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Provisional Peer-Reviewed Toxicity Values for

Methylcyclohexane
(CASRN 108-87-2)

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

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https://www.epa.gov/pprtv

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Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
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Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development (ORD) Center for Public Health and Environmental Assessment (CPHEA) website at https://ecomments.epa.gov/pprtv.

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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.

DRAFT PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR METHYLCYCLOHEXANE (CASRN 108-87-2)

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

Methylcyclohexane (CASRN 108-87-2) is a saturated cyclic hydrocarbon; its structure consists of a six-membered ring substituted with one methyl group. Methylcyclohexane is used as a solvent and as a raw material in synthetic processes for pharmaceuticals and dyes (OECD, 2014). It is also used in jet fuel and in cleaning solutions. Methylcyclohexane is listed on the U.S. EPA's Toxic Substances Control Act (TSCA) public inventory (U.S. EPA, 2021d) and is registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2021).

Methylcyclohexane is synthesized by catalytic hydrogenation of toluene (NCBI, 2021; Campbell, 2011) or by reacting benzene with methane at elevated temperatures (Baxter, 2012). Methylcyclohexane can also be distilled from crude petroleum oils via the acidic hydrocracking of polycyclic aromatics (Baxter, 2012). The U.S. national aggregate production volume in 2015 ranged from 500,000 to <1,000,000 pounds (U.S. EPA, 2021a).

The empirical formula for methylcyclohexane is C_7H_{14}. The chemical structure is shown in Figure 1. Table 1 summarizes the physicochemical properties of methylcyclohexane. Methylcyclohexane is a clear, colorless liquid that is slightly soluble in water (14 mg/L at 25°C). In the air, methylcyclohexane will exist in the vapor (gas) phase, based on a measured vapor pressure of 46 mm Hg. Methylcyclohexane will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals with a half-life of 1.1 days, calculated from an estimated hydroxyl radical reaction rate constant of 1.02×10^{-11} cm^3/molecule-second at 25°C. Volatilization from dry soil surfaces is expected, based upon its vapor pressure. Volatilization from water or moist soil surfaces is expected based upon the Henry's law constant of 0.43 atm-m^3/mole. The estimated soil adsorption coefficients for methylcyclohexane indicate low to moderate potential for mobility in soil and low to moderate potential to adsorb to suspended solids and sediment in aquatic environments. Methylcyclohexane does not contain functional groups that are likely to hydrolyze under environmental conditions; therefore, hydrolysis is not expected to be an important fate process.

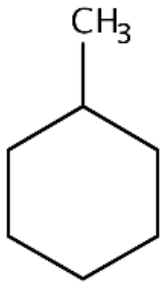

Figure 1. Methylcyclohexane (CASRN 108-87-2) Structure

Table 1. Physicochemical Properties of Methylcyclohexane (CASRN 108-87-2)

Property (unit)	Value[a]
Physical state	Liquid[b]
Boiling point (°C at 25 mm Hg)	101
Melting point (°C)	−127
Density (g/cm^3 at 20°C)	0.798
Vapor pressure (mm Hg at 25°C)	46
pH (unitless)	NA
Acid dissociation constant (pKa) (unitless)	NA
Solubility in water (mg/L at 25°C)	14 (reported as 1.47×10^{-4} mol/L)
Octanol-water partition coefficient (log K_{ow})	3.61
Henry's law constant (atm-m^3/mol at 25°C)	0.43
Soil adsorption coefficient (K_{oc}) (L/kg)	302 (estimated)
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	1.02×10^{-11}
Atmospheric half-life (d)	1.052 (calculated based on 1.5×10^6 OH/cm^3 and a 12-h day)[c]
Relative vapor density (air = 1)	3.39[b]
Molecular weight (g/mol)	98.189
Flash point (open cup in °C)	−4[b]

[a]U.S. EPA (2021b); data were extracted from the U.S. EPA CompTox Chemicals Dashboard (methylcyclohexane, CASRN 108-87-2; https://comptox.epa.gov/dashboard/chemical/details/DTXSID0047749; accessed February 16, 2022).
[b]NCBI (2021).
[c]U.S. EPA (2012b) (with user-entered inputs for boiling point = 101, melting point = −127, water solubility = 14 mg/L, vapor pressure = 46 mm Hg, Henry's law constant = 0.43, log K_{ow} = 3.61, and SMILES = C(CCCC1)(C1)C).

NA = not applicable; SMILES = simplified molecular input line entry system.

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

Table 2. Summary of Available Toxicity Values for Methylcyclohexane (CASRN 108-87-2)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference[c]
Noncancer			
IRIS	NV	NA	U.S. EPA (2021c)
HEAST (chronic and subchronic RfCs)	3 mg/m^3	Based on renal mineralization and papillary hyperplasia in 1-yr rat inhalation study	U.S. EPA (1997)
DWSHA	NV	NA	U.S. EPA (2018)
ATSDR	NV	NA	ATSDR (2021)
IPCS	NV	NA	IPCS (2021)
CalEPA	NV	NA	CalEPA (2021); CalEPA (2020)
OSHA (PEL)	500 ppm (2,000 mg/m^3)	8-h TWA (for general industry, construction, and shipyard employment)	OSHA (2021a); OSHA (2021b); OSHA (2021c)
NIOSH (REL)	400 ppm (1,600 mg/m^3)	10-h TWA	NIOSH (2019)
NIOSH (IDLH)	1,200 ppm	Based on 10% of the lower explosive limit of 1.2%	NIOSH (1994)
ACGIH (TLV)	400 ppm	8-h TWA; based on upper respiratory tract irritation, CNS impairment, and liver and kidney damage	ACGIH (2021)
Cancer			
IRIS	NV	NA	U.S. EPA (2021c)
HEAST	NV	NA	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2018)
NTP	NV	NA	NTP (2016)
IARC	NV	NA	IARC (2021)
CalEPA	NV	NA	CalEPA (2021); CalEPA (2020)
ACGIH	NV	NA	ACGIH (2021)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration.
[b]Parameters: IDLH = immediately dangerous to life or health; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = reference concentration; TLV = threshold limit value.
[c]Reference date is the publication date for the database and not the date the source was accessed.

CNS = central nervous system; NA = not applicable; NV = not available; TWA = time-weighted average.

Non-date limited literature searches were conducted in July 2019 and updated in June 2023 for studies relevant to the derivation of provisional toxicity values for methylcyclohexane. Searches were conducted using the U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE[1] (including TSCATS1), Scopus, and Web of Science. The National Technical Reports Library (NTRL) was searched for government reports from 2018 through September 2020[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), the U.S. EPA 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 IPCS INCHEM, Japan Existing Chemical Data Base (JECDB), Organisation for Economic Co-operation and Development (OECD) Screening Information Data Sets (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD HPV, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

[1]Note that this version of TOXLINE is no longer updated (https://www.nlm.nih.gov/databases/download/toxlinesubset.html); therefore, it was not included in the literature search update from June 2023.

