EPA/690/R-24/001F | March 2024 | FINAL

United States Environmental Protection Agency

Provisional Peer-Reviewed Toxicity Values for

1-Methylnaphthalene (CASRN 90-12-0)

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

EPA/690/R-24/001F
March 2024
https://www.epa.gov/pprtv

Provisional Peer-Reviewed Toxicity Values for

1-Methylnaphthalene
(CASRN 90-12-0)

Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Allison L. Phillips, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

CONTRIBUTOR

Q. Jay Zhao, PhD, MPH, DABT
Center for Public Health and Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

PRIMARY INTERNAL REVIEWERS

M. Margaret Pratt, PhD
Center for Public Health and Environmental Assessment, Washington, DC

J. Andre Weaver, PhD
Center for Public Health and Environmental Assessment, Research Triangle Park, NC

PRIMARY EXTERNAL REVIEWERS

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

PPRTV PROGRAM MANAGEMENT

Teresa L. Shannon
Center for Public Health and Environmental Assessment, Cincinnati, OH

Allison L. Phillips, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

J. Phillip Kaiser, PhD, DABT
Center for Public Health and Environmental Assessment, Cincinnati, OH

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 assessment.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1-METHYLNAPHTHALENE (CASRN 90-12-0)

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 toxicologically relevant 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 assessment 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 assessment 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 toxicologically relevant 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

1-Methylnaphthalene, CASRN 90-12-0, is an organic chemical and a member of the polycyclic aromatic compounds (PAC) class of chemicals. 1-Methylnapthalene is a component of petroleum and coal tar (NLM, 2024). It is used as a solvent, an intermediate for pesticides and drug manufacture (Mason, 2002), a dye carrier (de Guzman and Sutton, 2013), and a flavoring agent in food (NLM, 2024). 1-Methylnaphthalene is listed as active in commerce on the Toxic Substances Control Act (TSCA) public inventory (U.S. EPA, 2024c). 1-Methylnaphthalene is no longer registered with Europe's Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) program and is not currently permitted to be manufactured or imported into the European Economic Area (EEA) (ECHA, 2024).

The U.S. EPA's Chemical Data Reporting (CDR) database reported that the aggregate production volume was 1,882,047 pounds, domestically manufactured, in 2020 (U.S. EPA, 2022). More recent manufacturing data were not available. 1-Methylnaphthalene is generally recovered by fractional distillation of coal tar and petroleum (NLM, 2024).

The empirical formula for 1-methylnaphthalene is $C_{11}H_{10}$; its chemical structure is shown in Figure 1. Table 1 summarizes the physicochemical properties of 1-methylnapthalene. Physicochemical properties were collected from the U.S. EPA's CompTox Chemicals Dashboard (U.S. EPA, 2024a) and the PubChem website (NLM, 2024), except where noted (see Table 1). 1-Methylnaphtalene's high vapor pressure indicates that it will exist primarily in the vapor phase if released to the atmosphere. 1-Methylnapthalene is moderately volatile from water and moist soil surfaces based on its reported Henry's law constant. The soil adsorption coefficient indicates that it may have moderate sorption to soil and moderate to very strong sorption to sediment, which will reduce its mobility in the environment. Due to its expected sorption, the potential to leach to groundwater or undergo runoff after precipitation is low.

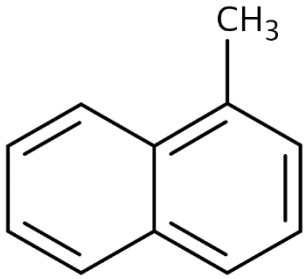

Figure 1. 1-Methylnaphthalene (CASRN 90-12-0) Structure

Table 1. Physicochemical Properties for 1-Methylnaphthalene (CASRN 90-12-0)

Property (unit)	Value[a]
Physical state	Liquid
Boiling point (°C)	242
Melting point (°C)	−3.10
Density (g/cm^3)	1.01 (predicted average)
Vapor pressure (mm Hg at 25°C)	0.0670
pH (unitless)	NA
Acid dissociation constant (pKa) (unitless)	NA
Solubility in water (mol/L)	0.000195
Octanol-water partition coefficient (log K_{ow})	3.87
Henry's law constant (atm-m^3/mo at 25°C)	5.14×10^{-4}
Soil adsorption coefficient (L/kg)	2,290[b]
Atmospheric OH rate constant (cm^3/molecule)	5.30×10^{-11} [b]
Atmospheric half-life (d)	0.20 (calculated based on its measured OH rate constant)[b]
Relative vapor density (air = 1)	4.91[b]
Molecular weight (g/mol)	142.20
Flash point (°C)	91.4 (predicted average)

[a]Unless otherwise noted, data were extracted from the U.S. EPA CompTox Chemicals Dashboard (1-methylnaphthalene, CASRN 90-12-0. https://comptox.epa.gov/dashboard/DTXSID9020877. Accessed January 31, 2024). All values are experimental averages unless otherwise specified.
[b]NLM (2024); all values are measured unless noted otherwise.

NA = not available.

A summary of available toxicity values for 1-methylnaphthalene from the U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values and Qualitative Conclusions Regarding Carcinogenicity for 1-Methylnaphthalene (CASRN 90-12-0)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2024b)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2018)
ATSDR (MRL, oral, chronic)	0.07 mg/kg-d	Based on increased incidence of pulmonary alveolar proteinosis in female mice.	ATSDR (2024); ATSDR (2005)
WHO	"No safety concern" when used as a flavoring agent	Safety evaluation based on a human intake threshold value of 90 µg/d (for chemicals in WHO structural class III).	WHO (2024); WHO (2006)
CalEPA	NV	NA	CalEPA (2024); CalEPA (2023)
OSHA	NV	NA	OSHA (2022a); OSHA (2022b); OSHA (2022c)
NIOSH	NV	NA	NIOSH (2018)
ACGIH (TLV-TWA)	0.5 ppm; skin notation	Based on upper respiratory tract irritation and lung damage in mice; skin notation based on alveolar proteinosis in mice with chronic skin painting.	ACGIH (2007)
Cancer			
IRIS	NV	NA	U.S. EPA (2024b)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2018)
NTP	NV	NA	NTP (2021)
IARC	NV	NA	IARC (2024)
CalEPA	NV	NA	CalEPA (2024) ; CalEPA (2023)
ACGIH (WOE)	A4, not classifiable as a human carcinogen	Based on limited evidence of lung adenomas in male mice with 2-methylnaphthalene but not 1-methylnaphthalene.	ACGIH (2020); ACGIH (2007)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Research; 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: MRL = minimum risk level; TLV = threshold limit value; TWA = time-weighted average; WOE = weight of evidence.

NA = not applicable; NV = not available.

Non-date limited literature searches were conducted in July 2019 and updated most recently in November 2023 for studies relevant to the derivation of provisional toxicity values for 1-methylnaphthalene, CASRN 90-12-0. Search results were conducted using the U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE (including TSCATS1)[1], Scopus, and Web of Science. The National Technical Reports Library (NTRL) was searched for government reports from 2018 through November 2023[2]. The following resources were searched outside of HERO for 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), the U.S. EPA Chemical Data Access Tool (CDAT), U.S. EPA's ChemView, the U.S. EPA Integrated Risk Information System (IRIS), the U.S. EPA Health Effects Assessment Summary Tables (HEAST), the U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), the U.S. EPA TSCATS2/TSCATS8e, the 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 Cooperation 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).

[1]TOXLINE was retired in December 2019. Searches of this database were conducted through July 2019.
[2]NTRL was a subset of TOXLINE until December 2019 when TOXLINE was discontinued. Searches of NTRL were conducted starting in 2018 to ensure that references were not missed due to delays in importing items into the database.

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

Tables 3A and 3B provide overviews of the relevant noncancer and cancer databases, respectively, for 1-methylnaphthalene, and include all potentially relevant repeated short-term, subchronic, and chronic studies, as well as reproductive and developmental toxicity studies. These tables include studies for which no-observed-adverse-effect levels (NOAELs)/lowest-observed-adverse-effect levels (LOAELs) could be identified (principal studies are identified in bold). All NOAELs/LOAELs were identified by the U.S. EPA unless noted otherwise. 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 1-Methylnaphthalene (CASRN 90-12-0)							
Category[a]	**Number of Male/Female, Strain Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							
Animal							
1. Oral (mg/kg-d)							
Subchronic	**12 breeding pairs/group, Sprague Dawley Crl:CD rat, gavage, at least 42 d (from 2 wk prior to mating, and throughout mating, gestation, and lactation until PND 4 in females or for 42 d total in males).** **Satellite group: 5 unmated F/per control and high-dose groups, gavage, 42 d.**	**0, 10, 50, 250**	**Increased absolute and relative liver weights and increased relative kidney weights in males and increased relative liver weights in females.**	**50**	**250**	**METI (2009b) (study in Japanese)**	**PS, NPR**
Subchronic	10 M/10 F, B6C3F1 *gpt* delta mouse, diet, 13 wk. Reported treatment: 0, 0.075, or 0.15% in the diet. Doses reported as ADDs by study authors.	M: 0, 120, 220 F: 0, 170, 280	No treatment-related effects at any dose.	220 (M) 280 (F)	NDr	Jin et al. (2012)	PR
Chronic	**50 M/50 F, B6C3F1 mouse, diet, 81 wk.** **Reported treatment: 0, 0.075, or 0.15% in the diet.** **Doses reported as ADDs by study authors.**	**M: 0, 71.6, 140** **F: 0, 75.1, 144**	**Pulmonary alveolar proteinosis (PAP) in males and females.**	**NDr**	**71.6 (M) 75.1 (F)**	Murata et al. (1993)	**PS, PR**

Table 3A. Summary of Potentially Relevant Noncancer Data for 1-Methylnaphthalene (CASRN 90-12-0)

Category[a]	Number of Male/Female, Strain Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Reproductive/ developmental	12 breeding pairs/group, Sprague Dawley Crl:CD rat, gavage, at least 42 d (from 2 wk prior to mating, and throughout mating, gestation, and lactation until PND 4 in females or for 42 d total in males).	0, 10, 50, 250	Reproductive: No effects Developmental: No effects	250	NDr	METI (2009b) (study in Japanese)	NPR
2. Inhalation (mg/m^3)							
Subchronic	**10 M/10 F, F344 rat, whole-body by vapor inhalation, 6 h/d, 5 d/wk, 13 wk.** **Reported analytical concentrations: 0, 0.52, 4.08, or 30.83 ppm.**	**M: 0, 0.099, 0.773, 5.833** **F: 0.065, 0.510, 3.736**	**Mucous cell hyperplasia in nasopharyngeal tissues in males.** **Transitional cell hyperplasia in nasopharyngeal tissues observed in males and mucous cell hyperplasia in nasopharyngeal tissues observed in females at higher exposure concentrations.**	**NDr**	**0.099 (M)**	Kim et al. (2020)	**PS, PR**

[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 to ≤10% life span (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% life span (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002b).
[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. Because the observed inhalation effects occurred in nasopharyngeal tissues, HEC values were calculated for the ET region by treating 1-methylnaphthalene as a Category 1 gas and using the following equation from U.S. EPA (1994): HEC = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × RGDR. $RGDR_{ET}$ values of 0.184, 0.183, and 0.182 for males and 0.121, 0.120, and 0.117 for females in the low-, mid-, and high-dose groups, respectively, were calculated as per U.S. EPA (1994) using default values for human VE and human and animal respiratory tissue surface area and animal VE values calculated using study-specific TWA body-weight values of 0.268, 0.266, and 0.265 kg for low-, mid-, and high-dose males, respectively, and 0.161, 0.160, and 0.154 kg for low-, mid-, and high-dose females, respectively, determined for this review.
[c]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; ET = extrathoracic; 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; PND = postnatal day; RGDR = regional gas dose ratio (animal:human); TWA = time-weighted average; VE = ventilation rate.

Table 3B. Summary of Potentially Relevant Cancer Data for 1-Methylnaphthalene (CASRN 90-12-0)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[a]**	**Critical Effects**	**Reference (comments)**	**Notes[b]**
Human					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					
Animal					
1. Oral (mg/kg-d)					
Carcinogenicity	**50 M/50 F, B6C3F1 mouse, diet, 81 wk.** **Reported treatment: 0, 0.075, or 0.15% in the diet.** **Reported ADDs: 0, 71.6, or 140 mg/kg-d (M); 0, 75.1, or 144 mg/kg-d (F).**	**M: 0, 10.7, 21.1** **F: 0, 11.1, 20.9**	**Increased adenoma and combined adenoma or carcinoma in the lungs of low- and high-dose male mice.**	Murata et al. (1993)	**PS, PR**
2. Inhalation (mg/m^3)					
ND					

[a]Dosimetry: Oral exposures are expressed as HEDs (mg/kg-day) for oral cancer effects; HEDs are calculated using DAFs, as recommended by U.S. EPA (2011b): HED = ADD (mg/kg-day) × DAF. DAFs of 0.149 and 0.150 (males) and 0.147 and 0.145 (females) were calculated as follows: DAF = $(BW_a \div BW_h)^{1/4}$, where BW_a = animal body weight, and BW_h = human body weight. Study-specific TWA animal body weights of 0.035 and 0.036 kg for low- and high-dose males, respectively, and 0.033 and 0.031 kg for low- and high-dose females, respectively, were determined for this review. For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).
[b]PS = principal study; PR = peer reviewed.

ADD = adjusted daily dose; BW = body weight; DAF = dosimetric adjustment factor; F = female(s); HED = human equivalent dose; M = male(s); ND = no data; TWA = time-weighted average.

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 of animals to 1-methylnaphthalene were evaluated in a combined repeated-dose reproductive/developmental toxicity screening study in rats (METI, 2009b), a subchronic toxicity study in transgenic mice (Jin et al., 2012), and a chronic/ carcinogenicity toxicity study in mice (Murata et al., 1993). Supporting acute, short-term, and subchronic oral studies are described in Section 2.3.2.

Subchronic Studies (Including Combined Reproductive and Developmental Screening)

METI (2009a); METI (2009b); NITE (2009)

METI (2009b) is an unpublished, oral, repeated-dose, reproductive/developmental toxicity screening study in rats, written in Japanese, with some text, figures, and tables in English. Additional brief summaries in English are available as separate documents (METI, 2009a; NITE, 2009). The Japanese text was also translated using Google Translate for the purposes of this review; this was not a comprehensive or certified translation. A combination of these documents was used to generate the summary of this OECD 422 guideline study below.

Commercially obtained Sprague Dawley Crl:CD rats (12 breeding pairs/group), aged approximately 9 weeks at the time of treatment, were administered 1-methylnaphthalene (97.2% purity) in olive oil daily, via gavage, at doses of 0, 10, 50, or 250 mg/kg-day. For the main group of animals, dosing began 2 weeks prior to mating and continued throughout mating, gestation, and lactation until postnatal day (PND) 4 (females) or for a total of 42 days (males). An additional satellite group of females (five per control and high-dose groups) were left unmated and were dosed for a total of 42 days. Five males/group and all satellite unmated females were allowed to recover for 14 days prior to sacrifice. The remaining males and mated females were sacrificed 1 day after the last administered dose. Stability of the test substance was confirmed to assure accuracy dosing.

Rats were observed twice daily during the administration period and once a day during the recovery period for mortality and clinical signs of toxicity. More detailed behavioral observations from an open field test (rises, clonic and tonic involuntary movements, pace, mobility, wakefulness, behavior, defecations, and urinations) were recorded once per week. Body weights and food intake were measured at intervals throughout the study. Functional observational battery [FOB] tests (visual, auditory and pain responses, pupillary reflex aerial righting reflex, grip strength, and spontaneous locomotor activity) were performed on five males during the last week of administration and on five selected females on PND 4. Blood was drawn at terminal necropsy from five parental males and females per group, and from the five recovery males and unmated females at the end of the recovery period. Hematology (total red blood cell [RBC] count, hemoglobin [HGB], hematocrit [HCT], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], platelet [PLT], total white blood cell [WBC], differential WBC count [neutrophil, stab and segmented],

lymphocyte, monocyte, eosinophil, and basophil), prothrombin time [PT], and activated partial thromboplastin time [APTT]), and serum clinical chemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total protein [TP], plasma protein patterns (albumin [Alb], α-globulin, α-2 globulin, β-globulin, γ-globulin, and albumin/globulin ratio [A/G ratio]), glucose, total cholesterol [TC], triglyceride [TG], total bilirubin [TBIL], blood urea nitrogen [BUN], creatinine [CRN], inorganic phosphate [IP], calcium [Ca], sodium [Na], potassium [K] and chloride [Cl]) endpoints were measured. Urinalysis was performed on samples collected from five control and five high-dose males on the last day of dosing or the last day of recovery (pH, protein, sugar, ketone bodies, bilirubin, occult blood, and urobilinogen). Measured organ weights (absolute and relative) included brain, thymus, heart, liver, spleen, kidneys, adrenals, testes, and epididymis. Gross necropsy was performed on all animals; histopathological examinations were performed on any gross findings and on >25 tissues from control and high-dose animals (five per group for males and six per group for females). Nasal tissues were not examined.

Assessment of reproductive endpoints included determinations of the fertility index of males and females, length of estrous cycle, number of days to copulation, conception rate, number of pregnant dams, implantation scars and corpora lutea, implantation index, gestation period, pre- and post-implantation loss, delivery and birth indices, and nursing status. Limited developmental endpoints included pup survival rate at birth, sex ratio, pup body weight and number of live/dead pups on PNDs 0 and 4, and examination of pups at sacrifice on PND 4 for external abnormalities.

Statistical analyses were performed using Williams' multiple comparison, Fisher's exact test (one-sided), Bartlett's test, Dunnett's multiple comparison, Kruskal-Wallis rank, Student's *t*-test and/or Aspin Welch t-test, and a multiple comparison of Steel when appropriate. Each pup was used as a sample unit for statistical analysis.

No deaths or moribund rats were observed in any group. No general signs of toxicity were seen in males from any group during normal or detailed clinical observations. In 10-mg/kg-day females, vaginal bleeding on the 23rd day of pregnancy was observed in one female; this female did not complete delivery by gestation day (GD) 25. Another female from this group showed signs of yellowish-green mucus from the vagina on PND 3. Behavioral observations in the open field test showed no consistent differences across dose groups, and there were no significant differences between treated and control groups in the FOB.

Body weights were similar to controls in the main study group males and females throughout the study at all dose levels. Body weight was reduced relative to controls starting on the 8th day of the study in the high-dose unmated satellite female group, with the deficit reaching approximately 10% at the end of exposure and persisting through the recovery period. Unmated high-dose satellite females also generally showed somewhat lower food consumption than controls at times during the exposure and recovery periods; the difference was statistically significant on Study Day 42, the last day of exposure. No changes in food consumption during the exposure period were observed in main study group males or females at any dose level. Hematology and clinical chemistry findings were unremarkable; the few statistically significant findings were sporadic in occurrence and were slight changes that fell within normal ranges (see Tables B-1 and B-2). Urinary endpoints in treated animals of both sexes were comparable to controls. At the end of dosing and in the absence of significant changes in body weights in main

group animals, high-dose males had significantly increased absolute and relative liver weights (increases of 17 and 26%, respectively) and increased relative (15% increase), but not absolute (8% increase), kidney weights, compared with controls (see Table B-3). No organ weight changes were observed in low- or mid-dose males, and none of the organ weight changes in high-dose males persisted to the end of the recovery period. Compared to control animals, mated high-dose females showed a significant increase in relative (10% increase), but not absolute (7% increase), liver weight. No liver weight changes were seen in mated females from the low- or mid-dose groups. Relative liver weights were also significantly increased (12% increase, compared to controls) in unmated females on Recovery Day 14.

No gross pathological changes were observed in males. The single female in the 10-mg/kg-day dose group that exhibited yellow-green mucus from the vagina showed slight atrophy of the thymus and spleen and slight to moderate discoloration of the liver and kidney. Thymic atrophy also occurred in one other female at 10 mg/kg-day, and single females in both the 10- and 50-mg/kg-day groups showed unilateral implantation in the uterus. No gross changes occurred in high-dose females. Histopathological examinations revealed no remarkable changes or statistically significant increased incidences of lesions in the tissues examined, including the lungs, liver, or kidney; however, tissues from only five control and high-dose males and six control and high-dose mated females (in addition to tissues from three females at 10 mg/kg-day with gross lesions) were examined. No histological data were collected from unmated females immediately following dosing.

Compared to controls, there were no statistically significant, treatment-related reproductive or screening-level developmental changes in any of the endpoints examined at any dose level. Conception rates were 100, 91.7, 100, and 100% in the control, low-, mid-, and high-dose groups, respectively, reflecting the one infertile female at 10 mg/kg-day. Another female in the 10-mg/kg-day group failed to deliver by GD 25; due to this single female, the birth rate was 90.9% in the 10-mg/kg-day group, compared with 100% in the other treatment groups and controls. Single incidences of poor nesting or breastfeeding behaviors, along with low viability indices from single litters, were reported across all groups, including controls. There were no treatment-related differences in pup body weights at birth or on PND 4, and no external abnormalities were found in any group.

A systemic NOAEL of 50 mg/kg-day and a LOAEL of 250 mg/kg-day were determined based on statistically and biologically significant increases in absolute and relative liver weights in male rats, relative liver weight in female rats, and relative kidney weight in male rats (METI, 2009b). The organ weight changes occurred in the absence of supporting serum chemistry or histopathological findings but exceed the U.S. EPA criteria for biological significance (a ≥10% increase in absolute and relative liver and kidney weight is considered biologically significant by the U.S. EPA (U.S. EPA, 2012)). The high dose of 250 mg/kg-day was a reproductive/ developmental NOAEL, based on the absence of effects on these endpoints at any dose. The administered doses of 0, 10, 50, and 250 mg/kg-day correspond to human equivalent doses

(HEDs) of 0, 2.8, 14, and 70.1 mg/kg-day in males and 0, 2.6, 13, and 64.0 mg/kg-day in mated females. For unmated females administered 250 mg/kg-day, the HED is 62.0 mg/kg-day.[3]

Jin et al. (2012)

In a peer-reviewed, published study, Jin et al. (2012) investigated in vivo genotoxicity in combination with systemic toxicity effects in B6C3F1 *gpt* delta mice[4] fed 1-methylnaphthalene in the diet for 13 weeks (Masumura et al., 1999; Nohmi et al., 1996).

Commercially obtained B6C3F1 *gpt* delta mice (10/sex/group), aged 6 weeks at the start of treatment, were fed diets containing 0, 0.075, or 0.15% 1-methylnaphthalene for 13 weeks. Doses were selected as they were previously determined to be carcinogenic in a chronic carcinogenicity study (Murata et al., 1993). Corresponding measured intakes provided by the study authors, based on body weight and food consumption data, were 0, 120, and 220 mg/kg-day for males and 0, 170, and 280 mg/kg-day for females. Diets were prepared fresh weekly by mixing 1-methylnaphthalene dissolved in corn oil (5% in each diet) with powdered CFR-1 diet. It is not explicitly stated whether control animals were fed diets containing the corn oil vehicle alone. Diets were stored in light-shielded containers at 4°C; the study does not indicate whether the containers were sealed or whether measures were taken to account for possible volatility. Analytical analysis of 1-methylnaphthalene stability in food during storage or at the time of feeding was not included in the study.

Animals were observed daily for clinical signs of toxicity; body weight and food consumption were recorded once per week. Blood was drawn at necropsy for hematology (WBC, RBC, HGB, HCT, MCV, MCH, MCHC, PLT, and differential leukocyte counts including band and segmented neutrophils, eosinophils, basophils, lymphocytes, monocytes, and reticulocytes) and clinical chemistry (AST, ALT, ALP, TP, TBIL, Alb, TG, TC, phospholipid, BUN, CRN, Na, Cl, K, Ca, and IP). Organ weights (brain, heart, lungs, liver, kidneys, spleen, thymus, adrenal glands, and testes) were recorded and microscopic examinations were performed for all dose groups on these and other tissues (arteries, bone/marrow, coagulation gland, esophagus, epididymides, large intestine [cecum, colon, and rectum], lymph node, mammary glands, pancreas, peripheral nerve, prostate gland, pituitary gland, thyroid glands, salivary gland, skeletal muscle, skin, small intestine [duodenum, jejunum, and ileum], spinal cord, stomach, urinary bladder, tongue, trachea, vagina, uterus, and ovaries). Additionally, right lung lobes were fixed

[3]Adjusted daily doses (ADDs) were converted to HEDs of 2.8, 14, and 70.1 mg/kg-day in low-, mid-, and high-dose males; 2.6, 13, and 64.0 mg/kg-day in mated low-, mid-, and high-dose females; and 62.0 mg/kg-day in unmated high-dose females using respective dosimetric adjustment factors (DAFs) of approximately 0.28 (males), and 0.26 (females), where HED = ADD × DAF. The DAFs were 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. Individual animal body weights were provided in the study; group time-weighted average (TWA) body weights determined for this review were 0.441, 0.442, and 0.433 kg (for low-, mid-, and high-dose males); 0.308, 0.308, and 0.300 kg (for mated low-, mid-, and high-dose females, respectively); and 0.268 (for unmated high-dose females, respectively). For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).

[4]The transgenic *gpt* delta mouse was developed by Nohmi et al. (1996) for in vivo genotoxicity assays. These mice have approximately 80 copies of λ EG10 DNA at a single site in chromosome 17 of C57 BL/6J mice, allowing for in vivo detection of point and deletion mutations (Masumura et al., 1999). B6C3F1 *gpt* delta mice result from crossing 57BL/6J *gpt* delta mice with C3H/He mice. There is uncertainty regarding interpretation of the systemic toxicity data in Jin et al. (2012) due to the use of transgenic *gpt* delta mice. Although comparison studies validating use of *gpt* delta rats for evaluating general toxicity responses are available (Matsushita et al., 2021; Akagi et al., 2015), similar validation studies were not located for *gpt* delta mice.

for histopathological and immunohistopathological examination; remaining lungs were used for genomic deoxyribonucleic acid (DNA) extraction for the in vivo mutation assays. Statistical analysis of continuous data (body weight, food and water consumption, organ weights, hematology, and serum biochemistry) was performed using analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. Incidences of histopathological lesions were evaluated using Fisher's exact probability test.

No mortalities or clinical signs of toxicity were observed. Body weights in treated animals were statistically indistinguishable from controls throughout the study, including final body weights. Food consumption was lower in high-dose males and low- and high-dose females than in controls for much of the study, but overall average food consumption did not differ significantly from controls in any treated group.

Hematological changes were limited to differential leukocyte counts that either showed no consistency between sexes or no clear relation to dose (see Table B-4). Compared to control animals, treated male mice showed a decrease in band form (immature) neutrophils, which was statistically significant in the low-dose group (51% decrease), and an increase in segmented (mature) neutrophils, which was statistically significant in the high-dose group (86% increase). In females, a non-dose-related, but statistically significant, increase in the percentage of basophils, relative to controls, was observed in both treatment groups; comparison to males, however, suggests that this apparent increase reflects a low control value rather than a change in the treated animals. Statistically significant serum chemistry changes in high-dose males included slight increases in AST and ALT (increases <1.5-fold compared with controls), along with small decreases in phospholipids (11% less than controls), BUN (14% less than controls), CRN (18% less than controls), and Ca (3% less than controls) (see Table B-5). Except for a slight decrease in serum Ca, there were no significant changes in low-dose males. The only statistically significant serum chemistry changes in females were slight decreases in phospholipids (9% less than controls) and total cholesterol (7% less than controls) and a slight (2%) increase in chloride at 280 mg/kg-day. Although increases in serum AST and ALT are sometimes associated with liver toxicity, that does not appear to be the case in this study (see discussion of liver lesions below). It is unclear whether any of the other observed serum chemistry or hematology changes have any toxicological significance.

Organ weight data showed no effect on relative liver weight in male or female mice at either dose (see Table B-6). Small decreases in absolute liver weights in the high-dose males and females reflect slightly reduced necropsy body weights in these groups. Absolute and relative spleen weights were significantly reduced in males of both treated groups, but the magnitude of change did not increase with dose and no change was seen in treated females. Significant decreases in absolute and relative heart weights were also reported in males only; however, the reported heart weights, including those from control animals, were ~6 times greater than mean absolute heart weights in similarly aged wild-type B6C3F1 males (Marino, 2012), which suggests caution in using data from these animals. In contrast, heart weight data reported for females were consistent with historical controls, and no effect of treatment was seen. There was an increase in thymus weight in females that was attributed by the study authors to one mouse with lymphoma. No effect on thymus weight was seen in males.

