Values in Male and Female Sprague Dawley Rats After Oral Treatment with Dibenzothiophene for 28 Days[a]

Endpoint	Best-Fitting Model	BMR	BMDL (HED) (mg/kg-d)	POD type	POD (HED) (mg/kg-d)
Increased relative liver weight in males	Exponential 3 (constant variance)	10% RD from control (0.1 RD)	2.01	BMDL	2.01
Increased relative liver weight in females	Linear (constant variance)	10% RD from control (0.1 RD)	2.19	BMDL	2.19
Increased hepatocyte hypertrophy in males	Data not amenable for BMD modeling[b]			NOAEL	2.5
Increased hepatocyte hypertrophy in females	Probit (constant variance)	10% ER from control (0.1 ER)	1.04	BMDL	1.04
Increased relative kidney weight in males	Exponential 4 (constant variance)	10% RD from control (0.1 RD)	1.36	BMDL	1.36

[a]JECDB (2011).
[b]Data were not considered amenable for BMD modeling given that incidence was 100% at the highest dose and 0% at lower doses.

BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; BMR = benchmark response; ER = Extra Risk; HED = human equivalent dose; NOAEL = no-observed-adverse-effect level; POD = point of departure; RD = relative deviation.

The 10% benchmark dose lower confidence limit ($BMDL_{10}$) (HED) of 1.04 mg/kg-day for increased hepatocyte hypertrophy in female rats in the JECDB (2011) study is the lowest POD in the available database and is expected to be protective of other health effects associated with dibenzothiophene oral exposure. The significance of dibenzothiophene-induced liver effects is based on coherent evidence across organ weights (increased relative liver weight), histopathology (primarily hypertrophy with some evidence of necrosis), and serum markers of liver function (decreased albumin protein fraction and A/G ratio) in rats at ≥10 mg/kg-day after 28-day oral exposure (JECDB, 2011). Supportive evidence of potential liver toxicity was also found after dietary exposure for 165 days in males rats (increased liver weight and fatty accumulation in the liver at ≥27 mg/kg-day) (Thomas et al., 1942) and acute gavage range-finding and median lethal dose (LD_{50}) experiments in mice (centrilobular degeneration and necrosis across 260−1,609 mg/kg) (Leighton, 1989). Altogether, the weight of evidence suggests that the liver is a primary target for dibenzothiophene via oral exposure and the $BMDL_{10}$ [HED] of 1.04 mg/kg-day for increased hepatocyte hypertrophy in female rats exposed for 28 days (JECDB, 2011) is selected as the most sensitive POD for the derivation of the subchronic p-RfD.

The screening subchronic p-RfD of 3×10^{-3} mg/kg-day for dibenzothiophene is derived by applying a composite uncertainty factor (UF_C) of 300 (reflecting an interspecies uncertainty factor [UF_A] of 3, an interindividual variability uncertainty factor [UF_H] of 10, and a database uncertainty factor [UF_D] of 10) to the selected POD of 1.04 mg/kg-day, as follows:

Screening Subchronic p-RfD = POD (HED) ÷ UF_C
= 1.04 mg/kg-day ÷ 300
= **3×10^{-3} mg/kg-day**

Table A-3 summarizes the uncertainty factors for the screening subchronic p-RfD for dibenzothiophene.

Table A-3. Uncertainty Factors for the Screening Subchronic p-RfD for Dibenzothiophene (CASRN 132-65-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following oral dibenzothiophene exposure. The toxicokinetic uncertainty has been accounted for by calculation of 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, 2011c).
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The repeat-dose oral database for dibenzothiophene includes a non-peer-reviewed, 28-day rat study in Japanese and a chronic rat study with significant limitations (primarily lack of a concurrent control and reporting on the number of test animals). No reproductive or developmental toxicity studies are available by any route of exposure.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of dibenzothiophene in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because the POD was derived from a study of suitable duration (28 days) for a subchronic value.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

DAF = dosimetric adjustment factor; HED = human equivalent dose; POD = point of departure; BMDL = benchmark dose lower confidence limit; 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.

Derivation of Screening Chronic Provisional Reference Dose

The POD used for derivation of the screening subchronic p-RfD based on increased hepatocyte hypertrophy in female rats ($BMDL_{10}$ [HED] of 1.04 mg/kg-day) from the 28-day study by JECDB (2011), cannot be used directly for derivation of the screening chronic p-RfD, due to the short duration of the critical study. The available 165-day chronic study by Thomas et al. (1942) reported increases in liver weight and liver histopathology at ≥27 mg/kg-day, which are similar to the doses associated with liver effects in the 28-day JECDB (2011) study (≥10 mg/kg-day). However, the limitations in the study design and data reporting in Thomas et

al. (1942) raise significant concerns regarding the interpretation of the study findings. Overall, the lack of adequate data to inform whether the liver or other health effects associated with dibenzothiophene worsen with chronic exposure prevent the derivation of a screening chronic p-RfD.

APPLICATION OF AN ALTERNATIVE ANALOGUE APPROACH (METHODS)

The analogue approach allows for the use of data from related compounds to calculate screening values when data for the compound of interest are limited or unavailable. Details regarding searches and methods for analogue analysis are presented in Wang et al. (2012). Three types of potential analogues (structural, metabolic, and toxicity-like) are identified to facilitate the final analogue chemical selection. The analogue approach may or may not be route-specific or applicable to multiple routes of exposure. All information was considered together as part of the final weight-of-evidence (WOE) approach to select the most suitable analogue both toxicologically and chemically.

An expanded analogue identification approach was developed to collect a more comprehensive set of candidate analogues for the compounds undergoing a U.S. EPA PPRTV screening-level assessment. As described below, this method includes application of a variety of tools and methods for identifying candidate analogues that are similar to the target chemical based on chemical structure and key features; metabolic relationships; or related toxic effects and mechanisms of action.

To identify structurally-related compounds, an initial pool of analogues is identified using automated tools, including ChemIDplus (ChemIDplus, 2021), CompTox Chemicals Dashboard (U.S. EPA, 2021b), and Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox (OECD, 2021), to conduct structural similarity searches. Additional analogues identified as ChemIDplus-related substances, parent, salts, and mixtures, and CompTox-related substances are considered. CompTox GenRA analogues are collected using the methods available on the publicly available GenRA Beta version, which may include Morgan fingerprints, Torsion fingerprints, ToxPrints and ToxCast, Tox21, and ToxRef data. For compounds that have very few analogues identified by structure similarity using a similarity threshold of 0.8 or 80%, substructure searches in the QSAR Toolbox may be performed, or similarity searches may be rerun using a reduced similarity threshold (e.g., 70 or 60%). The compiled list of candidate analogues is batch run through the CompTox Chemicals Dashboard where QSAR-ready simplified molecular-input line-entry system (SMILES) are collected and toxicity data availability is determined (e.g., from the Agency for Toxic Substances and Disease Registry [ATSDR], Office of Environmental Health Hazard Assessment [OEHHA), California Environmental Protection Agency [CalEPA], U.S. EPA Integrated Risk Information System [IRIS], PPRTVs). The batch output information is then uploaded into the Chemical Assessment Clustering Engine (ChemACE) (U.S. EPA, 2011a), which clusters the chemicals based on chemical fragments and displays the toxicity data availability for each candidate. The ChemACE output is reviewed by an experienced chemist, who narrows the list of structural analogues based on known or expected structure-toxicity relationships, reactivity, and known or expected metabolic pathways.