[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 evidence bases, respectively, for methylcyclohexane and include all potentially relevant repeated-dose short-term, subchronic, and chronic studies, as well as reproductive and developmental toxicity studies. Principal studies used in the PPRTV assessment for derivation of provisional toxicity values are identified in bold. The phrase "statistical significance" and term "significant," used throughout the document, indicate a *p*-value of <0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for Methylcyclohexane (CASRN 108-87-2)							
Category[a]	**Number of Male/Female, Strain, Species, Exposure Route, 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)							
Short-term	**5−10 M/5−10 F, Crj:CD (Sprague Dawley) rat, gavage (corn oil), 28 d** **Reported doses: 0, 100, 300, 1,000 mg/kg-d**	**0, 100, 300, 1,000**	**Increased incidence of renal tubule hyaline droplet degeneration in males.**	**100**	**300**	**ECHA (2001c)**	**PS, NPR**
Short-term	12 M/5−12 F group, Crl:CD (Sprague Dawley) rat, gavage (corn oil), from 14 d prior to mating, through mating and gestation until LD 4 (mated females), or for 28 d (males and unmated females) Reported doses: 0, 62.5, 250, 1,000 mg/kg-d	0, 62.5, 250, 1,000	Increased liver and kidney weights in males and unmated females and increased incidence of renal tubule hyaline droplets in males.	250	1,000	JECDB (2013) (This study is published in Japanese with some tables and figures in English, or reported in secondary sources.); ECHA (2011a); ECHA (2011b)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for Methylcyclohexane (CASRN 108-87-2)							
Category[a]	**Number of Male/Female, Strain, Species, Exposure Route, Reported Doses, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Reproductive/ developmental	12 M/12 F group, Crl:CD (Sprague Dawley) rat, gavage (corn oil), from 14 d prior to mating, through mating and gestation until LD 4 (females), or for 28 d (males) Reported doses: 0, 62.5, 250, 1,000 mg/kg-d	0, 62.5, 250, 1,000	No reproductive or developmental effects.	1,000	NDr	JECDB (2013) (This study is published in Japanese with some tables and figures in English, or reported in secondary sources.); ECHA (2011a); ECHA (2011b)	NPR
2. Inhalation (mg/m^3)							
Subchronic	10 M/10 F, Sprague Dawley rat, whole-body vapor inhalation, 6 h/day, 5 d/wk for 13 wk Reported analytical concentrations: 0, 101.9, 339.4, 1,608 ppm	0, 73.07, 243.4, 1,153	None identified due to lack of details in English on crucial endpoints.	NDr	NDr	Kim et al. (2006) (This study is published in Korean with English abstract, tables, and figures.)	PR
Chronic	65 M/65 F, CDF F344/CrlBR rat, whole-body vapor inhalation, 6 h/d, 5 d/wk for 12 mo Reported analytical concentrations: 0, 400.2, 2,004 ppm	0, 287.0, 1,437	Increased incidences of renal medullary mineralization and papillary hyperplasia in males.	287.0	1,437	AFRL (1985); API (1985)	PS, NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for Methylcyclohexane (CASRN 108-87-2)							
Category[a]	**Number of Male/Female, Strain, Species, Exposure Route, Reported Doses, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Chronic	0 M/200 F, C57BL/6J mouse, whole-body vapor inhalation, 6 h/d, 5 d/wk for 12 mo Reported analytical concentrations: 0, 400.2, 2,004 ppm	0, 287.0, 1,437	No clear treatment-related, toxicologically relevant effects applicable to human health risk assessment[d].	1,437	NDr	AFRL (1985); API (1985)	NPR
Chronic	**100 M/0 F, Syrian golden hamster, whole-body vapor inhalation, 6 h/d, 5 d/wk for 12 mo** **Reported analytical concentrations: 0, 400.2, 2,004 ppm**	**0, 287.0, 1,437**	**Decreased body weight in males.**	**NDr**	**287**	AFRL (1985); API (1985)	**PS, NPR**

Table 3A. Summary of Potentially Relevant Noncancer Data for Methylcyclohexane (CASRN 108-87-2)

Category[a]	Number of Male/Female, Strain, Species, Exposure Route, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Chronic	4 M/4 F, beagle dog, whole-body vapor inhalation, 6 h/d, 5 d/wk for 12 mo Reported analytical concentrations: 0, 400.2, 2,004 ppm	0, 287.0, 1,437	No clear treatment-related, toxicologically relevant effects applicable to human health risk assessment[d].	1,437	NDr	AFRL (1985); API (1985)	NPR

[a]Duration categories are defined as follows: acute = exposure for ≤24 hours; short-term = repeated exposure for >24 hours to ≤30 days; subchronic = repeated exposure for >30 days or ≤10% life span for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% life span for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: Doses are presented as ADDs (mg/kg-day) for oral noncancer effects and as HECs (in mg/m^3) for inhalation noncancer effects. The HEC from animal studies was calculated using the equation for ER effects from a Category 3 gas (U.S. EPA, 1994): HEC_{ER} = continuous concentration in mg/m^3 × ratio of animal:human blood-gas partition coefficients using a default coefficient of 1 because the blood-air partition coefficients (logK_{blood}) for mice, hamsters, and dogs are unknown and the rat logK_{blood} (0.79) is greater than the human logK_{blood} (0.61), as indicated by Abraham et al. (2005).
[c]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study.
[d]Limited endpoints were evaluated. In addition, details on the collection of chamber concentrations and exposure to control animals were not provided.

ADD = adjusted daily dose; ER = extrarespiratory; F = female(s); HEC = human equivalent concentration; LD = lactation day;
LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level.

Table 3B. Summary of Potentially Relevant Cancer Data for Methylcyclohexane (CASRN 108-87-2)					
Category	**Number of Male/Female, Strain, Species, Exposure Route, 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)					
ND					
2. Inhalation (mg/m^3)					
Carcinogenicity	65 M/65 F, CDF F344/CrlBR rat, whole-body vapor inhalation, 6 h/d, 5 d/wk for 12 mo Reported analytical concentrations: 0, 400.2, 2,004 ppm	0, 287.0, 1,437	No evidence of carcinogenicity in a limited study.	AFRL (1985); API (1985)	NPR
Carcinogenicity	0 M/200 F, C57BL/6J mouse, whole-body vapor inhalation, 6 h/d, 5 d/wk for 12 mo Reported analytical concentrations: 0, 400.2, 2,004 ppm	0, 287.0, 1,437	No evidence of carcinogenicity in a limited study.	AFRL (1985); API (1985)	NPR
Carcinogenicity	100 M/0 F, Syrian golden hamster, whole-body vapor inhalation, 6 h/d, 5 d/wk for 12 mo Reported analytical concentrations: 0, 400.2, 2,004 ppm	0, 287.0, 1,437	No evidence of carcinogenicity in a limited study.	AFRL (1985); API (1985)	NPR

Table 3B. Summary of Potentially Relevant Cancer Data for Methylcyclohexane (CASRN 108-87-2)

Category	Number of Male/Female, Strain, Species, Exposure Route, Reported Doses, Study Duration	Dosimetry[a]	Critical Effects	Reference (comments)	Notes[b]
Carcinogenicity	4 M/4 F, beagle dog, whole-body vapor inhalation, 6 h/d, 5 d/wk for 12 mo Reported analytical concentrations: 0, 400.2, 2,004 ppm	0, 287.0, 1,437	No evidence of carcinogenicity in a limited study.	AFRL (1985); API (1985)	NPR

[a]Dosimetry: Inhalation exposure units are expressed as HECs (mg/m^3). The HEC from animal studies was calculated using the equation for ER effects from a Category 3 gas (U.S. EPA, 1994): HEC_{ER} = continuous concentration in mg/m^3 × ratio of animal:human blood-gas partition coefficients using a default coefficient of 1 because the blood-air partition coefficients ($\log K_{blood}$) for mice, hamsters, and dogs are unknown and the rat $\log K_{blood}$ (0.79) is greater than the human $\log K_{blood}$ (0.61), as indicated by Abraham et al. (2005).
[b]Notes: NPR = not peer reviewed.

ER = extrarespiratory; F = female(s); HEC_{ER} = human equivalent concentration; M = male(s).

2.1. HUMAN STUDIES

2.1.1. Oral Exposures

No studies were identified.

2.1.2. Inhalation Exposures

No human studies adequate for determination of no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) values were identified. Studies that reported human data were confounded by co-exposures to other volatile organic compounds (VOCs) and were not considered suitable for hazard identification or dose-response.

2.2. ANIMAL STUDIES

2.2.1. Oral Exposures

The effects of oral exposure to methylcyclohexane in animals have been evaluated in short-term studies in rats (JECDB, 2013; ECHA, 2001c), one of which incorporated a screen for reproductive and developmental effects (JECDB, 2013).

Short-Term Studies (Including Combined Reproductive and Developmental Screening)

ECHA (2001c)

An unpublished, Good Laboratory Practice (GLP)-compliant OECD guideline 407 repeated-dose 28-day oral toxicity study in rats was summarized in secondary sources (ECHA, 2001c), which included select data tables for some endpoints that were adequate for review; the primary report was not available.