Histopathological examinations revealed liver lesions in treated male and female mice as well as in untreated (control) female mice. The observed lesions included single cell (necrosis

involving single hepatocytes) and focal necrosis (necrosis involving small clusters of hepatocytes), although neither represents extensive injury (Krishna, 2017). Female mice were more susceptible to these liver lesions than males. In females, incidences of both single cell and focal necrosis were 50−70% in the control and treated groups (see Table B-7). Vacuolization was also noted in treated females (1 and 30% in low- and high-dose mice vs. 0% in controls). In males, the incidence of single cell necrosis was increased relative to controls in the high-dose group (50 vs. 0% in controls), but focal necrosis was not observed at any dose. The study authors did not consider the increase in single cell necrosis in high-dose males to be toxicologically significant. No other statistically significant histopathological changes were observed in any tissue, including the lungs. Proliferating cell nuclear antigen (PCNA) immunostaining in the lungs also showed no changes in treated animals, compared to controls, suggesting no increases in proliferation of type II pneumonocytes, which has been described in other studies (Murata et al., 1992). Mutagenicity assays in lung tissue were negative. There were no increases in *gpt* or Spi^- mutation frequencies in lung tissue from any treatment group, although a positive control for the mutagenicity assay was not used.

This study provided no consistent evidence of toxicologically significant, treatment-related effects on any endpoint in male or female mice. Slight, statistically significant increases in serum AST and ALT were seen in high-dose male mice (which showed an increase in incidence of single cell necrosis, but no focal necrosis, in the liver). However, female mice, which showed high incidences of both single cell and larger focal necrosis in control and both dose groups, had AST and ALT levels close to, or lower than, the values in males at all doses. This suggests a disconnect between the serum chemistry and histopathology results; the slight increases in AST and ALT in high-dose males cannot reasonably be attributed to the minimal liver necrosis observed in this group while the females, with a greater degree of necrosis, showed baseline levels of AST and ALT. The toxicological significance of the slight serum AST and ALT increases in high-dose males is, therefore, unknown. Similarly, as discussed above, it is unclear that the increased incidence of single cell necrosis in high-dose male mice represents a toxicologically significant effect, given the high incidence of necrotic liver lesions in female mice (including controls) and the absence of the larger, focal necrotic lesions in male mice. Spleen weights were reduced in both low- and high-dose males, but the magnitude of change did not increase with dose, and no effect on spleen weight was seen in females. There were no histopathological findings in the spleen in either sex. None of the observed hematology or serum chemistry changes are known indicators of damage to the spleen. In the absence of demonstrated treatment-related toxicologically relevant effects, the high dose (220 mg/kg-day in males and 280 mg/kg-day in females) is identified as a NOAEL for male and female mice fed 1-methylnaphthalene in the diet for 13 weeks in this study. The administered doses of 0, 120, and 220 mg/kg-day in males and 0, 170, and 280 mg/kg-day in females correspond to HEDs of 0, 17.1, and 31.1 mg/kg-day in males and 0, 23.1, and 37.7 mg/kg-day in females, respectively.[5]

[5]ADDs were converted to HEDs of 17.1 and 31.1 mg/kg-day for low- and high-dose males, respectively, and 23.1 and 37.7 mg/kg-day for low- and high-dose females, respectively, using DAFs of approximately 0.143 (males) and 0.135 (females), where HED = daily dose × DAF. The DAFs were 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. Animal body-weight data reported graphically in the study were extracted using GrabIT™ software. TWA animal body weights of 0.030 and 0.029 kg and 0.024 and 0.023 kg for low- and high-dose males and females, respectively, were determined. For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).

Chronic/Carcinogenicity Studies

Murata et al. (1993)

In a published, peer-reviewed study, B6C3F1 mice (50/sex/group), aged 6 weeks at study initiation, were given diets containing 0, 0.075, or 0.15% 1-methylnaphthalene (>97% purity) for 81 weeks. Based on cumulative intake data provided by the study authors, doses of 1-methylnaphthalene were estimated as 71.6 and 140 mg/kg-day for the low- and high-dose males, respectively, and 75.1 and 144 mg/kg-day for the low- and high-dose females, respectively. Doses were selected based on results of a subacute toxicity test in which mice given diets of 0.44 and 1.33% 1-methylnaphthalene for 13 weeks exhibited growth retardation in both sexes, likely due to refusal of food intake. Food was prepared fresh monthly but the stability of 1-methylnaphthalene in the diet was not monitored and the study authors noted that control animals may have been exposed to 1-methylnaphthalene vapors. Mice were observed daily for abnormalities, and body weights were recorded weekly for the first 16 weeks and every 2 weeks thereafter. Food consumption was monitored throughout the study. At the end of the 81-week treatment period, blood was collected for hematology (WBC, RBC, HGB, HCT, MCV, MCH, MCHC, and percentage of different leukocytes [stab cells, segmented, eosinophil, basophil, lymphocytes, and monocytes]) and serum biochemical analysis (AST, ALT, ALP, lactate dehydrogenase [LDH], cholinesterase, gamma-glutamyl transpeptidase [γ-GTP], TBIL, TP, A/G ratio, Alb, BUN, uric acid, CRN, Na, K, Cl, iron, lipid, phospholipid, nonesterified fatty acid, neutral fat, cholesterol, esterified cholesterol, high-density lipoprotein [HDL], β-lipoprotein, and lipid peroxide). Organ weights were recorded for brain, salivary glands, heart, thymus, lung, liver, pancreas, spleen, kidneys, and testis. These organs and adrenals, trachea, stomach, small intestine, large intestine, seminal vesicle, ovary, uterus, vagina, mammary gland, skeletal muscle, eye, Harderian glands, spinal cord, bone (sternal, rib, vertebral), skin, and other tissues with abnormal appearance were prepared for histopathological examination. Nasal tissues were not examined. Histopathological examinations were also performed on all mice found dead or sacrificed moribund prior to scheduled sacrifice. A χ^2 test was used for analysis of neoplastic and non-neoplastic incidence data. Body weights, organ weights, and blood and serum endpoints were analyzed by Student's *t*-test without adjustment for multiple comparisons.

One control male mouse and one high-dose female mouse died of leukemia at Weeks 60 and 68, respectively. All other mice survived to scheduled sacrifice. There were no statistically significant, treatment-related effects on food consumption, growth, or terminal body weights. The only dose-related, statistically significant hematological changes in treated animals were increases in the percentages of monocytes in males and females in both the low- and high-dose groups, compared with controls (see Table B-8). The study authors hypothesized that the increase in monocytes may have been a physiological response to the pulmonary alveolar proteinosis (PAP) seen in the exposed animals. Other changes in leukocyte classifications and RBC parameters either showed no relation to dose or were directionally inconsistent between sexes or dose groups (see Table B-8). Serum biochemistry changes were generally sporadic and not related to dosing. The only changes appearing to be dose-related were statistically significant decreases in LDH and BUN in males (increases are typically expected as indicators of toxicity) and increased phospholipids and neutral fats in females (see Table B-9). These changes were not clearly associated with any pathologies, although the study authors previously speculated that the lipid changes may be related to PAP (Murata et al., 1992). Statistical analysis of both hematology and serum chemistry data were performed using simple t-tests, without adjustment for multiple comparisons, increasing the likelihood of false positive findings.

As shown in Table B-10, the statistically significant organ weight changes were generally either small in magnitude (5−9%, relative to controls), did not exhibit a clear relationship with dose, occurred only in one sex, and/or had questionable toxicological significance. As for the blood data, the use of simple t-tests by the study authors without adjustment for multiple comparisons means that there is a likelihood of false positive results. The study authors indicated that thymus weights in control female mice were abnormally high due to the development of lymphoma in this group, producing the apparent decrease in thymus weights in the treated mice.

Exposure-related lesions were restricted to the lung. Statistically significant increased incidences of male and female mice with PAP were observed following 81 weeks of 1-methylnaphthalene treatment in both the low- and high-dose groups (see Table B-11). This lesion was characterized by an accumulation of phospholipids in the alveolar lumens that appeared grossly as white protuberant nodules approximately 1−5 mm in diameter. Histologically, there was visible filling of alveolar lumens with cholesterol crystals, foamy cells, and an amorphous acidophilic material. Alveolar walls and epithelial cells were generally intact and the interstitium did not exhibit evidence of prominent edema, alveolitis, lipidosis, or fibrosis. The incidences of PAP lesions in controls, low-dose, and high-dose groups were 4/49, 23/50, and 19/50 in males and 5/50, 23/50, and 17/49 in females, respectively. The study authors stated that this effect had not been observed previously in >5,000 B6C3F1 mice housed in the same room and speculated that the incidences in control mice may have been due to exposure to volatilized 1-methylnaphthalene and 2-methylnaphthalene from the treatment groups housed in the same room for this experiment.

For non-neoplastic effects, a LOAEL of 71.6 mg/kg-day, the lowest dose in male mice exposed to dietary 1-methylnaphthalene for 81 weeks, was determined based on statistically significantly increased incidences of PAP. Incidences of PAP were also increased in the low-dose females (75.1 mg/kg-day). A NOAEL was not identified.

Tumor incidences in the lungs of mice are provided in Table B-12. Statistically significant increases in incidences of lung adenomas and lung adenomas or adenocarcinomas (combined) were seen in both low- and high-dose male mice treated with 1-methylnaphthalene in the diet for 81 weeks. Lung tumors were not increased in the female mice. No tumor increases were seen in other tissues.

The administered doses of 0, 71.6, and 140 mg/kg-day in males and 0, 75.1, and 144 mg/kg-day in females correspond to HEDs of 0, 10.7, and 21.1 mg/kg-day in males and 0, 11.1, and 20.9 mg/kg-day in females, respectively.[6]

[6]ADDs were converted to HEDs of 10.7 and 21.1 mg/kg-day for low- and high-dose males, respectively, and 11.1 and 20.9 mg/kg-day for low- and high-dose females, respectively, using respective DAFs of 0.149 and 0.150 (males) and 0.147 and 0.145 (females). The DAFs were calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$), BW_a = animal body weight and BW_h = human body weight. Animal body-weight data reported graphically in the study were extracted using GrabIT™ software. TWA animal body weights of 0.035 and 0.036 kg for low- and high-dose males, respectively, and 0.033 and 0.031 kg for low- and high-dose females, respectively, were determined. For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).

2.2.2. Inhalation Exposures

Relevant studies on the effects of inhalation exposure of animals to 1-methylnaphthalene were limited to a single subchronic repeated-dose inhalation toxicity study in rats (Kim et al., 2020). Supporting acute and short-term inhalation studies are described in Section 2.3.2.

Subchronic Studies

Kim et al. (2020)

In a published, peer-reviewed study, Kim et al. (2020) reported the effects of repeat exposure to 1-methylnaphthalene (97.3% pure) in rats. F344 rats (10/sex/group) were commercially obtained at 6 weeks of age, and exposed, whole-body, to 1-methylnaphthalene vapors at nominal concentrations of 0, 0.5, 4, and 30 ppm for 6 hours/day, 5 days/week for 13 weeks. Measured analytical concentrations (mean ± standard deviation [SD]) were 0, 0.52 ± 0.05, 4.08 ± 0.25, and 30.83 ± 1.28 ppm for the low-, middle-, and high-exposure groups, respectively; maintaining significant figures, these concentrations correspond to 0, 3.0, 23.7, and 179.3 mg/m^3, respectively[7]. A low dose of 0.5 ppm was selected to correspond with the concentration that American Conference of Governmental Industrial Hygienists (ACGIH) recommended as an 8-hour TWA Threshold Limit Value (TLV) on the basis of respiratory irritation (ACGIH, 2007).

Animals were observed daily for mortality and clinical signs of toxicity. Body weights were recorded twice per week for the first 4 weeks then once per week for the remainder of the study. Monitoring of food consumption was mentioned without details on frequency. At terminal necropsy, blood was drawn for hematology (RBC, HGB, HCT, MCV, MCH, MCHC, platelets, WBC, differential WBC count [neutrophil, lymphocyte, monocyte, eosinophil, and basophil], reticulocyte, PT, and APTT), and serum clinical chemistry (ALT, AST, ALP, BUN, CRN, creatinine phosphokinase [CPK], TBIL, TP, Alb, TC, TG, and Na). Bronchoalveolar lavage (BAL) fluid from five rats/sex/group was analyzed for LDH, total cell counts, macrophages, polymorphonuclear leukocyte (PMN), and lymphocyte counts. Necropsies consisted of external examinations of body surfaces, orifices, and contents of cranial, thoracic, and abdominal cavities of all rats. Organs (adrenal glands, brain, heart, kidneys, liver, spleen, testes, thymus, epididymides, lung, ovaries, and uterus) were weighed (absolute weights only) and select tissues (adrenal glands, aorta, bone marrow, brain, cecum, colon, duodenum, epididymides, esophagus, femur, Harderian glands, heart, ileum, jejunum, kidneys, larynx, liver, lung, lymph nodes [tracheobronchial and mesenteric], mammary gland, nasopharyngeal tissue, nerve [sciatic], pancreas, parathyroids, pituitary, prostate, rectum, salivary glands [submandibular, sublingual, and parotid], seminal vesicles, skeletal muscle, skin, spinal cord [cervical, lumbar, and thoracic], spleen, sternum, stifle joint, stomach, teeth, thymus, thyroids, tongue, trachea, urinary bladder, ovaries, uterus, eyes/optic nerve, and testes) were preserved. Histological analysis was performed on fixed tissues from the control and high-exposure animals only, except for nasopharyngeal tissue, which was examined from animals from all exposure groups. Depending on tissue type, tissues were preserved in either 10% neutral buffered formalin or Davidson's solution. Preserved tissues were paraffin-embedded, sectioned, and stained with

[7]Analytical concentrations of 0.52, 4.08, and 30.83 ppm were converted to mg/m^3 using the following formula: mg/m^3 = (ppm × MW)/24.45, where MW = 142.2 g/mol (the molecular weight of 1-methylnaphthalene) and 24.45 is the volume occupied by 1 g/mol of any compound in a gaseous state at 0°C and 760 mm Hg.

hematoxylin and eosin. Statistical analysis was performed using the PASW Statistics 18 or SigmaPlot 12 programs. One-way ANOVA was used to evaluate BAL fluid and organ weight data; hematological and serum chemistry endpoints were analyzed using Dunnett's test. The statistical test used for body-weight data was not specified.

No deaths or exposure-related clinical signs were observed (data not shown). Mean body weights of treated males from all groups were comparable to controls throughout the study. In females, body weights in the high-exposure group were slightly (≤5%) lower than controls throughout the study (statistically significant only on Day 16), while body weights in the low- and mid-exposure groups were similar to controls. No significant changes in food consumption were reported (data not shown). Results from BAL fluid analysis showed no differences in cell differential counts or in levels of LDH across groups. Observed hematological and clinical chemistry changes were small in magnitude and fell within normal ranges. Statistically significant hematological changes were limited to increases in PT in high-exposure males (10% increase) and females (8% increase) and APTT (8% increase) in high-exposure males (see Table B-13). Statistically significant serum chemistry changes were limited to a small (16%) decrease in ALT (increases are considered toxicologically relevant) and small (≤5%) increases in albumin and sodium levels in high-exposure males (see Table B-13). No serum chemistry changes occurred in low- or mid-exposure males or in any exposed female group. There were no statistically significant differences in absolute organ weights between exposed and control groups and magnitudes of change were <5%; relative organ weights were not reported.

Results from gross examinations were not reported. The incidence of mucous cell hyperplasia in nasopharyngeal tissues was significantly increased in male rats of all exposed groups and in high-exposure female rats. Both the incidence (from 40 to 100%) and severity (from minimal to moderate) of this lesion increased with exposure level in the male rats (see Table B-14). In females, the incidence and severity increased with exposure, from 30% with minimal lesions in the mid-exposure group to 100% with minimal-to-moderate lesions in the high-exposure group. Males in the mid- and high-exposure groups also showed significantly increased incidences of hyperplasia in transitional epithelial cells of nasopharyngeal tissues (50% incidence, minimal severity). Aside from nasopharyngeal tissues, all other microscopic findings, including in the lungs, were reported to be consistent with those normally found in rats of the same age group, and were considered by the study authors to be spontaneous (data not shown in study report).

A LOAEL of 3.0 mg/m^3 was identified based on statistically significantly increased incidence of mucous cell hyperplasia in nasopharyngeal tissues in male F344 rats exposed to 1-methylnaphthalene vapors for 6 hours/day, 5 days/week for 13 weeks. A NOAEL was not determined. Nasal mucous cell hyperplasia increased in incidence and severity with exposure concentration in both sexes. Nasal transitional epithelial cell hyperplasia was also observed in males in the higher exposure groups. Analytical concentrations of 0, 3.0, 23.7, and 179.3 mg/m^3 correspond to human equivalent concentrations based on extrathoracic effects (HEC_{ET}) values of

0, 0.099, 0.773, and 5.833 mg/m^3, respectively, for males and 0, 0.065, 0.510, and 3.736 mg/m^3, respectively, for females for extrathoracic effects (maintaining the stated significant figures).[8]

Chronic, Reproductive, Developmental, and Carcinogenicity Studies

No inhalation chronic, reproductive, developmental, or carcinogenicity studies on 1-methylnaphthalene in animals were identified.

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

2.3.1. Genotoxicity

Table 4A provides an overview of genotoxicity studies of 1-methylnaphthalene. Limited genotoxicity data are available for 1-methylnaphthalene but results generally show that 1-methylnaphthalene is non-genotoxic. The chemical produced negative results in the Ames test with *Salmonella typhimurium* strains TA98 and TA100 both in the presence and absence of rat liver S9 metabolic activation (Florin et al., 1980). These results were consistent with those obtained in a second Ames test in which *S. typhimurium* strains TA97, TA98, TA100, and TA1535 showed negative results both with and without activation (rat and hamster S9) (NTP, 2018). Positive results were reported in a forward mutation assay using *S. typhimurium* strain TM677 in the presence of preinduced rat S9, but only at a concentration inducing cytotoxicity (Kaden et al., 1979). 1-Methylnaphthalene did not induce chromosomal aberrations (CAs) or sister chromatid exchanges (SCEs) in human peripheral lymphocytes in the absence or presence of S9 hepatic microsomal fractions (Kulka et al., 1988). The micronuclei frequency in V79 hamster fibroblasts exposed to 1-methylnaphthalene did not differ significantly from the controls, although urine extracts from rats exposed to 1-methylnaphthalene induced a significant increase in the frequency of micronuclei compared to urine extracts from the group of control animals (Świercz et al., 2022). The study authors concluded that it was likely that 1-methylnaphthalene metabolites present in the rat urine induced increased micronuclei frequency. In an in vivo transgenic rodent mutation assay, Jin et al. (2012) analyzed mutation frequencies for *gpt* and Spi$^-$ in the lungs of B6C3F1 *gpt* delta mice administered diets containing 0, 0.075, and 0.15% 1-methylnaphthalene for 13 weeks. There were no significant differences among groups for either sex, indicating that 1-methylnaphthalene was negative for in vivo genotoxicity in this test; however, no positive controls were included in the assay.

[8]HEC values based on extrathoracic effects are calculated by treating 1-methylnaphthalene as a Category 1 gas and using the following equation from U.S. EPA (1994): HEC = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × RGDR, where RGDR is the regional gas dose ratio (animal:human). $RGDR_{ET}$ values of 0.184, 0.183, and 0.182 for males and 0.121, 0.120, and 0.117 for females in the low-, mid-, and high-dose groups, respectively, were calculated as per U.S. EPA (1994) using default values for human VE (ventilation rate) and human and animal respiratory tissue surface area and animal VE values calculated using study-specific TWA body-weight values of 0.268, 0.266, and 0.265 kg for low-, mid-, and high-dose males and 0.161, 0.160, and 0.154 kg for low, mid-, and high-dose females determined for this review.

Table 4A. Summary of 1-Methylnaphthalene Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested[a]	Results Without Activation[b]	Results With Activation[b]	Comments	References
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* TA98 and TA100; bacteria were tested with and without metabolic activation by S9 rat liver fraction (0 or 0.03−30 µmol/plate)	30 µmol/plate (4,300 µg/plate[c]).	−	−	Ames assay. No evidence of mutagenicity in any of the strains tested with or without S9 activation. Toxic to bacteria at ≥3 µmol/plate.	Florin et al. (1980)
Mutation	*S. typhimurium* strains TA97, TA98, TA100, and TA1535; bacteria were tested with and without metabolic activation by rat or hamster S9 (0 or 0.3−100.0 µg/plate)	100.0 µg/plate.	−	−	Ames assay. No evidence of mutagenicity in any of the strains tested with or without S9 activation.	NTP (2018)
Mutation	*S. typhimurium* TM677; bacteria were tested in the presence of preinduced rat liver homogenate (0 or 0.7−7 mM)	7 mM (1,000 µg/mL[c]).	NDr	+ (T)	Forward mutation assay. Positive for mutations at 7mM. Cytotoxicity at ≥3.5 mM.	Kaden et al. (1979)
Genotoxicity studies in mammalian cells—in vitro						
Clastogenicity (CA)	Human peripheral lymphocytes; cells were tested with or without activation by S9 hepatic microsomal fraction (without S9: 0, 1.0, or 2.0 mM; with S9: 0 or 0.25−2.0 mM)	Without activation: 2.0 mM (280 µg/mL[c]). With activation: 2.0 mM (280 µg/mL[c]).	−	−	No increase in chromatid breaks, gaps, or number of S-cells with or without S9 activation.	Kulka et al. (1988)

Table 4A. Summary of 1-Methylnaphthalene Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested[a]	Results Without Activation[b]	Results With Activation[b]	Comments	References
Clastogenicity (SCE)	Human peripheral lymphocytes; cells were tested with and without activation by S9 hepatic microsomal fraction (without S9: 0, 1.0, or 2.0 mM; with S9: 0 or 0.25−2.0 mM)	Without activation: 2.0 mM (280 µg/mL[c]) With activation: 2.0 mM (280 µg/mL[c])	−	−	No increase in SCEs without activation. Slight increase in SCEs with activation did not meet criteria for a positive test (<twofold).	Kulka et al. (1988)
Clastogenicity (MN)	Chinese hamster fibroblasts (binucleated V79 cells); cells were tested with and without activation by S9 hepatic fraction (0, 0.035, 0.070, or 0.40 mM)	Without activation: 0.40 mM (25 µg/mL[c]) With activation: 0.40 mM (25 µg/mL[c])	−	−	No increase in MN frequency compared to vehicle control. However, a significant increase in MN frequency was observed after exposure to the urine extracts from animals exposed to single and repeated doses of 1-methylnaphthalene at 50−200 mg/m^3.	Świercz et al. (2022)
Genotoxicity studies—in vivo						
MFs for *gpt* and red/gam (Spi$^-$) in the lungs of B6C3F1 *gpt* delta mice	An in vivo transgenic rodent mutation assay; B6C3F1 *gpt* delta mice were administered diets containing 0, 0.075, or 0.15% 1-methylnaphthalene for 13 wk; MFs in lungs were examined (males: 0, 120, or 220 mg/kg-d; females: 0, 170, or 280 mg/kg-d)	Males: 220 mg/kg-d Females: 280 mg/kg-d	−	NA	No significant increases in *gpt* or Spi$^-$ MF among any groups for either sex; however, no positive controls were included in the assay.	Jin et al. (2012)

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]− = negative; + = positive.
[c]Molarity conversion based on molecular weight of 142.197 g/mol.

CA = chromosomal aberration; MF = mutation frequency; MN = micronuclei; NA = not applicable; NDr = not determined; MF = mutation frequency; SCE = sister chromatid exchange; T = cytotoxicity.

2.3.2. Supporting Animal Studies

A limited number of supporting acute, short-term, subchronic, and chronic studies are summarized in Table 4B. These include inadequately reported studies, studies that evaluate only one endpoint, studies with short exposure durations, studies conducted via routes of exposure other than oral or inhalation (e.g., dermal, injection), and select mixture studies. Supporting oral studies include a poorly described acute oral toxicity study in rats (DuPont, 1992), a 14-day study in rats reporting transient weight loss and no histopathological findings (DuPont, 1992), and a preliminary 13-week study in B6C3F1 mice, briefly mentioned in another study report (Murata et al., 1993), that reported growth retardation at ≥624.4 mg/kg-day and no abnormal histopathology (doses up to 1,887 mg/kg-day). Acute and short-term inhalation studies provide limited support that 1-methylnaphthalene may have mild neurotoxic effects, such as decreasing pain sensitivity and reducing corticosterone stress responses (Świercz and Stępnik, 2020; Korsak et al., 1998), and possibly produce immune and/or hematological effects (Lorber, 1972) or induce changes in liver function (Świercz et al., 2022). The chemical was shown to be an acute respiratory irritant (Korsak et al., 1998). Intraperitoneal (i.p.) injection studies found minimal lung lesions (swollen Clara cells) in the bronchiolar epithelium of treated mice (Rasmussen et al., 1986), but not in rats (Dinsdale and Verschoyle, 1987). A series of chronic dermal studies in mice performed using a mixture of 1- and 2-methylnaphthalene found lung lesions described in the earlier studies as lipid pneumonia or proliferation of type II pneumocytes (Taki et al., 1986; Emi and Konishi, 1985) and in the later study as PAP (Murata et al., 1992), as observed in the chronic dietary study of Murata et al. (1993) described above.