Toxicokinetic studies identified from the literature searches performed for this PPRTV assessment were used to identify metabolic analogues (metabolites and metabolic precursors). Metabolites were also identified from the two OECD QSAR Toolbox metabolism simulators (in vivo rat metabolism simulator and rat liver S9 metabolism simulator). Targeted PubMed searches were conducted to identify metabolic precursors and other compounds that share any of the observed or predicted metabolites identified for the target chemical. Metabolic analogues are then added to the pool of candidate analogues and toxicity data availability is determined (e.g., from ATSDR, OEHHA, CalEPA, U.S. EPA IRIS, PPRTVs).

In vivo toxicity data for the target chemical (if available from the literature searches) are evaluated to determine whether specific or characteristic toxicity was observed (e.g., cholinesterase inhibition, inhibition of oxidative phosphorylation). In addition, in vitro mechanistic data identified from the literature searches or obtained from tools including GenRA, ToxCast/Tox21, and Comparative Toxicogenomics Database (CTD) (Davis et al., 2021) were evaluated for this purpose. Data from CompTox Chemicals Dashboard ToxCast/Tox21 are collected to determine bioactivity of the target chemical in in vitro assays that may indicate potential mechanism(s) of action. The GenRA option within the Dashboard also offers an option to search for analogues based on similarities in activity in ToxCast/Tox21 in vitro assays. Using the ToxCast/Tox21 bioactivity data, nearest neighbors identified with similarity indices of ≥0.5 may be considered potential candidate analogues. The CTD (Davis et al., 2021) is searched to identify compounds with gene interactions similar to interactions induced by the target chemical; compounds with gene interactions similar to the target chemical (with a similarity index >0.5) may be considered potential candidate analogues. These compounds are then added to the pool of candidate analogues, and toxicity data availability is determined (e.g., from ATSDR, OEHHA, CalEPA, U.S. EPA IRIS, PPRTVs).

The tools used for the expanded analogue searches were selected because they are publicly available, which allows for transparency and reproducibility of the results, and because they are supported by U.S. and OECD agencies, updated regularly, and widely used. The application of a variety of different tools and methods to identify candidate analogues serves to minimize the limitations of any individual tool with respect to the pool of chemicals included, chemical fragments considered, and methods for assessing similarity. Further, the inclusion of techniques to identify analogues based on metabolism and toxicity or bioactivity expands the pool of candidates beyond those based exclusively on structural similarity.

Analogue Search Results for Dibenzothiophene

Candidate analogues for dibenzothiophene were identified based on structural relationships, metabolic relationships, and toxicity/mechanisms/mode-of-action (MOA) relationships. For candidates identified through these approaches, U.S. EPA (IRIS and PPRTV), ATSDR, and CalEPA sources were searched for subchronic, intermediate, and chronic inhalation toxicity values. No candidate analogues with inhalation toxicity values were identified. Details are provided below.

Identification of Structural Analogues with Established Toxicity Values

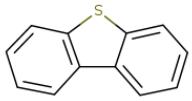
Dibenzothiophene is not a member of an existing OECD or New Chemical category. Candidate structural analogues for dibenzothiophene were identified using similarity searches in the OECD Toolbox, U.S. EPA CompTox Chemicals Dashboard, and ChemIDplus tools. A total of 24 unique structural analogues were identified for dibenzothiophene in the Dashboard, OECD QSAR Toolbox, and ChemIDplus (≥80% similarity threshold) (NLM, 2021a; OECD, 2020).

The list of potential analogues was manually reviewed and the following criteria were applied to select candidate analogues for further evaluation based on the structural features expected to influence toxicokinetics and/or toxicity,:

- Contains one thiophene ring fused with 1–3 benzene rings, and
- Only methyl, ethyl, or propyl alkyl substituents are present.

Using these criteria, all 24 structural analogues initially identified were considered candidate analogues for dibenzothiophene (see Table A-4). No inhalation toxicity values were identified for any of the candidate structural analogues.

Table A-4. Candidate Structural Analogues Identified for Dibenzothiophene



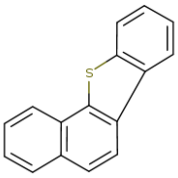
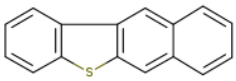
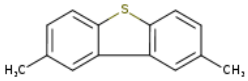
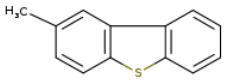
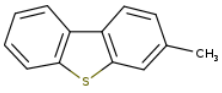
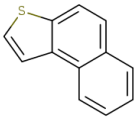
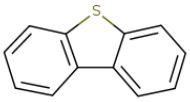
Tool (Method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches	Structure
Dashboard (Tanimoto), OECD Toolbox, and ChemIDplus (method not described)	Benzo[*b*]naphtho[2,1-*d*]thiophene (239-35-0)	
	Benzo[*b*]naphtho[2,3-*d*]thiophene (243-46-9)	
Dashboard (Tanimoto) ChemIDplus (method not described)	2,8-Dimethyldibenzo[*b*,*d*]thiophene (1207-15-4)	
	2-Methyldibenzothiophene (30995-64-3)	
OECD Toolbox, and ChemIDplus (method not described)	3-Methyldibenzothiophene (16587-52-3)	
Dashboard (Tanimoto)	Naphtho(2,1-*b*)thiophene (233-02-3)	

Table A-4. Candidate Structural Analogues Identified for Dibenzothiophene



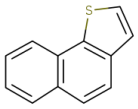
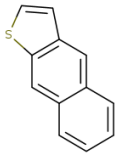
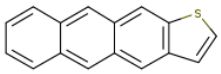
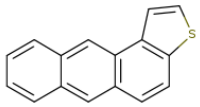
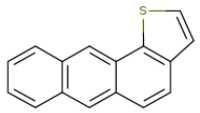
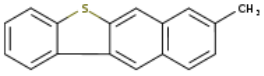
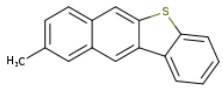
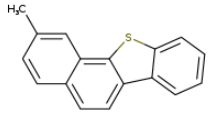
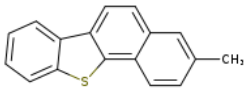
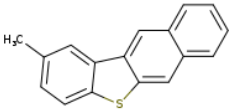
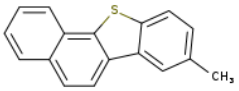
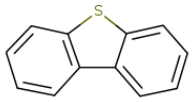
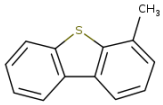
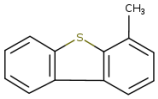
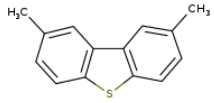
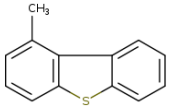
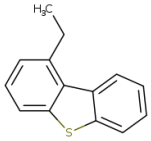
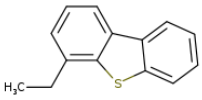
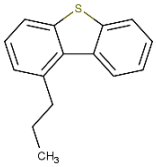
Tool (Method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches	Structure
	Naphtho(1,2-*b*)thiophene (234-41-3)	
	Naphtho(2,3-*b*)thiophene (268-77-9)	
	Anthra(2,3-*b*)thiophene (22108-55-0)	
	Anthra(2,1-*b*)thiophene (227-56-5)	
	Anthra(1,2-*b*)thiophene (227-86-1)	
	Benzo(*b*)naphtho(2,3-*d*)thiophene, 8-methyl- (24964-07-6)	
	Benzo(*b*)naphtho(2,3-*d*)thiophene, 9-methyl- (41895-72-1)	
	Benzo(*b*)naphtho(2,1-*d*)thiophene, 2-methyl- (4567-43-5)	
	Benzo(*b*)naphtho(2,1-*d*)thiophene, 3-methyl- (4567-45-7)	
	Benzo(*b*)naphtho(2,3-*d*)thiophene, 2-methyl- (83656-84-2)	
	Benzo(*b*)naphtho(2,1-*d*)thiophene, 8-methyl- (83821-53-8)	

Table A-4. Candidate Structural Analogues Identified for Dibenzothiophene



Tool (Method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches	Structure
ChemIDplus (method not described)	Dibenzothiophene, 2-methyl- (20928-02-3)	
	Dibenzothiophene, 1-methyl- (31317-07-4)	
	Dimethyldibenzothiophene (70021-47-5)	
	Dibenzothiophene, 4-methyl- (7372-88-5)	
	1-Ethyldibenzo[*b*,*d*]thiophene (79313-22-7)	
	4-Ethyldibenzothiophene (89816-99-9)	
	1-Propyldibenzo[*b*,*d*]thiophene (79313-23-8)	

[a]80% similarity threshold was applied.