Crj:CD (Sprague Dawley) rats (five/sex/group), aged 5 weeks at study initiation, were administered methylcyclohexane (99.8% pure) doses of 0, 100, 300, or 1,000 mg/kg-day in corn oil, via gavage, for 28 days. An additional five animals/sex were included in the control and high-dose groups to evaluate reversal of effects following a 14-day recovery period. Analytical measurements were taken at the first and last preparation of gavage solutions and were within 99.5 and 107.1%, respectively, of nominal concentrations. Doses were selected based on a preliminary 14-day oral toxicity study that reported salivation in both sexes at 1,000 mg/kg-day. Rats were checked 3 times/day during dosing for mortality and cage-side observations. Detailed clinical observations and body-weight measurements were made once a week. Food consumption was measured throughout the study. On the first and last day of dosing, neurobehavioral endpoints (grip strength, motor activity, and hindlimb foot splay) were examined. Urine was collected in the last week of dosing by placing the rats in metabolic cages and was tested for volume, color, sediment, osmotic pressure, pH, occult blood, ketones, glucose [GLU], protein, bilirubin, and urobilinogen. The day after the last dose, rats (five/sex/group) were euthanized and examined. During the recovery period, the remaining rats in the control and high-dose groups were checked twice a day for mortality and cage-side observations, body weights continued to be recorded weekly, and urine was collected during the last week of recovery and examined as above. Endpoints examined at the times of sacrifice included hematology (hematocrit [HCT], hemoglobin [HGB], red blood cell [RBC] count, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], platelets [PLT], differential white blood cell [WBC] counts, reticulocytes, prothrombin time [PT], activated partial thromboplastin time [APTT]), and fibrinogen) and clinical biochemistry (alkaline phosphatase [ALP], aspartate aminotransferase [AST], GLU, total cholesterol [TC], triglyceride [TG], blood urea nitrogen [BUN], creatinine [CRN], total bilirubin [TBIL], total

protein [TP], albumin [ALB], albumin:globulin ratio [A/G], sodium [Na], potassium [K], chloride [Cl], calcium [Ca], and inorganic phosphorus [IP]). Organs that were weighed were not specified (only data for absolute and relative liver and ovary weights and relative epididymis weights were provided in the secondary sources). Animals were grossly examined, and histopathology was performed on 29−30 tissues. Statistical tests included the Bartlett test, Dunnett test, Steel test, Fisher's exact test, and Mann-Whitney U test.

No rats died during the study. The only clinical sign reported was salivation occurring within 1 hour of dosing in males at ≥300 mg/kg-day and in females at 1,000 mg/kg-day. Data on body weight were presented only as body-weight gain. Statistically significant increases in body-weight gain during dosing (days 0−27) were observed in males at 300 mg/kg-day (26% increase) and 1,000 mg/kg-day (20% increase) compared to controls (see Table B-1). Food consumption was increased in the same dose groups. Treated females showed no increase in body-weight gain. There were no functional neurobehavioral changes at any dose in either sex.

No treatment-related hematological effects were observed (data not shown). Serum chemistry results were unremarkable (see Table B-2). Sporadic statistically significant changes either showed no relationship to dose, fell within expected normal ranges for age-matched CD (Sprague Dawley) rats (Giknis and Clifford, 2006), were not consistent with other findings, occurred during the recovery period only, and/or were of unclear toxicological significance.

Statistically significantly increases in total protein (by 7%, relative to controls) and total bilirubin (by 100% relative to controls) were in males at 1,000 and 300 mg/kg-day, respectively, at the end of treatment. In addition, ALP was statistically significantly decreased (by 34% relative to controls) in the high-dose males. In females treated with 1,000 mg/kg-day, total cholesterol was statistically significantly increased (by 46% relative to controls) and AST was statistically significantly decreased (by −11% relative to controls). In addition, the A/G ratio was statistically significantly increased (by 14% relative to controls) at 100 mg/kg-day at the end of treatment in females.

Absolute and relative liver weights were statistically significantly increased (by 22%, relative to controls) in high-dose males at the end of treatment; increases persisted through the recovery period (see Table B-3). An increase of 16% in absolute liver weight was seen in males at 300 mg/kg-day, but the change in relative liver weight at this dose was only 6%. In females at 1,000 mg/kg-day, an increase in absolute weight of 10% and a significant 13% increase in relative weight compared to controls were reported. After recovery, female liver weights were increased <10% relative to controls. No changes in other organ weights at the end of treatment were reported in either sex.

Microscopic examination showed a significant increase in the incidence of hepatocellular hypertrophy in 5/5 high-dose males and 1/5 high-dose females at the end of the treatment period (see Table B-4); this lesion was not seen in animals euthanized after the recovery period. Male rats also showed kidney hyaline droplet degeneration in 0/5, 1/5, 5/5, and 5/5 animals in the control, 100, 300, and 1,000 mg/kg-day groups, respectively, at the end of treatment. This lesion was observed in 1/5 high-dose males after recovery. In addition to "hyaline droplet degeneration," which was observed only in males, the secondary source for this study also reported "hyaline droplet formation" separately, an effect that was seen only in females. There is no description in the secondary report of the two lesions or explanation for considering them separately. Hyaline droplet formation was reported in 2/5 high-dose females at the end of dosing and reached statistical significance in high-dose females (5/5) at the end of recovery. The study authors of the secondary report considered the hyaline droplet degeneration in the kidneys of male rats to be alpha 2u-globulin (α2u-g)-related and thus not relevant for humans, although it was not specified whether the presence of α2u-g was actually assessed in this study. No increase was reported in the incidence of other lesions that typically occur as part of the known progression in α2u-g-associated nephrotoxicity (e.g., single cell necrosis in epithelium of P2 segment of proximal tubule, accumulation of granular casts at junction of P3 segment and loop of Henle, cell proliferation within the P2 segment, linear mineralization of tubules within the renal papilla)(U.S. EPA, 1991). The study authors of the secondary report considered the hyaline droplets in females to be of unclear etiology. U.S. EPA (1991) noted that hyaline droplets may occur in female rats, albeit less frequently than in male rats, due to accumulation of proteins other than α2u-g. As a result, the relationship to treatment and the toxicological significance of the formation of these droplets in high-dose female rats are unclear.

A NOAEL of 100 mg/kg-day and a LOAEL of 300 mg/kg-day were identified from this study based on increased incidence of renal hyaline droplet degeneration in male rats. Chemicals inducing excessive accumulation of α2u-g in the hyaline droplets of male kidneys bind reversibly to the α2u-g protein specifically produced in male rats, thus leading to hyaline droplet accumulation and subsequent development of nephrotoxicity and possible renal tumor formation (U.S. EPA, 1991). According to the U.S. EPA guidelines, the fulfillment of three criteria is necessary to determine that renal toxicity is associated with α2u-g and therefore not relevant to human health: (1) increased size and number of hyaline droplets; (2) identification of the accumulating protein as α2u-g; and (3) the presence of other lesions associated with α2u-g nephropathy (e.g., single cell necrosis, granular casts formation, and linear mineralization) (U.S. EPA, 1991). Although the final step in the α2u-g pathway is the formation of kidney tumors, the presence of kidney tumors is not always evident and should not invalidate other findings characteristic of α2u-g toxicity. Other factors such as dose, other toxicities not related to α2u-g, and length of exposure may complicate the ability to detect kidney tumors (U.S. EPA, 1991). Details included in the secondary report did not indicate that α2u-g was measured in the study. The secondary report also did not demonstrate a pathological sequence of other lesions associated with α2u-g progression. Finally, hyaline droplet formation was observed in 2/5 high-dose females at the end of treatment and 5/5 females at the end of the recovery period, suggesting that kidney effects not related to α2u-g may be occurring (ECHA, 2001c); together, the data provide insufficient evidence to meet two of the three criteria outlined in U.S. EPA (1991) to definitively attribute the observed hyaline droplet degeneration in male rats to α2u-g nephropathy. Therefore, these effects are considered to be potentially relevant to human health. At higher doses, biologically and statistically significant increases in absolute and relative liver weights in male and female rats and significantly increased liver cell hypertrophy in male rats

were observed. In this study, the administered doses of 100, 300, and 1,000 mg/kg-day correspond to human equivalent doses (HEDs) of 24.9, 74.6, and 249 mg/kg-day for males and 23.2, 69.7, and 232 mg/kg-day in females[3].

JECDB (2013); ECHA (2011a); ECHA (2011b)

A GLP-compliant, unpublished OECD guideline 422 repeated-dose toxicity study with an reproductive/developmental screening test is available as a report in Japanese (JECDB, 2013) with some text, figures, and tables in English. The same study was described in detail in secondary sources (ECHA, 2011a, b). The summary below was generated using the data from the main study, along with additional methodological details provided in the secondary sources.