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Supporting evidence—noncancer effects in animals following oral exposure				
Acute (oral)	Rats (strain, sex, and number not specified) were dosed orally with 1-methylnaphthalene at up to 7,500 mg/kg.	Marked incoordination and muscle weakness lasting 24−48 h were observed in rats at doses ≥3,375 mg/kg. A rat given 7,500 mg/kg died. Congestion of internal organs and kidney damage were observed in the animal that died.	A single dose was lethal to a rat at 7,500 mg/kg.	DuPont (1992)
Short-term (oral)	Rats (six rats, strain, and sex not specified) were orally administered 10 treatments of 1,500 mg/kg 1-methylnaphthalene over 14 d.	No deaths were observed. Transient weight loss was reported, but animals regained weight and were in "good condition" 14 d after the last treatment. No gross or histopathological changes were observed in animals 14 d after the last treatment.	There was limited evidence of transient weight loss in rats treated at 1,500 mg/kg.	DuPont (1992)
Subchronic (oral)	B6C3F1 mice (10/sex/group) were administered diets containing 0, 0.0163, 0.049, 0.147, 0.44, or 1.33% 1-methylnaphthalene for 13 wk (approximately 0, 23.13, 69.54, 208.6, 624.4, or 1,887 mg/kg-d, respectively, as determined for this review)[a]. Endpoints evaluated were not clearly specified but included growth and histopathology.	Growth retardation was observed at ≥0.44% (624.4 mg/kg-d), likely due to refusal to eat. No histopathological lesions were observed in any group (data not shown).	There was limited evidence of growth retardation in mice at ≥624.4 mg/kg-d. This was a preliminary study, which was poorly described in the main study report.	Murata et al. (1993)
Supporting evidence—noncancer effects in animals following inhalation exposure				
Acute (inhalation)	Wistar rats (10 males/group) were exposed, whole-body, to 1-methylnapthalene vapor concentrations of 0, 152, 253, or 407 mg/m^3 for 4 h. Endpoints evaluated included mortality, rotarod performance (measured before and immediately after exposure), and a hot plate test.	No deaths occurred. Increased latency of the paw-lick response was seen (increases of 143 and 254% at 253 and 405 mg/m^3, respectively), compared with controls. There was no effect on rotarod performance.	There was evidence of a concentration-related decrease in pain sensitivity in rats exposed to ≥253 mg/m^3 for 4 h.	Korsak et al. (1998)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute (inhalation)	Balb/C mice (8−10 males/group) were exposed, whole-body, to 1-methylnapthalene vapor concentrations of 54, 103, 203, 310, or 416 mg/m^3 for 6 min. Respiratory rates were recorded continuously before exposure, during 6 min of exposure, and for 12 min after exposure and used to determine an RD_{50} value.	Concentration-dependent decreases in respiratory rates were seen in mice, with maximum decreases in the first 2 min of exposure.	Mouse RD_{50} (95% CI) = 129 (61−228) mg/m^3.	Korsak et al. (1998)
Acute (inhalation)	Wistar rats (four males per group) were exposed to 1-methylnaphthalene vapors (nose-only) for 6 h (single exposure) at analytical concentrations of 0, 50.3, and 194.5 mg/m^3. Tissue and blood samples were collected at the end of the exposure and urine samples were collected at 0, 24, 48, and 72 h following exposure. Endpoints evaluated included body weight, organ weight (lung, liver, spleen, and kidney), and tissue metabolite distribution.	Significant increases in absolute but not relative liver weight (22−43% higher than controls) were observed in both dose groups; a significant reduction in relative, but not absolute, spleen weight (30−36% lower than controls) was observed in the low-dose group only; a significant increase in absolute, but not relative, kidney weight (18−19% higher than controls) was observed in the high-dose group only.	There was limited evidence of renal and hematological changes in rats.	Świercz et al. (2022)
Short-term (inhalation)	Dogs (intact, recently splenectomized, or chronically splenectomized; at least 2−6 group; sex and strain not specified) were exposed to mists containing pure or practical-grade 1-methynaphthalene for 5-min periods, with 7−10 min pauses in between, over a period of 4 consecutive days. Animals were observed for up to 10 d. Endpoints evaluated included differential WBC, reticulocyte and platelet counts, and RBC survival. Blood and bone marrow were collected pre- and post-exposure.	Pure 1-methylnaphthalene increased the percent of reticulocytes in six of six chronic splenectomized dogs and in one of four intact dogs and decreased platelets in one of six chronic splenectomized dogs. Practical-grade 1-methylnaphthalene increased the mean leucocyte counts in both intact and recently splenectomized dogs (four per group) and increased the mature and mean immature neutrophil counts in intact dogs.	There was limited evidence of hematological changes in dogs. Based on the information provided, exposure concentrations could not be determined.	Lorber (1972)

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Short-term (inhalation)	Wistar rats (three males/group) were exposed to 1-methylnaphthalene vapors (nose-only in glass restrainer tubes) 6 h/day for 5 d at analytical concentrations of 0, 53.7, or 195.5 mg/m^3. A second unrestrained control group was included. Endpoints evaluated included body weights, food and water intake, and measurements of serum corticosterone (as a biomarker for stress). A 3-h time course analysis of serum corticosterone levels was performed during the first 3 h after termination of the 6-h exposure on Study Day 5.	Restrained control rats had significantly higher serum corticosterone levels than unrestrained controls. Exposing restrained rats to 1-methylnaphthalene significantly reduced serum corticosterone levels (more so in the 57.3 mg/m^3 group than in the 195.5 mg/m^3 group) measured immediately after exposure ended. The 3-h time course after the end of exposure showed an initial increase in serum corticosterone levels in rats that had been exposed to 1-methylnaphthalene, followed by a decline to levels similar to unrestrained controls.	The study presents some evidence that 1-methylnaphthalene reduced the corticosterone stress response in rats, but the results are questionable, as the observed effect was stronger at the lower exposure level.	Świercz and Stępnik (2020)
Short-term (inhalation)	Wistar rats (four males per group) were exposed to 1-methylnaphthalene vapors (nose-only) 6 h/day for 5 d at analytical concentrations of 0, 53.7, and 198.1 mg/m^3. Tissue and blood samples were collected at the end of the exposure and urine samples were collected at 0, 24, 48, and 72 h following exposure. Endpoints evaluated included body weights, organ weights (lung, liver, spleen, and kidney), serum ALT and AST activity, liver CYP1A1 and CYP1A2 activity, and tissue metabolite distribution and urinary excretion.	Significant reductions in absolute and relative spleen weights (19−39% lower than controls) were observed in both dose groups; significantly higher ALT activity (40% higher than controls) was observed in serum of rats exposed to the high dose only; liver CYP1A1 activity was increased (32% higher than controls) at the high dose only; and liver CYP1A2 activity was increased (54−71% higher than controls) in both dose groups.	Inhalation exposure to 1-methylnaphthalene may induce changes in liver function at ≥53.7 mg/m^3.	Świercz et al. (2022)

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Supporting evidence−noncancer effects in animals following other exposure routes				
Acute (i.p.)	Male Swiss-Webster mice (two per group) were given single doses of 0, 1, or 2 mmol/kg (equivalent to 0, 142, or 284 mg/kg) of 1-methylnaphthalene in peanut oil via i.p. injection. Animals were sacrificed 1, 3, 7, or 14 d post-treatment. Endpoints evaluated included light microscopic examination of lung, liver, and kidney tissues and electron microscopic examination of lung tissue.	Minimal morphology changes were observed in bronchiolar epithelium, consisting of swelling of Clara cells with occasional sloughed cells in terminal bronchioles at ≥142 mg/kg. No effects on liver or kidneys were observed.	There was evidence for minimal lesions in the lungs of male mice at ≥142 mg/kg i.p.	Rasmussen et al. (1986)
Acute (i.p.)	Female Wistar-derived rats (number not reported) were given single doses of 0 or 1.0 mmol/kg (equivalent to 142 mg/kg) of 1-methylnaphthalene via i.p. injection. Use of vehicle was not reported. Animals were sacrificed 24 h post-dosing and lung tissues were examined microscopically.	No lesions in the lungs were detected.	There was no evidence of lung lesions in female rats at 142 mg/kg i.p.	Dinsdale and Verschoyle (1987)
Acute (dermal)	Rabbits (strain, sex, and number treated not reported).	A rabbit exposed to 3,750 mg/kg on the skin was inactive and refused food for 24 h after treatment. A rabbit exposed to 7,500 mg/kg on the skin refused food and was almost completely inactive until it died 48 h after treatment. Possible kidney damage was reported. Skin irritation was observed.	Acute dermal exposure to 7,500 mg/kg was lethal to a rabbit.	DuPont (1992)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Chronic (dermal) Mixture (composition not reported)	Female B6C3F1 mice (4, 11, and 32/group, respectively) were dermally exposed to 0, 29.7, or 118.8 mg/kg of a mixture containing 1-methylnaphthalene and 2-methylnaphthalene in acetone 2 times/wk for 61 wk. Mortality was recorded, and histology was performed on skin, lungs, and unspecified organs.	Mortality was observed as early as 10 wk and peaked at 38 wk; deaths were attributed to lipid pneumonia. Lipid pneumonia was observed in 0/4, 3/11, and 31/32 animals at 0, 29.7, and 118.8 mg/kg, respectively. White spots with demarcated nodules were grossly visible. Histological observations included hypertrophy and hyperplasia of type II pneumocytes, alveolar wall thickening, and multinucleated giant cells, foamy cells, and cholesterol crystals in the alveolar lumen.	Dermal exposure to a mixture of 1- and 2-methylnaphthalene for 61 weeks produced lung lesions described as lipid pneumonia in mice.	Emi and Konishi (1985)
Chronic (dermal) Mixture (composition not reported)	Female B6C3F1 mice (three, eight, or seven per group, respectively) were dermally administered 0, 118.8, or 237.6 mg/kg of a mixture containing 1-methylnaphthalene and 2-methylnaphthalene dissolved in acetone 2 times/wk for 50 wk. Lipids were extracted from lung tissues for lipid profiling.	Increased levels of triglyceride, cholesterol, cholesteryl ester, and phospholipids were seen in the lungs of exposed mice at ≥118.8 mg/kg, compared to control.	The study authors considered the observed pulmonary lipid changes to be indicative of proliferation of Type II pneumocytes, because these cells are known to produce some of the increased lipids.	Taki et al. (1986)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Chronic (dermal) Mixture (approximate 2:1 2-methylnaphthalane: 1-methylnaphthalene ratio)	Female B6C3F1 mice (15/group) were dermally exposed to 0 or 119 mg/kg of a mixture containing 1-methylnaphthalene and 2-methylnaphthalene in acetone 2 times/wk for 30 wk. Lungs were fixed for light and electron microscopy.	Final body weight was reduced 14% in exposed animals, compared with control. PAP occurred in 100% of the exposed animals and was characterized by grey-white nodules on lung surfaces, alveoli filled with eosinophilic material, mononucleated giant cells with foamy cytoplasm, and myelinoid structures present in areas of proteinosis. The study also reported 100% PAP in animals similarly exposed dermally to 238 mg/kg 2 times/wk for 20 wk (data not shown).	Dermal exposure to a mixture of 1- and 2-methylnaphthalene for 30 wk produced lung lesions described as PAP in 100% of exposed mice.	Murata et al. (1992)

[a]Reported dietary intakes (% 1-methylnaphthalene in food) were converted to ADDs using the following equation: ADD = [1-methylnaphthalene (% in diet) × food intake (kg food/day)]/average body weight (kg) × 10^6 (mg/kg), where reference values for body weight and food intake were used as recommended by U.S. EPA (1988). An average value of food intake for males and females of 0.003555 kg/day was used (average of female B6C3F1 84–93-day intake [0.00344 kg/day] and male B6C3F1 84–91-day intake [0.00367 kg/day]) and an average body weight for males and females of 0.02505 kg was used (average of female B6C3F1 84–93-day body weight [0.0214 kg] and male B6C3F1 84–91-day body weight [0.0287 kg]).

1-NA = 1-naphtholic acid; ADD = adjusted daily dose; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CYP = cytochrome P450; i.p. = intraperitoneal; PAP = pulmonary alveolar proteinosis; RBC = red blood cell; RD_{50} = concentration depressing respiratory rate to 50%; WBC = white blood cell.

2.3.3. Metabolism/Toxicokinetic Studies

No studies are available that quantify the rate or extent of 1-methylnaphthalene uptake following oral exposure; however, oral toxicity studies, such as those discussed in Section 2.2.1, show that 1-methylnaphthalene is absorbed via the gastrointestinal tract. Inhalation and dermal toxicokinetic studies indicate that 1-methylnaphthalene is rapidly absorbed through the lungs (Świercz et al., 2022; Świercz and Wąsowicz, 2018) and the skin (Mcdougal et al., 2000). 1-Methylnaphthalene was detected in blood samples taken immediately after exposure from male Wister rats exposed, nose-only, to vapor concentrations of 50 or 200 mg/m^3 for 6 hours (Świercz and Wąsowicz, 2018) and for 6 hours/day for 5 days (Świercz et al., 2022). Examination of the absorption and penetration examination of methylnaphthalene (assumed mixture) using excised rodent skin, exposed for 4 hours in static diffusion cells, demonstrated a flux of 1.55 µg/cm^2/hour and a skin permeability coefficient of 1.6×10^{-4} (Mcdougal et al., 2000).

No data on distribution following oral or dermal exposure were identified. After inhalation exposure in rats, elimination from blood was rapid and followed a two-compartment model (Świercz et al., 2022; Świercz and Wąsowicz, 2018). Half-lives for phase I were similar following single or repeat exposures (1.08 and 2.46 minutes, respectively). Half-lives and areas under the curve (AUCs) during phase II were concentration-dependent; after a single 6-hour exposure, the half-lives in blood during phase II were 39.1 minutes at an exposure concentration of 50 mg/m^3 and 104 minutes at an exposure concentration of 200 mg/m^3. 1-Methylnaphthalene concentration in rat tissues was also dependent on the concentration of exposure. After inhalation, 1-methylnaphthalene immediately distributed primarily to kidney and fat, with greater distribution to fat at increasing exposure concentrations (Świercz and Wąsowicz, 2018). Lower concentrations of 1-methylnaphthalene were found in the lungs, spleen, liver, and brain. Twenty-four hours post-exposure, the parent compound was only detected in fat (single and repeat exposures) and kidney (single exposure only). No 1-methylnaphthalene was detected in any tissues at 72 hours following termination of exposure. In general, 1-methylnaphthalene concentrations in tissues were lower in animals repeatedly exposed to 1-methylnaphthalene for 5 days, compared with those exposed for a single 6-hour period, suggesting increased metabolism following repeated exposure (Świercz and Wąsowicz, 2018). Świercz et al. (2022) monitored levels of 1-naphtholic acid (1-NA), a metabolite of 1-methylnaphthalene, following single (6-hour) or repeated (6 hours/day for 5 days) exposure to 1-methylnapthalene via nose-only inhalation in rats (see Table 4B). The highest 1-NA concentrations were observed in kidney tissue following exposure, although no 1-NA was detected 72 hours after the end of the exposure in any analyzed tissues. In collected urine samples (3 days, 24 hours/day), 95% of total measured 1-NA was detected in the first 0−24 hours, suggesting rapid metabolism of 1-methylnaphthalene at the administered doses (up to 200 mg/m^3).

No in vivo animal studies on 1-methylnaphthalene metabolism are available. Based on similarities to the 2-methylnaphthalene isomer, 1-methylnaphthalene is expected to be oxidized by cytochrome P450 (CYP450) monooxygenases to dihydrodiols or alcohols that are further modified to glucuronides and sulfates, which are then excreted (Lin et al., 2009). Metabolism is expected to occur in the nose and respiratory tract, which contain CYP450 monooxygenases and are known targets of 1-methylnaphthalene toxicity (Kim et al., 2020; Murata et al., 1993). However, no studies directly linking metabolic activation with toxic effects are available (Lin et al., 2009). Based on in vitro studies in human and rat liver microsomes, 1-methylnaphthalene can also be metabolized in the liver. Using inhibition studies, (Wang et al., 2020) showed that the CYP450 enzyme, CYP1A, was involved in aromatic ring and alkyl chain oxidation of

1-methylnaphthalene in human microsomes but may not play an important role in oxidation of 1-methylnaphthalene in the liver of rats. Incubations with human and rat liver microsomes identified 1-(hydroxymethyl)naphthalene, resulting from side-chain oxidation, as the primary metabolite of 1-methylnaphthalene (Wang et al., 2020). Minor metabolites included dihydro-1-methylnaphthalenediol and 1-methylnapthol. Apparent K_m, V_{max} values, and intrinsic clearance Cl_{int} (V_{max}/K_m) were calculated for each metabolite. The metabolic rate for formation of dihydro-1-methylnaphthalenediol was significantly higher in humans compared with rats (V_{max} of 163 vs. 56 pmol/minute/mg microsomal protein, respectively), whereas V_{max} values for 1-methylnaphthol were higher in rat microsomes (Wang et al., 2020). A human biomarker study (Li et al., 2014) identified five purported metabolites of 1-methylnaphthalene [8-methyl-2-naphthol, 4-methyl-1-napthol, 5-methyl-1-napthol, 4-methyl-2-napthol, and 5-methyl-2-napthol] at higher levels in the urine of smokers compared with nonsmokers.

No data on elimination following oral exposures in animals are available. After termination of inhalation exposure in rats, Świercz and Wąsowicz (2018) measured levels of the 1-methylnaphthalane parent compound in urine over a 72-hour period. Approximately 85% of the total amount of parent 1-methylnaphthalene detected in urine was eliminated during the first 24 hours of collection and urinary parent levels showed dependence on the concentration but not duration of exposure. Daily elimination in repeat-exposure animals showed a reduction in 1-methylnaphthalene removal over consecutive days in the 50 mg/m^3 group, but not in the 200 mg/m^3 group. In humans, Li et al. (2014) suggested that metabolites of 1-methylnaphthalene are excreted in urine, predominantly as conjugates (data not shown).

2.3.4. Mode-of-Action/Mechanistic Studies

Available data on 1-methylnaphthalene indicate the lung as one of the primary target organs. In a mouse chronic dietary study, 1-methylnaphthalene caused an increase in incidences of PAP in both male and female mice (Murata et al., 1993). The same study authors reported a similar effect in 100% of treated female mice in a 30-week skin painting study (see Table 4B) using a methylnaphthalene mixture that contained both 1- and 2-methylnaphthalene isomers (Murata et al., 1992). Earlier dermal studies in female mice reported similar lung changes, which were described as endogenous lipid pneumonia or proliferation of type II pnuemocytes in response to the methylnaphthalene mixture (Taki et al., 1986; Emi and Konishi, 1985). 1-Methylnaphthalene induced minimal changes (swelling of Clara cells) in the lungs of male mice given a single intraperitoneal (i.p.) injection (Rasmussen et al., 1986). No lung toxicity has been observed in rats (Kim et al., 2020; METI, 2009b; Dinsdale and Verschoyle, 1987), indicating that similar to naphthalene (U.S. EPA, 1998), 1-methylnaphthalene-induced lung injury may be species-specific, with mice being the more sensitive species.

The mechanism underlying 1-methylnaphthalene-induced PAP was proposed by Murata et al. (1992). Murata et al. (1992) hypothesized that 1-methylnaphthalene first induces injury to type I pneumocytes, leading to compensatory hyperplasia and hypertrophy of type II pneumocytes, along with intercellular structural changes to lamellar bodies and myelinoid structures (Murata et al., 1993; Murata et al., 1992). Swollen type II pneumocytes are then thought to detach from the alveolar wall, becoming mononucleated balloon cells that eventually accumulate lipid droplets and ascicular crystals in the cytoplasm. Rupture of these cells is then thought to release proteinaceous materials into the surrounding tissue, thus causing PAP (Murata et al., 1992).

It is not clear whether this proposed sequence of events is compatible with the current understanding of PAP pathogenesis in humans (reviewed in Kumar and Cummings, 2021; Trapnell et al., 2019). PAP, which can be classified into primary, secondary, or congenital PAP, each with distinct etiologies, is characterized by excessive accumulation of surfactants, which are composed of primarily phospholipids, such as phosphatidylcholine, as well as neutral lipids, in the lung alveoli. This can occur from disruptions in granulocyte-macrophage colony-stimulating factor (GM-CF), dysfunctional changes or reductions in the numbers of alveolar macrophages, or changes in neutrophils that lead to the disruption of surfactant homeostasis (Salvaterra and Campo, 2020; Trapnell et al., 2019). Taki et al. (1986) showed an accumulation of surfactant phospholipids in the lungs of female mice exposed dermally to 1-methylnaphthalene that the study authors presumed to be due to proliferation of type II pneumocytes. Alterations in percentages of neutrophil and or monocyte (macrophage precursor) cells in animals exposed to 1-methylnaphthalene were also reported in two studies in mice, although no functional tests were performed (Jin et al., 2012; Murata et al., 1993). These observations could be in line with the current understanding of PAP pathogenesis, but more mechanistic studies are needed.

1-Methylnaphthalene has been shown to produce nasal lesions by inhalation exposure in male and female rats (Kim et al., 2020), but no known mechanisms have been proposed. The olfactory and respiratory epithelia of the nose are known targets of naphthalene, a structurally related compound (U.S. EPA, 1998). The mode of action (MOA) of naphthalene toxicity is hypothesized to involve metabolism by CYP1A1 and other enzymes via ring epoxidation to reactive species such as 1,2-epoxides and 1,2-quinones (Lin et al., 2009; U.S. EPA, 1998). The reactive species then interact with cellular components. It is currently unknown whether reactive metabolites generated via CYP450-mediated oxidation are responsible for 1-methylnaphthalene-induced toxicities. Based on in vitro metabolism studies with human liver microsomes, 1-methylnaphthalene undergoes ring epoxidation mediated, in part, by CYP1A (Wang et al., 2020), which is similar to naphthalene, although to a lesser extent.

Increased absolute and/or relative liver weight was found in rats of both sexes treated orally with 1-methylnaphthalene (METI, 2009b). The liver is a site of 1-methylnaphthalene metabolism (Wang et al., 2020), and stimulation of metabolism is a known cause of increased liver weight for many chemicals (U.S. EPA, 2002a). There are, however, no specific data available relating metabolic activity to liver weight following 1-methylnaphthalene exposure.

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF ORAL REFERENCE DOSES

3.1.1. Derivation of a Subchronic Provisional Reference Dose

The database of relevant studies for derivation of a subchronic provisional reference dose (p-RfD) for 1-methylnaphthelene is limited. No data in humans were located. Animal studies available via the oral route include an unpublished, non-peer-reviewed OECD 422 guideline study written in Japanese (METI, 2009b) and a published study performed in transgenic mice, which presents interpretation challenges for use in a toxicity assessment (Jin et al., 2012). The Jin et al. (2012) study also had some notable study limitations.

There is uncertainty regarding interpretation of the systemic toxicity data in Jin et al. (2012) due to the use of transgenic *gpt* delta mice. Although comparison studies validating use of *gpt* delta rats for evaluating general toxicity responses are available (Matsushita et al., 2021; Akagi et al., 2015), similar validation studies were not located for *gpt* delta mice. The current OECD test guideline for transgenic rodent gene mutation assays (Test Guideline 488) anticipates that these assays could be combined with OECD Test Guideline 407 (28-day repeated-dose toxicity studies), but an official guideline for this integration is not yet available. It is unclear whether the transgene would make mice susceptible to potential systemic effects compared with wild-type counterparts. Other limitations of the Jin et al. (2012) 13-week feeding study include the lack of stability measurements of 1-methylnaphthalene in food preparations and analytical measurements of 1-methylnaphthalene concentrations in food at the time of feeding. Although the study specified that food preparations were stored in light-shielded containers, it was not indicated whether other precautions were taken to prevent loss from volatilization. The lack of these evaluations in the Jin et al. (2012) feeding study is especially significant, because no treatment-related effects were seen in any group to indicate that the 1-methylnaphthalene added to the diet was received by the test animals. Due to the limitations of this study, Jin et al. (2012) was not considered further for RfD derivation.

Although unpublished, METI (2009b) is a well-conducted guideline study that reported adequate information with which to derive a screening subchronic level p-RfD value for 1-methylnaphthalene (see Appendix A).

3.1.2. Derivation of a Chronic Provisional Reference Dose

The only study applicable for derivation of a chronic p-RfD (Murata et al., 1993) has several limitations. Although well-conducted in many respects, there was probable confounding from possible inhalation and dermal exposure of all animals (controls and treated) to volatilized 1-methylnaphthalene and 2-methylnaphthalene. In addition, the resulting loss from the feedstock, which was prepared monthly and stored at room temperature, was not quantified. Therefore, the exact dosage of 1-methylnaphthalene and the fraction of the response attributable to oral ingestion cannot be estimated with accuracy. These factors add uncertainty to the dose-response relationship between oral exposure to 1-methylnaphthalene and PAP assessed from the Murata et al. (1993) study. As the toxicity of 1-methylnaphthalene and 2-methylnaphthalene is similar (both methylnaphthalene isomers are associated with PAP following oral exposure), additional insight into the uncertainty in the use of these data can be obtained from the *Toxicological Review of 2-Methylnaphthalene* (U.S. EPA, 2003), with particular reference to Chapters 5 and 6, where a more extensive discussion of the uncertainties is presented. Due to the uncertainties

associated with the Murata et al. (1993) study, a chronic p-RfD cannot be confidently derived. However, the study provides sufficient data to develop a screening value that may be useful in certain instances (see Appendix A).

3.2. DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No human data are available regarding the toxicity of 1-methylnaphthalene following repeated inhalation exposure. The database on repeat-exposure inhalation toxicity of 1-methylnaphthalene is limited to a single published, peer-reviewed, subchronic study in rats exposed to 1-methylnaphthalene vapors for 13 weeks (Kim et al., 2020). Although the study did not follow any guidelines, it was conducted in a manner similar to OECD Test Guideline 413 (90-day subchronic inhalation toxicity study). According to the study authors, "the test material was generated in the form of vapor by a liquid vapor generator and gas chromatography was used for the analysis of concentrations in the inhalation chambers sequentially, approximately every 40 minutes." Nominal concentrations (0.5, 4, and 30 ppm) were confirmed to be 0.52 ± 0.05, 4.08 ± 0.25, and 30.83 ± 1.28 ppm, respectively. Although potential exposure from coat cleaning cannot be discounted with the whole-body exposure paradigm used by Kim et al. (2020), whole-body exposures introduce less stress to test animals compared to nose-only exposures (Oyabu et al., 2015). Whole-body exposure chambers also simulate environmental or work-places exposures (Wong, 2007). The critical effects identified in this study were increased incidence of mucous cell hyperplasia in nasopharyngeal tissues in males at ≥3.0 mg/m^3 and females at 179.3 mg/m^3 and increased incidence of transitional epithelial cell hyperplasia in nasopharyngeal tissues in males at ≥23.7 mg/m^3 (see Table 5). There is additional support for 1-methylnaphthalene as a respiratory irritant; an acute study of sensory irritation in mice found concentration-dependent decreases in respiratory rates during acute inhalation exposure and calculated an RD_{50} (concentration depressing respiratory rate to 50% of control) of 129 mg/m^3 (Korsak et al., 1998).

Table 5. Data for Sensitive Endpoints in F344 Rats Exposed to 1-Methylnaphthalene Vapors for 6 Hours/Day, 5 Days/week for 13 Weeks[a]

Lesion	Analytical Concentration [HEC_{ET}] in (mg/m^3)[b]			
	0	**3.0 [0.099]**	**23.7 [0.773]**	**179.3 [5.833]**
Males				
Hyperplasia, mucous cell in nasopharyngeal tissues (total)	0/10 (0%)[c]	**4/10 (40%)***	**10/10 (100%)***	**10/10 (100%)***
Hyperplasia, transitional epithelial cell in nasopharyngeal tissues (total)	0/10 (0%)	0/10 (0%)	**5/10 (50%)***	**5/10 (50%)***
Lesion	**Analytical Concentration [HEC_{ET}] in (mg/m^3)**			
	0	**3.0 [0.065]**	**23.7 [0.510]**	**179.3 [3.736]**
Females				
Hyperplasia, mucous cell in nasopharyngeal tissues (total)	0/10 (0%)	0/10 (0%)	3/10 (30%)	**10/10 (100%)***

[a]Kim et al. (2020).
[b]HEC_{ET} values are calculated by treating 1-methylnaphthalene as a Category 1 gas and using the following equation from U.S. EPA (1994): HEC = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × RGDR. $RGDR_{ET}$ values of 0.184, 0.183, and 0.182 for males and 0.121, 0.120, and 0.117 for females in the low-, mid-, and high-dose groups, respectively, were calculated as per U.S. EPA (1994) using default values for human VE and human and animal respiratory tissue surface area and animal VE values calculated using study-specific TWA body-weight values of 0.268, 0.266, and 0.265 kg for low-, mid-, and high-dose males, respectively, and 0.161, 0.160, and 0.154 kg for low, mid-, and high-dose females, respectively, determined for this review.
[c]Values denote number of animals showing changes/total number of animals examined (% incidence).
*Significantly different from control by Fisher's exact test (one-sided $p < 0.05$), conducted for this review.

HEC_{ET} = human equivalent concentration based on extrathoracic effects; RGDR = regional gas dose ratio (animal:human); TWA = time-weighted average; VE = ventilation rate.

The Kim et al. (2020) hyperplasia data were modeled using the available dichotomous models in the U.S. EPA's Benchmark Dose Software (BMDS; Version 3.2). Human equivalent concentration based on extrathoracic effects (HEC_{ET}) values were used as the dose metric, and a reporting benchmark response (BMR) of 10% extra risk for incidence data was used. Table 6 summarizes the benchmark concentration (BMC) modeling results and provides candidate points of departure (PODs) for the modeled endpoints. Details of model fit for each data set are presented in Appendix C.

Table 6. BMC and BMCL Values from Best Fitting Models for Mucous Cell and Transitional Epithelial Hyperplasia in Male and Female F344 Rats Exposed to 1-Methylnaphthalene Vapors for 6 Hours/Day, 5 Days/week for 13 Weeks[a]

Endpoint	Best Fitting Model	BMR	BMC_{10} (HEC_{ET}) (mg/m^3)	$BMCL_{10}$ (HEC_{ET}) (mg/m^3)
Mucous cell hyperplasia in nasopharyngeal tissues in males	Multistage 1-degree	10% extra risk	0.018	0.009
Transitional epithelial cell hyperplasia in nasopharyngeal tissues in males	Log-logistic	10% extra risk	0.26	0.12
Mucous cell hyperplasia in nasopharyngeal tissues in females	Multistage 1-degree	10% extra risk	0.12	0.066

[a]Kim et al. (2020).

BMC = benchmark concentration; BMC_{10} = 10% benchmark concentration; BMCL = benchmark concentration lower confidence limit; $BMCL_{10}$ = 10% benchmark concentration lower confidence limit; BMR = benchmark response; HEC_{ET} = human equivalent concentration based on extrathoracic effects.

3.2.1. Derivation of a Subchronic Provisional Reference Concentration

The 10% benchmark concentration lower confidence limit ($BMCL_{10}$) (HEC_{ET}) of 0.009 mg/m^3 for increased incidence of mucous cell hyperplasia in nasopharyngeal tissues in male F344 rats in the 13-week inhalation study by Kim et al. (2020) is selected as the most health-protective POD for derivation of the subchronic p-RfC.

The subchronic provisional reference concentration (p-RfC) of 3×10^{-5} mg/m^3 is derived by applying a composite uncertainty factor (UF_C) of 300 (reflecting an interspecies uncertainty factor [UF_A] of 3, a database uncertainty factor [UF_D] of 10, and an intraspecies uncertainty factor [UF_H] of 10) to the selected POD of 0.009 mg/m^3, as follows:

Subchronic p-RfC = POD (HEC_{ET}) ÷ UF_C
= 0.009 mg/m^3 ÷ 300
= **3×10^{-5} mg/m^3**

Table 7 summarizes the uncertainty factors for the subchronic p-RfC for 1-methylnaphthalene.