OECD = Organisation for Economic Co-operation and Development.

Identification of Toxicokinetic Precursors or Metabolites with Established Toxicity Values

The main metabolite in urine from a rabbit exposed orally to dibenzothiophene was mono-hydroxy-diphenylene sulfone (Thomas et al., 1942). In rat liver microsomes incubated with dibenzothiophene, the identified metabolites were dibenzothiophene-5-oxide and dibenzothiophene-5-dioxide (dibenzothiophene sulfone) (Jacob et al., 1991; Vignier et al., 1985). Predicted metabolites were collected from the OECD QSAR Toolbox. PubMed searches (searching "dibenzothiophene" or "132-65-0" and "metabolite") were conducted to identify metabolic precursors to dibenzothiophene. No metabolic precursors were identified. PubMed was also searched to identify other compounds that are metabolized to any of the observed or predicted metabolites of dibenzothiophene (searching the metabolite name or [CASRN if

available] and "metabolite"). No compounds that share at least one metabolite with dibenzothiophene were identified in these searches.

Table A-5 summarizes the 18 candidate metabolic analogues for dibenzothiophene (3 observed metabolites and an additional 15 unique predicted metabolites). Searches for relevant toxicity values for the candidate metabolic analogues of dibenzothiophene did not identify inhalation toxicity values for any of the observed/predicted metabolites.

Table A-5. Candidate Metabolic Analogues of Dibenzothiophene

Relationship to Dibenzothiophene	Compound
Metabolic precursor	None identified
Metabolite	Mono-hydroxy-dibenzothiophene sulfone (location of hydroxy group not specified)
	Dibenzothiophene 5-oxide (CASRN 1013-23-6)
	Dibenzothiophene sulfone (CASRN 1016-05-3)
	2-Hydroxydibenzothiophene (CASRN 22439-65-2)
	3-Hydroxydibenzothiophene (CASRN 69747-77-9)
	4-Hydroxydibenzothiophene (CASRN 24444-75-5)
	2,3-Dihydroxydibenzothiophene[a]
	3,4-Dihyroxydibenzothiophene[a]
	3,7-Dihydroxydibenzothiophene[a]
	3,4,7-Trihydroxydibenzothiophene[a]
	2,3,7-Trihydroxydibenzothiophene[a]
	2-Hydroxydibenzothiophene 5-oxide[a]
	3-Hydroxydibenzothiophene 5-oxide[a]
	4-Hydroxydibenzothiophene 5-oxide[a]
	2,3-Hydroxydibenzothiophene 5-oxide[a]
	3,4-Hydroxydibenzothiophene 5-oxide[a]
	3,7-Hydroxydibenzothiophene 5-oxide[a]
	1-Hydroxydibenzothiophene (CASRN 69747-83-7)
Shares common metabolite(s)	None identified

[a]CASRN not available for this metabolite.

Identification of Analogues on the Basis of Toxicity/Mechanistic/Mode-of-Action Information and Established Toxicity Values

Available toxicity and mechanistic data for dibenzothiophene were evaluated to determine whether these data would suggest candidate analogues. The data were reviewed to determine whether there were in vivo toxicity data suggesting specific, characteristic toxicity (e.g., cholinesterase inhibition, inhibition of oxidative phosphorylation) that could be used to identify candidate analogues. The limited available in vivo animal data on dibenzothiophene administered orally indicate that the liver is the primary target organ and increased hepatocyte

hypertrophy in female rats exposed for 28 days. JECDB (2011) was used as a critical effect for the derivation of the screening subchronic p-RfD value (see "DERIVATION OF SCREENING PROVISIONAL REFERENCE DOSES" section for more details). However, the available information was not sufficient to suggest specific, characteristic toxicity that could be used to identify candidate analogues.

Dibenzothiophene was active in 25 ToxCast/Tox21, 6 EDSP21, and 83 PubChem bioactivity assays reported in the U.S. EPA CompTox Chemicals Dashboard. The GenRA option within the Dashboard offers an option to search for analogues based on similarities in activity in ToxCast in vitro assays. Using the ToxCast bioactivity data, none of the nearest neighbors identified by GenRA had similarity indices ≥0.5 (the highest index was 0.28 for pentachloroanisole).

The CTD identified several compounds with gene interactions similar to interactions induced by dibenzothiophene (Davis et al., 2021). In the CTD, similarity is measured by the Jaccard index, calculated as the size of the intersection of interacting genes for chemical A and chemical B divided by the size of the union of those genes (range 0 [no similarity] to 1 [complete similarity]). Among the compounds with gene interactions similar to dibenzothiophene, the numbers of common gene interactions ranged from 23 to 145, and similarity indices ranged from 0.03 to 0.16; the compound with the highest similarity index (0.16) was pyrene. There were no compounds with a similarity index over 0.5.

Summary

Searches for structural, metabolic, and toxicity/mechanistic analogues for dibenzothiophene yielded a total of 42 unique candidate analogues: 24 structural analogues and 18 metabolites. None of the identified candidate analogues have inhalation toxicity values from authoritative sources such as U.S. EPA, ATSDR, or CalEPA.

Because no candidate analogues with inhalation toxicity values were identified for dibenzothiophene, the alternative analogue approach was unable to derive screening reference inhalation concentrations for dibenzothiophene.

APPENDIX B. DATA TABLES

Table B-1. Selected Endpoints in Male and Female Sprague Dawley Rats After Oral Treatment with Dibenzothiophene for 28 Days[a]