Ten-week-old Crl:CD (Sprague Dawley) rats (12 breeding pairs/group) were administered methylcyclohexane (99.9% purity) in a corn oil vehicle, via gavage, at (nominal) doses of 0, 62.5, 250, or 1,000 mg/kg-day. Males were dosed from 14 days prior to mating and during the mating period for a total of 28 days. Females were dosed from 14 days prior to mating and throughout mating and gestation until day 4 of lactation. A satellite set of unmated females (10 per control and high-dose groups and 5 per low- and mid-dose groups) were dosed for a total of 28 days. Half of the males from all groups (6/12 animals) and 5/10 unmated females from the control and high-dose groups were allowed to recover for 14 days following the end of the dosing period. Animals were euthanized either 1 day after the last administered dose or after 14 days of recovery, respectively.

Rats were checked twice a day during dosing for mortality and to make cage-side observations. Detailed clinical signs (functional observational battery), including posture, palpebral closure, excessive grooming, repetitive circling, biting behavior, clonic convulsions, tonic convulsions, ease of removal from cage, ease of handling, muscle tone, fur condition, mucous membranes condition, lacrimation, salivation, piloerection, pupil size, respiration, and behavior in an open field test (frequency of urination, defecation, rearing and grooming, gait, palpebral closure, consciousness, behavioral abnormalities, and righting reflex) were evaluated in all groups before treatment and once a week during the dosing period. Sensory reactivity (pupillary reflex, approaching behavior, response to touch, auditory reflex, and pain reflex), grip strength, and spontaneous motor activity were measured at the end of dosing in males and unmated females. Body weights were measured twice a week during dosing and on recovery days 1, 4, 8, 11, 14, and 15. Food and water consumption were measured throughout the study. Blood was drawn from males and unmated females at the end of dosing and after the recovery period for hematology (RBC, HGB, HCT, MCV, MCH, MCHC, PLT, reticulocytes, PT, APTT, fibrinogen, WBCs, lymphocytes, neutrophils, eosinophils, basophils, monocytes) and clinical chemistry (AST, alanine aminotransferase [ALT], ALP, γ-glutamyl transferase [GGT], TP, ALB, A/G, TBIL, BUN, CRN, GLU, TC, TG, Na, K, Cl, Ca, IP, and iron [Fe]) measurements. Thyroid hormone (triiodothyronine [T_3], thyroxin [T_4], and thyroid stimulating hormone [TSH]) levels were measured in both sexes at the end of dosing. Other endpoints included urinalysis (volume,

[3]The adjusted daily doses (ADDs) were converted to HEDs of 24.9, 74.6, and 249 mg/kg-day in low-, mid-, and high-dose males and 23.2, 69.7, and 232 mg/kg-day in low-, mid-, and high-dose females using dosimetric adjustment factors (DAFs) of 0.249 (males) and 0.232 (females), where HED = ADD × DAF. 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. In the absence of body-weight data in the study, reference body weights of 0.267 kg for male and 0.204 kg for female Sprague Dawley rats in a subchronic study were used (U.S. EPA, 1988). For humans, the reference body-weight value of 70 kg was used (U.S. EPA, 1988).

color, pH, presence of protein, GLU, ketone bodies, bilirubin, occult blood, urobilinogen, epithelial cells, RBC, WBC, casts, and crystals) and organ weights (brain, pituitary, salivary glands, thyroids, thymus, heart, liver, spleen, kidneys, adrenals, testes, epididymides, ventral prostate, seminal vesicles, ovaries, and uterus) in males and unmated females at the end of dosing and after the recovery period. Gross necropsy was performed on males and unmated females after dosing and after the recovery period and on mated females at the time of sacrifice. With the exception of kidney tissues, which were examined in all male dose groups, histological examinations after dosing were done on 44 tissues in 6/12 male and 5/10 unmated females in the control and high-dose groups and in recovery animals. Histological examination of mated females was performed on ovaries, uterus, vagina, and mammary gland tissues only.

Females in the mating groups were monitored for estrous cycle length and normality. Reproductive indices (copulation index, fertility index, implantation index, gestation index, delivery index, and birth index) were calculated. Female reproductive organ weights (ovaries and uterus) were measured, and histopathological analysis included examinations of the mammary gland, ovary, uterus, and vagina. Reproductive analysis in males was limited to organ weights (testis, epididymis, ventral prostate, and seminal vesicles) and histopathology of those tissues; sperm parameters were not evaluated. Litter observations included the number and sex of pups, live and stillbirths, postnatal mortality, physical or behavioral abnormalities, pup body weights and litter weights (lactation days [LDs] 0−4) and weight gain, and presence of gross anomalies. Sex ratio at birth, live birth index, and viability indices were determined.

Details of statistical analyses were reported in Japanese in the primary study. Statistical analysis, as described in the secondary sources (ECHA, 2011a, b), indicates the use of Bartlett's test, Dunnett's test, Steel's test, F test, Student's *t*-test, Aspin-Welch *t*-test, Fisher's exact test, and/or Cochran-Armitage test. Litter observations included the number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, weight gain, and physical or behavioral abnormalities.

No rats died during the study. Transient salivation was seen in some high-dose animals immediately after dosing. Body weights of treated rats were comparable to controls throughout the study. No treatment-related changes in food or water consumption were seen. There were no changes in sensory reactivity, grip strength, or spontaneous motor activity in any group. At the end of the treatment period, there were no significant hematological changes in males and only small increases in reticulocyte and monocyte counts (within expected ranges) in the high-dose unmated females; these changes were not seen in the treated recovery group females. Serum chemistry changes are shown in Table B-5. Potential noteworthy findings were limited and included statistically significant increases in ALT (74% increase), GGT (93% increase), and TC (80% increase) in high-dose males at the end of treatment; an increase in ALT (34% increase) and TC (60% increase) was seen after the recovery period as well. These and all other observed serum chemistry changes were, however, within the range expected for age- and sex-matched rats of this strain (Giknis and Clifford, 2006). Thyroid hormone levels were comparable across groups in both sexes. Urinalysis showed no treatment-related changes.

At the end of the treatment period, statistically and biologically (>10%) significant increases in absolute and relative liver and kidney weights were found in the high-dose male rats and in relative liver and kidney weights in unmated females relative to controls (see Table B-6). Smaller changes that were not statistically significant were seen in the treated recovery group

males. High-dose unmated females also showed statistically significant increases in absolute and relative adrenal weights and relative uterus weights. Increased relative uterus weight was within the historical normal range of the testing facility and was not considered treatment related. These changes were not biologically significant or were not seen at all in the treated recovery group females. Uterus weights were not increased in the mated females at any dose (evaluated on LD 5).

No treatment-related gross findings were observed at necropsy. The only treatment-related finding identified by histopathological examination was an increased incidence of hyaline droplets in the kidneys of male rats at the end of the treatment period (observed in 0/6, 0/6, 4/6, and 6/6 males in the control, low-, mid-, and high-dose groups, respectively). The pairwise increase in the high-dose group was statistically significant, as was the overall trend. Lesion severity was reported to be slight in all cases. The lesion was not seen in the male rats examined after the recovery period. The study authors of the secondary report of this study (ECHA, 2011a) considered this lesion likely related to α2u-g accumulation, which is specific to male rats and not relevant to humans. It is unclear, however, whether α2u-g was measured in this study. There is no indication that such measurements were made in the English language portions of the original Japanese study report. There is also no detailed discussion of this issue in the secondary source (ECHA, 2011a). No increased incidences of other lesions typically associated with progression of α2u-g nephrotoxicity were observed in any treatment group.

One animal in each of the control, 62.5 mg/kg-day, and 1,000 mg/kg-day groups did not become pregnant. There were no significant maternal effects or differences in any of the reproductive endpoints measured, including the copulation index, fertility index, length of gestation, number of corpora lutea, implantation scars, and implantation index, between control and treated animals. All the pups from one dam in the 250 mg/kg-day group died, presumably due to hypothermia resulting from faulty nesting; this was likely accidental and not treatment-related. Litter endpoints, including pups born, sex ratios, live birth, and viability indices, were comparable across all groups. There were no statistically significant changes in pup or litter body weights. No external abnormalities in pups were observed.