Table 7. Uncertainty Factors for the Subchronic p-RfC for 1-Methylnaphthalene (CASRN 90-12-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HEC calculation) is performed.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The repeat-exposure inhalation database is limited to a single published, peer-reviewed, 13-wk inhalation study in rats. Reproductive and developmental endpoints were studied in rats following oral exposure and no effects were found, but only a limited screening-level assessment was performed.
UF_H	10	A UF_H of 10 is applied to account for human variability and susceptibility, in the absence of information to assess toxicokinetics and toxicodynamic variability of 1-methylnaphthalene in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMCL.
UF_S	1	A UF_S of 1 is applied because the subchronic POD was derived from subchronic data.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Confidence in the subchronic p-RfC for 1-methylnaphthalene is low, as described in Table 8.

Table 8. Confidence Descriptors for the Subchronic p-RfC for 1-Methylnaphthalene

Confidence in study	M	Confidence in the principal study by Kim et al. (2020) is medium. The study was conducted in a manner similar to OECD Test Guideline 413 but there were some deficiencies in reporting (e.g., organ weights were reported only as absolute, and not relative, values).
Confidence in database	L	Confidence in the database is low. The database comprises a single repeat-exposure inhalation study. Some supporting information for the critical effect in this study (nasal irritation in rats) was provided by an acute inhalation study in mice. Reproductive and developmental endpoints were studied in rats following oral exposure and no effects were found, but only a limited screening-level assessment was performed.
Confidence in subchronic p-RfC	L	Overall, the confidence in the subchronic p-RfC is low.

L = low; M = medium; OECD = Organisation for Economic Co-operation and Development; p-RfC = provisional reference concentration.

3.2.2. Derivation of a Chronic Provisional Reference Concentration

No chronic inhalation studies were identified for 1-methylnaphthalene. In the absence of available chronic inhalation studies, the POD from the subchronic study by Kim et al. (2020) was selected as a suitable basis for the chronic p-RfC. As discussed above, the POD from this

study is a $BMCL_{10}$ (HEC_{ET}) of 0.009 mg/m^3 for increased incidence of mucous cell hyperplasia in nasopharyngeal tissues in male rats.

The chronic p-RfC of 3×10^{-6} mg/m^3 is derived by applying a UF_C of 3,000 (reflecting a UF_A of 3, UF_D of 10, UF_H of 10, and a subchronic to chronic uncertainty factor [UF_S] of 10) to the selected POD of 0.009 mg/m^3.

Chronic p-RfC = POD (HEC_{ET}) ÷ UF_C
= 0.009 mg/m^3 ÷ 3,000
= **3×10^{-6} mg/m^3**

Table 9 summarizes the uncertainty factors for the chronic p-RfC for 1-methylnaphthalene.

Table 9. Uncertainty Factors for the Chronic p-RfC for 1-Methylnaphthalene (CASRN 90-12-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HEC calculation) is performed.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The repeat-exposure inhalation database is limited to a single published, peer-reviewed, 13-wk inhalation study in rats. Reproductive and developmental endpoints were studied in rats following oral exposure and no effects were found, but only a limited screening-level assessment was performed.
UF_H	10	A UF_H of 10 is applied to account for human variability and susceptibility, in the absence of information to assess toxicokinetics and toxicodynamic variability of 1-methylnaphthalene in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMCL
UF_S	10	A UF_S of 10 is applied because the chronic POD was derived from subchronic data.
UF_C	3,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Confidence in the chronic p-RfC for 1-methylnaphthalene is low, as described in Table 10.

Table 10. Confidence Descriptors for the Chronic p-RfC for 1-Methylnaphthalene

Confidence in study	M	Confidence in the principal study by Kim et al. (2020) is medium. The study was conducted in a manner similar to OECD Test Guideline 413 but there were some deficiencies in reporting (e.g., organ weights were reported only as absolute and not relative values).
Confidence in database	L	Confidence in the database is low. The database comprises a single repeat-exposure inhalation study that was subchronic, not chronic, in duration. Some supporting information for the critical effect in this study (nasal irritation in rats) was provided by an acute inhalation study in mice. Reproductive and developmental endpoints were studied in rats following oral exposure and no effects were found, but only a limited screening-level assessment was performed.
Confidence in Chronic RfC	L	Overall, the confidence in the chronic p-RfC is low

L = low; M = medium; OECD = Organisation for Economic Co-operation and Development; p-RfC = provisional reference concentration.

3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

Table 11 presents a summary of noncancer references values.

Table 11. Summary of Noncancer Reference Values for 1-Methylnaphthalene (CASRN 90-12-0)

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/M	Increased relative liver weight	2×10^{-1}	$BMDL_{0.1RD}$	24.12	100	METI (2009b)
Screening chronic p-RfD (mg/kg-d) (see Appendix A)	Mouse/M	PAP	1×10^{-2}	LOAEL	10.7	1,000	Murata et al. (1993)
Subchronic p-RfC (mg/m^3)	Rat/M	Mucous cell hyperplasia in nasopharyngeal tissues	3×10^{-5}	$BMCL_{10}$	0.009	300	Kim et al. (2020)
Chronic p-RfC (mg/m^3)	Rat/M	Mucous cell hyperplasia in nasopharyngeal tissues	3×10^{-6}	$BMCL_{10}$	0.009	3,000	Kim et al. (2020)

BMDL = benchmark dose lower confidence limit; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; HEC = human equivalent concentration; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; M = male; PAP = pulmonary alveolar proteinosis; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; RD = relative deviation; UF_C = composite uncertainty factor.

3.4. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Following the U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment*, 1-methylnaphthalene has "*Suggestive Evidence of Carcinogenic Potential*" by oral exposure and "*Inadequate Information to Assess Carcinogenic Potential*" by inhalation exposure (see Table 12). There are no human studies to indicate cancer risk. The database of information regarding the carcinogenicity of 1-methylnaphthalene in animals is limited to a single carcinogenicity study in which male and female B6C3F1 mice (50/sex/group) were given 1-methylnaphthalene in the diet for 81 weeks at concentrations resulting in doses of 0, 71.6, or 140 mg/kg-day (males) or 0, 75.1, or 144 mg/kg-day (females) (Murata et al., 1993). Under the conditions of the study, significantly increased incidences of lung adenoma and combined lung adenoma or adenocarcinoma were observed in male mice of both dose groups, but not in female mice (see Table B-12 for tumor incidence data). No information was located regarding the potential carcinogenicity of 1-methylnaphthalene by oral exposure in a second animal species or via inhalation or other routes of exposure. Genotoxicity studies were largely negative, including two Ames tests for mutation in bacteria (NTP, 2018; Florin et al., 1980), assays for CAs and SCEs in human peripheral lymphocytes (Kulka et al., 1988), a subchronic in vivo assay for *gpt* and Spi$^-$ mutations in the lungs of mice (Jin et al., 2012), and a micronucleus test in Chinese hamster fibroblasts (Świercz et al., 2022). One of the only positive responses reported, in a forward mutation assay in bacteria (Kaden et al., 1979), was confounded by high cytotoxicity at the same dose level. The other positive response was observed when urine extracts from rats exposed to 1-methylnaphthalene were used in a micronucleus test in Chinese hamster fibroblasts (Świercz et al., 2022).

Table 12. Cancer WOE Descriptor for 1-Methylnaphthalene (CASRN 90-12-0)

Possible WOE Descriptor	Designation	Route of Entry (Oral, Inhalation, or Both)	Comments
"Carcinogenic to Humans"	NS	NA	No human data are available.
"Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.
"Suggestive Evidence of Carcinogenic Potential"	**Selected**	**Oral**	**Lung tumors were significantly increased in male, but not female, mice in an 81-wk feeding study of 1-methylnaphthalene. No other oral cancer bioassays were located.**
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Inhalation**	**No information is available on the carcinogenicity of 1-methylnaphthalene by inhalation exposure.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.

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

3.4.1. Mode-of-Action Discussion

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) define MOA "…as a sequence of key events and processes, starting with interaction of an agent with a cell,

proceeding through operational and anatomical changes, and resulting in cancer formation." Examples of possible modes of carcinogenic action for any given chemical include "mutagenicity, mitogenesis, programmed cell death, cytotoxicity with reparative cell proliferation, and immune suppression."

The MOA for tumor formation in male mice in the Murata et al. (1993) study is not known. The available data do not support the hypothesis that PAP might be a precursor to lung tumor formation (Murata et al., 1997; Murata et al., 1993). For example, compared with 2-methylnaphthalene, 1-methylnaphthalene induced equal or slightly lower incidences of PAP, but higher incidences of lung tumors. In addition, Murata et al. (1993) reported that the numbers of mice developing PAP and lung tumors following exposure to 1-methylnaphthalene were not statistically correlated, and the sites of development of alveolar proteinosis and lung tumors were not always clearly linked. Furthermore, lung tumors were increased only in male mice, while PAP was increased in both male and female mice. Genotoxicity data for 1-methylnaphthalene are limited but are mostly consistent in finding that 1-methylnaphthalene is not genotoxic or mutagenic. A mutagenic MOA has also not been established for either of the structurally related compounds, 2-methylnaphthalene (U.S. EPA, 2007) and naphthalene (U.S. EPA, 1998).

3.5. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES

Table 13 presents a summary of cancer risk estimates values.

Table 13. Summary of Cancer Risk Estimates for 1-Methylnaphthalene (CASRN 90-12-0)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
Screening p-OSF $(mg/kg\text{-}d)^{-1}$ (see Appendix A)	Mouse/M	Combined lung adenoma or adenocarcinoma	0.051	Murata et al. (1993)
p-IUR $(mg/m^3)^{-1}$	NDr			

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

3.5.1. Derivation of Provisional Oral Slope Factor (p-OSF)

Murata et al. (1993) is the only available cancer bioassay for 1-methylnaphthalene. As noted in Section 3.1.2, this study has several limitations. The exposure of all animals (including treated and controls), to volatilized 1- and 2-methylnaphthalene originating from the diets introduces considerable uncertainty into the quantitative analysis. Some of the lung tumors in these animals may have arisen (at least in part) with contributions from inhalation exposure, and some of these with contributions from 2-methylnaphthalene exposure. It is possible that the two lung adenomas in the control animals were a result of unintentional inhalation exposure to methylnaphthalene vapors, although historical control data are lacking to verify that conjecture. Although solubilization in corn oil used in the preparation of animal diets was anticipated to minimize 1-methylnaphthalene loss due to volatilization, loss from the feedstock, which was prepared monthly and stored at room temperature, was not quantified. Therefore, the exact dosage of 1-methylnaphthalene and the fraction of the response attributable to oral ingestion cannot be estimated with accuracy. It could be assumed that inhalation exposure was the same

for all animals, and the control incidence could still serve as an approximate measure of background incidence, with respect to secondary inhalation exposure; however, the assumption of equal exposure for all animals is somewhat tenuous since proximity to the possible emission source was not the same for all animals, with treated animals being closer. As such, a modeled p-OSF based on these data might reflect a health-protective bias, resulting from potential differences in unintentional inhalation exposure across treatment groups. Due to the limitations described, Murata et al. (1993) was considered inadequate for derivation of a p-OSF. However, the study provided sufficient data to develop a screening value that may be useful in certain instances (see Appendix A).

3.5.2. Derivation of Provisional Inhalation Unit Risk (p-IUR)

There is inadequate information to assess the carcinogenic potential of 1-methylnaphthalene by inhalation exposure. There are no suitable human or animal inhalation data available.

APPENDIX A. SCREENING PROVISIONAL VALUES

Due to the lack of evidence described in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment, it is inappropriate to derive a provisional toxicity value for 1-methylnaphthalene. 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.

Screening subchronic and chronic provisional reference doses (p-RfDs) and a screening provisional oral slope factor (p-OSF) were derived for 1-methylnaphthalene, as described in the sections below.

DERIVATION OF SCREENING PROVISIONAL REFERENCES DOSES

As discussed in the main body of the report, the 42-day gavage rat study (METI, 2009b) and the chronic dietary mouse study (Murata et al., 1993) provide sufficient information for derivation of screening subchronic and chronic p-RfD values, respectively, for 1-methylnaphthalene. Due to several limitations of these studies, they were only considered suitable to support the derivation of screening values. Although a well-conducted guideline study, (METI, 2009b) is unpublished, not peer-reviewed, and written primarily in Japanese. Although well-conducted in many respects, data presented in Murata et al. (1993) were likely confounded by possible inhalation and dermal exposure of all animals (controls and treated) to volatilized 1-methylnaphthalene and 2-methylnaphthalene. Resulting loss from the feedstock was not quantified, making the administered dose of 1-methylnaphthalene and the fraction of the response attributable to oral ingestion difficult to estimate with accuracy.

Derivation of Screening Subchronic p-RfD

METI (2009b) exposed 12 breeding pairs of Sprague Dawley Crl:CD rats to 1-methylnaphthalene doses of 0, 10, 50, or 250 mg/kg-day by gavage beginning 2 weeks prior to mating, and continuing through mating, gestation, and lactation until postnatal day (PND) 4 (females) or for a total of 42 days (males). The most sensitive effects in this study were increased absolute and relative liver weights and increased relative kidney weights in males and increased relative liver weights in females at 250 mg/kg-day (see Table A-1). When amenable, these data were used for benchmark dose (BMD) modeling. Modeling of these endpoints was performed using all available dichotomous models in the U.S. Environmental Protection Agency (U.S. EPA) Benchmark Dose Software (BMDS) (Version 3.2). Human equivalent dose (HED) values in mg/kg-day were used as the dose metric (see Table A-1). A benchmark response (BMR) of 10% relative deviation (RD) was used, because a 10% change in liver and/or kidney weight was considered biologically significant.

Table A-1. Data for Increased Liver and Kidney Weights in Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene via Gavage During Premating, Mating, Gestation, and Lactation Until PND 4 or for 42 Days[a]

Endpoint	Males: ADD [HED] (mg/kg-d)[b]			
	0	**10 [2.8]**	**50 [14]**	**250 [70.1]**
Number of animals (n)	7	12	12	**7**
Liver weight				
Absolute (g)	12.94 ± 1.905[c]	12.895 ± 1.604 (−0%)[d]	13.043 ± 1.272 (+1%)	**15.159 ± 1.934 (+17%)***
Relative (g%)	2.628 ± 0.233	2.678 ± 0.223 (+2%)	2.685 ± 0.17 (+2%)	**3.309 ± 0.416 (+26%)****
Kidney weight				
Absolute (g)	2.905 ± 0.299	3.006 ± 0.298 (+3%)	3.006 ± 0.285 (+3%)	3.127 ± 0.287 (+8%)
Relative (g%)	0.593 ± 0.057	0.626 ± 0.053 (+6%)	0.62 ± 0.053 (+5%)	**0.683 ± 0.06 (+15%)***
Endpoint	**Mated Females: ADD [HED] (mg/kg-d)**			
	0	**10 [2.6]**	**50 [13]**	**250 [64.0]**
Number of animals (n)	11	8	12	11
Liver weight				
Absolute (g)	9.859 ± 0.808[c]	9.563 ± 0.599 (−3%)[d]	9.929 ± 0.63 (+1%)	10.588 ± 0.988 (+7%)
Relative (g%)	3.193 ± 0.227	3.148 ± 0.275 (−1%)	3.188 ± 0.169 (−0%)	**3.521 ± 0.373 (+10%)***

[a]METI (2009b).
[b]ADDs were converted to HEDs of 2.8, 14, and 70.1 mg/kg-day in low-, mid-, and high-dose males, respectively, and 2.6, 13, and 64.0 mg/kg-day in low-, mid-, and high-dose females, respectively, using DAFs of approximately 0.28 (males), and 0.26 (females), where HED = ADD × DAF. The DAFs were 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. Individual animal body weights were provided in the study; group TWA body weights determined for this review were 0.441, 0.442, and 0.433 kg for low-, mid-, and high-dose males, respectively, and 0.308, 0.308, and 0.300 kg for low-, mid-, and high-dose females, respectively. For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).
[c]Data are mean ± SD.
[d]Value in parentheses is percent change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*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; PND = postnatal day; SD = standard deviation; TWA = time-weighted average.

Table A-2 summarizes the BMD modeling results and provides candidate points of departure (PODs) for the organ weight data from METI (2009b). Details of model fit for each data set are presented in Appendix C.

Table A-2. BMD and BMDL Values from Best Fitting Models for Increased Organ Weights in Male and Female Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene via Gavage During Premating, Mating, Gestation, and Lactation Until PND 4 or for 42 Days[a]

Endpoints	Best Fitting Model	BMR	BMD (HED) (mg/kg-d)	BMDL (HED) (mg/kg-d)
Increased absolute liver weight (males)	No selected model[b]	10% RD from control (0.1RD)	NA	NA
Increased relative liver weight (males)	Polynomial 2-degree (nonconstant variance)	10% RD from control (0.1RD)	44.79	24.12
Increased relative kidney weight (males)	No selected model[b]	10% RD from control (0.1RD)	NA	NA
Increased relative liver weight (females)	Polynomial 3-degree (nonconstant variance)	10% RD from control (0.1RD)	62.40	42.30

[a]METI (2009b).
[b]Data were not amenable to BMD modeling.

BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; BMR = benchmark response; HED = human equivalent dose; NA = not applicable; PND = postnatal day; RD = relative deviation.

The benchmark dose lower confidence limit with 10% relative deviation ($BMDL_{0.1RD}$) (HED) of 24.12 mg/kg-day based on increased relative liver weight in male rats in the 42-day gavage study (METI, 2009b) is the most health-protective POD identified and is selected as the POD for derivation of the screening subchronic p-RfD.

The screening subchronic p-RfD of 2×10^{-1} mg/kg-day is derived by applying a composite uncertainty factor (UF_C) of 100 (reflecting an interspecies uncertainty factor [UF_A] of 3, a database uncertainty factor [UF_D] of 3, and an intraspecies uncertainty factor [UF_H] of 10) to the selected POD of 24.12 mg/kg-day, as follows:

Screening Subchronic p-RfD = POD (HED) ÷ UF_C
= 24.12 mg/kg-day ÷ 100
= **2×10^{-1} mg/kg-day**

Table A-3 summarizes the uncertainty factors for the screening subchronic p-RfD for 1-methylnaphthalene.

Table A-3. Uncertainty Factors for the Screening Subchronic p-RfD for 1-Methylnaphthalene (CASRN 90-12-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HED calculation) is performed.
UF_D	3	A UF_D of 3 is applied to account for deficiencies and uncertainties in the database. Subchronic oral studies include an unpublished, Japanese-language, 42-d gavage study in rats that collected comprehensive systemic data (METI, 2009b) and a published 13-wk dietary study in transgenic mice that had significant limitations (Jin et al., 2012). Reproductive and developmental endpoints were studied in rats following 42-d gavage exposure and no effects were found (METI, 2009a); although a wide variety of reproductive endpoints were collected, only a limited screening-level assessment for developmental endpoints was performed.
UF_H	10	A UF_H of 10 is applied to account for human variability and susceptibility in the absence of information to assess the toxicokinetic and toxicodynamic variability of 1-methylnaphthalene 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 (42 days) for a subchronic value.
UF_C	100	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

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

Derivation of Screening Chronic p-RfD

Murata et al. (1993), the only available oral chronic study on 1-methylnaphthalene, was identified as the principal study for derivation of a screening chronic p-RfD. Pulmonary alveolar proteinosis (PAP) observed in both male and female rats at the lowest doses tested was selected as the critical effect (see Table A-4). Although this lesion was not seen in other oral or inhalation studies of 1-methylnapthalene, there is some supporting evidence for the observed effect. An isomer of 1-methylnaphthalene, 2-methylnaphthalene has also been associated with PAP following chronic dietary exposure in mice, and derivation of an Integrated Risk Information System (IRIS) oral reference dose (RfD) value for 2-methylnaphthalane was based on this effect (U.S. EPA, 2003; Murata et al., 1997). The same study authors reported PAP in 100% of treated female mice in a 30-week skin painting study using a mixture of 1- and 2-methylnaphthalene (Murata et al., 1992). Earlier dermal studies in female mice reported similar lung changes, which were described as endogenous lipid pneumonia, in response to a methylnaphthalene mixture (Taki et al., 1986; Emi and Konishi, 1985). Lipid pneumonia and PAP are distinct conditions but share similar features and can coexist (Salvaterra and Campo, 2020), and although rare, lipid pneumonia may precede development of PAP in some cases in humans (Trapnell et al., 2019; Antoon et al., 2016). The absence of supporting data by oral or inhalation exposure could reflect the relatively short duration of the available studies. A 13-week preliminary study briefly described in Murata et al. (1993) using the same mouse strain did not report any incidences of PAP, suggesting that development of PAP may require longer durations of oral exposure.

Table A-4. Incidence of Pulmonary Alveolar Proteinosis in B6C3F1 Mice Fed 1-Methylnaphthalene in the Diet for 81 Weeks[a]

Males: ADD [HED] (mg/kg-d)[b]		
0	**71.6 [10.7]**	**140 [21.1]**
4/49 (8.2%)[b]	**23/50 (46.0%)***	**19/50 (38.0%)***
Females: ADD [HED] (mg/kg-d)		
0	**75.1 [11.1]**	**144 [20.9]**
5/50 (10.0%)	**23/50 (46.0%)***	**17/49 (34.7%)***

[a]Murata et al. (1993).
[b]The ADDs were converted to HEDs of 10.7 and 21.1 mg/kg-day for low- and high-dose males and 11.1 and 20.9 mg/kg-day for low- and high-dose females using respective DAFs of 0.149 and 0.150 (males) and 0.147 and 0.145 (females). The DAFs were calculated as follows: DAF = ($Bw_a^{1/4} \div Bw_h^{1/4}$), where DAF = dosimetric adjustment factor, BW_a = animal body weight and BW_h = human body weight. Animal body weight data reported graphically in the study were extracted using GRABIT™ software. TWA animal body weights of 0.035 and 0.036 kg for low- and high-dose males, respectively, and 0.033 and 0.031 kg for low- and high-dose females, respectively, were determined. For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).
[c]Values denote number of animals showing changes / total number of animals examined (% incidence).
*Significantly different from control ($p < 0.01$) value by χ^2 test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose

The PAP data from Murata et al. (1993) were modeled using the available dichotomous models in the U.S. EPA's BMDS (Version 3.2). HED values were used as the dose metric, and the standard reporting BMR of 10% extra risk for incidence data was used. None of the available models provided adequate fit to either data set. Therefore, the lowest lowest-observed-adverse-effect level (LOAEL) of 71.6 mg/kg-day in males, corresponding to an HED of 10.7 mg/kg-day, is selected as the POD for the screening chronic p-RfD value.

The screening chronic p-RfD of 1×10^{-2} mg/kg-day is derived by applying a UF_C of 1,000 (reflecting a UF_A of 3, UF_D of 3, UF_H of 10, and LOAEL-to-no-observed-adverse-effect level [NOAEL] uncertainty factor [UF_L] of 10) to the selected POD of 10.7 mg/kg-day, as follows:

Screening Chronic p-RfD = LOAEL (HED) ÷ UF_C
= 10.7 mg/kg-day ÷ 1,000
= **1×10^{-2} mg/kg-day**

Table A-5 summarizes the uncertainty factors for the screening chronic p-RfD for 1-methylnaphthalene.

Table A-5. Uncertainty Factors for the Screening Chronic p-RfD for 1-Methylnaphthalene (CASRN 90-12-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HED calculation) is performed.
UF_D	3	A UF_D of 3 is applied to account for deficiencies and uncertainties in the database. The animal oral database for chronic studies consists of a single chronic dietary study in mice that investigated comprehensive systemic endpoints (Murata et al., 1993). Reproductive and developmental endpoints were studied in rats following 42-d gavage exposure and no effects were found (METI, 2009b) although a wide variety of reproductive endpoints were collected only a limited screening-level assessment for developmental endpoints was performed.
UF_H	10	A UF_H of 10 is applied to account for human variability and susceptibility in the absence of information to assess toxicokinetic and toxicodynamic variability of 1-methylnaphthalene in humans.
UF_L	10	A UF_L of 10 is applied because the POD is a LOAEL.
UF_S	1	A UF_S of 1 is applied because the POD was derived from chronic data.
UF_C	1,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

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

Derivation of a Screening Provisional Oral Slope Factor (p-OSF)

The Murata et al. (1993) 81-week oral cancer bioassay in mice provides sufficient data to derive a screening p-OSF for 1-methylnaphthalene, based on significantly increased incidence of lung tumors (combined adenomas or adenocarcinomas) in treated male mice (see Table A-6). Due to several limitations of the study, it was only considered suitable to support the derivation of a screening value. Limitations include potential exposure of all animals to volatilized 1- and 2-methylnaphthalene and the lack of monitoring 1-methylnaphthalene loss from the feedstock. These limitations introduce uncertainty to the exact dosage of 1-methylnaphthalene administered and the fraction of the response attributable to oral ingestion.

Table A-6. Incidence Data for Lung Tumors in Male B6C3F1 Mice Fed 1-Methylnaphthalene in the Diet for 81 Weeks[a]

Endpoint	Males: ADD [HED] (mg/kg-d)		
	0	71.6 [10.7]	140 [21.1]
Lung adenoma or adenocarcinoma (combined)	2/49 (4.1%)[b]	**13/50 (26.0%)***	**15/50 (30.0%)***

[a]Murata et al. (1993).
[b]Values denote number of animals showing changes / total number of animals examined (% incidence).
*Significantly different from control ($p < 0.01$) value by χ^2 test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose.

To obtain a POD for a quantitative assessment of cancer risk, BMD analysis was performed on the incidence data for lung adenoma or carcinoma (combined) in the male mice. The POD is an estimated dose (expressed in human-equivalent terms) near the lower end of the observed range that marks the starting point for extrapolation to lower doses. Multistage cancer models in the U.S. EPA BMDS (Version 3.2) were fit to the incidence data shown above (see Table A-6). The BMR used was 10% extra risk, and the HED in mg/kg-day was used as the dose metric. The modeling results are summarized in Table A-7 (see additional BMD details in Appendix C).

Table A-7. Modeling Results Based on the Incidence of Lung Tumors in Male B6C3F1 Mice Fed 1-Methylnaphthalene in the Diet for 81 Weeks[a]

Tumor Endpoint	Selected Model	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
Lung adenoma or adenocarcinoma (combined)	Multistage (1-degree)	6.01	4.16

[a]Murata et al. (1993).

BMD_{10} = 10% benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; HED = human equivalent dose

The Multistage 1-degree model provided adequate fit to the data for combined lung adenoma or carcinoma in male mice (see Table A-7). The Multistage 2-degree model took the form of the 1-degree model. Higher-degree models were not applied to the data set because only three dose groups were available. The predicted 10% benchmark dose (BMD_{10}) (HED) associated with 10% extra risk is 6.01 mg/kg-day and the 95% lower confidence limit, the 10% benchmark dose lower confidence limit ($BMDL_{10}$) (HED), is 4.16 mg/kg-day for lung adenoma or carcinoma (combined). The $BMDL_{10}$ (HED) of 4.16 mg/kg-day is used as the POD for derivation of the p-OSF.

In the absence of data for the MOA of 1-methylnaphthalene induced tumorigenesis, the screening p-OSF for 1-methylnaphthalene, based on the $BMDL_{10}$ (HED) of 4.16 mg/kg-day, is derived using a linear approach, as follows:

$$\textbf{Screening p-OSF (unadjusted)} = \text{BMR} \div BMDL_{10}\text{ (HED)} = 0.1 \div 4.16\text{ mg/kg-day} = \mathbf{0.024\ (mg/kg\text{-}day)^{-1}}$$

An adjustment was applied to account for the less-than-lifetime observation period (U.S. EPA, 1980). The (Murata et al., 1993) bioassay exposed mice to 1-methylnaphthalene for only 81 weeks. Thus, due to the short duration of the study, it cannot be known how an increased duration (i.e., 2-year lifetime exposure) might have influenced tumor incidence. Therefore, an adjustment factor of $(L \div L_e)^3$ was applied to the unadjusted screening p-OSF, where L = the lifetime of the animal and L_e = duration of the experimental dosing (U.S. EPA, 1980). Using this adjustment, an adjusted screening p-OSF is derived as follows:

Screening p-OSF (adjusted) = p-OSF (unadjusted) × $(L \div L_e)^3$
= 0.024 $(mg/kg\text{-}day)^{-1}$ × $(104 \text{ weeks} \div 81 \text{ weeks})^3$
= **0.051 $(mg/kg\text{-}day)^{-1}$**

It is important to note that the (Murata et al., 1993) bioassay raises concern for exposures of longer duration. Although there is uncertainty associated with the degree of adjustment, the adjusted estimate is more health-protective than the estimate without the $(L \div L_e)^3$ adjustment, which is likely to be underestimated. Because 1-methylnaphthalene shows "*Suggestive Evidence of Carcinogenic Potential*" by oral exposure (see Table 12), derivation of a screening p-OSF for this chemical is warranted despite the aforementioned uncertainty arising from the application of the less-than-lifetime adjustment factor.