Males: ADD [HED] in mg/kg-d[b]				
Endpoint[c,d]	**0**	**3 [0.75]**	**10 [2.5]**	**30 [7.4]**
Motor activity (total count)	1,399.3 ± 407.4	1388.3 ± 480.2 (−0.8%)	516.7 ± 238.8** (−63%)	661.8 ± 322.1** (−53%)
PT (sec)	16.62 ± 0.87	17.35 ± 1.23 (+4%)	20.48 ± 2.37** (+23%)	22.62 ± 4.19** (+36%)
APTT (sec)	28.23 ± 2.79	28.23 ± 3.37 (+0%)	33.23 ± 2.16 (+18%)	39.92 ± 6.67** (+41%)
Calcium (mg/dL)	9.55 ± 0.1	9.57 ± 0.28 (+0.2%)	9.82 ± 0.38 (+3%)	10.07 ± 0.34 (+5%)*
A/G ratio	1.208 ± 0.123	1.185 ± 0.065 (−2%)	1.175 ± 0.049 (−3%)	1.055 ± 0.07 (−13%)**
Albumin protein fraction (%)	54.65 ± 1.66	54.22 ± 1.35 (−0.8%)	53.97 ± 1.07 (−1%)	51.30 ± 1.67 (−6%)**
α2u-g protein fraction (%)	7.93 ± 0.35	7.52 ± 0.69 (−5%)	8.27 ± 0.2 (+4%)	9.03 ± 0.41 (+14%)**
Beta globulin protein fraction (%)	14.85 ± 0.48	15.02 ± 0.44 (+1%)	15.42 ± 0.47 (+4%)	16.95 ± 0.6 (+14%)**
Terminal body weight (g)	341.8 ± 13.7	345.8 ± 19.3 (+1%)	327.3 ± 28.7 (−4%)	323.3 ± 26.1 (−5%)
Absolute liver weight (g)	11.082 ± 1.213	12.170 ± 1.438 (+10%)	11.708 ± 1.117 (+6%)	14.468 ± 1.736** (+31%)
Relative liver weight (%)	3.233 ± 0.247	3.512 ± 0.271 (+9%)	3.578 ± 0.153* (+11%)	4.465 ± 0.208** (+38%)
Absolute kidney weight (g)	2.498 ± 0.204	2.535 ± 0.088 (+1%)	2.615 ± 0.355 (+5%)	2.653 ± 0.172 (+6%)
Relative kidney weight (%)	0.732 ± 0.040	0.735 ± 0.023 (+0%)	0.798 ± 0.052* (+9%)	0.823 ± 0.031** (+12%)

Table B-1. Selected Endpoints in Male and Female Sprague Dawley Rats After Oral Treatment with Dibenzothiophene for 28 Days[a]

Females: ADD [HED] in mg/kg-d				
Endpoint	**0**	**3 [0.68]**	**10 [2.2]**	**30 [6.7]**
Terminal body weight (g)	192.7 ± 21.4	211.7 ± 7.9 (+10%)	195.7 ± 12.8 (+2%)	195.7 ± 18.3 (+2%)
Total cholesterol (mg/dL)	51.8 ± 14.5	58.3 ± 13.8 (+13%)	51.5 ± 11.6 (+0.6%)	79.7 ± 23.4* (+54%)
Absolute liver weight (g)	6.008 ± 0.644	7.100 ± 0.347* (+18%)	6.733 ± 0.555 (+12%)	7.767 ± 0.795** (+29%)
Relative liver weight (%)	3.123 ± 0.170	3.355 ± 0.145 (+7%)	3.450 ± 0.299* (+10%)	3.970 ± 0.187** (+27%)
Absolute kidney weight (g)	1.548 ± 0.141	1.765 ± 0.154* (+14%)	1.613 ± 0.124 (+4%)	1.593 ± 0.154 (+3%)
Relative kidney weight (%)	0.808 ± 0.059	0.837 ± 0.074 (+4%)	0.827 ± 0.058 (+2%)	0.818 ± 0.058 (+1%)

[a]JECDB (2011).
[b]ADDs were converted into HEDs (HED = ADD × DAF) using DAFs of 0.250, 0.248, and 0.247 for low-, mid-, and high-dose males and 0.226, 0.223, and 0.222 for low-, mid-, and high-dose females 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. Study-specific TWA animal body weights of 0.272, 0.264, and 0.259 kg for low-, mid-, and high-dose males, and 0.182, 0.174, and 0.171 kg for low-, mid-, and high-dose females were used. For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).
[c]Data are means ± SD; n = 6 for all data points, except n = 12 for motor activity in control and high-dose groups.
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$) by Dunnett's test (motor activity, hematology, serum chemistry and organ weights) or Mann-Whitney U-test (PT time), as reported by the study authors.
**Significantly different from control ($p < 0.01$) by Dunnett's test (motor activity, hematology, serum chemistry and organ weights) or Mann-Whitney U-test (PT time), as reported by the study authors.

α2u-g = alpha 2u-globulin; ADD = adjusted daily dose; A/G = albumin/globulin; APTT = activated partial thromboplastin time; DAF = dosimetric adjustment factor; HED = human equivalent dose; PT = prothrombin time; SD = standard deviation; TWA = time-weighted average.

Table B-2. Selected Histopathological Endpoints in Male and Female Sprague Dawley Rats After Oral Treatment with Dibenzothiophene for 28 Days[a]

Males: ADD [HED] in mg/kg-d[b]				
Endpoint[c]	**0**	**3 [0.75]**	**10 [2.5]**	**30 [7.4]**
Liver (all lesions graded as slight):				
Hepatocyte hypertrophy, centrilobular	0/6 (0%)	0/6 (0%)	0/6 (0%)	6/6 (100%)
Fatty change, periportal	0/6 (0%)	2/6 (33%)	0/6 (0%)	0/6 (0%)
Microgranuloma	4/6 (67%)	2/6 (33%)	2/6 (33%)	1/6 (17%)
Necrosis, focal	0/6 (0%)	0/6 (0%)	0/6 (0%)	1/6 (17%)
Kidney (proximal tubular epithelium; all lesions graded as slight):				
Hyaline droplet	0/6 (0%)	1/6 (17%)	2/6 (33%)	6/6 (100%)
Eosinophilic body	0/6 (0%)	1/6 (17%)	2/6 (33%)	6/6 (100%)
Regeneration	1/6 (17%)	2/6 (33%)	0/6 (0%)	0/6 (0%)
Females: ADD [HED] in mg/kg-d				
Endpoint	**0**	**3 [0.68]**	**10 [2.2]**	**30 [6.7]**
Liver (all lesions graded as slight):				
Hepatocyte hypertrophy, centrilobular	0/6 (0%)	0/6 (0%)	1/6 (17%)	6/6 (100%)
Fatty change, periportal	3/6 (50%)	2/6 (33%)	0/6 (0%)	0/6 (0%)
Microgranuloma	4/6 (67%)	3/6 (50%)	3/6 (50%)	2/6 (33%)

[a]JECDB (2011).
[b]ADDs were converted into HEDs (HED = ADD × DAF) using DAFs of 0.250, 0.248, and 0.247 for low-, mid-, and high-dose males and 0.226, 0.223, and 0.222 for low-, mid-, and high-dose females 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. Study-specific TWA animal body weights of 0.272, 0.264, and 0.259 kg for low-, mid-, and high-dose males, and 0.182, 0.174, and 0.171 kg for low-, mid-, and high-dose females were used. For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).
[c]Data are number of animals showing changes/ total number of animals examined (% incidence).

ADD = adjusted daily dose; DAF = dosimetric adjustment factor; HED = human equivalent dose; SD = standard deviation; TWA = time-weighted average.

Table B-3. Body, Liver, and Spleen Weights of Male Albino Rats After Dietary Exposure to Dibenzothiophene for 165 Days[a,b]

	Percent in diet ADD [HED] in mg/kg-d[d,e,f]					
	0[g]	0.025%	0[h]	0.050%	0[i]	0.100%
Endpoint[c]	0	13 [2.9]	0	27 [5.9]	0	63 [13]
Terminal body weight (g)	310	310	273	273	212	212
Absolute liver weight (g)	10.00 ± 0.11	10.70 ± 0.29 (+7%)	9.50 ± 0.27	12.80 ± 0.48 (+35%)	8.40 ± 0.22	18.10 ± 0.74 (+115%)
Absolute spleen weight (g)	0.97 ± 0.062	0.69 ± 0.015 (−29%)	0.92 ± 0.072	0.64 ± 0.067 (−30%)	0.83 ± 0.041	0.36 ± 0.010 (−57%)