A systemic NOAEL of 250 mg/kg-day and LOAEL of 1,000 mg/kg-day were identified from this study. Statistically and biologically (>10%) significant increases in liver and kidney weights were seen in both male and female rats at 1,000 mg/kg-day. An effect on the liver was also suggested by the small, but significant, increases in serum ALT and GGT found in the 1,000-mg/kg-day male rats. In the kidney, hyaline droplets were seen in male rats at ≥250 mg/kg-day and were significantly increased at 1,000 mg/kg-day. Although considered by the study authors of the secondary report to be associated with α2u-g accumulation (and therefore not relevant to humans), it is not clear that α2u-g was measured in this study or that the issue was considered in detail. No other lesions associated with α2u-g nephrotoxicity were observed. Altogether, two of the three criteria (α2u-g protein verification and lesions associated with α2u-g) required to demonstrate α2u-g nephrotoxicity due to methylcyclohexane exposure were not satisfied based on the U.S. EPA's guidance (U.S. EPA, 1991). Because the available data fail to provide sufficient evidence that the α2u-g process was operative, the hyaline droplets are considered a human-relevant endpoint for this study. The high dose of 1,000 mg/kg-day is a reproductive/developmental NOAEL, based on the absence of effects on these endpoints at any dose. The administered doses of 62.5, 250, and 1,000 mg/kg-day correspond to HEDs of 17.1,

68.6, and 273 mg/kg-day for males; 15.7, 63.0, and 251 mg/kg-day for unmated females; and 16.1, 64.2, and 255 mg/kg-day for mated females, respectively[4].

Subchronic/Chronic Studies

No oral subchronic or chronic studies on methylcyclohexane in animals were identified.

2.2.2. Inhalation Exposures

Relevant studies on the effects of inhalation exposure of animals to methylcyclohexane were limited to a subchronic study in rats (Kim et al., 2006) and a chronic study in rats, mice, hamsters, and dogs (AFRL, 1985; API, 1985).

Subchronic Studies

Kim et al. (2006)

A 13-week inhalation toxicity study published in Korean evaluated the effects of methylcyclohexane inhalation exposure in rats. Due to the lack of available details in English on crucial endpoints (e.g., organ weights and histopathology) and the poor quality of the available translation, NOAEL and LOAEL values for this study were not determined.

Chronic/Carcinogenicity Studies

AFRL (1985); API (1985)

In an unpublished, non-peer-reviewed study with deficiencies in methods and data reporting, AFRL (1985) exposed groups of 10-week-old CDF F344/CrlBR rats (65/sex/group), 8-week-old C57BL/6J mice (200 females/group), 12-week-old Syrian golden hamsters (100 males/group), and 8−13-month-old purebred beagle dogs (4/sex/group), whole-body, to nominal concentrations of 0, 400, or 2,000 ppm methylcyclohexane (~99% pure) vapors for 6 hours/day, 5 days/week for 1 year. Exposures were performed in two 840-cubic-foot exposure chambers (two for each concentration). The measured methylcyclohexane mean concentrations in each chamber were 401.5 and 398.9 ppm for the low-exposure group, respectively, and 1,998 and 2,009 ppm for the high-exposure group, respectively; the pair-averaged chamber concentrations were 400.2 ppm (1,607 mg/m^3) and 2,004 ppm (8,048 mg/m^3), respectively[5]. At the end of the exposure period, a small number of animals (10 rats/sex, 20 female mice, and 10 male hamsters) from each group were necropsied for histological analysis. The remaining rodents were monitored for an additional year prior to sacrifice, and all dogs were held for 5 years postexposure. Overall, several deficiencies were identified in this study. For example, three different lots of the test agent were used with purities ranging from 98.50 to 98.66%, with the identified impurities being *n*-heptane (0.74−0.97%) and toluene (0.52−0.60%); details on the

[4]The ADDs were converted to HEDs of 17.1, 68.6, and 273 mg/kg-day in low-, mid-, and high-dose males; 15.7, 63.0, and 251 mg/kg-day in unmated low-, mid-, and high-dose females; and 16.1, 64.2, and 255.2 in mated low-, mid-, and high-dose females using DAFs of 0.27 (males), 0.25 (unmated females), and 0.26 (mated 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 0.395, 0.398, and 0.391 kg (for low-, mid-, and high-dose males, respectively); 0.282, 0.283, and 0.279 kg (for low-, mid-, and high-dose unmated females, respectively); and 0.305, 0.305, and 0.297 kg (for mated 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).

[5]Analytical concentrations of 400.2 and 2,004 ppm were converted to mg/m^3 using the following formula: mg/m^3 = (ppm × molecular weight [MW])/24.45, where MW = 98.186 g/mol (the molecular weight of methylcyclohexane) and 24.45 is the volume occupied by 1 g/mol of any compound in a gaseous state at 25°C and 760 mm Hg.

collection of chamber concentrations were not provided; details on the exposure to control animals; and details on animal husbandry during exposures were omitted.

All animals were observed hourly during exposure and at least 6 times daily during recovery. Body weights of rats, hamsters, and dogs were measured every 2 weeks during exposure and biweekly (rats and hamsters) or biannually (dogs) during recovery. For the mice, group weights were measured monthly (data not provided). Blood samples were collected from the rats euthanized at the end of the 12-month exposure period and from dogs every 2 weeks during the exposure period and every 6 months thereafter. Blood analyses included the measurement of routine hematology (not further defined) and serum chemistry (electrolytes, GLU, CRN, TBIL, TP, ALB, ALT, AST, and ALP) endpoints. At sacrifice (either after the 12-month exposure or the recovery period), organ weights were measured in rats and dogs (organs not specified and data not shown). All animals were necropsied at death, and histopathological examination of "approximately 33 tissues" was performed. The report provided limited lesion incidence data for select tissues and excluded lesions of very low incidence (AFRL, 1985).

The statistical methods used to evaluate data were not specified, but it was noted in the study, for most endpoints, whether the values from the exposure groups were significantly different from controls (i.e., $p < 0.05$ or $p < 0.01$). Body weight, hematology, and clinical chemistry values were reported as group means without measures of variance, precluding performance of independent statistical analysis for these data. Some of the data presented in the report that were not statistically analyzed by the study authors (e.g., early mouse deaths) were analyzed by Fisher's exact test (two-tailed; $p < 0.05$) for this review. The results from each species are reported separately below.

Rats

No differences in mortality across groups were discernable at the end of the 1-year exposure period (based on the number of animals examined for histopathology, one male each from the control and high-exposure groups and one control female died). Body-weight data were graphically reported as means with no measures of variance. Based on the data, digitized using the MATLAB tool, GRABIT[6], body weights of exposed males were slightly decreased compared to controls throughout the exposure period and continuing to the end of the study; however, the magnitudes of change were small (<10% in both the low- and high-exposure groups). Body weights of exposed female rats were similar to controls throughout exposure and recovery. Hematological and serum chemistry data were reported as means from 9 or 10 animals/sex group with no measure of variance, although changes reaching statistical significance were indicated by the study authors. Decreases in WBCs were observed in males (19 and 21% in the low- and high-exposure groups, respectively) and in high-exposure females (33% decrease, compared with controls) (see Table B-7), but the reported values fall within the normal range (Giknis and Clifford, 2006). Differential counts were not reported. Statistically significant changes in HGB and HCT in high- and low-exposure males, respectively, were not biologically relevant, and no effect on RBCs was observed. Serum chemistry changes in males were unremarkable, and serum chemistry data for end-of-exposure females were not reported due to hemolysis in most samples

[6]GRABIT (https://www.mathworks.com/matlabcentral/fileexchange/7173-grabit) is an application of MATLAB and extracts data points from an image file using a graphical user interface.

of female rat blood. The study authors did not consider any of these changes to be biologically significant. No organ weight data were presented.

Histopathology data were available for a limited number of tissues from animals euthanized at 12 months or that died earlier (see Table B-8). No statistically significant non-neoplastic lesions were observed at 12 months in exposed rats, although renal tubular dilatation in male rats (1/11, 2/10, and 4/11 in control, low-, and high-exposure rats, respectively) was considered by the study authors to be biologically significant. In recovery animals, insufficient data were provided to allow estimation of mortality incidence during the recovery period. Histopathology findings were the only results reported at the end of the recovery period (see Table B-8). At 24 months, high incidences of chronic progressive nephropathy (CPN), a spontaneous age-related condition, were observed in all male (ranging from 92 to 100%) and female (ranging from 14 to 29%) rat groups, including controls, regardless of dose. Medullary mineralization and papillary hyperplasia, changes not typically associated with CPN (U.S. EPA, 1991), were significantly increased in the high-exposure males, but not in females, relative to controls. Unlike α2u-g nephropathy, CPN affects both sexes of rats and mice but represents a different spectrum of lesions not limited to those associated with α2u-g nephropathy (e.g., basement membrane thickening, nuclear crowding) and is more pronounced in older animals (Hard et al., 2009). In addition, renal tubular degeneration was seen in one control and two exposed male rats. The study authors considered the renal lesions in males to be consistent with α2u-g "hydrocarbon" nephropathy.