APPENDIX B. DATA TABLES

Table B-1. Select Hematology Findings in Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene via Gavage During Premating, Mating, Gestation, and Lactation Until PND 4 or for 42 Days[a]

Endpoint	Males (main group): ADD [HED] (mg/kg-d)[b]				Males (recovery): ADD [HED] (mg/kg-d)	
	0	10 [2.8]	50 [14]	250 [70.1]	0	250 [70.1]
RBC (× 10^4/µL)	902 ± 47[c]	932 ± 72 (+3%)[d]	892 ± 23 (−1%)	900 ± 34 (−0%)	922 ± 65	882 ± 35 (−4%)
HGB (g/dL)	16.8 ± 0.6	16.9 ± 1.2 (+1%)	16.7 ± 0.9 (−1%)	16 ± 0.6 (−5%)	17 ± 0.7	**15.9 ± 0.2 (−6%)***
HCT (%)	49 ± 2.6	49 ± 4.5 (+0%)	50.1 ± 3.9 (+2%)	48.5 ± 1.4 (−1%)	50.5 ± 2	**46.5 ± 0.6 (−8%)****
MCV (fL)	54.3 ± 1.3	52.5 ± 1 (−3%)	56.1 ± 3.2 (+3%)	53.9 ± 2.1 (−1%)	55 ± 3.2	52.8 ± 1.8 (−4%)
MCH (pg)	18.6 ± 0.8	18.1 ± 0.4 (−3%)	18.7 ± 0.6 (+1%)	17.8 ± 0.6 (−4%)	18.5 ± 1	18.1 ± 0.8 (−2%)
MCHC (g/dL)	34.3 ± 1.1	34.5 ± 0.9 (+1%)	33.3 ± 1.5 (−3%)	33.1 ± 1.6 (−3%)	33.6 ± 1	34.2 ± 0.8 (+2%)
WBC (× 10^2/µL)	91 ± 21	78 ± 23 (−14%)	117 ± 117 (+29%)	117 ± 29 (+29%)	110 ± 10	100 ± 15 (−9%)
Leukocyte classification						
Basophil (%)	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Eosinophil (%)	1.4 ± 0.5	1.4 ± 0.9 (+0%)	1 ± 0.7 (−29%)	1.8 ± 1.8 (+29%)	1.2 ± 1.3	1.4 ± 0.5 (+17%)
Stab neutrophil (%)	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Segmented neutrophil (%)	18.4 ± 2.9	20.6 ± 10.3 (+12%)	17.2 ± 7.3 (−7%)	22.2 ± 5.6 (+21%)	11.8 ± 4.1	16.4 ± 4.4 (+39%)
Lymphocyte (%)	80.2 ± 2.9	78 ± 10.3 (−3%)	81.8 ± 7.8 (+2%)	76 ± 6.4 (−5%)	87 ± 4.7	82.2 ± 4.1 (−6%)
Monocyte (%)	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Other (%)	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0

Table B-1. Select Hematology Findings in Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene via Gavage During Premating, Mating, Gestation, and Lactation Until PND 4 or for 42 Days[a]

	Mated Females: ADD [HED] (mg/kg-d)				Unmated Females (recovery): ADD [HED] (mg/kg-d)	
Endpoint	**0**	**10 [2.6]**	**50 [13]**	**250 [64.0]**	**0**	**250 [62.0]**
RBC (× 10^4/µL)	696 ± 80	699 ± 90 (+0%)	700 ± 34 (+1%)	723 ± 24 (+4%)	817 ± 28	838 ± 31 (+3%)
HGB (g/dL)	14 ± 1.2	14.2 ± 1.5 (+1%)	14.5 ± 0.8 (+4%)	14.8 ± 0.5 (+6%)	15.7 ± 0.2	16.3 ± 0.6 (+4%)
HCT (%)	42 ± 3.2	42.9 ± 3.2 (+2%)	40.4 ± 2.1 (−4%)	42.3 ± 1.9 (+1%)	44.9 ± 1.2	46.7 ± 3.1 (+4%)
MCV (fL)	60.6 ± 3	61.9 ± 4.5 (+2%)	57.6 ± 1.1 (−5%)	58.5 ± 2.5 (−3%)	55 ± 1.6	55.7 ± 2.7 (+1%)
MCH (pg)	20.1 ± 1.4	20.4 ± 1 (+1%)	20.7 ± 0.4 (+3%)	20.4 ± 0.5 (+1%)	19.3 ± 0.6	19.5 ± 0.7 (+1%)
MCHC (g/dL)	33.2 ± 0.09	33.1 ± 1.7 (−0%)	**35.9 ± 1.1 (+8%)***	35 ± 1.7 (+5%)	35 ± 0.5	34.9 ± 1.2 (−0%)
WBC (× 10^2/µL)	101 ± 7	121 ± 47 (+20%)	101 ± 23 (+23%)	117 ± 18 (+16%)	49 ± 7	54 ± 15 (+10%)
Leukocyte classification						
Basophil (%)	0 ± 0	0 ± 0	0 ± 0	0.2 ± 0.4 (100%)	0 ± 0	0 ± 0
Eosinophil (%)	0.3 ± 0.5	0.4 ± 0.9 (+33%)	0.2 ± 0.4 (−33%)	0.6 ± 0.9 (+100%)	2.0 ± 1.4	0.8 ± 0.8 (−60%)
Stab neutrophil (%)	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Segmented neutrophil (%)	29 ± 11.7	30.6 ± 18.9 (+6%)	27.6 ± 6.6 (−5%)	25 ± 5.1 (−14%)	17.8 ± 8	10.4 ± 4.6 (−42%)
Lymphocyte (%)	70.3 ± 12.3	69 ± 18.6 (−2%)	72.2 ± 6.4 (+3%)	74.2 ± 5.8 (−6%)	80.2 ± 8.6	88.8 ± 4.2 (+11%)
Monocyte (%)	0.5 ± 1	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Other (%)	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0

[a]METI (2009b).
[b]ADDs (mg/kg-day) were reported by the study authors; calculated HEDs appear in brackets.
[c]Data are mean ± SD (g) for five animals/group with the following exceptions: one mated and one unmated control female were excluded due to death during anesthesia.
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$) by Student's *t*-test, Aspin-Welch's test, or Dunnett's test as reported by the study authors.
**Significantly different from control ($p < 0.01$) by Student's *t*-test, Aspin-Welch's test, or Dunnett's test as reported by the study authors.

ADD = adjusted daily dose; HCT = hematocrit; HED = human equivalent dose; HGB = hemoglobin; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PND = postnatal day; RBC = red blood cell; SD = standard deviation; WBC = white blood cell.

Table B-2. Select Serum Chemistry Findings in Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene via Gavage During Premating, Mating, Gestation, and Lactation Until PND 4 or for 42 Days[a]

	Males (main group): ADD [HED] (mg/kg-d)[b]				Males (recovery): ADD [HED] (mg/kg-d)	
Endpoint	**0**	**10 [2.8]**	**50 [14]**	**250 [70.1]**	**0**	**250 [70.1]**
AST (IU/L)	70 ± 7[c]	70 ± 9 (+0%)[d]	76 ± 8 (+9%)	83 ± 27 (+19%)	70 ± 7	62 ± 8 (−11%)
ALT (IU/L)	30 ± 4	31 ± 7 (+3%)	31 ± 6 (+3%)	42 ± 18 (+40%)	36 ± 4	30 ± 7 (−17%)
ALP (IU/L)	259 ± 52	253 ± 50 (−2%)	238 ± 18 (−8%)	253 ± 36 (−2%)	241 ± 53	207 ± 18 (−14%)
TP (g/dL)	6.3 ± 0.3	6.4 ± 0.2 (+2%)	6.4 ± 0.3 (+2%)	6.5 ± 0.4 (+3%)	6.4 ± 0.1	6.4 ± 0.3 (+0%)
α1-globulin (%)	21.4 ± 1.6	21.5 ± 1.3 (+0%)	22.2 ± 0.9 (+4%)	22 ± 1.2 (+3%)	22.8 ± 2.3	22.7 ± 1.1 (−0%)
K (mEq/L)	4.42 ± 0.28	4.47 ± 0.33 (+1%)	4.27 ± 0.26 (−3%)	4.37 ± 0.22 (−1%)	4.49 ± 0.13	**5.01 ± 0.4 (+12%)***
IP (mg/dL)	6.2 ± 0.8	6.1 ± 0.8 (−2%)	6.5 ± 0.7 (+5%)	6.3 ± 0.3 (+2%)	5.4 ± 0.4	5.6 ± 0.6 (+4%)
	Mated Females: ADD [HED] (mg/kg-d)				**Unmated Females (recovery): ADD [HED] (mg/kg-d)**	
Endpoint	**0**	**10 [2.6]**	**50 [13]**	**250 [64.0]**	**0**	**250 [62.0]**
AST (IU/L)	93 ± 22	95 ± 40 (+2%)	75 ± 9 (−19%)	76 ± 7 (−18%)	62 ± 4	70 ± 34 (+13%)
ALT (IU/L)	53 ± 9	45 ± 19 (−15%)	40 ± 7 (−25%)	44 ± 11 (−17%)	20 ± 3	31 ± 20 (+55%)
ALP (IU/L)	123 ± 25	127 ± 56 (+3%)	114 ± 26 (−7%)	123 ± 48 (+0%)	103 ± 10	**79 ± 9 (−23%)****
TP (g/dL)	5.9 ± 0.2	**6.3 ± 0.2 (+7%)***	6.3 ± 0.2 (+7%)	**6.4 ± 0.3 (+8%)****	6.8 ± 0.4	**7.5 ± 0.3 (+10%)***
α1-globulin (%)	18.6 ± 0.8	19.1 ± 1.8 (+3%)	**21.2 ± 1.2 (+14%)***	20.3 ± 1.2 (+9%)	17.3 ± 1.3	17.7 ± 0.9 (+2%)
K (mEq/L)	4.09 ± 0.32	4.05 ± 0.41 (−1%)	4.39 ± 0.26 (+7%)	4.52 ± 0.16 (+11%)	3.79 ± 0.37	3.7 ± 0.13 (−2%)
IP (mg/dL)	6.8 ± 1.4	6.5 ± 1 (−4%)	7.1 ± 0.4 (+4%)	**8.5 ± 0.9 (+25%)***	5.2 ± 1.1	5.1 ± 1.4 (−2%)

[a]METI (2009b).
[b]ADD (mg/kg-day) values were reported by the study authors; calculated HEDs appear in brackets.
[c]Data are mean ± SD (g) for five animals/group with the following exceptions: one mated and one unmated control female were excluded due to death during anesthesia.
[d]Value in parentheses is % change relative to control = ([treatment mean – control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$) by Student's *t*-test, Asprin-Welch's test, or Dunnett's test as reported by the study authors.
**Significantly different from control ($p < 0.01$) by Student's *t*-test, Asprin-Welch's test, or Dunnett's test as reported by the study authors.

ADD = adjusted daily dose; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HED = human equivalent dose; IP = inorganic phosphate; K = potassium; PND = postnatal day; SD = standard deviation; TP = total protein.

Table B-3. Select Organ Weights in Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene via Gavage During Premating, Mating, Gestation, and Lactation Until PND 4 or for 42 Days[a]

	Males (main group): ADD [HED] (mg/kg-d)[b]				Males (recovery): ADD [HED] (mg/kg-d)	
Endpoint	**0**	**10 [2.8]**	**50 [14]**	**250 [70.1]**	**0**	**250 [70.1]**
Number of animals (n)	7	12	12	**7**	5	5
Necropsy body weight	491.4 ± 46.8[c]	480.7 ± 34.5 (−2%)[d]	485.5 ± 30 (−1%)	458.9 ± 27.3 (−7%)	523.5 ± 54.8	520.2 ± 19 (−1%)
Liver weight						
Absolute (g)	12.94 ± 1.905	12.895 ± 1.604 (−0%)	13.043 ± 1.272 (+1%)	**15.159 ± 1.934 (+17%)***	14.219 ± 1.381	14.131 ± 0.78 (−1%)
Relative (g%)	2.628 ± 0.233	2.678 ± 0.223 (+2%)	2.685 ± 0.17 (+2%)	**3.309 ± 0.416 (+26%)****	2.726 ± 0.248	2.723 ± 0.241 (−0%)
Kidney weight						
Absolute (g)	2.905 ± 0.299	3.006 ± 0.298 (+3%)	3.006 ± 0.285 (+3%)	3.127 ± 0.287 (+8%)	2.944 ± 0.223	2.939 ± 0.249 (−0%)
Relative (g%)	0.593 ± 0.057	0.626 ± 0.053 (+6%)	0.62 ± 0.053 (+5%)	**0.683 ± 0.06 (+15%)***	0.565 ± 0.049	0.566 ± 0.053 (+0%)
Spleen weight						
Absolute (g)	0.759 ± 0.114	0.768 ± 0.128 (+1%)	0.775 ± 0.072 (+2%)	0.794 ± 0.116 (+5%)	0.875 ± 0.135	0.759 ± 0.1 (−13%)
Relative (g%)	0.155 ± 0.023	0.159 ± 0.022 (+3%)	0.16 ± 0.016 (+3%)	0.173 ± 0.026 (+12%)	0.167 ± 0.012	**0.146 ± 0.016 (−13%)***

Table B-3. Select Organ Weights in Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene via Gavage During Premating, Mating, Gestation, and Lactation Until PND 4 or for 42 Days[a]

Endpoint	Mated Females: ADD [HED] (mg/kg-d)				Unmated Females (recovery): ADD [HED] (mg/kg-d)	
	0	**10 [2.6]**	**50 [13]**	**250 [64.0]**	**0**	**250 [62.0]**
Number of animals (n)	11	8	12	11	5	5
Necropsy body weight	308.9 ± 14.9	304.7 ± 16.8 (−1%)	311.6 ± 14.3 (+1%)	302 ± 24.5 (−2%)	322.7 ± 34.1	288.9 ± 21.2 (−10%)
Liver weight						
Absolute (g)	9.859 ± 0.808	9.563 ± 0.599 (−3%)	9.929 ± 0.63 (+1%)	10.588 ± 0.988 (+7%)	7.626 ± 0.714	7.69 ± 0.606 (+1%)
Relative (g%)	3.193 ± 0.227	3.148 ± 0.275 (−1%)	3.188 ± 0.169 (−0%)	**3.521 ± 0.373 (+10%)***	2.368 ± 0.138	**2.663 ± 0.106 (+12%)****
Kidney weight						
Absolute (g)	1.956 ± 0.109	1.852 ± 0.122 (−5%)	1.935 ± 0.128 (−1%)	1.957 ± 0.209 (+0%)	1.845 ± 0.194	1.762 ± 0.125 (−4%)
Relative (%)	0.634 ± 0.04	0.609 ± 0.048 (−4%)	0.622 ± 0.04 (−2%)	0.65 ± 0.072 (+3%)	0.574 ± 0.06	0.612 ± 0.044 (+7%)
Spleen weight						
Absolute (g)	0.693 ± 0.095	0.652 ± 0.096 (−6%)	0.655 ± 0.041 (−5%)	0.601 ± 0.066 (−13%)	0.574 ± 0.15	0.472 ± 0.038 (−18%)
Relative (%)	0.225 ± 0.033	0.214 ± 0.028 (−5%)	0.211 ± 0.014 (−6%)	0.199 ± 0.021 (−12%)	0.179 ± 0.046	0.164 ± 0.015 (−8%)

[a]METI (2009b).
[b]ADD (mg/kg-day) values were reported by the study author; calculated HEDs appear in brackets.
[c]Data are mean ± SD (g).
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$), by Student's *t*-test, or Dunnett's test, as reported by the study authors.
**Significantly different from control ($p < 0.01$), by Student's *t*-test, or Dunnett's test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; PND = postnatal day; SD = standard deviation.

Table B-4. Select Hematological Results of Male and Female B6C3F1 *gpt* Delta Mice Treated with 1-Methylnaphthalene in the Diet for 13 Weeks[a]

Endpoint	Males: ADD [HED] in (mg/kg-d)[b]		
	0	**120 [17.1]**	**220 [31.1]**
WBC (× 10^2/µL)	24.2 ± 15[c]	22 ± 9 (−9%)[d]	15 ± 7 (−38%)
Leukocyte classification			
Band form neutrophils (%)	5.3 ± 1.8	**2.6 ± 0.9 (−51%)***	3.9 ± 2.4 (−26%)
Segmented neutrophils (%)	14.8 ± 3.2	16.8 ± 3.9 (+14%)	**27.5 ± 13.5 (+86%)***
Eosinophils	1.3 ± 0.9	0.6 ± 0.4 (−54%)	1.1 ± 0.4 (−15%)
Basophils (%)	0.3 ± 0.5	0.4 ± 0.2 (+33%)	0.3 ± 0.3 (+0%)
Lymphocytes (%)	77 ± 7.5	79 ± 3.7 (+3%)	66.4 ± 16 (−14%)
Monocytes (%)	0.9 ± 0.3	0.6 ± 0.3 (−33%)	0.6 ± 0.3 (−33%)
Endpoint	**Females: ADD [HED] in (mg/kg-d)**		
	0	**170 [23.1]**	**280 [37.7]**
WBC (× 10^2/µL)	16 ± 8	17 ± 11 (+6%)	17 ± 8 (+6%)
Leukocyte classification			
Band form neutrophils (%)	3.1 ± 1.7	2.2 ± 1.1 (−29%)	2.6 ± 1.5 (−16%)
Segmented neutrophils (%)	10.7 ± 3.9	10.4 ± 3.2 (−3%)	10.9 ± 3.4 (+2%)
Eosinophils	1 ± 0.6	1.1 ± 0.7 (+10%)	1.1 ± 0.6 (+10%)
Basophils (%)	0.1 ± 0.2	**0.4 ± 0.2 (+300%)***	**0.4 ± 0.2 (+300%)***
Lymphocytes (%)	84.7 ± 5.1	85.3 ± 3.8 (+1%)	84.4 ± 4.2 (−0%)
Monocytes (%)	0.5 ± 0.3	0.5 ± 0.3 (+0%)	0.4 ± 0.3 (−20%)

[a]Jin et al. (2012).
[b]Doses equivalent to 0, 0.075, and 0.15% 1-methylnaphthalene in the diet; calculated HEDs appear in brackets.
[c]Data are mean ± SD; n = 10 animals per group.
[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, 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; HED = human equivalent dose; SD = standard deviation; WBC = white blood cell.

Table B-5. Select Serum Biochemistry Results of Male and Female B6C3F1 *gpt* Delta Mice Treated with 1-Methylnaphthalene in the Diet for 13 Weeks[a]

Endpoint	Males: ADD [HED] in (mg/kg-d)[b]		
	0	**120 [17.1]**	**220 [31.1]**
AST (IU/L)	37.1 ± 2.8[c]	37.3 ± 3.2 (+1%)[d]	**50.6 ± 15.6 (+36%)***
ALT (IU/L)	20.3 ± 2.1	20.9 ± 4.5 (+3%)	**30.1 ± 10.4 (+48%)***
Phospholipid (mg/dL)	232.3 ± 22.8	218.9 ± 15.2 (−6%)	**207.4 ± 5.6 (−11%)***
TC (mg/dL)	119.6 ± 12.5	121.3 ± 8.1 (+1%)	113.9 ± 5.8 (−5%)
CRN (mg/dL)	0.11 ± 0.01	0.1 ± 0.01 (−9%)	**0.09 ± 0.01 (−18%)****
Ca (mg/dL)	9.2 ± 0.3	**8.9 ± 0.2 (−3%)***	**8.9 ± 0.3 (−3%)***
Cl (mEQ/L)	115.4 ± 1.4	115.4 ± 1.3 (+0%)	116.9 ± 3 (+1%)
BUN (mg/dL)	31.1 ± 3.8	28.6 ± 20 (−8.0)	**26.6 ± 3.7 (−14%)***
Endpoint	**Females: ADD [HED] in (mg/kg-d)**		
	0	**170 [23.1]**	**280 [37.7]**
AST (IU/L)	39.6 ± 2.4	38.6 ± 3.4 (−3%)	40.3 ± 4.1 (+2%)
ALT (IU/L)	18 ± 2.1	16.7 ± 1.2 (−7%)	18.4 ± 2.5 (+2%)
Phospholipid (mg/dL)	189.2 ± 8.1	181 ± 7.9 (−4%)	**172.3 ± 16.6 (−9%)***
TC (mg/dL)	104.6 ± 4.8	98.6 ± 7.1 (−6%)	**97.1 ± 7.1 (−7%)***
CRN (mg/dL)	0.09 ± 0.01	0.11 ± 0.02 (+22%)	0.09 ± 0.02 (+0%)
Ca (mg/dL)	8.9 ± 0.2	9 ± 0.3 (+1%)	8.7 ± 0.2 (−2%)
Cl (mEQ/L)	115.6 ± 1.5	115.9 ± 1.4 (+0%)	**117.6 ± 2.1 (+2%)***
BUN (mg/dL)	20.9 ± 4.1	24.4 ± 10.4 (+16%)	25.3 ± 5.4 (+21%)

[a]Jin et al. (2012).
[b]Doses equivalent to 0, 0.075, and 0.15% 1-methylnaphthalene in the diet; calculated HEDs appear in brackets.
[c]Data are mean ± SD; n = 10 animals per group.
[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, 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; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Ca = calcium; Cl = chloride; CRN = creatinine; HED = human equivalent dose; SD = standard deviation; TC = total cholesterol.

Table B-6. Select Organ Weights of Male and Female B6C3F1 *gpt* Delta Mice Treated with 1-Methylnaphthalene in the Diet for 13 Weeks[a]

Endpoint	Males: ADD [HED] in (mg/kg-d)[b]		
	0	**120 [17.1]**	**220 [31.1]**
Necropsy body weight (g)	33.1 ± 1.8[c]	33.1 ± 3.7 (+0%)[d]	30.7 ± 2 (−7%)
Liver weight			
Absolute (g)	1.35 ± 0.1	1.32 ± 0.18 (−2%)	1.21 ± 0.11 (−10%)
Relative (%)	4.09 ± 0.27	3.99 ± 0.19 (−2%)	3.93 ± 0.23 (−4%)
Kidney weight			
Absolute (g)	0.46 ± 0.08	0.45 ± 0.03 (−2%)	0.45 ± 0.04 (−2%)
Relative (%)	1.38 ± 0.24	1.38 ± 0.11 (+0%)	1.47 ± 0.12 (+7%)
Spleen			
Absolute (g)	0.09 ± 0.01	**0.07 ± 0.02* (−22%)***	**0.06 ± 0.01 (−33%)****
Relative (%)	0.27 ± 0.04	**0.21 ± 0.04 (−22%)***	**0.21 ± 0.05 (−22%)***
Heart weight			
Absolute (g)	0.97 ± 0.06	**0.81 ± 0.24 (−16%)***	**0.72 ± 0.03 (−26%)****
Relative (%)	2.94 ± 0.21	2.48 ± 0.77 (−16%)	**2.35 ± 0.19 (−20%)****
Thymus weight			
Absolute (g)	0.03 ± 0.01	0.03 ± 0.01 (+0%)	0.03 ± 0.01 (+0%)
Relative (%)	0.09 ± 0.02	0.08 ± 0.04 (−11%)	0.08 ± 0.01 (−11%)
Endpoint	**Females: ADD [HED] in (mg/kg-d)**		
	0	**170 [23.1]**	**280 [37.7]**
Necropsy body weight (g)	25.6 ± 1.4	25.5 ± 2.6 (−0%)	24.8 ± 1.3 (−3%)
Liver weight			
Absolute (g)	1.08 ± 0.06	1.04 ± 0.06 (−4%)	**1.00 ± 0.07 (−7%)***
Relative (%)	4.28 ± 0.43	4.12 ± 0.29 (−4%)	4.05 ± 0.27 (−5%)
Kidney weight			
Absolute (g)	0.34 ± 0.02	0.33 ± 0.02 (−3%)	0.33 ± 0.02 (−3%)
Relative (%)	1.33 ± 0.13	1.29 ± 0.11 (−3%)	1.32 ± 0.1 (−1%)
Spleen weight			
Absolute (g)	0.08 ± 0.01	0.08 ± 0.01 (+0%)	0.07 ± 0.01 (−13%)
Relative (%)	0.32 ± 0.03	0.3 ± 0.04 (−6%)	0.3 ± 0.04 (−6%)
Heart weight			
Absolute (g)	0.13 ± 0.01	0.12 ± 0.01 (−8%)	0.12 ± 0.01 (−8%)
Relative (%)	0.51 ± 0.02	0.49 ± 0.04 (−4%)	0.47 ± 0.04 (−8%)
Thymus weight			
Absolute (g)	0.04 ± 0.01	0.04 ± 0.01 (+0%)	**0.08 ± 0.10 (+100%)**[, e]**
Relative (%)	0.14 ± 0.02	0.15 ± 0.02 (+7%)	0.35 ± 0.44 (+150%)

[a]Jin et al. (2012).
[b]Doses equivalent to 0, 0.075, and 0.15% 1-methylnaphthalene in the diet; calculated HEDs appear in brackets.
[c]Data are mean ± SD; n = 10 animals per group.
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[e]Lymphoma was observed in one mouse.
*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; HED = human equivalent dose; SD = standard deviation.

Table B-7. Histopathological Changes in Male and Female B6C3F1 *gpt* Delta Mice Treated with 1-Methylnaphthalene in the Diet for 13 Weeks[a]

Males			
	ADD [HED] in (mg/kg-d)[b]		
Endpoints	**0**	**120 [17.1]**	**220 [31.1]**
Liver			
Single cell necrosis	0/10 (0%)[c]	3/10 (30%)	**5/10 (50%)***
Focal necrosis	0/10 (0%)	0/10 (0%)	0/10 (0%)
Vacuolization	0/10 (0%)	0/10 (0%)	0/10 (0%)
Females			
	ADD [HED] in (mg/kg-d)		
Endpoints	**0**	**170 [23.1]**	**280 [37.7]**
Liver			
Single cell necrosis	7/10 (70%)	5/10 (50%)	5/10 (50%)
Focal necrosis	5/10 (50%)	5/10 (50%)	7/10 (70%)
Vacuolization	0/10 (0%)	1/10 (1%)	3/10 (30%)

[a]Jin et al. (2012).
[b]Doses equivalent to 0, 0.075, and 0.15% 1-methylnaphthalene in the diet; calculated HEDs appear in brackets.
[c]Values denote number of animals showing changes / total number of animals examined (% incidence).
*Significantly different from control ($p < 0.01$) by Fisher's exact test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose.