[a]Thomas et al. (1942).
[b]Statistical analysis was not reported and is not conducted because number of animals per group was not reported.
[c]Organ weights are expressed as mean ± probable error; value in parentheses is % change relative to matched laboratory historical control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Animals were provided dibenzothiophene in the food at 0.25, 0.50, or 1.00% for the first 4 days. Because of low food intakes and decreases in body weight, doses were then decreased to 0.025, 0.050, or 0.100% dibenzothiophene for the remainder of the 165-day study period. The study authors provided the amount of dibenzothiophene consumed. The following equation was used to convert that information to mg/kg-day:
ADD = total dibenzothiophene consumption per animal over study duration × (1 ÷ body weight) × (1 ÷ days dosed)
[e]ADDs were converted to HEDs by multiplying by DAFs of 0.225, 0.219, and 0.208 for low-, mid-, and high-dose rats calculated as follows: DAF = ($BW_a^{1/4}$ ÷ $BW_h^{1/4}$), where BW_a = animal body weight, and BW_h = human body weight. Study-specific estimated average animal body weights of 0.179, 0.161, and 0.130 kg for low-, mid-, and high-dose rats were used. For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).
[f]Data for each exposure group were compared with data for laboratory historical controls. For the evaluation of organ weights, historical controls were matched according to body weight.
[g]Matched laboratory historical controls for 13-mg/kg-day dose group.
[h]Matched laboratory historical controls for 27-mg/kg-day dose group.
[i]Matched laboratory historical controls for 63-mg/kg-day dose group.

ADD = adjusted daily dose; DAF = dosimetric adjustment factor; HED = human equivalent dose; TWA = time-weighted average.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE FOR DICHOTOMOUS DATA

The benchmark dose (BMD) modeling of dichotomous data was conducted with the U.S. Environmental Protection Agency (U.S. EPA) Benchmark Dose Software (BMDS; version 3.2). For these data, the Gamma, Logistic, Log-Logistic, Probit, Log-Probit, Hill, Multistage, and Weibull dichotomous models available within the software were fit using a benchmark response (BMR) of 10% extra risk. In general, the BMR should be near the low end of the observable range of increased risk in the study. BMRs that are too low can result in widely disparate benchmark dose lower confidence limit (BMDL) estimates from different models (high model dependence). Adequacy of model fit is judged based on the $\chi 2$ goodness-of-fit *p*-value ($p > 0.1$), magnitude of scaled residuals (absolute value <2.0), and visual inspection of the model fit. Among all models providing adequate fit, the BMDL from the model with the lowest Akaike's information criterion (AIC) is selected as a potential point of departure (POD), if the BMDLs are sufficiently close (less than approximately threefold); if the BMDLs are not sufficiently close (greater than approximately threefold), model dependence is indicated, and the model with the lowest reliable BMDL is selected.

MODELING PROCEDURE CONTINUOUS DATA MODELING

The BMD modeling of continuous data was conducted with the U.S. EPA BMDS (version 3.2). For these data, the Exponential, Linear, Polynomial, and Power continuous models available within the software were used. The continuous Hill model was not considered for the derivation of a POD because it has five parameters and requires a data set with a minimum of six data points (including control). The continuous models available within the software were fit using a BMR of 1 standard deviation (SD) or alternative BMRs where appropriate as outlined in the Benchmark Dose Technical Guidance (U.S. EPA, 2012). A BMR 10% relative deviation (RD) for liver and kidney weights is considered a minimally biologically significant response in adult animals and was applied in this assessment for benchmark dose (BMD) modeling purposes. An adequate fit was judged based on the χ^2 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 as to whether the variance across dose groups was constant. If a constant variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2; *p*-value > 0.1), the final BMD results were estimated from a constant variance model. If the test for homogeneity of variance was rejected (*p*-value < 0.1), the model was run again while modeling the variance as a power function of the mean to account for this nonconstant variance. If this nonconstant variance model did not adequately fit the data (i.e., Test 3; *p*-value < 0.1), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL has been selected if the BMDLs estimated from different models varied more than threefold; otherwise, the BMDL from the model with the lowest AIC has been selected as a potential POD from which to derive the proposed reference value.

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

Increased Relative Liver Weight in Male Sprague Dawley Rats After Oral Treatment with Dibenzothiophene for 28 Days (***JECDB, 2011***)

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in male Sprague Dawley rats orally exposed to dibenzothiophene for 28 days (JECDB, 2011). The constant variance model provided an adequate fit to the variance data, and the Exponential models 2 and 3, and the Linear model provided adequate fit to the means. Visual inspection of the dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest nonzero dose, and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for models providing adequate fit were sufficiently close (differed by less than threefold), so the model with the lowest AIC was selected (Exponential model 3). The estimated human equivalent benchmark dose associated with 10% relative deviation from the control ($BMD_{0.1RD}$) and benchmark dose lower confidence limit associated with 10% relative deviation from the control ($BMDL_{0.1RD}$) values of 2.33 and 2.01 mg/kg-day, respectively, were selected from this model. The results of the BMD modeling are summarized in Table C-1. Figure C-1 shows the fit of the Exponential model 3 model to the data.

Table C-1. BMD Modeling Results (Constant Variance) for Relative Liver Weight in Male Sprague Dawley Rats Orally Exposed to Dibenzothiophene for 28 Days[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	$BMD_{0.1RD}$ (HED, (mg/kg-d)	$BMDL_{0.1RD}$ (HED, (mg/kg-d)
Exponential (model 2)[c]	0.56101604	0.2269728	−0.767558354	0.935991293	2.330715	2.011481
Exponential (model 3)[c,d]	**0.56101604**	**0.226973**	**−0.767697226**	**0.935989576**	**2.330708**	**2.011754**
Exponential (model 4)[c]	0.56101604	0.0691553	−1.045102633	3.273097499	2.071878	1.36167
Exponential (model 5)[c]	0.56101604	NA	−1.042495246	5.26907005	2.07426	1.362246
Polynomial (3-degree)[e]	0.56101604	0.0985958	−0.429504946	2.698252338	1.771026	4.6872224
Polynomial (2-degree)[e]	0.56101604	0.0890464	−0.53754105	2.861669325	1.761492	4.2908893
Power[c]	0.56101604	0.0737363	−0.763984146	3.167966089	1.743172	4.5119764
Linear[e]	0.56101604	0.1921587	−1.042667628	1.269007639	1.737413	2.5442898

[a]JECDB (2011).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Selected model.
[e]Coefficients restricted to be positive.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = lower confidence limit on the BMD (subscripts denote BMR: i.e., 0.1RD = dose associated with 10% relative deviation from the control); BMR = benchmark response; NA = test for fit is not valid; HED = human equivalent dose.