Tumor incidence data show no relationship between exposure to methylcyclohexane and tumor formation under the conditions of the study (see Table B-9). The only statistically significant finding was an increase in the incidence of unspecified testicular tumors in males from the low-exposure group, but not the high-exposure group, at the 12-month sacrifice (0/11, 5/10, and 2/10 for the control, low-, and high-exposure groups, respectively). The study authors noted that these were common spontaneous tumors in their rats; incidences of testicular interstitial cell tumors were 89−96% in the male rats (including controls) at 24 months. There was no increase in renal tumors in the male rats, which is noteworthy relative to the study author's contention that nonneoplastic renal lesions seen in male rats at 24 months may have been related to α2u-g nephropathy, a condition associated with development of kidney tumors. In females, there was only a nonsignificant increase in the incidence of mammary gland fibroadenomas (0/47, 4/50, and 6/48 in the control, low-, and high-exposure groups, respectively). The study authors indicated that all the neoplastic changes seen were those expected in aging animals of this species.

A NOAEL of 1,607 mg/m^3 and a LOAEL of 8,048 mg/m^3 were identified based on significantly increased incidences of medullary mineralization and papillary hyperplasia in male rats at the end of the observation period at 24 months. The study authors considered these lesions to be related to α2u-g nephropathy, and therefore not relevant to humans, but the extent to which the data support that conclusion is unclear. There was no detailed discussion in the document. Medullary mineralization and papillary hyperplasia are both known to occur in the later stages of the progression in α2u-g-associated nephrotoxicity (U.S. EPA, 1991). Changes that typically occur in the earlier stages of α2u-g-associated nephrotoxicity, such as increases in hyaline droplets containing α2u-g, single cell necrosis, and granular casts, were not observed, but the study did not include examination of rats before 12 months, when observation of these changes (especially hyaline droplets and single cell necrosis) would have been more likely. Exacerbation

of spontaneous CPN is another feature of α2u-g nephropathy that was not seen in this study (possibly, however, because almost all male rats had the lesion, obscuring any potential difference across groups, and lesion severity was not reported). The lack of renal tumors is noteworthy, as α2u-g nephropathy is often associated with development of kidney tumors, but not definitive, because tumor development depends on many factors (e.g., dose, exposure duration, etc.). Altogether, two of the three criteria (increased hyaline droplet accumulation and positive identification of the α2u-g protein) required by the U.S. EPA guidance (U.S. EPA, 1991) to demonstrate α2u-g nephropathy due to methylcyclohexane exposure are not satisfied; thus, the male rat kidney data are considered relevant for humans. The reported concentrations of 0, 1,607, or 8,048 mg/m^3 correspond to human equivalent concentration for extrarespiratory effects (HEC_{ER}) values of 0, 287.0, and 1,437 mg/m^3, respectively[7].

Mice

Limited results were reported for female mice. Based on the number of animals examined for histopathology at or before the 1-year sacrifice, there appeared to be a slight increase in mortality with exposure (9/200, 15/200, and 19/200 early deaths in the control, low-, and high-exposure groups, respectively), but differences from control were not statistically significant ($p > 0.05$ by two-tailed Fisher's exact test performed for this review). The study authors did not report any effect on mortality. The timing and causes of death were not reported, hindering any further analysis or interpretation of these results. For mice allowed to recover for 1 year after inhalation exposure to methylcyclohexane (161−171/group), insufficient data precluded the estimation of the mortality incidence during the recovery period. Clinical signs and body-weight results were not reported. Hematology and serum chemistry analyses were not performed. No organ weights were reported. At 24 months, the incidences of multiple uterine cysts were higher than controls at both exposure concentrations (10/164, 22/158, and 23/152 for the control, low-, and high-exposure groups, respectively) and the incidences of malignant lymphoma were higher than controls in the high-exposure group (45/171, 44/162, and 56/155 for the control, low-, and high-exposure groups, respectively). However, the increases were within the range of normal variation for these common lesions in aged mice (Ward, 2006). The study authors did not consider any histopathological findings to be statistically or biologically significant.

The high concentration of 8,048 mg/m^3 is tentatively identified as a NOAEL based on the lack of adverse effects seen in female mice. There is some uncertainty due to the limited endpoints evaluated. The reported concentrations of 0, 1,607, or 8,048 mg/m^3 correspond to HEC_{ER} values of 0, 287.0, and 1,437 mg/m^3, respectively[8].

[7]HEC values based on extrarespiratory effects were calculated by treating methylcyclohexane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure concentration (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (logK_{blood}) (animal:human), using a default coefficient of 1 since the rat logK_{blood} (0.79) is greater than the logK_{blood} (0.61) as indicated by Abraham et al. (2005).

[8]HEC values based on extrarespiratory effects were calculated by treating methylcyclohexane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure concentration (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (logK_{blood}) (animal:human), using a default coefficient of 1 since the mouse logK_{blood} is unknown; the human logK_{blood} is 0.61.

Hamsters

No changes in the incidence of male hamster mortality during the 1-year exposure period were discernable. Male hamsters exposed to either 1,607 or 8,048 mg/m^3 methylcyclohexane for 1 year showed mean body-weight deficits exceeding 10% relative to controls, but not differing between the two exposed groups. The data were not statistically analyzed, and no variance data were provided. The decreases in mean body weight were evident within a month of the start of exposure and continued to the end of the exposure period; however, body weight changes did not persist following recovery. Hematology and serum chemistry endpoints were not measured in hamsters. Histopathological examinations of tissues from male hamsters showed no treatment-related findings at the end of exposure at 12 months or the end of observation at 24 months.

A LOAEL of 1,607 mg/m^3 was determined for decreased body weight in male hamsters. Deficits in mean values were seen in both dose groups and exceeded 10%, but did not differ between dose groups. Statistical analysis could not be performed due to failure of the study authors to provide any measure of variance. The reported concentrations of 0, 1,607, and 8,048 mg/m^3 correspond to HEC_{ER} values of 0, 287.0, and 1,437 mg/m^3, respectively[9].

Dogs

All beagle dogs (four/sex/group) exposed by inhalation to methylcyclohexane for 1 year survived through another 5 years postexposure. Canine body-weight data were not provided. The only biochemistry results provided in the study were serum ALT levels. The data were graphically presented by study week with no measure of variance. Transient increases (Week 7 and Weeks 39−43) seen in the 8,048 mg/m^3 group were attributed to one dog, and changes in the 1,607 mg/m^3 group observed during Weeks 39−43 were attributed to two animals. No significant differences in ALT levels were observed during the 5-year postexposure period. The study authors noted that during the 5-year observation period, there were no indications of renal effects (API, 1985). The study authors did not consider any of the observed lesions in the dogs to be biologically or statistically significant. There were no treatment-related increased incidences of neoplastic tumors in dogs.

A NOAEL of 8,048 mg/m^3 was determined for the lack of clearly adverse effects in dogs exposed to methylcyclohexane for 1 year. This determination is tentative due to the small numbers of dogs used, the limited number of endpoints evaluated, and the long postexposure observation period prior to their histopathologic examination. The reported concentrations of 0, 1,607, and 8,048 mg/m^3 correspond to HEC_{ER} values of 0, 287.0, and 1,437 mg/m^3, respectively[10].

[9]HEC values based on extrarespiratory effects were calculated by treating methylcyclohexane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure concentration (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (logK_{blood}) (animal:human), using a default coefficient of 1 since the hamster logK_{blood} is unknown; the human logK_{blood} is 0.61.

[10]HEC values based on extrarespiratory effects were calculated by treating methylcyclohexane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure concentration (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (logK_{blood}) (animal:human), using a default coefficient of 1 since the hamster logK_{blood} is unknown; the human logK_{blood} is 0.61.

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

2.3.1. Genotoxicity

Table 4A provides an overview of genotoxicity studies of methylcyclohexane. The limited data suggest that methylcyclohexane is not genotoxic. The chemical produced negative results in two Ames tests with *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2*uvrA* both in the presence and absence of rat liver S9 metabolic activation (JECDB, 2011a; ECHA, 2001a). Methylcyclohexane also did not induce chromosomal aberrations in Chinese hamster lung cells in the presence or absence of rat liver S9 metabolic activation (JECDB, 2011b; ECHA, 2001b).