Table B-8. Select Hematological Results in Male and Female B6C3F1 Mice Fed 1-Methylnaphthalene in the Diet for 81 Weeks[a]

Endpoint	Males: ADD [HED] (mg/kg-d)[b]		
	0	**71.6 [10.7]**	**140 [21.1]**
RBC (× 10^{-3}/µL)[c]	8.42 ± 0.84[d]	8.13 ± 0.39 (−3%)[e]	8.49 ± 0.66 (+1%)
HGB (g/dL)[c]	14.1 ± 1.98	13.3 ± 0.57 (−6%)	14 ± 1.23 (−1%)
HCT (%)[c]	40.5 ± 5.26	**36.8 ± 1.8 (−9%)***	41 ± 3.51 (+1%)
MCV (fL)[c]	48 ± 2.7	**45 ± 2.1 (−6%)***	48 ± 0.6 (+0%)
MCH (pg)[c]	16.7 ± 1.85	16.4 ± 0.8 (−2%)	16.5 ± 0.6 (−1%)
MCHC (%)[c]	35 ± 3.31	36.3 ± 1.68 (+4%)	34.2 ± 1.04 (−2%)
WBC (× 10^{-3}/µL)[c]	2.8 ± 1.22[b]	2.2 ± 0.71 (−21%)[c]	2.9 ± 0.99 (+4%)
Leukocyte classification			
Stab cell (%)[f]	0.42 ± 0.44	**2.57 ± 1.5 (+512%)***	**1.5 ± 0.98 (+257%)***
Segmented (%)[f]	13.77 ± 16	**20.94 ± 13.63 (+52%)***	**13.98 ± 8.42 (+2%)**
Eosinophil (%)[f]	0.05 ± 0.28	0.13 ± 0.36 (+160%)	0.04 ± 0.2 (−20%)
Basophil (%)[f]	0 ± 0	0 ± 0	0 ± 0
Lymphocyte (%)[e]	85.61 ± 16.54	**75.54 ± 14.51 (−12%)***	**81.3 ± 8.91 (−5%)***
Monocyte (%)[e]	0.17 ± 0.41	**0.81 ± 0.9 (+376%)***	**1.18 ± 0.97 (+594%)***
Endpoint	**Females: ADD [HED] (mg/kg-d)**		
	0	**75.1 [11.1]**	**144 [20.9]**
RBC (× 10^{-3}/µL)[c]	8.19 ± 0.36	8.43 ± 0.23 (+3%)	8.31 ± 0.35 (+1%)
HGB (g/dL)[c]	12.8 ± 0.87	**14.4 ± 0.57 (+13%)***	**14.2 ± 0.41 (+11%)***
HCT (%)[c]	38.3 ± 1.97	40.6 ± 3.89 (+6%)	39.2 ± 1.33 (+2%)
MCV (fL)[c]	47 ± 0.6	47 ± 3.9 (+0%)	46 ± 1 (−2%)
MCH (pg)[c]	15.6 ± 0.49	**17.1 ± 0.21 (+10%)***	**17 ± 0.69 (+9%)***
MCHC (%)[c]	33.2 ± 1.27	**35.8 ± 2.08 (+8%)***	**36.1 ± 0.75 (+9%)***
WBC (× 10^{-3}/µL)[c]	2.8 ± 0.78	1.8 ± 0.79 (−36%)	2.2 ± 0.42 (−21%)
Leukocyte classification			
Stab cell (%)[f]	1.55 ± 0.8	**2.46 ± 1.49 (+59%)***	1.22 ± 1.01 (−21%)
Segmented (%)[f]	15.55 ± 9.01	15.21 ± 8.32 (−2%)	**10.86 ± 7.48 (−30%)***
Eosinophil (%)[f]	0.11 ± 0.33	0.07 ± 0.26 (−36%)	0.14 ± 0.42 (+27%)
Basophil (%)[f]	0 ± 0	0 ± 0	0 ± 0

Table B-8. Select Hematological Results in Male and Female B6C3F1 Mice Fed 1-Methylnaphthalene in the Diet for 81 Weeks[a]

Endpoint	Females: ADD [HED] (mg/kg-d)		
	0	**75.1 [11.1]**	**144 [20.9]**
Lymphocyte (%)[f]	82.35 ± 9.35	81.37 ± 8.52 (−1%)	**86.69 ± 8.6 (+5%)***
Monocyte (%)[f]	0.42 ± 0.51	**0.91 ± 0.95 (+117%)***	**1.1 ± 1.15 (+162%)***

[a]Murata et al. (1993).
[b]ADD (mg/kg-day) values were reported by the study authors; calculated HEDs appear in brackets.
[c]Number of animals = 4−15 per group.
[d]Data are mean ± SD.
[e]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[f]Number of animals = 49−50 per group.
*Significantly different from control ($p < 0.05$) by Student's *t*-test, as reported by the study authors.

ADD = adjusted daily dose; HCT = hematocrit; HED = human equivalent dose; HGB = hemoglobin; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; SD = standard deviation; WBC = white blood cell.

Table B-9. Select Serum Chemistry Results in Male and Female B6C3F1 Mice Fed 1-Methylnaphthalene in the Diet for 81 Weeks[a]

Endpoint	Males: ADD [HED] (mg/kg-d)[b]		
	0	**71.6 [10.7]**	**140 [21.1]**
AST (U/L)	101 ± 28[c,d]	127 ± 66 (+26%)[e]	117 ± 136 (+16%)
ALT (U/L)	46 ± 34	73 ± 86 (+59%)	74 ± 115 (+61%)
ALP (K-AU)	5.3 ± 1.68	5.2 ± 1.11 (−2%)	9.6 ± 14 (+81%)
LDH (U/L)	815 ± 329	579 ± 511 (−29%)	**397 ± 246 (−51%)***
γ-GTP (U/L)	5 ± 1.4	**3 ± 2 (−40%)***	7 ± 7.1 (+40%)
TBIL (mg/dL)	0.4 ± 0.259	**0.2 ± 0.091 (−50%)***	0.2 ± 0.077 (−50%)
A/G ratio	0.37 ± 0.025	**0.32 ± 0.05 (−14%)***	**0.4 ± 0.037 (+8%)***
Alb (g/dL)	1.6 ± 0.13	**1.4 ± 0.25 (−13%)***	1.6 ± 0.14 (+0%)
BUN (mg/dL)	22 ± 4.5	**20 ± 6.5 (−9%)**	**18 ± 4.6 (−18%)***
Uric acid (mg/dL)	4 ± 0.82	3.8 ± 0.87 (−5%)	4.4 ± 1.53 (+10%)
Na (mEQ/L)	154 ± 3	**148 ± 4 (−4%)***	**151 ± 4 (−2%)***
K (mEQ/L)	4.9 ± 0.39	**4.3 ± 0.3 (−12%)***	**4.6 ± 0.34 (−6%)***
Cl (mEQ/L)	119 ± 8	**111 ± 5 (−7%)***	116 ± 5 (−3%)
Fe (μg/dL)	151 ± 32	**107 ± 16 (−29%)***	145 ± 34 (−4%)
Lipid (mg/dL)	436 ± 85	**512 ± 105 (+17%)***	441 ± 50 (+1%)
Phospholipid (mg/dL)	165 ± 40	190 ± 36 (+15%)	233 ± 200 (+41%)
Neutral fat (mg/dL)	81 ± 22	**101 ± 20 (+25%)***	83 ± 22 (+2%)
Cholesterol (mg/dL)	122 ± 41	153 ± 53 (+25%)	128 ± 22 (+5%)
Esterified cholesterol ratio (%)[f]	90 ± 4	91 ± 3 (+1%)	88 ± 3 (−2%)
HDL cholesterol (mg/dL)	97 ± 3	**93 ± 5 (−4%)***	90 ± 13 (−7%)
β-Lipoprotein (mg/dL)	260 ± 75	316 ± 104 (+22%)	263 ± 44 (+1%)
Lipid peroxide (nmol/dL)	4.1 ± 0.97	3.7 ± 1 (−10%)	3.7 ± 0.78 (−10%)
Endpoint	**Females: ADD [HED] (mg/kg-d)**		
	0	**75.1 [11.1]**	**144 [20.9]**
AST (U/L)	113 ± 158	67 ± 6 (−41%)	182 ± 269 (+61%)
ALT (U/L)	38 ± 20	33 ± 4 (−13%)	87 ± 164 (+129%)
ALP (K-AU)	9.6 ± 1.71	9 ± 1.96 (−6%)	10 ± 2.61 (+4%)
LDH (U/L)	435 ± 386	457 ± 170 (+5%)	338 ± 190 (−22%)
γ-GTP (U/L)	4 ± 2.4	3 ± 0.9 (−25%)	6 ± 7.2 (+50%)
TBIL (mg/dL)	0.2 ± 0.043	0.2 ± 0.033 (+0%)	0.2 ± 0.046 (+0%)
A/G ratio	0.35 ± 0.07	**0.45 ± 0.05 (+29%)***	**0.39 ± 0.037 (+11%)***
Alb (g/dL)	1.4 ± 0.21	**1.7 ± 0.13 (+21%)***	**1.6 ± 0.13 (+14%)***
BUN (mg/dL)	19 ± 15	15 ± 2.2 (−21%)	16 ± 3.1 (−16%)
Uric acid (mg/dL)	3.8 ± 1.22	**4.7 ± 1.31 (+24%)***	3.9 ± 1.15 (+3%)
Na (mEQ/L)	153 ± 4	152 ± 1 (−1%)	152 ± 2 (−1%)

Table B-9. Select Serum Chemistry Results in Male and Female B6C3F1 Mice Fed 1-Methylnaphthalene in the Diet for 81 Weeks[a]

Endpoint	Females: ADD [HED] (mg/kg-d)		
	0	**75.1 [11.1]**	**144 [20.9]**
K (mEQ/L)	4.2 ± 0.43	4.2 ± 0.38 (+0%)	**3.8 ± 0.69 (−10%)**
Cl (mEQ/L)	115 ± 4	115 ± 2 (+0%)	115 ± 4 (+0%)
Fe (μg/dL)	138 ± 32	**160 ± 28 (+16%)***	157 ± 26 (+14%)
Lipid (mg/dL)	430 ± 48	**473 ± 49 (+10%)***	467 ± 65 (+9%)
Phospholipid (mg/dL)	147 ± 29	154 ± 22 (+5%)	**171 ± 19 (+16%)***
Neutral fat (mg/dL)	111 ± 22	130 ± 31 (+17%)	**138 ± 44 (+24%)***
TC (mg/dL)	109 ± 20	**121 ± 13 (+11%)***	114 ± 16 (+5%)
Esterified cholesterol ratio (%)	89 ± 3	**87 ± 2 (−2%)***	**86 ± 3 (−3%)***
HDL cholesterol (mg/dL)	88 ± 19	92 ± 3 (+5%)	91 ± 16 (+3%)
β-Lipoprotein (mg/dL)	229 ± 40	**254 ± 28 (+11%)***	242 ± 34 (+6%)
Lipid peroxide (nmol/dL)	3.4 ± 0.57	**3.9 ± 0.7 (+15%)***	3.4 ± 0.62 (+0%)

[a]Murata et al. (1993).
[b]ADD (mg/kg-day) values were reported by the study authors; calculated HEDs appear in brackets.
[c]Data are mean ± SD.
[d]Number of samples = 11−16, pooled sera from 3 or 4 mice.
[e]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$) by Student's *t*-test, as reported by the study authors.

ADD = adjusted daily dose; A/G = albumin to globulin ratio; Alb = albumin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Cl = chloride; Fe = iron; HED = human equivalent dose; γ-GTP = gamma-glutamyl transpeptidase; HDL = high-density lipoprotein; K = potassium; LDH = lactate dehydrogenase; Na = sodium; SD = standard deviation; TBIL = total bilirubin; TC = total cholesterol.

Table B-10. Select Organ Weights of Male and Female B6C3F1 Mice Fed 1-Methylnaphthalene in the Diet for 81 Weeks[a]

Endpoint	Males: ADD [HED] (mg/kg-d)[b]		
	0	**71.6 [10.7]**	**140 [21.1]**
Necropsy body weight (g)	41 ± 3.6[c]	40 ± 3.7 (−2%)[d]	42 ± 3.4 (+2%)
Liver weight			
Absolute (mg)	1,667 ± 760	1,664 ± 656 (−0%)	1,732 ± 484 (+4%)
Relative[e]	41.4 ± 21	41.9 ± 21.3 (+1%)	41.5 ± 10.6 (+0%)
Kidney weight (right)			
Absolute (mg)	310 ± 32	303 ± 32 (−2%)	**295 ± 31 (−5%)***
Relative	7.7 ± 0.8	7.5 ± 0.9 (−3%)	**7.1 ± 0.8 (−8%)***
Kidney weight (left)			
Absolute (mg)	300 ± 31	299 ± 37 (−0%)	290 ± 31 (−3%)
Relative	7.4 ± 0.8	7.4 ± 0.9 (+0%)	**7 ± 0.6 (−5%)***
Brain weight			
Absolute (mg)	425 ± 42	**455 ± 25 (+7%)***	**457 ± 25 (+8%)***
Relative	10.5 ± 1.5	**11.3 ± 1.1 (+8%)***	**11 ± 1 (+5%)***
Salivary gland weight			
Absolute (mg)	316 ± 48	307 ± 42 (−3%)	313 ± 53 (−1%)
Relative	7.8 ± 1.2	7.6 ± 1 (−3%)	7.5 ± 1.3 (−4%)
Thymus weight			
Absolute (mg)	48 ± 22	49 ± 33 (+2%)	51 ± 22 (+6%)
Relative	1.2 ± 0.6	1.2 ± 0.8 (+0%)	1.2 ± 0.5 (+0%)
Heart weight			
Absolute (mg)	177 ± 23	**167 ± 20 (−6%)***	**162 ± 20 (−8%)***
Relative	4.4 ± 0.6	**4.1 ± 0.7 (−7%)***	**3.9 ± 0.4 (−11%)***
Lung weight			
Absolute (mg)	292 ± 43	293 ± 45 (+0%)	289 ± 60 (−1%)
Relative	7.2 ± 1.1	7.3 ± 1.2 (+1%)	6.9 ± 1.3 (−4%)
Spleen weight			
Absolute (mg)	115 ± 124	**101 ± 40 (−12%)***	112 ± 107 (−3%)
Relative	2.8 ± 2.9	2.5 ± 1.1 (−11%)	2.7 ± 2.6 (−4%)
Pancreas weight			
Absolute (mg)	386 ± 194	381 ± 97 (−1%)	412 ± 183 (+7%)
Relative	9.5 ± 4.6	9.5 ± 2.4 (+0%)	9.9 ± 4.3 (+4%)
Testis weight (right)			
Absolute (mg)	98 ± 12	99 ± 17 (+1%)	**103 ± 10 (+5%)***
Relative	2.4 ± 0.3	2.5 ± 0.4 (+4%)	2.5 ± 0.3 (+4%)

Table B-10. Select Organ Weights of Male and Female B6C3F1 Mice Fed 1-Methylnaphthalene in the Diet for 81 Weeks[a]

Endpoint	Females: ADD [HED] (mg/kg-d)		
	0	**75.1 [11.1]**	**144 [20.9]**
Testis weight (left)			
Absolute (mg)	100 ± 13	103 ± 18 (+3%)	102 ± 13 (+2%)
Relative	2.5 ± 0.5	2.6 ± 0.5 (+4%)	2.5 ± 0.3 (+0%)
Necropsy body weight (g)	45 ± 7.5	46 ± 7.7 (+2%)	46 ± 6.6 (+2%)
Liver weight			
Absolute (mg)	1,428 ± 458	1,348 ± 183 (−6%)	1,450 ± 192 (+2%)
Relative	32.6 ± 16.3	29.9 ± 3.8 (−8%)	32.3 ± 5.6 (−1%)
Kidney weight (right)			
Absolute (mg)	224 ± 28	**205 ± 26 (−8%)***	213 ± 28 (−5%)
Relative	5 ± 1	**4.6 ± 0.9 (−8%)***	4.8 ± 1.2 (−4%)
Kidney weight (left)			
Absolute (mg)	219 ± 30	**199 ± 27 (−9%)***	212 ± 22 (−3%)
Relative	5 ± 1.2	**4.5 ± 0.9 (−10%)***	4.8 ± 1.1 (−4%)
Brain weight			
Absolute (mg)	468 ± 27	469 ± 22 (+0%)	460 ± 31 (−2%)
Relative	10.6 ± 2.2	10.6 ± 2.2 (+0%)	10.3 ± 1.9 (−3%)
Salivary gland weight			
Absolute (mg)	235 ± 74	**192 ± 34 (−18%)***	**190 ± 44 (−19%)***
Relative	5.2 ± 1.5	**4.3 ± 1.1 (−17%)***	**4.2 ± 0.9 (−19%)***
Thymus weight[c,d]			
Absolute (mg)	82 ± 58	**53 ± 25 (−35%)***	**54 ± 29 (−34%)***
Relative	1.8 ± 1.1	**1.2 ± 0.6 (−33%)***	**1.2 ± 0.6 (−33%)***
Heart weight			
Absolute (mg)	131 ± 20	**122 ± 22 (−7%)***	**123 ± 18 (−6%)***
Relative	2.9 ± 0.8	2.7 ± 0.8 (−7%)	2.7 ± 0.7 (−7%)
Lung weight			
Absolute (mg)	309 ± 67	**279 ± 64 (−10%)***	293 ± 129 (−5%)
Relative	6.9 ± 1.6	**6.3 ± 2.1 (−9%)***	6.9 ± 5.9 (+0%)
Spleen weight			
Absolute (mg)	153 ± 222	118 ± 36 (−23%)	134 ± 77 (−12%)
Relative	3.7 ± 7.2	2.7 ± 1 (−27%)	3.1 ± 2.2 (−16%)
Pancreas weight			
Absolute (mg)	366 ± 175	330 ± 63 (−10%)	**306 ± 81 (−16%)***
Relative	8.2 ± 3.6	7.3 ± 1.7 (−11%)	**6.8 ± 2 (−17%)***

[a]Murata et al. (1993).
[b]ADD (mg/kg-day) values were reported by the study authors; calculated HEDs appear in brackets.
[c]Data are mean ± SD; n = 49−50 animals per group.
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[e]Reported as ratio to body weight × 10^3.
*Significantly different from control ($p < 0.05$) by Student's *t*-test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; SD = standard deviation.

Table B-11. Incidence of Nonneoplastic Lung Lesions in B6C3F1 Mice Fed 1-Methylnaphthalene in the Diet for 81 Weeks[a]

Observation	Males: ADD [HED] (mg/kg-d)[b]		
	0	**71.6 [10.7]**	**140 [21.1]**
Pulmonary alveolar proteinosis	4/49 (8.2%)[c]	**23/50 (46.0%)***	**19/50 (38.0%)***
	Females: ADD [HED] (mg/kg-d)		
	0	**75.1 [11.1]**	**144 [20.9]**
Pulmonary alveolar proteinosis	5/50 (10.0%)	**23/50 (46.0%)***	**17/49 (34.7%)***

[a]Murata et al. (1993).
[b]ADD (mg/kg-day) values were reported by the study authors; calculated HEDs appear in brackets.
[c]Values denote number of animals showing changes / total number of animals examined (% incidence).
*Significantly different from control ($p < 0.01$) value by χ^2 test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose.

Table B-12. Tumor Incidences in the Lungs of B6C3F1 Mice Fed 1-Methylnaphthalene in the Diet for 81 Weeks[a]

Observation	Males: ADD [HED] (mg/kg-d)[b]		
	0	**71.6 [10.7]**	**140 [21.1]**
Lung adenoma	2/49 (4.1%)[c]	**13/50 (26.0%)***	**12/50 (24.0%)***
Lung adenocarcinoma	0/49 (0%)	0/50 (0%)	3/50 (6.0%)
Combined lung adenoma or adenocarcinoma	2/49 (4.1%)	**13/50 (26.0%)***	**15/50 (30.0%)***
	Females: ADD [HED] (mg/kg-d)		
	0	**75.1 [11.1]**	**144 [20.9]**
Lung adenoma	4/50 (8.0%)	2/50 (4.0%)	4/49 (8.2%)
Lung adenocarcinoma	1/50 (2.0%)	0/50	1/49 (2.0%)
Combined lung adenoma or adenocarcinoma	5/50 (10.0%)	2/50 (4.0%)	5/50 (10.2%)

[a]Murata et al. (1993).
[b]ADD (mg/kg-day) values were reported by the study authors; calculated HEDs appear in brackets.
[c]Values denote number of animals showing changes / total number of animals examined (% incidence).
*Significantly different from control ($p < 0.01$) value by χ^2 test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose.

Table B-13. Select Hematological and Serum Biochemistry Results in Male and Female F344 Rats Exposed to 1-Methylnaphthalene Vapors for 6 Hours/Day, 5 Days/week for 13 Weeks[a]

Endpoint	Analytical Concentration [HEC_{ER}][b] in mg/m^3			
	0	**3.0 [0.540]**	**23.7 [4.237]**	**179.3 [31.552]**
Males				
APTT (s)	17.5 ± 1.7[c]	18 ± 0.8 (+3%)[d]	18.6 ± 0.8 (+6%)	**18.9 ± 0.5 (+8%)***
PT (s)	10.2 ± 0.3	10.5 ± 0.4 (+3%)	10.6 ± 0.3 (+4%)	**11.2 ± 0.6 (+10%)****
ALT (IU/L)	50.8 ± 5.6	51.2 ± 8.8 (+1%)	45.2 ± 4.6 (−11%)	**42.9 ± 5.8 (−16%)***
AST (IU/L)	91.5 ± 13.1	95.7 ± 12.8 (+5%)	88.7 ± 10.6 (−3%)	89.5 ± 36 (−2%)
ALP (IU/L)	456 ± 27.5	445.6 ± 35.2 (−2%)	455.9 ± 43 (−0%)	443 ± 44.9 (−3%)
Alb (g/dL)	4.1 ± 0.1	4.2 ± 0.1 (+2%)	4.1 ± 0.1 (+0%)	**4.3 ± 0.2 (+5%)****
Na (mmol/L)	144.3 ± 0.8	144.6 ± 0.8 (+0%)	145.1 ± 1 (+1%)	**145.7 ± 1.8 (+1%)***
Endpoint	**Analytical Concentration [HEC_{ER}] in mg/m^3**			
	0	**3.0 [0.540]**	**23.7 [4.237]**	**179.3 [31.552]**
Females				
APTT (s)	17.9 ± 0.8	18.5 ± 1.4 (+3%)	18.2 ± 1 (+2%)	19.1 ± 0.6 (+7%)
PT (s)	9.9 ± 0.4	10 ± 0.6 (+1%)	10.1 ± 0.2 (+2%)	**10.7 ± 0.7 (+8%)****
ALT (IU/L)	38.4 ± 7.2	44.7 ± 11.3 (+16%)	40.9 ± 11 (+7%)	38.8 ± 5.2 (+1%)
AST (IU/L)	81.6 ± 14.6	94.5 ± 18.4 (+16%)	86.5 ± 12.6 (+6%)	81.9 ± 7.3 (+0%)
ALP (IU/L)	362.5 ± 33.3	365.6 ± 50.9 (+1%)	367 ± 32 (+1%)	365.3 ± 51.8 (+1%)
Alb (g/dL)	4.3 ± 0.2	4.4 ± 0.2 (+2%)	4.3 ± 0.2 (+0%)	4.2 ± 0.2 (−2%)
Na (mmol/L)	146.3 ± 1.3	147.2 ± 2.4 (+1%)	146.1 ± 0.6 (−0%)	146.4 ± 0.9 (+0%)

[a]Kim et al. (2020).
[b]Reported concentrations; calculated HEC_{ER} values appear in brackets. Systemic effects from inhalation exposure to 1-methylnaphthalene were considered to be extrarespiratory effects of a Category 3 gas, as defined in the U.S. EPA guidance for deriving RfCs (U.S. EPA, 1994). Following this guidance, experimental exposures were adjusted to a mg/m^3 basis (3.0, 23.7, and 179.3 mg/m^3), adjusted to a continuous exposure basis (mg/m^3 × 6 hours/24 hours × 5 days/7 days = mg/m^3 × 0.1786: 0, 0.540, 4.237 and 31.552 mg/m^3), and converted to HECs by multiplying the adjusted concentrations by the ratio of rat:human blood/gas partition coefficients. Because the blood/gas coefficients for 1-methylnaphthalene were not available, the default ratio of 1 was used.
[c]Data are mean ± SD; n = 10/group.
[d]Value in parentheses is percent change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$) by Dunnett's test, as reported by the study authors.
**Statistically different from control ($p < 0.01$) by Dunnett's test, as reported by the study authors.

Alb = albumin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; HEC = human equivalent concentration; HEC_{ER} = human equivalent concentration based on extrarespiratory effects; Na = sodium; PT = prothrombin time; RfC = oral reference concentration; SD = standard deviation; U.S. EPA = U.S. Environmental Protection Agency.

Table B-14. Incidence and Severity of Histopathological Lesions in Nasopharyngeal Tissues in F344 Rats Exposed to 1-Methylnaphthalene Vapors for 6 Hours/Day, 5 Days/week for 13 Weeks[a]

Lesion and Severity	Analytical Concentration [HEC_{ET}][b] in mg/m^3			
	0	**3.0 [0.099]**	**23.7 [0.773]**	**179.3 [5.833]**
Males				
Hyperplasia, mucous cell in nasopharyngeal tissues				
Minimal	0/10 (0%)[c]	**4/10 (40%)***	**4/10 (40%)***	0/10 (0%)
Mild	0/10 (0%)	0/10 (0%)	**6/10 (60%)***	0/10 (0%)
Moderate	0/10 (0%)	0/10 (0%)	0/10 (0%)	**10/10 (100%)***
Total	0/10 (0%)	**4/10 (40%)***	**10/10 (100%)***	**10/10 (100%)***
Hyperplasia, transitional epithelial cell in nasopharyngeal tissues				
Minimal	0/10 (0%)	0/10 (0%)	**5/10 (50%)***	**5/10 (50%)***
Mild	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Moderate	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Total	0/10 (0%)	0/10 (0%)	**5/10 (50%)***	**5/10 (50%)***
Lesion and Severity	**Analytical Concentration [HEC_{ET}] in mg/m^3**			
	0	**3.0 [0.065]**	**23.7 [0.510]**	**179.3 [3.736]**
Females				
Hyperplasia, mucous cell in nasopharyngeal tissues				
Minimal	0/10 (0%)	0/10 (0%)	3/10 (30%)	2/10 (20%)
Mild	0/10 (0%)	0/10 (0%)	0/10 (0%)	**6/10 (60%)***
Moderate	0/10 (0%)	0/10 (0%)	0/10 (0%)	2/10 (20%)
Total	0/10 (0%)	0/10 (0%)	3/10 (30%)	**10/10 (100%)***

[a]Kim et al. (2020).
[b]Reported concentrations; calculated HEC_{ET} values appear in brackets.
[c]Values denote number of animals showing changes/total number of animals examined (% incidence).
*Significantly different from control by Fisher's exact test (one-sided $p < 0.05$) conducted for this review.

HEC_{ET} = human equivalent concentration based on extrathoracic effects.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE

Dichotomous Noncancer Data

The benchmark dose (BMD) modeling of dichotomous data is conducted with the U.S. Environmental Protection Agency (U.S. EPA) Benchmark Dose Software (BMDS) (Version 3.2 was used for this document). For these data, the Gamma, Logistic, Log-Logistic, Log-Probit, Multistage, Probit, and Weibull dichotomous models available within the software are fit using a benchmark response (BMR) of 10% extra risk. The Dichotomous Hill model was not considered for the derivation of a point of departure (POD) because it has four parameters and requires a data set with a minimum of five data points (including control). Alternative BMRs may also be used where appropriate, as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012). 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 χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of scaled residuals for the dose group nearest to the BMD (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 POD if the BMDLs are sufficiently close (less than threefold); if the BMDLs are not sufficiently close (greater than threefold), model-dependence is indicated, and the model with the lowest reliable BMDL is selected.

Cancer Data

The model-fitting procedure for dichotomous cancer incidence is as follows. The Multistage cancer model in the U.S. EPA's BMDS (Version 3.2) is fit to the incidence data using the extra risk option. The Multistage cancer model is run for all polynomial degrees up to n−1 (where n is the number of dose groups including control). An adequate model fit is judged by three criteria: (1) goodness-of-fit *p*-value ($p < 0.1$); (2) visual inspection of the dose-response curve; and (3) scaled residual at the data point (except the control) for the dose group nearest to the BMD (absolute value <2.0). Among all of the models providing adequate fit to the data, the BMDL for the model with the lowest AIC is selected as the POD. In accordance with the U.S. EPA (2012) and U.S. EPA (2005) guidance, BMD and BMDL values associated with an extra risk of 10% are calculated, which should be within the observable range of increased risk in a cancer bioassay. Modeling is performed for each individual tumor type with at least a statistically significant trend. Where applicable, the MS Combo model is used to evaluate the combined cancer risk of multiple tumor types. MS Combo is run using the incidence data for the individual tumor types and the polydegrees identified in the model runs for the individual tumor types.

Continuous Data

The BMD modeling of continuous data is conducted with the U.S. EPA's BMDS (Version 3.2) as well. For these data, the Exponential, Linear, Polynomial, and Power continuous models were fit using a standard reporting BMR of 1 standard deviation (SD) relative risk or 10% relative deviation as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012). 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). An

adequate fit is judged based on the χ^2 goodness-of-fit p value ($p > 0.1$), magnitude of the scaled residuals for the dose group nearest to the BMD (absolute value <2.0), 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 by greater 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 (p-RfD)
Increased Relative Liver Weight in Male Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene by Gavage for 42 Days (METI, 2009b)

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in male Sprague Dawley Crl:CD rats orally exposed to 1-methylnaphthalene for 42 days (METI, 2009b). The constant variance model did not provide adequate fit to the variance data (test 2 *p*-value < 0.1), but the nonconstant variance model did. With the nonconstant variance model applied, all available models provided adequate fit to the means, except for the Exponential 5 model. Visual inspection of the dose-response curves suggested adequate fit, and scaled residuals did not exceed ±2 units at the data point closest to the BMD. BMDLs for models providing adequate fit were sufficiently close (differed by less than threefold), so the model with the lowest AIC was selected (Polynomial 2-degree). The Polynomial 2-degree model estimated human equivalent benchmark dose with 10% relative deviation ($BMD_{0.1RD}$) and benchmark dose lower confidence limit with 10% relative deviation ($BMDL_{0.1RD}$) values of 44.79 and 24.12 mg/kg-day, respectively. The results of the BMD modeling are summarized in Table C-1 and plotted in Figure C-1.