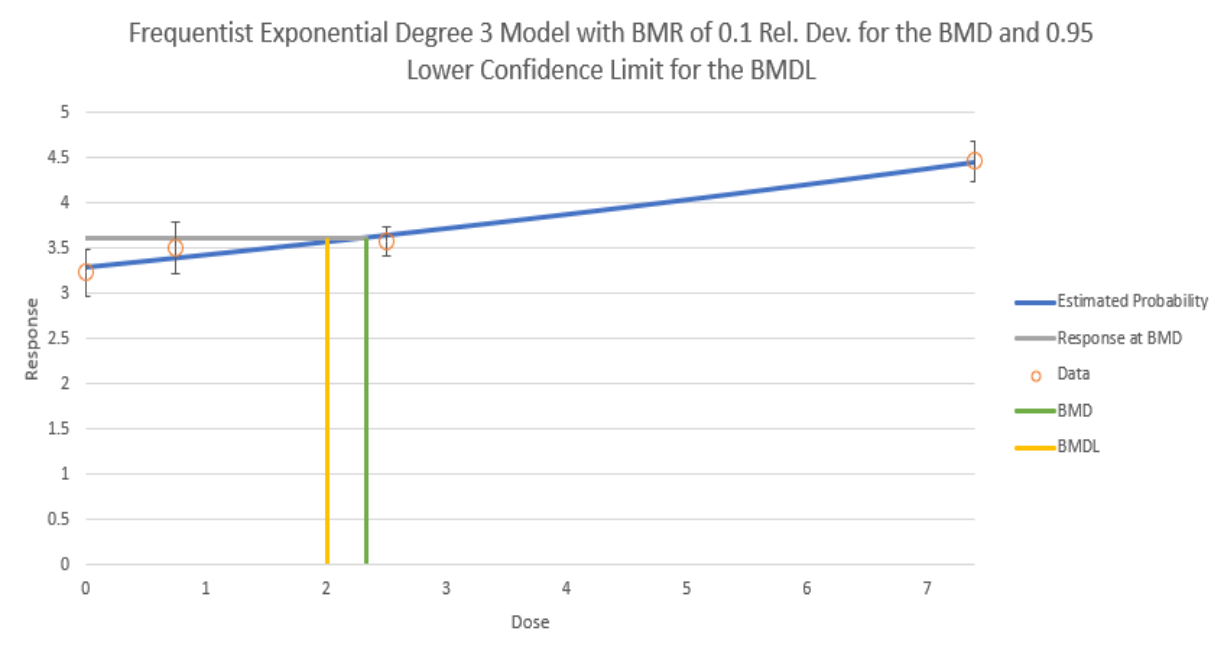


Figure C-1. Fit of Exponential Model 3 to Data for Relative Liver Weight in Male Sprague Dawley Rats Exposed to Dibenzothiophene for 28 Days (JECDB, 2011)

BMD Model Output for Figure C-1

Data

Relative liver weight in males (JECDB 2011)			
[Add user notes here]			
Dose	N	Mean	Std. Dev.
HED (mg/kg-d)	[Custom]	[Custom]	[Custom]
0	6	3.233	0.247
0.75	6	3.512	0.271
2.5	6	3.578	0.153
7.4	6	4.465	0.208

Model Results

Benchmark Dose	
BMD	2.33070755
BMDL	2.011754168
BMDU	2.774379473
AIC	0.935989576
Test 4 P-value	0.226972953
D.O.F.	2

Model Parameters	
# of Parameters	4
Variable	Estimate
a	3.291898107
b	0.040893213
d	Bounded
log-alpha	−3.04887724

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	6	3.291898107	3.233	3.233	0.21774326	0.247	0.247	−0.662570721
0.75	6	3.394424526	3.512	3.512	0.21774326	0.271	0.271	1.322658242
2.5	6	3.64624315	3.578	3.578	0.21774326	0.153	0.153	−0.767697226
7.4	6	4.455209601	4.465	4.465	0.21774326	0.208	0.208	0.110136507

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	4.014929631	5	1.97014074
A2	5.042561625	8	5.91487675
A3	4.014929631	5	1.97014074
fitted	2.532005212	3	0.93598958
R	−17.66965809	2	39.3393162

* Includes additive constant of −22.05452. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	−2*Log (Likelihood Ratio)	Test df	p-value
1	45.42443942	6	<0.0001
2	2.055263988	3	0.56101604
3	2.055263988	3	0.56101604
4	2.965848839	2	0.22697295

***Increased Relative Liver Weight in Female Sprague Dawley Rats After Oral Treatment with Dibenzothiophene for 28 Days* (*JECDB, 2011*)**

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in female Sprague Dawley rats orally exposed to dibenzothiophene for 28 days (JECDB, 2011). The constant variance model provided an adequate fit to the variance data and all models provided adequate fit to the means. Visual inspection of the dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest nonzero dose, and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for models providing adequate fit were sufficiently close (differed by less than threefold), so the model with the lowest AIC was selected (Linear). The Polynomial and Power models converged to the Linear model. The Linear model estimated human equivalent $BMD_{0.1RD}$ and $BMDL_{0.1RD}$ values of 2.73 and 2.19 mg/kg-day, respectively. The results of the BMD modeling are summarized in Table C-2. Figure C-2 shows the fit of the Linear model to the data.

Table C-2. BMD Modeling Results (Constant Variance) for Relative Liver Weight in Female Sprague Dawley Rats Orally Exposed to Dibenzothiophene for 28 Days[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	$BMD_{0.1RD}$ (HED, (mg/kg-d)	$BMDL_{0.1RD}$ (HED, (mg/kg-d)
Exponential (model 2)[c]	0.27880585	0.354743	0.121794767	−3.39315347	2.94462	2.417078
Exponential (model 3)[c]	0.27880585	0.3547431	0.121823756	−3.393153703	2.944643	2.419279
Exponential (model 4)[c]	0.27880585	0.2060485	−0.451460518	−1.866901424	2.210648	1.105419
Exponential (model 5)[c]	0.27880585	0.2060467	−0.45428488	−1.866889072	2.20753	1.105422
Polynomial (3-degree)[d]	0.27880585	0.3935635	−0.021131946	−3.600850872	2.733293	2.185768
Polynomial (2-degree)[d]	0.27880585	0.3935635	−0.021131946	−3.600850872	2.733293	2.185768
Power[c]	0.27880585	0.3935635	−0.02113139	−3.600850872	2.733292	2.185999
Linear[d,e]	**0.27880585**	**0.3935635**	**−0.021131734**	**−3.600850872**	**2.733293**	**2.185768**

[a]JECDB (2011).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Coefficients restricted to be positive.
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = lower confidence limit on the BMD (subscripts denote BMR: i.e., 0.1RD = dose associated with 10% relative deviation from the control); BMR = benchmark response; HED = human equivalent dose.

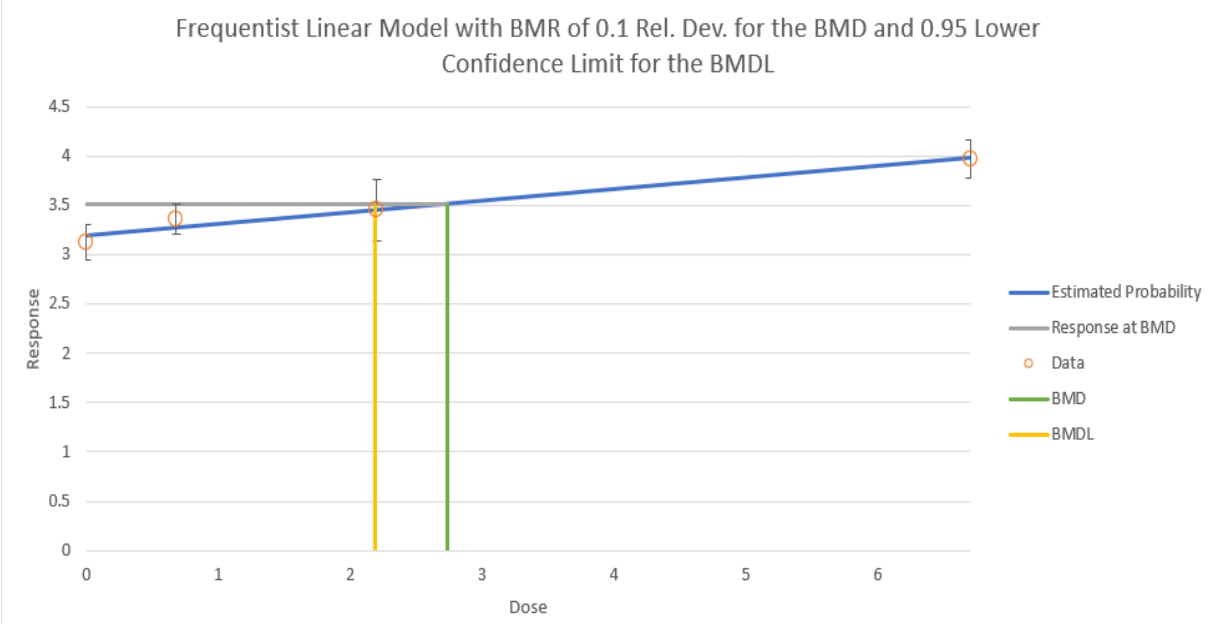


Figure C-2. Fit of Linear Model to Data for Relative Liver Weight in Female Sprague Dawley Rats Exposed to Dibenzothiophene for 28 Days (JECDB, 2011)