Methylcyclohexane coating on standard carbon black particles enhanced the effect of the carbon black particles to reduce viability and increase oxidative deoxyribonucleic acid (DNA) damage (fragment length analysis with restriction enzyme assay) in RAW 264.7 murine macrophages (Rim et al., 2011), but the relevance of these findings to genotoxicity of methylcyclohexane is unclear.

Table 4A. Summary of Methylcyclohexane 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, TA100, TA1535, and TA1537 and *Escherichia coli* WP2*uvrA*; bacteria were tested with (0 or 0.781−200 µg/plate) and without (0 or 0.097−25 µg/plate) metabolic activation by S9 rat liver fraction	Without activation: TA98 (25 µg/plate), TA100 and TA1535 (3.13 µg/plate), TA1537 (12.5 µg/plate), WP2urvA (25 µg/plate) With activation: TA98, TA100, and TA1535 (25 µg/plate), TA1537 (100 µg/plate), WP2urvA (200 µg/plate)	−	−	Ames assay. No evidence of mutagenicity in any of the strains tested with or without S9 activation. Adequate study. Cytotoxicity was seen at the highest one or two concentrations tested in each strain, with and without activation, as expected based on a preliminary study.	ECHA (2001a)
Mutation	*S. typhimurium* TA98, TA100, TA1535, and TA1537 and *E. coli* WP2*uvrA*; bacteria were tested with and without metabolic activation by S9 rat liver fraction (0 or 4.69−150 µg/plate for *S. typhimurium* or 4.69−600 µg/plate for *E. coli*)	With and without activation: TA98, TA100, TA1535, and TA1537 (150 µg/plate), WP2*uvrA* (600 µg/plate)	−	−	Ames assay. No evidence of mutagenicity in any of the strains tested with or without S9 activation. Adequate study. Cytotoxicity was seen at the highest one or two concentrations tested in each strain, with and without activation, as expected based on a preliminary study. It was noted that no precipitates were seen at any concentration.	JECDB (2011a)
Genotoxicity studies in mammalian cells—in vitro						
CA	CHL/IU cells; tested for 6 h with and without metabolic activation by S9 rat liver fraction and for 24 and 48 h without metabolic activation (0 or 245−980 µg/mL)	980 µg/mL	−	−	No increase in CAs in any test condition. Adequate study. No cytotoxicity was seen.	ECHA (2001b)

Table 4A. Summary of Methylcyclohexane Genotoxicity

Endpoint	Test System	Doses/Concentrations Tested[a]	Results Without Activation[b]	Results With Activation[b]	Comments	References
CA	CHL/IU cells; tested for 6 h with and without metabolic activation by S9 rat liver fraction and for 24 h without metabolic activation (0 or 40−160 µg/mL)	160 µg/mL	−	−	No increase in CAs in any test condition. Adequate study. Cytotoxicity interfered with detection of CAs only at the highest concentrations tested (160 µg/mL in the 6-h test and 120 µg/mL in the 24-h test). It was noted that no precipitates were seen at any concentration.	JECDB (2011b)

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b] − = negative.

CA = chromosomal aberration; CHL = Chinese hamster lung.

2.3.2. Supporting Human Studies

Table 4B summarizes epidemiological studies that investigated health effects in populations with exposure to multiple VOCs that included methylcyclohexane. Due to the confounding exposures to mixed VOCs in these studies, they are of limited use for methylcyclohexane hazard identification and do not provide data for quantitative dose-response analysis.