Table C-1. BMD Modeling Results (Nonconstant Variance) for Increased Relative Liver Weight in Male Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene by Gavage for 42 Days[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	$BMD_{0.1RD}$ (mg/kg-d) HED	$BMDL_{0.1RD}$ (mg/kg-d) HED
Exponential (model 2)[c]	0.54	0.35	−0.86	3.69	30.08	22.32
Exponential (model 3)[c]	0.54	0.62	−0.00017	3.85	61.29	25.20
Exponential (model 4)[c]	0.54	0.12	−0.95	6.05	28.46	17.82
Exponential (model 5)[c]	0.54	NA	−0.00036	5.85	61.32	14.69
Polynomial (3-degree)[d]	0.54	0.62	−0.0062	3.84	51.81	24.46
Polynomial (2-degree)[d,*]	0.54	**0.84**	**0.0071**	**1.94**	**44.79**	**24.12**

Table C-1. BMD Modeling Results (Nonconstant Variance) for Increased Relative Liver Weight in Male Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene by Gavage for 42 Days[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	$BMD_{0.1RD}$ (mg/kg-d) HED	$BMDL_{0.1RD}$ (mg/kg-d) HED
Power[c]	0.54	0.62	−0.0026	3.85	54.58	24.45
Linear[d]	0.54	0.30	−0.95	4.05	28.62	20.37

[a]METI (2009b).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Coefficients restricted to be positive.
*Selected model. The constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, all models except the Exponential 5 model provided adequate fit to the means. BMDLs for models providing adequate fit were sufficiently close (differed by <threefold), so the model with the lowest AIC was selected (Polynomial 2-degree).

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; HED = human equivalent dose; NA = not applicable (computation failed); RD = relative deviation.

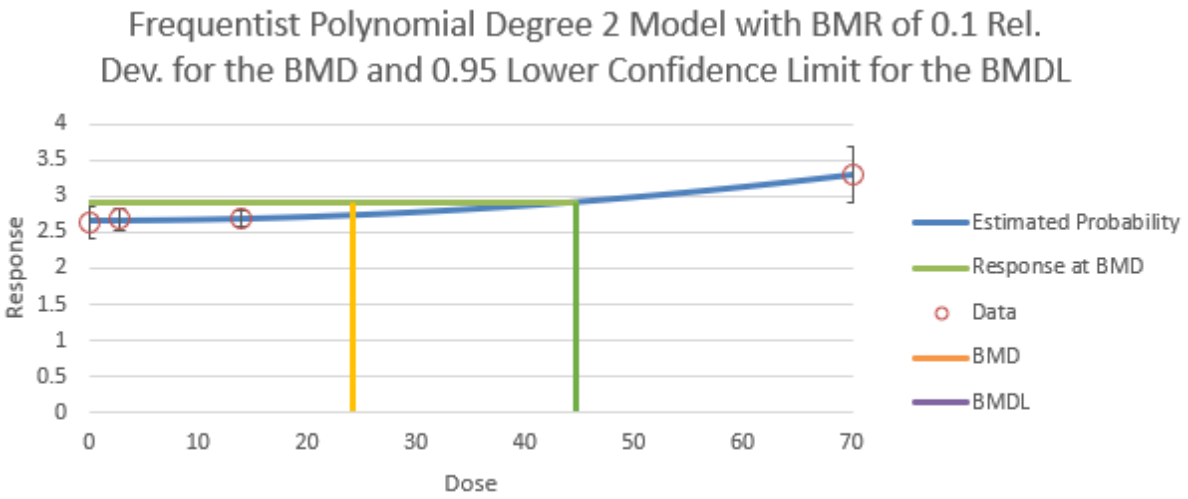

Figure C-1. Fit of Polynomial 2-Degree Model to the Data for Increased Relative Liver Weight in Male Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene by Gavage for 42 Days (METI, 2009b)

BMD Model Output of Polynomial 2-Degree Model for Increased Relative Liver Weight in Male Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene by Gavage for 42 Days (METI, 2009b)

Frequentist Polynomial Degree 2 Restricted

User Input

Info	
Model	frequentist Polynomial degree 2 v1.1
Dataset Name	Relative Liver Weights in Males
User notes	[Add user notes here]
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...
Variance Model	Var[i] = alpha * mean[i] ^ rho

Model Options	
BMR Type	Rel. Dev.
BMRF	0.1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Non-Constant

Model Data	
Dependent Variable	HED
Independent Variable	mean
Total # of Observations	4
Adverse Direction	Upward

Model Results

Benchmark Dose	
BMD	44.79469795
BMDL	24.12204139
BMDU	58.76085228
AIC	1.943404034
Test 4 P-value	0.844416786
D.O.F.	2

Model Parameters	
# of Parameters	5
Variable	Estimate
g	2.658868348
beta1	Bounded
beta2	0.000132509
rho	6.009127996
alpha	-9.135257856

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	7	2.658868348	2.628	2.628	0.19603462	0.233	0.233	-0.41660994
2.8	12	2.659907215	2.678	2.678	0.19626484	0.223	0.223	0.319340154
14	12	2.684840031	2.685	2.685	0.20184444	0.17	0.17	0.002745434
70.1	7	3.310016862	3.309	3.309	0.37858821	0.416	0.416	-0.00710631

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-0.034941499	5	10.069883
A2	3.810519056	8	8.37896189
A3	3.197407068	6	5.60518586
fitted	3.028297983	4	1.94340403
R	-13.72096852	2	31.441937

* Includes additive constant of -34.91966. 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	35.06297515	6	<0.0001
2	7.69092111	3	0.05285056
3	1.226223977	2	0.5416626
4	0.338218169	2	0.84441679

Increased Relative Liver Weights in Female Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene via Gavage for 42 Days (METI, 2009b)

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in female Sprague Dawley Crl:CD rats orally exposed to 1-methylnaphthalene for 42 days (METI, 2009b). The constant variance model did not provide adequate fit to the variance data (test 2 *p*-value < 0.1), but the nonconstant variance model did. With the nonconstant variance model applied, all available models provided adequate fit to the means, except for the Exponential 5 model. Visual inspection of the dose-response curves suggested adequate fit and scaled residuals did not exceed ±2 units at the data point closest to the BMD. BMDLs for models providing adequate fit were sufficiently close (differed by less than threefold), so the model with the lowest AIC was selected (Polynomial 3-degree). The Polynomial 3-degree model estimated human equivalent $BMD_{0.1RD}$ and $BMDL_{0.1RD}$ values of

62.40 and 42.30 mg/kg-day, respectively. The results of the BMD modeling are summarized in Table C-2 and plotted in Figure C-2.

Table C-2. BMD Modeling Results (Nonconstant Variance) for Increased Relative Liver Weight in Female Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene by Gavage for 42 Days[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	$BMD_{0.1RD}$ (mg/kg-d) HED	$BMDL_{0.1RD}$ (mg/kg-d) HED
Exponential (model 2)[c]	0.33	0.44	0.16	9.21	58.03	39.35
Exponential (model 3)[c]	0.33	0.68	−0.00022	9.74	63.54	42.79
Exponential (model 4)[c]	0.33	0.19	0.19	11.31	58.11	33.29
Exponential (model 5)[c]	0.33	NA	−0.00032	11.74	63.14	14.23
Polynomial (3-degree)[d,*]	**0.33**	**0.90**	**−0.0013**	**7.78**	**62.40**	**42.30**
Polynomial (2-degree)[d]	0.33	0.83	−0.042	7.95	60.73	41.52
Power[c]	0.33	0.68	0.00032	9.74	63.80	42.42
Linear[d]	0.33	0.42	0.19	9.31	58.07	36.85

[a]METI (2009b).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Coefficients restricted to be positive.
*Selected model. The constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, all models except the Exponential 5 model provided adequate fit to the means. BMDLs for models providing adequate fit were sufficiently close (differed by <threefold), so the model with the lowest AIC was selected (Polynomial 3-degree).

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; HED = human equivalent dose; NA = not applicable (computation failed); RD = relative deviation.

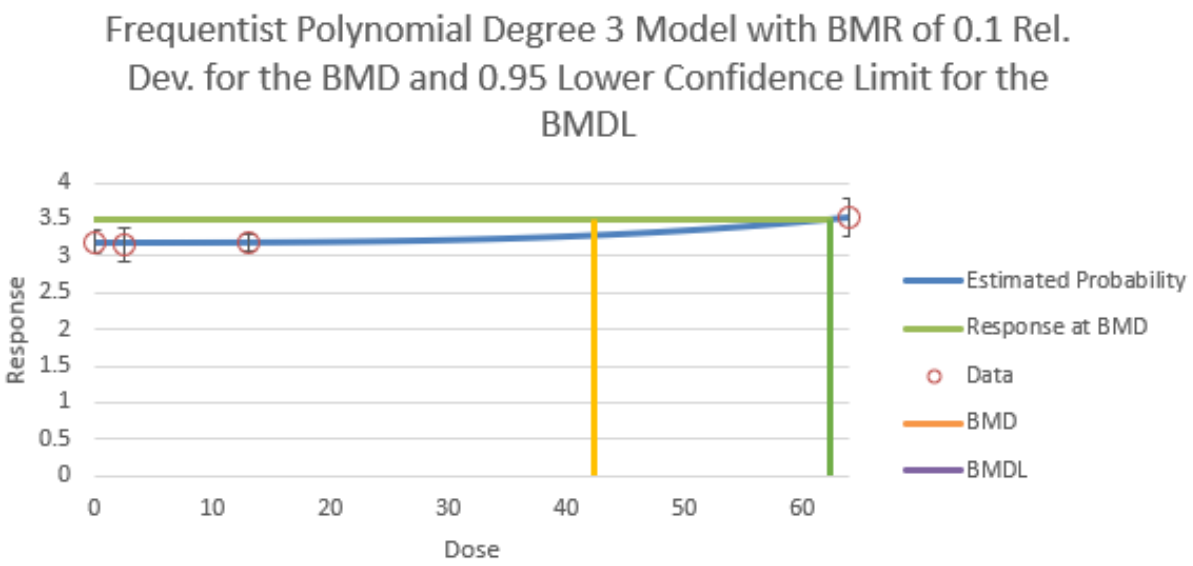

Figure C-2. Fit of Polynomial 3-Degree Model to the Data for Increased Relative Liver Weight in Female Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene by Gavage for 42 Days (METI, 2009b)

BMD Model Output of Polynomial 3-Degree Model for Increased Relative Liver Weight in Female Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene by Gavage for 42 Days (METI, 2009b)

Frequentist Polynomial Degree 3 Restricted

User Input

Info	
Model	frequentist Polynomial degree 3 v1.1
Dataset Name	Relative Liver Weights in Females
User notes	[Add user notes here]
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...
Variance Model	Var[i] = alpha * mean[i] ^ rho

Model Options	
BMR Type	Rel. Dev.
BMRF	0.1
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Non-Constant

Model Data	
Dependent Variable	[Custom]
Independent Variable	[Custom]
Total # of Observations	4
Adverse Direction	Upward

Model Results

Benchmark Dose	
BMD	62.40411377
BMDL	42.29521502
BMDU	91.70616072
AIC	7.777468742
Test 4 P-value	0.901815638
D.O.F.	2

Model Parameters	
# of Parameters	6
Variable	Estimate
g	3.178293321
beta1	Bounded
beta2	Bounded
beta3	1.30784E-06
rho	10.24003468
alpha	-14.96157255

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	11	3.178293321	3.193	3.193	0.2100766	0.227	0.227	0.23218455
2.6	8	3.178316307	3.148	3.148	0.2100844	0.275	0.275	-0.40815728
13	12	3.181166642	3.188	3.188	0.2110508	0.169	0.169	0.11215996
64	11	3.521135321	3.521	3.521	0.3549448	0.373	0.373	-0.00126445

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-2.348937716	5	14.697875
A2	1.330142963	8	13.339714
A3	0.214610802	6	11.570778
fitted	0.111265629	4	7.7774687
R	-8.625073638	2	21.250147

* Includes additive constant of -38.59542. 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	19.9104332	6	0.0028729
2	7.358161357	3	0.0613171
3	2.231064321	2	0.3277408
4	0.206690346	2	0.9018156

Increased Absolute Liver Weights and Increased Relative Kidney Weights in Male Sprague Dawley Crl:CD Rats Exposed to 1-Methylnaphthalene via Gavage for 42 Days (METI, 2009b)

BMD modeling results of the data for increased absolute liver weights in male rats or increased relative kidney weights in male rats (METI, 2009b) indicated that there was no significant dose-response (test 1 *p*-value > 0.05); therefore, BMD modeling of these data sets was not pursued.

BENCHMARK CONCENTRATION (BMC) MODELING TO IDENTIFY POTENTIAL PODS FOR DERIVATION OF A SUBCHRONIC PROVISIONAL REFERENCE CONCENTRATION

Increased Incidence of Mucous Cell Hyperplasia in Nasopharyngeal Tissues in Male F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week) (Kim et al., 2020)

The procedure outlined above for dichotomous noncancer data was applied to the incidence data for mucous cell hyperplasia in nasopharyngeal tissues in male F344 rats exposed to 1-methylnaphthalene via inhalation (vapor) for 13 weeks (6 hours/day, 5 days/week) (Kim et al., 2020). All the models provided an adequate fit according to the χ^2 goodness-of-fit *p*-value ($p > 0.1$), and scaled residuals did not exceed ± 2 units at the data point closest to the BMC (see Table C-3). However, the benchmark concentration lower confidence limit (BMCL) computation for the Weibull model failed so it was not considered for POD derivation. The BMCLs for the remaining models were not sufficiently close (differed by greater than approximately threefold), so the model with the lowest BMCL was selected (Multistage [degree = 1]). Figure C-3 shows the fit of the Multistage (degree = 1) model to the data. Based on human equivalent concentrations (HECs), the 10% benchmark concentration (BMC_{10}) and 10% benchmark concentration lower confidence limit ($BMCL_{10}$) for increased incidence of mucous cell hyperplasia in nasopharyngeal tissues in male F344 rats were 0.018 and 0.009 mg/m^3, respectively.

Table C-3. BMC Modeling Results for Increased Incidence of Mucous Cell Hyperplasia in Nasopharyngeal Tissues in Male F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week)[a]

Model	χ^2 Goodness-of-fit *p*-value[b]	AIC	Scaled Residual at Dose Nearest BMC	BMC_{10} (mg/m^3) HEC	$BMCL_{10}$ (mg/m^3) HEC
Gamma[c]	1.00	17.46	−0.000755448	0.042	0.010
Log-logistic[d]	1.00	17.46	−0.000457297	0.067	0.011
Multistage (degree = 3)[e]	1.00	19.46	−0.000390256	0.030	0.010
Multistage (degree = 2)[e]	1.00	17.46	−0.000390256	0.028	0.010
Multistage (degree = 1)[e,*]	**0.98**	**15.74**	**−0.000390256**	**0.018**	**0.009**

Table C-3. BMC Modeling Results for Increased Incidence of Mucous Cell Hyperplasia in Nasopharyngeal Tissues in Male F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week)[a]

Model	χ^2 Goodness-of-fit *p*-value[b]	AIC	Scaled Residual at Dose Nearest BMC	BMC_{10} (mg/m^3) HEC	$BMCL_{10}$ (mg/m^3) HEC
Weibull[c]	1.00	17.47	−0.001761315	0.029	0[f]
Logistic	0.76	17.40	0.538780371	0.051	0.029
Log-probit[d]	1.00	17.46	−0.000303782	0.060	0.010
Probit	0.29	21.66	0.825377764	0.087	0.057

[a]Kim et al. (2020).
[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]BMCL computation failed.
*Selected model. All models provided adequate fit to the data, but the Gamma, Multistage, Log-probit, and Weibull models were not considered for POD derivation due to issues with the BMCLs. BMCLs for the remaining models were not sufficiently close (differed by >threefold), so the one of these with the lowest BMCL (Log-logistic) was selected.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMC_{10} = 10% benchmark concentration; BMCL = benchmark concentration lower confidence limit; $BMCL_{10}$ = 10% benchmark concentration lower confidence limit; HEC = human equivalent concentration; POD = point of departure.

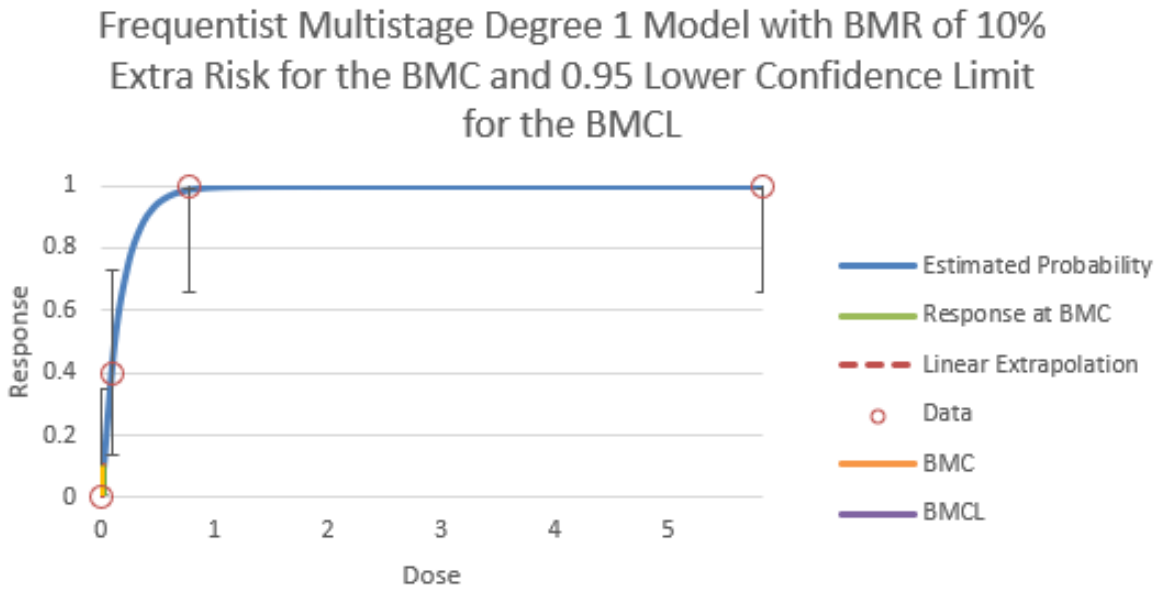

Figure C-3. Fit of Multistage (degree = 1) Model to the Data for Increased Incidence of Mucous in Nasopharyngeal Tissues Cell Hyperplasia in Male F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week) (Kim et al., 2020)

BMD Model Output of Multistage (degree = 1) Model for Increased Incidence of Mucous Cell Hyperplasia in Nasopharyngeal Tissues in Male F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week) (Kim et al., 2020)

Frequentist Multistage Degree 1 Restricted

User Input

Info	
Model	frequentist Multistage degree 1 v1.1
Dataset Name	Total mucous cell hyperplasia Male rats
User notes	[Add user notes here]
Dose-Response Model	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2 - ...)]

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	[Custom]
Independent Variable	[Custom]
Total # of Observations	4

Model Results

Benchmark Dose	
BMC	0.018083913
BMCL	0.009475298
BMCU	0.034878884
AIC	15.74287758
P-value	0.982050735
D.O.F.	3
Chi^2	0.171518085
Slope Factor	10.5537579

Model Parameters	
# of Parameters	2
Variable	Estimate
g	Bounded
b1	5.826201507

The value of this parameter, 1.52299795127603E-08, is within the tolerance of the bound (see user guide for tolerance limits)

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	1.523E-07	0	10	-0.0003903
0.099	0.438303699	4.383036988	4	10	-0.2441194
0.773	0.988931519	9.889315192	10	10	0.3345499
5.833	1	10	10	10	1.333E-07

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-6.73011667	4	-	-	NA
Fitted Model	-6.871438792	1	0.28264424	3	0.9632589
Reduced Model	-26.92046668	1	40.3807	3	<0.0001

Increased Incidence of Transitional Cell Hyperplasia in Male F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week) (Kim et al., 2020)

The procedure outlined above for dichotomous noncancer data was applied to the incidence data for transitional cell hyperplasia in male F344 rats exposed to 1-methylnaphthalene via inhalation (vapor) for 13 weeks (6 hours/day, 5 days/week) (Kim et al., 2020). Only the Log-logistic and Log-probit models provided an adequate fit according to the χ^2 goodness-of-fit *p*-value ($p > 0.1$) and scaled residuals (see Table C-4). However, the BMC/BMCL ratio for the Log-probit model was >20; therefore, this model was not considered for derivation of a POD, leaving only the Log-logistic model as a viable alternative. Figure C-4 shows the fit of the Log-logistic model to the data. Based on HECs, the BMC_{10} and $BMCL_{10}$ for increased incidence of transitional cell hyperplasia in male F344 rats were 0.26 and 0.12 mg/m^3, respectively.

Table C-4. BMC Modeling Results for Increased Incidence of Transitional Cell Hyperplasia in Male F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week)[a]

Model	χ^2 Goodness-of-fit *p*-value[b]	AIC	Scaled Residual at Dose Nearest BMC	BMC_{10} (mg/m^3) HEC	$BMCL_{10}$ (mg/m^3) HEC
Gamma[c]	0.003	40.75	3.06	0.51	0.30
Log-logistic[d,*]	**0.109**	**35.49**	**−0.65**	**0.26**	**0.12**
Multistage (degree = 3)[e]	0.003	40.75	3.06	0.51	0.30
Multistage (degree = 2)[e]	0.003	40.75	3.06	0.51	0.30
Multistage (degree = 1)[e]	0.003	40.75	3.06	0.51	0.30
Weibull[c]	0.003	40.75	3.06	0.51	0.30
Logistic	0.005	43.43	2.71	1.72	1.05
Log-probit[d]	0.177	35.84	−0.96	0.12	0.001[f]
Probit	0.005	43.29	2.72	1.61	1.01

[a]Kim et al. (2020).
[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]BMC/BMCL ratio is >20.
*Selected model. Only the Log-logistic and Log-probit models provided an adequate fit to the data. The Log-probit model was not considered for POD derivation because the BMC/BMCL ratio was >20, so the Log-logistic was selected.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMC_{10} = 10% benchmark concentration; BMCL = benchmark concentration lower confidence limit; $BMCL_{10}$ = 10% benchmark concentration lower confidence limit; HEC = human equivalent concentration; POD = point of departure.

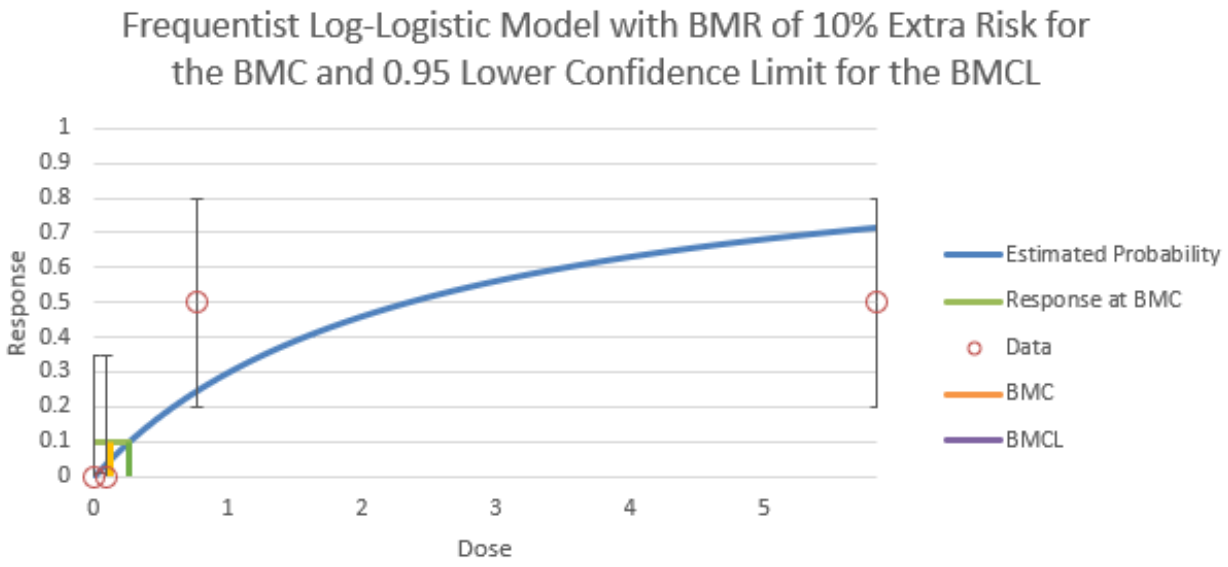

Figure C-4. Fit of Log-Logistic Model to the Data for Increased Incidence of Transitional Cell Hyperplasia in Male F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week) (Kim et al., 2020)

BMD Model Output of Log-Logistic Model for Increased Incidence of Transitional Cell Hyperplasia in Male F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week) (Kim et al., 2020)

Frequentist Log-Logistic Restricted Option Set #1

User Input

Info	
Model	frequentist Log-Logistic v1.1
Dataset Name	Transitional cell hyperplasia male rats
User notes	[Add user notes here]
Dose-Response Model	P[dose] = g+(1-g)/[1+exp(-a-b*Log(dose))]

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	[Custom]
Independent Variable	[Custom]
Total # of Observations	4

Model Results

Benchmark Dose	
BMC	0.261574763
BMCL	0.119303974
BMCU	0.590187836
AIC	35.49347532
P-value	0.108799645
D.O.F.	3
Chi^2	6.058475938

Model Parameters	
# of Parameters	3
Variable	Estimate
g	Bounded
a	-0.856189441
b	Bounded

The value of this parameter, 1.52299795127603E-08, is within the tolerance of the bound (see user guide for tolerance limits)

The value of this parameter, 1, is within the tolerance of the bound (see user guide for tolerance limits)

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	1.523E-07	0	10	-0.0003903
0.099	0.040355915	0.403559151	0	10	-0.6484829
0.773	0.247188137	2.471881373	5	10	1.8532773
5.833	0.712455952	7.124559517	5	10	-1.4843547

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-13.86294361	4	-	-	NA
Fitted Model	-16.74673766	1	5.7675881	3	0.1234816
Reduced Model	-22.49340578	1	17.2609243	3	0.0006246

Increased Incidence of Mucous Cell Hyperplasia in Nasopharyngeal Tissues in Female F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week) (Kim et al., 2020)

The procedure outlined above for dichotomous noncancer data was applied to the incidence data for mucous cell hyperplasia in nasopharyngeal tissues in female F344 rats exposed to 1-methylnaphthalene via inhalation (vapor) for 13 weeks (6 hours/day, 5 days/week) (Kim et al., 2020). All of the models provided adequate fit according to the $\chi 2$ goodness-of-fit *p*-value ($p > 0.1$) and scaled residuals (see Table C-5). The BMCLs for the models were not sufficiently close (differed by greater than approximately threefold), so the model with the lowest BMCL was selected (Multistage 1-degree). Figure C-5 shows the fit of the Multistage 1-degree model to the data. Based on HECs, the BMC_{10} and $BMCL_{10}$ for increased incidence of mucous cell hyperplasia in nasopharyngeal tissues in female F344 rats were 0.12 and 0.066 mg/m^3, respectively.

Table C-5. BMC Modeling Results for Increased Incidence of Mucous Cell Hyperplasia in Nasopharyngeal Tissues in Female F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week)[a]

Model	χ^2 Goodness-of-fit *p*-value[b]	AIC	Scaled Residual at Dose Nearest BMC	BMC_{10} (mg/m^3) HEC	$BMCL_{10}$ (mg/m^3) HEC
Gamma[c]	1.00	16.22	0.0003	0.40	0.090
Log-logistic[d]	1.00	14.22	3.32×10^{-8}	0.44	0.140
Multistage (degree = 3)[e]	1.00	14.23	0.004	0.34	0.087
Multistage (degree = 2)[e]	1.00	14.33	−0.24	0.28	0.087
Multistage (degree = 1)[e,*]	**0.57**	**18.29**	**−0.76**	**0.12**	**0.066**
Weibull[c]	0.99	16.24	0.01	0.33	0.090
Logistic	1.00	14.22	4.23×10^{-5}	0.46	0.23
Log-probit[d]	1.00	16.22	-8.2×10^{-9}	0.40	0.13
Probit	1.00	14.32	0.06	0.36	0.21

[a]Kim et al. (2020).
[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.
*Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >threefold), so the model with the lowest BMCL (Multistage 1-degree) was selected.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMC_{10} = 10% benchmark concentration; $BMCL_{10}$ = 10% benchmark concentration lower confidence limit; HEC = human equivalent concentration.