BMD Model Output for Figure C-2

Data

Relative liver weight in females (JECDB 2011)			
[Add user notes here]			
Dose	N	Mean	Std. Dev.
HED (mg/kg-day)	[Custom]	[Custom]	[Custom]
0	6	3.123	0.17
0.68	6	3.355	0.145
2.2	6	3.45	0.299
6.7	6	3.97	0.187

Model Results

Benchmark Dose	
BMD	2.733293247
BMDL	2.185768319
BMDU	3.595625864
AIC	−3.600850872
Test 4 P-value	0.393563466
D.O.F.	2

Model Parameters	
# of Parameters	3
Variable	Estimate
g	3.194580413
beta1	0.116876655
alpha	0.039245734

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	6	3.194580413	3.123	3.123	0.19810536	0.17	0.17	−0.885061798
0.68	6	3.274056538	3.355	3.355	0.19810536	0.145	0.145	1.000831977
2.2	6	3.451709054	3.45	3.45	0.19810536	0.299	0.299	−0.021131734
6.7	6	3.977654002	3.97	3.97	0.19810536	0.187	0.187	−0.094638521

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	5.732938375	5	−1.46587675
A2	7.654954357	8	0.69009129
A3	5.732938375	5	−1.46587675
fitted	4.800425436	3	−3.60085087
R	−9.782299848	2	23.5645997

* Includes additive constant of −22.05452. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	−2*Log(Likelihood Ratio)	Test df	p-value
1	34.87450841	6	<0.0001
2	3.844031964	3	0.27880585
3	3.844031964	3	0.27880585
4	1.865025877	2	0.39356347

Increased Hepatocyte Hypertrophy in Female Sprague Dawley Rats After Oral Treatment with Dibenzothiophene for 28 Days (JECDB, 2011)

The procedure outlined above for dichotomous data was applied to the data for increased hepatocyte hypertrophy in female Sprague Dawley rats orally exposed to dibenzothiophene for 28 days (JECDB, 2011). All models provided adequate fit (*p*-value > 0.10). However, based on visual inspection, the Multistage degree 1 model was not found to have an adequate fit (estimated probabilities consistently misrepresented the observed responses by ~20%). All other models provided adequate fit upon visual inspection and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for models providing adequate fit were sufficiently close (differed by less than threefold), so the model with the lowest AIC was selected (Probit). The Probit model estimated a human equivalent $BMD_{0.1ER}$ and $BMDL_{10}$ of 2.08 and 1.04 mg/kg-day, respectively. The results of the BMD modeling are summarized in Table C-3. Figure C-3 shows the fit of the Probit model to the data.

Table C-3. BMD Modeling Results for Hepatocyte Hypertrophy in Female Sprague Dawley Rats Orally Exposed to Dibenzothiophene for 28 Days[a]

Model	*p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	$BMD_{0.1ER}$ (HED, (mg/kg-d)	$BMDL_{10}$ (HED, (mg/kg-d)
Dichotomous Hill	0.9994799	−6.91397E−08	11.40673536	2.125982	1.13544
Gamma[c]	0.9999729	−0.000199249	9.406843019	2.027344	0.974324
Log-Logistic[d]	0.9971634	−4.82841E−06	11.40675978	2.104989	1.135448
Multistage Degree 3[e]	0.9957091	−0.085479764	7.528643645	1.781135	0.624666
Multistage Degree 2[e]	0.8345974	−0.433247713	8.79031287	1.257594	0.564518
Multistage Degree 1[e,f]	0.2663758	−0.991744547	13.67071077	0.471974	0.252068
Weibull[c]	0.9999858	0.002899612	7.409558632	1.99808	0.881564
Logistic	1	4.90622E−06	7.406763669	2.121106	1.125562
Log-Probit[d]	0.9999999	6.34854E−10	9.406734872	2.132271	1.119394
Probit[g]	**1**	**4.20484E−06**	**7.406737143**	**2.083075**	**1.035344**

[a]JECDB (2011).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Slope restricted to be ≥1.
[e]Betas restricted to be ≥0.
[f]Model did not pass visual fit inspection.
[g]**Selected model**.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; NA = test for fit is not valid; HED = human equivalent dose.

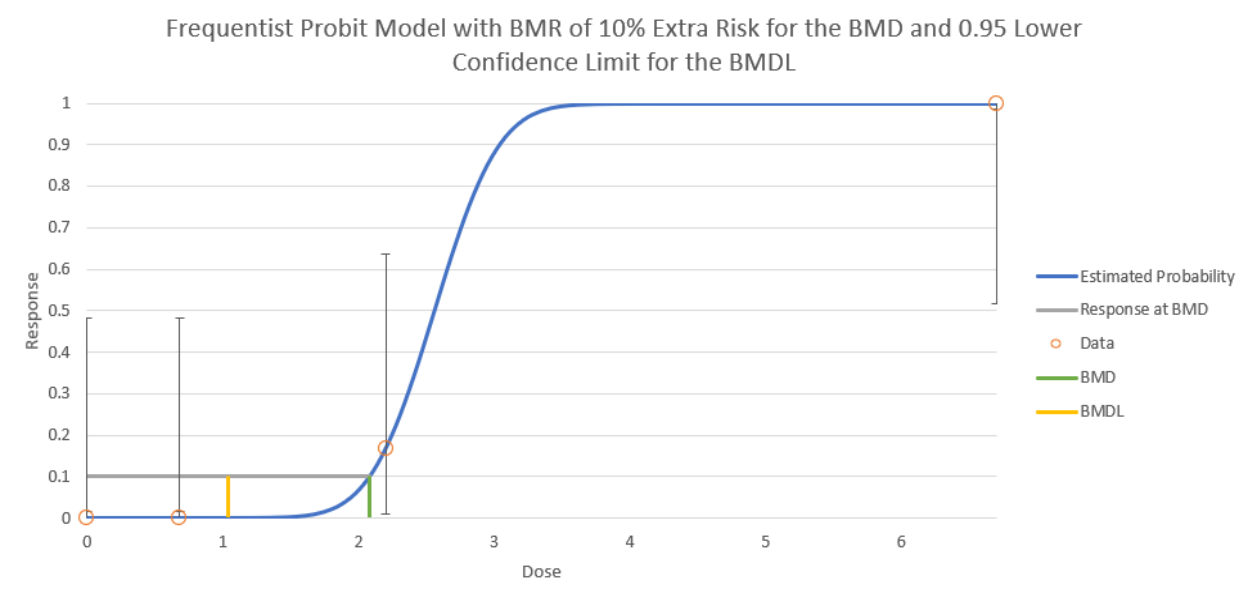


Figure C-3. Fit of Probit Model to Data for Increased Hepatocyte Hypertrophy in Female Sprague Dawley Rats Exposed to Dibenzothiophene for 28 Days (JECDB, 2011)

BMD Model Output for Figure C-3

Data

Increased hepatocyte hypertrophy in females		
[Add user notes here]		
Dose	N	Incidence
HED (mg/kg-day)	[Custom]	[Custom]
0	6	0
0.68	6	0
2.2	6	1
6.7	6	6

Model Results

Benchmark Dose	
BMD	2.083075
BMDL	1.035344
BMDU	3.0208465
AIC	7.406737143
P-value	1
D.O.F.	3
Chi^2	1.3185E−06

Model Parameters	
# of Parameters	2
Variable	Estimate
a	−6.877871888
b	Bounded

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	3.03766E−12	1.8226E−11	0	6	−4.269E−06
0.68	2.19744E−07	1.31847E−06	0	6	−0.0011482
2.2	0.166666027	0.999996162	1	6	4.205E−06
6.7	1	6	6	6	0

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	−2.703367253	4	–	–	NA
Fitted Model	−2.703368572	1	2.637E−06	3	1
Reduced Model	−14.48729404	1	23.5678536	3	<0.0001

Increased Relative Kidney Weight in Male Sprague Dawley Rats After Oral Treatment with Dibenzothiophene for 28 Days (JECDB, 2011)

The procedure outlined above for continuous data was applied to the data for increased relative kidney weight in male Sprague Dawley rats orally exposed to dibenzothiophene for 28 days (JECDB, 2011). The constant variance model provided an adequate fit to the variance data and only the Exponential degree 4 model provided adequate fit to the means. Visual inspection of the dose-response curve suggested adequate fit and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. Therefore, the human equivalent $BMD_{0.1RD}$ and $BMDL_{0.1RD}$ values of 3.08 and 1.36 mg/kg-day, respectively, for this model were selected. The results of the BMD modeling are summarized in Table C-4. Figure C-4 shows the fit of the Exponential 4 model to the data.

Table C-4. BMD Modeling Results (Constant Variance) for Relative Kidney Weight in Male Sprague Dawley Rats Orally Exposed to Dibenzothiophene for 28 Days[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	$BMD_{0.1RD}$ (HED, (mg/kg-d)	$BMDL_{0.1RD}$ (HED, (mg/kg-d)
Exponential (model 2)[c]	0.24433599	0.0810132	−0.493677602	−82.13382255	6.069332	4.448717
Exponential (model 3)[c]	0.24433599	0.0810136	−0.493536392	−82.13383205	6.069183	4.452747
Exponential (model 4)[c,d]	**0.24433599**	**0.1801994**	**0.64553924**	**−83.36413069**	**3.077499**	**1.364732**
Exponential (model 5)[c]	0.24433599	NA	0.002299382	−83.16003746	2.701189	0.816626
Polynomial (3-degree)[e]	0.24433599	0.0905573	−0.519162188	−82.35656545	5.918103	4.248669
Polynomial (2-degree)[e]	0.24433599	0.0905573	−0.519162176	−82.35656545	5.918103	4.248669
Power[c]	0.24433599	0.0905573	−0.519162289	−82.35656545	5.918105	4.249527
Linear[e]	0.24433599	0.0905573	−0.519162316	−82.35656545	5.918103	4.248669

[a]JECDB (2011).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Selected model.
[e]Coefficients restricted to be positive.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = lower confidence limit on the BMD (subscripts denote BMR: i.e., 0.1RD = dose associated with 10% relative deviation from the control); BMR = benchmark response; HED = human equivalent dose.

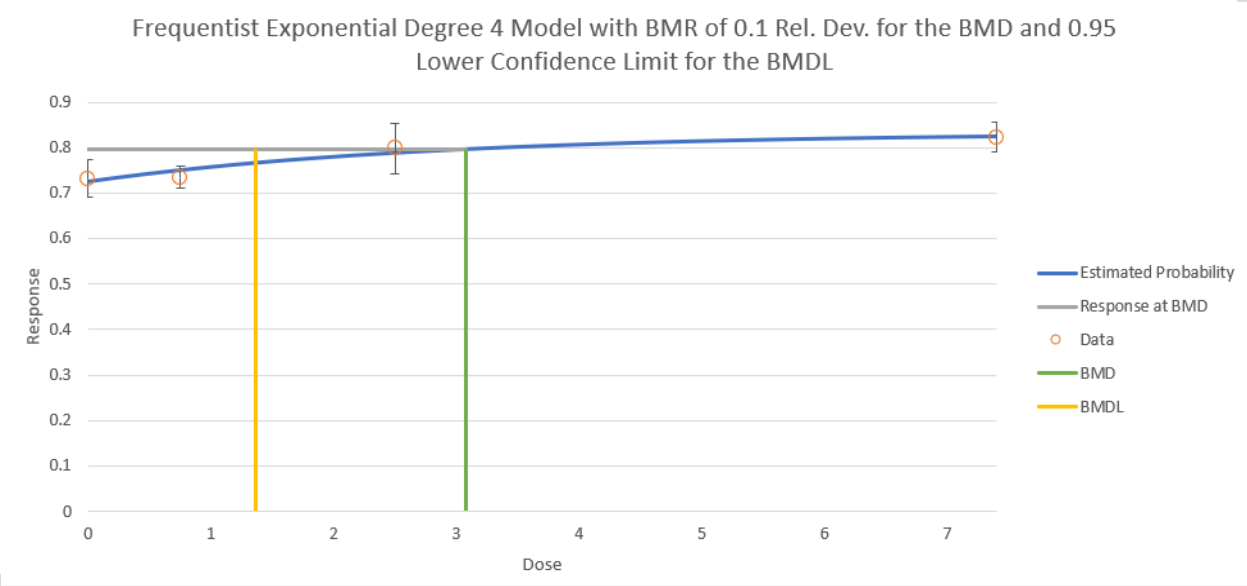


Figure C-4. Fit of Exponential Degree 4 Model to Data for Increased Relative Kidney Weight in Male Sprague Dawley Rats Exposed to Dibenzothiophene for 28 Days (JECDB, 2011)

BMD Model Output for Figure C-4

Data

Increased relative kidney weight in males			
[Add user notes here]			
Dose	N	Mean	Std. Dev.
HED (mg/kg-day)	[Custom]	[Custom]	[Custom]
0	6	0.732	0.04
0.75	6	0.735	0.023
2.5	6	0.798	0.052
7.4	6	0.823	0.031

Model Results

Benchmark Dose	
BMD	3.07749939
BMDL	1.364731935
BMDU	19.93656715
AIC	−83.36413069
Test 4 P-value	0.180199393
D.O.F.	1

Model Parameters	
# of Parameters	4
Variable	Estimate
a	0.724353256
b	0.356825599
c	1.150036123
log-alpha	−6.644715675

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	6	0.724353256	0.732	0.732	0.03606769	0.04	0.04	0.519318585
0.75	6	0.749871217	0.735	0.735	0.03606769	0.023	0.023	−1.009959186
2.5	6	0.788494711	0.798	0.798	0.03606769	0.052	0.052	0.64553924
7.4	6	0.825280877	0.823	0.823	0.03606769	0.031	0.031	−0.154902775

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	46.58005477	5	−83.1601095
A2	48.66183302	8	−81.323666
A3	46.58005477	5	−83.1601095
fitted	45.68206535	4	−83.3641307
R	36.61850946	2	−69.2370189

* Includes additive constant of −22.05452. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest

Test	−2*Log(Likelihood Ratio)	Test df	p-value
1	24.08664712	6	0.00050343
2	4.163556496	3	0.24433599
3	4.163556496	3	0.24433599
4	1.795978855	1	0.18019939

APPENDIX D. REFERENCES

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