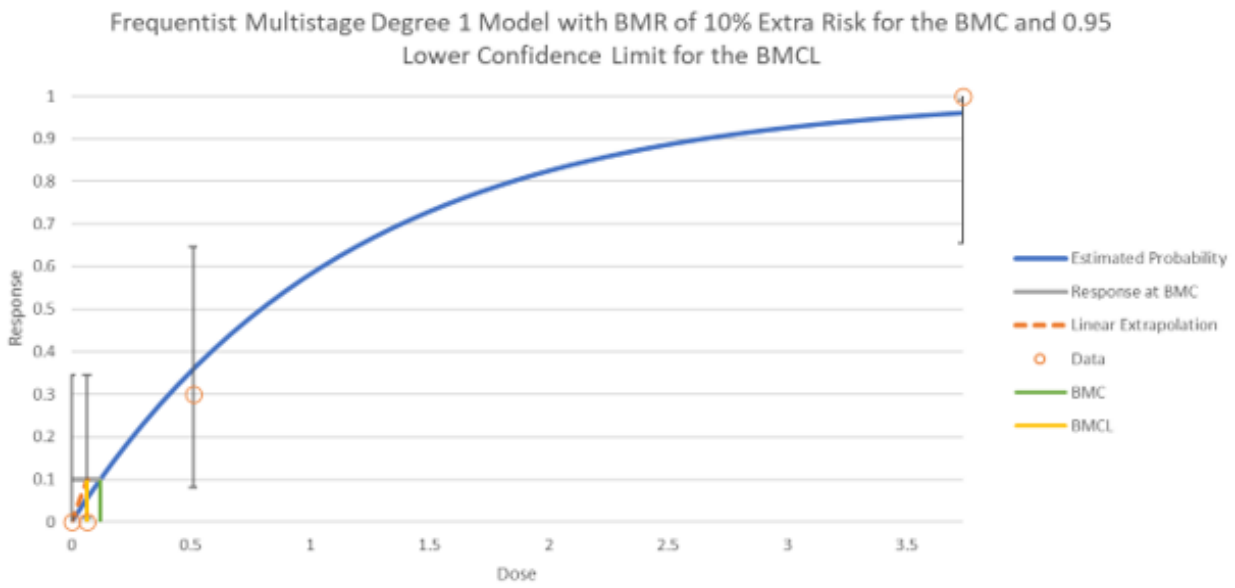

Figure C-5. Fit of Multistage 1-Degree Model to the Data for Increased Incidence of Mucous Cell Hyperplasia in Nasopharyngeal Tissues in Female F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week) (Kim et al., 2020)

BMC Model Output of Multistage 1-Degree Model for Increased Incidence of Mucous Cell Hyperplasia in Nasopharyngeal Tissues in Female F344 Rats Exposed to 1-Methylnaphthalene via Inhalation (Vapor) for 13 Weeks (6 Hours/Day, 5 Days/Week) (Kim et al., 2020)

Frequentist Multistage Degree 1 Restricted

User Input

Info	
Model	frequentist Multistage degree 1 v1.1
Dataset Name	Total mucous cell hyperplasia female rats
User notes	[Add user notes here]
Dose-Response Model	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2 - ...)]

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	[Custom]
Independent Variable	[Custom]
Total # of Observations	4

Model Results

Benchmark Dose	
BMC	0.120729623
BMCL	0.066284393
BMCU	0.223184123
AIC	18.29099358
P-value	0.566919696
D.O.F.	2
Chi^2	1.135075228
Slope Factor	1.508650756

Model Parameters	
# of Parameters	2
Variable	Estimate
g	1.52361E-08
b1	0.872698106

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.52361E-08	1.52361E-07	0	10	-0.0003903
0.065	0.055146502	0.55146502	0	10	-0.7639708
0.51	0.359224456	3.592244563	3	10	-0.3903599
3.736	0.96162696	9.616269596	10	10	0.6316984

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-6.108643021	4	-	-	NA
Fitted Model	-7.14549679	2	2.07370754	2	0.3545685
Reduced Model	-25.22324114	1	38.2291962	3	<0.0001

BMD MODELING TO IDENTIFY POTENTIAL PODS FOR DERIVATION OF A PROVISIONAL CANCER RISK ESTIMATE FOR ORAL EXPOSURE

Increased Incidence of Combined Lung Adenoma or Adenocarcinoma in Male B6C3F1 Mice Exposed to 1-Methylnaphthalene via Diet for 81 Weeks (Murata et al., 1993)

The procedure outlined above for cancer data was applied to the data for combined lung adenoma or adenocarcinoma in male B6C3F1 mice exposed to 1-methylnaphthalene via diet for 81 weeks (Murata et al., 1993). The Multistage 1-degree model provided adequate fit to the data, as shown by the $\chi 2$ goodness-of-fit p-value ($p > 0.1$) and scaled residuals (see Table C-6). The Multistage 2-degree model took the form of the 1-degree model. Higher-degree models were not applied to the data set because only three dose groups were present. Figure C-6 shows the fit of the Multistage 1-degree model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ values for increased incidence of combined lung adenoma or adenocarcinoma in male B6C3F1 mice were 6.01 and 4.16 mg/kg-day, respectively.

Table C-6. BMD Modeling Results for Increased Incidence of Combined Lung Adenoma or Adenocarcinoma in Male B6C3F1 Mice Exposed to 1-Methylnaphthalene via Diet for 81 Weeks[a]

Model	χ^2 Goodness-of-fit *p*-value[b]	AIC	Scaled Residual at Dose Nearest BMD	BMD_{10} (mg/kg-d) HED	$BMDL_{10}$ (mg/kg-d) HED
Multistage (degree = 2)[c]	0.28	140.26	0.87	6.01	4.16
Multistage (degree = 1)[c,*]	**0.28**	**140.26**	**0.87**	**6.01**	**4.16**

[a]Murata et al. (1993).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Betas restricted to ≥0.
*Selected model. The Multistage 1-degree model provided adequate fit to the data. The Multistage 2-degree model took the form of the 1-degree model.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMC_{10} = 10% benchmark concentration; $BMCL_{10}$ = 10% benchmark concentration lower confidence limit; HED = human equivalent dose.

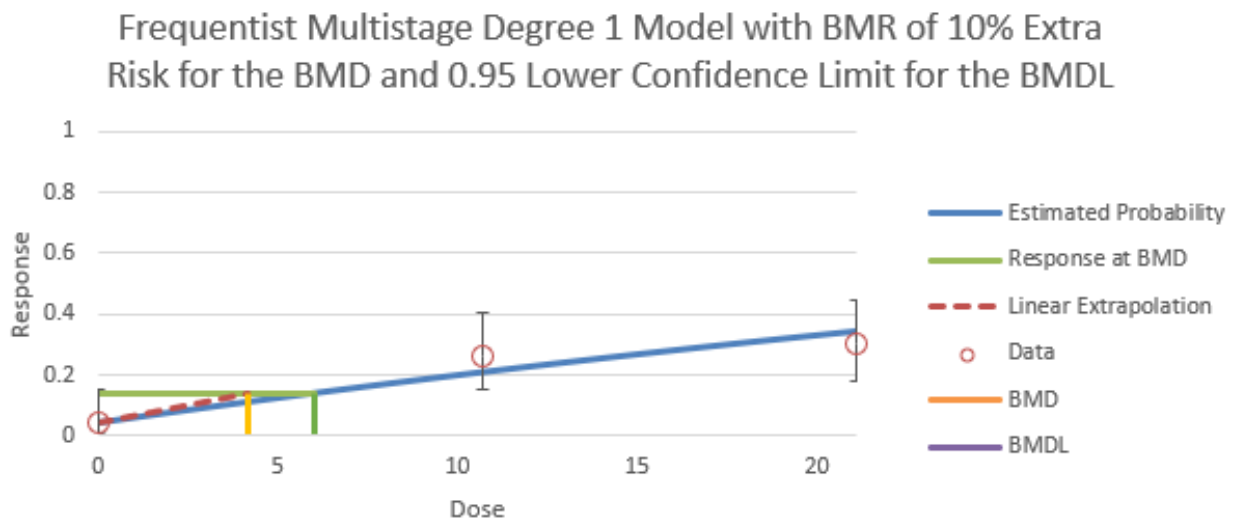

Figure C-6. Fit of Multistage 1-Degree Model to the Data for Increased Incidence of Combined Lung Adenoma or Adenocarcinoma in Male B6C3F1 Mice Exposed to 1-Methylnaphthalene via Diet for 81 Weeks (Murata et al., 1993)

BMD Model Output of Multistage 1-Degree Model for Increased Incidence of Combined Lung Adenoma or Adenocarcinoma in Male B6C3F1 Mice Exposed to 1-Methyl-naphthalene via Diet for 81 Weeks (Murata et al., 1993)

Frequentist Multistage Degree 1 Restricted

User Input

Info	
Model	frequentist Multistage degree 1 v1.1
Dataset Name	CombLungAdenoAdenocarcMMice
User notes	[Add user notes here]
Dose-Response Model	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2 - ...)]

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	HED
Independent Variable	Incidence
Total # of Observations	3

Model Results

Benchmark Dose	
BMD	6.005170966
BMDL	4.156604153
BMDU	10.38868258
AIC	140.2583658
P-value	0.276456526
D.O.F.	1
Chi^2	1.184427297
Slope Factor	0.0240581

Model Parameters	
# of Parameters	2
Variable	Estimate
g	0.046432018
b1	0.017544966

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.046432018	2.275168878	2	49	-0.1868171
10.7	0.209647076	10.4823538	13	50	0.8746912
21.11	0.341584303	17.07921516	15	50	-0.6200338

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-67.55202394	3	-	-	NA
Fitted Model	-68.12918292	2	1.154317958	1	0.28264707
Reduced Model	-74.83638246	1	14.56871703	2	0.00068619

APPENDIX D. REFERENCES

ACGIH. (2007). 1-Methylnaphthalene and 2-methylnaphthalene. In Documentation of the threshold limit values and biological exposure indices (7th ed.). Cincinnati, OH.

ACGIH. (2020). 2020 TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents & biological exposure indices. Cincinnati, OH.

Akagi, JI; Toyoda, T; Cho, YM; Mizuta, Y; Nohmi, T; Nishikawa, A; Ogawa, K. (2015). Validation study of the combined repeated-dose toxicity and genotoxicity assay using gpt delta rats. Cancer Sci 106: 529-541. http://dx.doi.org/10.1111/cas.12634

Antoon, JW; Hernandez, ML; Roehrs, PA; Noah, TL; Leigh, MW; Byerley, JS. (2016). Endogenous lipoid pneumonia preceding diagnosis of pulmonary alveolar proteinosis. Clin Respir J 10: 246-249. http://dx.doi.org/10.1111/crj.12197

ATSDR. (2005). Toxicological profile for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene [ATSDR Tox Profile]. (PB2006100004). Atlanta, GA: Department of Health and Human Services. https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=PB2006100004

ATSDR. (2024). Toxic substances portal: Toxicological profiles [Database]. Atlanta, GA. Retrieved from https://www.atsdr.cdc.gov/toxprofiledocs/index.html

CalEPA. (2023). Consolidated table of OEHHA/CARB approved risk assessment health values. Sacramento, California. https://ww2.arb.ca.gov/resources/documents/consolidated-table-oehha-carb-approved-risk-assessment-health-values

CalEPA. (2024). Oehha chemical database [Database]. Sacramento, CA: Office of Environmental Health Hazard Assessment. Retrieved from https://oehha.ca.gov/chemicals

de Guzman, E; Sutton, B, Jr. (2013). Dye carriers. In Kirk-Othmer encyclopedia of chemical technology. Hoboken, NJ: John Wiley & Sons. http://dx.doi.org/10.1002/0471238961.0425050307212613.a01.pub2

Dinsdale, D; Verschoyle, RD. (1987). Pulmonary toxicity of naphthalene derivatives in the rat. Arch Toxicol Suppl 11: 288-291. http://dx.doi.org/10.1007/978-3-642-72558-6_54

DuPont. (1992). Initial submission: preliminary toxicity investigation of alpha-methylnaphthalene and diisobutyl carbinol with cover letter dated 101892 [TSCA Submission]. (MR-183. OTS0556357. 88-920010961. 8EHQ-1192-13158. TSCATS/441533). Haskell Laboratory.

ECHA. (2024). Substance infocard: 1-methylnaphthalene. Available online at https://echa.europa.eu/bg/substance-information/-/substanceinfo/100.001.788

Emi, Y; Konishi, Y. (1985). Endogenous lipid pneumonia in female B6C3F1 mice. In TC Jones; U Mohr; RD Hunt (Eds.), Respiratory system (pp. 166-168). Berlin, Germany: Springer. http://dx.doi.org/10.1007/978-3-642-96846-4_25

Florin, I; Rutberg, L; Curvall, M; Enzell, CR. (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 15: 219-232. http://dx.doi.org/10.1016/0300-483X(80)90055-4

IARC. (2024). Agents classified by the IARC monographs. Lyon, France. http://monographs.iarc.fr/ENG/Classification/List_of_Classifications.pdf

Jin, M; Kijima, A; Suzuki, Y; Hibi, D; Ishii, Y; Nohmi, T; Nishikawa, A; Ogawa, K; Umemura, T. (2012). In vivo genotoxicity of 1-methylnaphthalene from comprehensive toxicity studies with B6C3F1 gpt delta mice. J Toxicol Sci 37: 711-721.

Kaden, DA; Hites, RA; Thilly, WG. (1979). Mutagenicity of soot and associated polycyclic aromatic hydrocarbons to Salmonella typhimurium. Cancer Res 39: 4152-4159.
Kim, YS; Lee, MJ; Seo, DS; Kim, TH; Kim, MH; Lim, CH. (2020). Thirteen-week inhalation toxicity study of 1-methylnaphthalene in F344 rats. Toxicological Research 36: 13-20. http://dx.doi.org/10.1007/s43188-019-00009-1
Korsak, Z; Majcherek, W; Rydzyński, K. (1998). Toxic effects of acute inhalation exposure to 1-methylnaphthalene and 2-methylnaphthalene in experimental animals. Int J Occup Med Environ Health 11: 335-342.
Krishna, M. (2017). Patterns of necrosis in liver disease [Review]. Clin Liver Dis (Hoboken) 10: 53-56. http://dx.doi.org/10.1002/cld.653
Kulka, U; Schmid, E; Huber, R; Bauchinger, M. (1988). Analysis of the cytogenetic effect in human lymphocytes induced by metabolically activated 1- and 2-methylnaphthalene. Mutat Res 208: 155-158. http://dx.doi.org/10.1016/0165-7992(88)90052-8
Kumar, A; Cummings, KJ. (2021). Pulmonary alveolar proteinosis secondary to occupational exposure. Curr Pulmonol Rep 10: 30-39. http://dx.doi.org/10.1007/s13665-021-00267-1
Li, Z; Romanoff, LC; Trinidad, DA; Pittman, EN; Hilton, D; Hubbard, K; Carmichael, H; Parker, J; Calafat, AM; Sjoedin, A. (2014). Quantification of 21 metabolites of methylnaphthalenes and polycyclic aromatic hydrocarbons in human urine. Anal Bioanal Chem 406: 3119-3129. http://dx.doi.org/10.1007/s00216-014-7676-0
Lin, CY; Wheelock, AM; Morin, D; Baldwin, RM; Lee, MG; Taff, A; Plopper, C; Buckpitt, A; Rohde, A. (2009). Toxicity and metabolism of methylnaphthalenes: comparison with naphthalene and 1-nitronaphthalene [Review]. Toxicology 260: 16-27. http://dx.doi.org/10.1016/j.tox.2009.03.002
Lorber, M. (1972). Hematoxicity of synergized pyrethrin insecticides and related chemicals in intact, totally and subtotally splenectomized dogs. Acta Hepatogastroenterol 19: 66-78.
Marino, DJ. (2012). Age-specific absolute and relative organ weight distributions for B6C3F1 mice. J Toxicol Environ Health A 75: 76-99. http://dx.doi.org/10.1080/15287394.2011.625548
Mason, RT. (2002). Naphthalene. In Kirk-Othmer encyclopedia of chemical technology. Hoboken, NJ: John Wiley & Sons. http://dx.doi.org/10.1002/0471238961.1401160813011915.a01.pub2
Masumura, K; Matsui, M; Katoh, M; Horiya, N; Ueda, O; Tanabe, H; Yamada, M; Suzuki, H; Sofuni, T; Nohmi, T. (1999). Spectra of gpt mutations in ethylnitrosourea-treated and untreated transgenic mice. Environ Mol Mutagen 34: 1-8.
Matsushita, K; Ishii, Y; Kijima, A; Takasu, S; Kuroda, K; Takagi, H; Nohmi, T; Ogawa, K; Umemura, T. (2021). Background data of 2-year-old male and female F344 gpt delta rats. J Toxicol Pathol 34: 23-31. http://dx.doi.org/10.1293/tox.2020-0060
Mcdougal, JN; Pollard, DL; Weisman, W; Garrett, CM; Miller, TE. (2000). Assessment of skin absorption and penetration of JP-8 jet fuel and its components. Toxicol Sci 55: 247-255. http://dx.doi.org/10.1093/toxsci/55.2.247
METI. (2009a). 1-Methylnapthalene summary: [Combined repeat dose and reproductive/developmental toxicity screening test of 1-methylnaphthalene by oral administration in rats]. Japan Ministry of Economy, Trade and Industry. Shiga Research Institute. National Institute of Technology and Evaluation. https://www.nite.go.jp/chem/jcheck/tempfile_list.action?tpk=23402&ppk=7239&kinou=100&type=ja

METI. (2009b). [1-Methylnapthalene: Combined repeat dose and reproductive/developmental toxicity screening test of 1-methylnaphthalene by oral administration in rats]. Japan Ministry of Economy, Trade and Industry. Shiga Research Institute. National Institute of Technology and Evaluation. https://www.nite.go.jp/chem/jcheck/tempfile_list.action?tpk=23403&ppk=7239&kinou=100&type=ja

Murata, Y; Denda, A; Maruyama, H; Konishi, Y. (1993). Chronic toxicity and carcinogenicity studies of 1-methylnaphthalene in B6C3F1 mice. Toxicol Sci 21: 44-51. http://dx.doi.org/10.1093/toxsci/21.1.44

Murata, Y; Denda, A; Maruyama, H; Nakae, D; Tsutsumi, M; Tsujiuchi, T; Konishi, Y. (1997). Chronic toxicity and carcinogenicity studies of 2-methylnaphthalene in B6C3F1 mice. Fundam Appl Toxicol 36: 90-93. http://dx.doi.org/10.1006/faat.1996.2283

Murata, Y; Emi, Y; Denda, A; Konishi, Y. (1992). Ultrastructural analysis of pulmonary alveolar proteinosis induced by methylnaphthalene in mice. Exp Toxicol Pathol 44: 47-54. http://dx.doi.org/10.1016/S0940-2993(11)80137-5

NIOSH. (2018). NIOSH pocket guide to chemical hazards. Index of chemical abstracts service registry numbers (CAS No.). Atlanta, GA. http://www.cdc.gov/niosh/npg/npgdcas.html

NITE. (2009). Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG422). Data sheet: 1-Methylnaphthalene (CAS no. 90-12-0). https://www.nite.go.jp/chem/jcheck/tempfile_list.action?tpk=23401&ppk=7239&kinou=100&type=ja

NLM. (2024). PubChem: 1-Methylnaphthalene [CASRN: 90-12-0] [Database]. Retrieved from https://pubchem.ncbi.nlm.nih.gov/compound/7002

Nohmi, T; Katoh, M; Suzuki, H; Matsui, M; Yamada, M; Watanabe, M; Suzuki, M; Horiya, N; Ueda, O; Shibuya, T; Ikeda, H; Sofuni, T. (1996). A new transgenic mouse mutagenesis test system using Spi- and 6-thioguanine selections. Environ Mol Mutagen 28: 465-470. http://dx.doi.org/10.1002/(SICI)1098-2280(1996)28:4<465::AID-EM24>3.0.CO;2-C

NTP. (2018). Genetic toxicity evaluation of 1-methylnaphthalene in Salmonella/E.coli mutagenicity test or Ames test. Study 404676: Summary data. (NTP Study Number: 404676). https://tools.niehs.nih.gov/cebs3/views/index.cfm?action=main.download&bin_id=11134&library_id=14541&fileIdsSelected=1de240ff65768bcc0165ee3f8e450582

NTP. (2021). 15th Report on carcinogens. Research Triangle Park, NC. https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc

OSHA. (2022a). Air contaminants: Occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. (OSHA Standard 1915.1000). Washington, DC. https://www.govinfo.gov/content/pkg/CFR-2022-title29-vol7/pdf/CFR-2022-title29-vol7-sec1915-1000.pdf

OSHA. (2022b). Safety and health regulations for construction: Occupational health and environmental controls: Gases, vapors, fumes, dusts, and mists. Washington, DC. https://www.govinfo.gov/content/pkg/CFR-2022-title29-vol8/pdf/CFR-2022-title29-vol8-sec1926-55.pdf

OSHA. (2022c). Table Z-1: Limits for air contaminants. Occupational safety and health standards, subpart Z, toxic and hazardous substances. Washington, DC. https://www.govinfo.gov/content/pkg/CFR-2022-title29-vol6/pdf/CFR-2022-title29-vol6-sec1910-1000.pdf

Oyabu, T; Morimoto, Y; Izumi, H; Yoshiura, Y; Tomonaga, T; Lee, BW; Okada, T; Myojo, T; Shimada, M; Kubo, M; Yamamoto, K; Kawaguchi, K; Sasaki, T. (2015). Comparison between whole-body inhalation and nose-only inhalation on the deposition and health effects of nanoparticles. Environ Health Prev Med 21: 42-48. http://dx.doi.org/10.1007/s12199-015-0493-z

Rasmussen, RE; Do, DH; Kim, TS; Dearden, LC. (1986). Comparative cytotoxicity of naphthalene and its monomethyl- and mononitro- derivatives in the mouse lung. J Appl Toxicol 6: 13-20. http://dx.doi.org/10.1002/jat.2550060104

Salvaterra, E; Campo, I. (2020). Pulmonary alveolar proteinosis: from classification to therapy [Review]. Breathe 16: 200018. http://dx.doi.org/10.1183/20734735.0018-2020

Świercz, R; Stępnik, M. (2020). The effects of 1-methylnaphthalene after inhalation exposure on the serum corticosterone levels in rats. Int J Occup Med Environ Health 33: 691-699. http://dx.doi.org/10.13075/ijomeh.1896.01476

Świercz, R; Stępnik, M; Gromadzińska, J; Domeradzka-Gajda, K; Roszak, J; Wąsowicz, W. (2022). Metabolism and in vitro assessment of the mutagenic activity of urinary extracts from rats after inhalation exposure to 1-methylnaphthalene. Int J Occup Med Environ Health 35: 731-746. http://dx.doi.org/10.13075/ijomeh.1896.01955

Świercz, R; Wąsowicz, W. (2018). The distribution and excretion of 1-methylnaphthalene in rats exposed to 1-methylnaphthalene by inhalation. Int J Occup Med Environ Health 31: 763-770. http://dx.doi.org/10.13075/ijomeh.1896.01224

Taki, T; Nakazima, T; Emi, Y; Konishi, Y; Hayashi, A; Matsumoto, M. (1986). Accumulation of surfactant phospholipids in lipid pneumonia induced with methylnaphthalene. Lipids 21: 548-552. http://dx.doi.org/10.1007/BF02534050

Trapnell, BC; Nakata, K; Bonella, F; Campo, I; Griese, M; Hamilton, J; Wang, T; Morgan, C; Cottin, V; McCarthy, C. (2019). Pulmonary alveolar proteinosis [Review]. Nat Rev Dis Primers 5: 17. http://dx.doi.org/10.1038/s41572-019-0066-3

U.S. EPA. (1980). Water quality criteria documents; availability Appendix C--Guidelines and methodology used in the preparation of health effects assessment chapters of the consent decree water quality criteria documents. Fed Reg 45: 79347-79357.

U.S. EPA. (1988). Recommendations for and documentation of biological values for use in risk assessment [EPA Report]. (EPA600687008). Cincinnati, OH. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. EPA. (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry [EPA Report]. (EPA600890066F). Research Triangle Park, NC. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=51174829&CFTOKEN=25006317

U.S. EPA. (1998). Toxicological review of naphthalene (CAS no. 91-20-3) in support of summary information on the Integrated Risk Information System (IRIS) [EPA Report]. Washington, DC: Integrated Risk Information System. https://iris.epa.gov/static/pdfs/0436tr.pdf

U.S. EPA. (2002a). Hepatocellular hypertrophy. HED guidance document #G2002.01 [EPA Report]. Washington, DC.

U.S. EPA. (2002b). A review of the reference dose and reference concentration processes [EPA Report]. (EPA630P02002F). Washington, DC. https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf

U.S. EPA. (2003). Toxicological review of 2-methylnaphthalene (CASRN 91-57-6) in support of summary information on the Integrated Risk Information System (IRIS) [EPA Report]. (EPA635R03010). Washington, DC. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1006tr.pdf

U.S. EPA. (2005). Guidelines for carcinogen risk assessment [EPA Report]. (EPA630P03001F). Washington, DC. https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

U.S. EPA. (2007). Provisional peer-reviewed toxicity values for 2-methylnaphthalene (CASRN 91-57-6) [EPA Report]. Cincinnati, OH. https://cfpub.epa.gov/ncea/pprtv/documents/Methylnaphthalene2.pdf

U.S. EPA. (2011a). Health effects assessment summary tables (HEAST) for superfund [EPA Report]. Washington, DC. https://epa-heast.ornl.gov/heast.php

U.S. EPA. (2011b). Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose. (EPA100R110001). Washington, DC. https://www.epa.gov/sites/production/files/2013-09/documents/recommended-use-of-bw34.pdf

U.S. EPA. (2012). Benchmark dose technical guidance [EPA Report]. (EPA100R12001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. https://www.epa.gov/risk/benchmark-dose-technical-guidance

U.S. EPA. (2018). 2018 Edition of the drinking water standards and health advisories tables [EPA Report]. (EPA822F18001). Washington, DC: U.S. Environmental Protection Agency, Office of Water. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100U7U8.txt

U.S. EPA. (2022). Access CDR data [Database]. Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. Retrieved from https://www.epa.gov/chemical-data-reporting/access-cdr-data

U.S. EPA. (2024a). CompTox chemicals dashboard: 1-methylnaphthalene. Available online at https://comptox.epa.gov/dashboard/chemical/details/DTXSID9020877 (accessed February 16, 2022).

U.S. EPA. (2024b). Integrated risk information system (IRIS) database [Database]. Washington, DC. Retrieved from http://www.epa.gov/iris/

U.S. EPA. (2024c). The Toxic Substances Control Act's (TSCA) inventory (non-CBI). Updated February 2024 [Database]. Washington, DC: U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. Retrieved from https://www.epa.gov/tsca-inventory/how-access-tsca-inventory#download

Wang, D; Bruyneel, B; Kamelia, L; Wesseling, S; Rietjens, IMC, M; Boogaard, PJ. (2020). In vitro metabolism of naphthalene and its alkylated congeners by human and rat liver microsomes via alkyl side chain or aromatic oxidation. Chem Biol Interact 315: 108905. http://dx.doi.org/10.1016/j.cbi.2019.108905

WHO. (2006). Aromatic hydrocarbons. In Safety evaluation of certain food additives and contaminants Prepared by the sixty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JEFCA) (pp. 291-316). (WHO Food Additives Series: 54). Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety. https://apps.who.int/iris/handle/10665/43265

WHO. (2024). Online catalog for the Environmental Health Criteria (EHC) monographs [Database]. Geneva, Switzerland: World Health Organization (WHO). Retrieved from https://www.inchem.org/pages/ehc.html

Wong, BA. (2007). Inhalation exposure systems: Design, methods and operation [Review]. Toxicol Pathol 35: 3-14. http://dx.doi.org/10.1080/01926230601060017