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Supporting evidence−noncancer effects in humans following inhalation exposure				
Case-control	Within a group of elementary school students in Seoul, Korea, asthma cases were identified based on a questionnaire and confirmed by a physician (n = 33); controls matched for age and sex were selected from the non-asthmatic students (n = 40). Personal, indoor, and outdoor sampling for 10 VOCs, including methylcyclohexane, was performed over 3 days. Levels of VOCs were compared across groups.	Cases were exposed to significantly higher levels of methylcyclohexane than controls in outdoor air, but to similar levels in indoor air and personal air samples, which contained higher levels overall. Cases also had significantly higher exposure than controls to benzene, toluene, and *o*-xylene. After adjusting for confounding factors in multiple regression analysis, no significant relationship was seen between VOC exposure and asthma.	The study found no evidence of an association between childhood asthma and exposure to methylcyclohexane.	Hwang et al. (2011)
Occupational	Liver function was assessed in a group of 42 workers who had been exposed to a variety of solvents at a single U.K. factory for an average of 11.4 yr and a group of 41 healthy U.K. workers with no history of occupational solvent exposure and a history of normal liver function test results in routine testing. Urine and blood samples were collected from each subject at the workplace. For solvent workers, personal exposure to solvents was monitored on the day of biological monitoring by using diffusive sampling tubes. Methylcyclohexane was among the primary exposures of the solvent workers (6 ppm or 20 mg/m^3). Other solvents detected at similar levels were toluene, *n*-heptane, and xylene.	Serum levels of ALT, AST, ALP, GGT, and bilirubin in the solvent-exposed workers did not differ from controls. The only findings in solvent-exposed workers relative to controls were increased prevalence of abnormally high urinary bile acid and increased mean urinary levels of 6 β-hydroxycortisol (and ratio of 6 β-hydroxycortisol to urinary free cortisol). Within the solvent-exposed group, there was no relationship between personal atmospheric measurements of solvents or years of employment and urinary bile acids or 6 β-hydroxycortisol levels.	The study found limited evidence of potential liver effects in workers exposed to multiple solvents but no toxicologically relevant effects specifically attributed to methylcyclohexane exposure.	Mason et al. (1994)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Occupational	Test subjects were 21 workers at jobs with moderate-to-high exposure to organic solvents employed for at least 2 years in one of five military offset print shops in Belgium or Germany. Personal air sampling conducted for each worker on a single normal workday showed that workers in each plant were exposed to an average of 10 organic solvents and the group as a whole was exposed to over 25 different solvents (methylcyclohexane was among the most common, along with trichloroethane and *n*-heptane). Methylcyclohexane concentrations in the exposed group ranged from not detected to 9.5 mg/m^3 in workplace air (<5% of the total concentration of measured solvents). Controls were 21 military drivers presumed to be without occupational solvent exposure matched for age, sex, education level, and spoken language (Dutch/French/German). Participants answered a general questionnaire on age and lifestyle factors, reported neurotoxicity symptoms, and provided medical history; were given a physical exam; and underwent digital oximetry and eight neurobehavioral tests.	Print shop workers had significantly more and longer-lasting nocturnal oxygen desaturations during sleep than controls; however, there was no quantitative relationship between exposure to solvents (estimated based on duration of employment and hygienic practices) and sleep-related events. In the questionnaire, exposed workers had more complaints than controls, particularly regarding mood. Hand-eye coordination was reduced in print shop workers compared to controls. There were no other neuropsychiatric or neurobehavioral differences between exposed workers and controls.	The study found some evidence for more and longer-lasting sleep disturbances in solvent-exposed print shop workers than in unexposed controls but no toxicologically relevant effects specifically attributed to methylcyclohexane exposure.	Laire et al. (1997)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Case-control	Cases were 108 women clinically diagnosed with spontaneous abortion at a single hospital in Italy (in a region where many women work in the shoe industry, where solvents are widely used) in 1987−1988. Controls were 108 women discharged from the same hospital following normal delivery, matched with cases for birth year, calendar year of hospital admission, and city of residence. All participants were interviewed using a standard questionnaire regarding pregnancy history, lifestyle factors, medications taken during pregnancy, and jobs during pregnancy (including details relating to use of solvents). Cases and controls were categorized based on solvent exposure (none, low, or high). Because solvent mixtures were generally used, no attempt was made to specify any particular solvent in detail. Out of 50 women exposed to solvents, 47 worked in shoemaking and 3 worked in a leather goods factory. In monitoring of 31 shoe factories from 1982 to 1992, 12 different solvents were detected, including methylcyclohexane (30−120 mg/m^3).	Raw ORs for spontaneous abortion were 1.0 (based on 78 cases and 88 controls) in women with no solvent exposure, 1.13 (based on 12 cases and 12 controls) in women with low solvent exposure, and 2.54 (based on 18 cases and 8 controls) in women with high solvent exposure. The elevated OR in women with high solvent exposure was not statistically significant. Significant increases in ORs were found for smoking, coffee consumption, previous abortions, and marital status as single. After adjustment for confounding factors using stepwise logistical regression, the RR for spontaneous abortion was significantly increased in women with high solvent exposure (3.85 [95% CI 1.24−11.9]).	The study found evidence that exposure to solvents may increase the risk of spontaneous abortion but no toxicologically relevant effects specifically attributed to methylcyclohexane exposure.	Agnesi et al. (1997)
Cross-sectional study	Within a cohort of 976 neonates born in Leipzig, Germany recruited between December 1997 and January 1999, 85 children (43 boys and 42 girls) in a randomly selected subgroup were evaluated for immune status at birth (umbilical cord blood taken at delivery and analyzed for T-cell function using intracellular cytokine staining) and exposure to VOCs, as assessed by passive sampling in the children's bedrooms for 4 wk after birth and questionnaires completed by the parents about possible sources of VOC exposure during pregnancy (e.g., painting, flooring, smoking, etc.). Methylcyclohexane was among 28 VOCs measured in the children's bedrooms, with a relatively low median concentration of 1.6 µg/m^3.	No significant association was found between exposure to methylcyclohexane and cytokine-producing cord blood T cells (i.e., percentages of T cells producing IFN-γ, TNF-α, IL-2, or IL-4). Statistically significant associations were found for several of the other VOCs.	The study found some evidence that exposure to VOCs may have an influence on immune status of the newborn child, but no toxicologically relevant effects specifically attributed to methylcyclohexane exposure.	Lehmann et al. (2002)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Supporting evidence−cancer effects in human following inhalation exposure				
Cancer cluster	After a professional football team moved to a new stadium in New Jersey in 1976, four team members developed cancer between 1980 and 1987: one each of non-Hodgkin's lymphoma, glioblastoma, angiosarcoma, and Hodgkin's disease. Measurements for VOCs were taken in June−July 1988 from a practice field, a natural grass field outside of the stadium, the new stadium, and a racetrack used by the athletes. Methylcyclohexane was among 16 VOCs detected, at relatively low levels ranging from 0.1 to 0.4 ppb (0.4−1.6 µg/m^3). A cohort of 7,889 people who had worked at least 1 d at the facility was constructed. A total of 146 cancer cases and 65 cancer deaths in the cohort occurring between January 1, 1978 and December 31, 1987 were analyzed in relation to New Jersey cancer morbidity and mortality data.	No significant excess of cancer incidence or mortality was observed for all tumors combined or for tumors at any specific site, even with consideration for latency, nor was there any difference between indoor and non-indoor workers.	The study found no evidence that tumors were increased in the cohort studied and was uninformative regarding the potential carcinogenicity of methylcyclohexane.	Kraut et al. (1991)
Supporting evidence−noncancer effects in animals following oral exposure				
Acute (oral)	Female rats (5/group, strain unknown) were administered single doses of 0, 1,250, 2,500, or 5,000 mg/kg of methylcyclohexane via gavage (vehicle appears to have been 0.2% carboxyl methyl cellulose). Animals were observed for 14 d. Endpoints evaluated included mortality, clinical findings, and body-weight changes. Gross necropsies and histopathological examinations were performed.	No deaths were observed. Clinical signs (depression, soft feces, decreased locomotion, solid perineal region, crouching position, and anorexia) were reportedly observed in all groups in a dose-related manner. Other effects, observed only at 5,000 mg/kg, were decreased body weight (<10%, NS), increased absolute (10−13%, NS) and relative (19−25%, $p < 0.05$) liver and kidney weights, and kidney lesions (glomerular atrophy, congestion/hemorrhage, and focal degeneration/necrosis each in 5/5 versus 0/5 in controls).	The rat LD_0 was >5,000 mg/kg. Increased liver and kidney weights and kidney lesions were seen at 5,000 mg/kg in female rats.	Kim et al. (2011c) (This study is published in Korean, with abstract and data tables in English.)
Acute (oral)	Rats (number, strain, and sex not specified) received a single oral dose of technical-grade methylcyclohexane (70% methylcyclohexane, 10% cyclohexane, 20% dimethylcyclohexane) neat. No additional details were provided.	ND	The rat LD_{50} was >3,200 mg/kg.	Eastman Kodak (1994)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute (oral)	Mice (number, sex, and strain not specified) were orally administered methylcyclohexane (purity not reported). No details were provided.	ND	The mouse LD_{50} was 2,250 mg/kg.	ECHA (1982b)
Acute (oral)	Young white rabbits (one per dose) were administered single doses of methylcyclohexane (97% pure, 3% toluene) at eight dose levels ranging from 1,000 to 10,000 mg/kg via gavage (use of vehicle not specified). Animals were observed for up to 14 d. Endpoints evaluated included mortality, clinical signs, body weights, and gross necropsy. Blood was analyzed for cellular elements.	Mortality occurred at ≥4,500 mg/kg; four rabbits at these dose levels died within 84 hours of dosing, while four rabbits at lower doses (up to 4,000 mg/kg) survived. Severe diarrhea was seen in the rabbits, including all that died, within 3 hours of dosing. All animals lost weight after dosing, but not in proportion to dose. No hematological changes were found. Necropsy of animals that died showed damage to the heart, liver, and kidneys that may have been due in part to intercurrent severe pulmonary infection.	The rabbit LD_0 and LD_{Lo} were 4,000 and 4,500 mg/kg, respectively.	Treon et al. (1943b)
Short-term (oral)	Male F344 rats (eight treated, six controls) were administered water or methylcyclohexane neat at a dose of 800 mg/kg every other day for 14 d. Kidneys were examined for histopathology and specifically for lesions associated with α2u-g nephropathy.	Only "very slight traces of nephropathy" were observed.	No increase in α2u-g nephropathy was found in male rats treated with 400 mg/kg-d for 14 d.	Parnell et al. (1988)
Short-term (oral)	Male and female Crj:CD (Sprague Dawley) rats (number not specified) were administered methylcyclohexane doses of 0, 100, 300, or 1,000 mg/kg-d via gavage in corn oil for 14 d.	No deaths occurred. Increased salivation was seen in both sexes at 1,000 mg/kg-d.	No mortality occurred in rats dosed by gavage with ≤1,000 mg/kg-d for 14 d.	ECHA (2001c) Preliminary range-finding study
Supporting evidence−noncancer effects in animals following inhalation exposure				
Acute (inhalation)	Rats (strain, sex, and number per group not reported) were exposed to technical-grade methylcyclohexane (70% pure) at concentrations of 11,000, 82,000, 184,000, or 260,000 mg/m^3 for 0.22−6 h. Endpoints included mortality and clinical signs.	Mortality was observed at ≥82,000 mg/m^3 within 14−70 min of exposure. Lethargy, ataxia, and terminal convulsions were observed in animals that died. At 11,000 mg/m^3, no deaths occurred, and lethargy was the only clinical sign.	The rat LC_0 (6 h) and LC_{Lo} were 11,000 mg/m^3 and 82,000 mg/m^3, respectively.	ECHA (1965)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute (inhalation)	Rats (number, strain, and sex not reported) were exposed to a cycloparaffinic solvent (90% methylcyclohexane) at a vapor concentration of 7,700 ppm (30,920 mg/m^3) for 4 h.	Sudden violent seizures were observed that resulted in traumatic injury in one animal, demonstrated by lesions to the spinal cord and surrounding tissues and clinical presentation of hindlimb paralysis.	Seizures occurred in rats at 30,900 mg/m^3.	Shell Chemical (1999)
Acute (inhalation)	Rats (strain, number, and sex not reported in English) were exposed to methylcyclohexane vapor concentrations of 0, 100, 500, 2,500, or 5,000 ppm (0, 402, 2,010, 10,040, or 20,100 mg/m^3, respectively) for 4 h.	ND	The rat LC_{50} (4 h) was 15,054 mg/m^3.	Kim et al. (2006) (This study is published in Korean, with abstract and data tables in English.)
Acute (inhalation)	Sprague Dawley rats (20 males/group) were exposed, whole-body, to methylcyclohexane vapor concentrations of 0, 4,172, or 6,565 ppm (0, 16,750, or 26,360 mg/m^3, respectively) for 1 h. Half of the animals (10/group) were euthanized at the end of the exposure period; the remaining animals were necropsied after a 28-d observation period. Endpoints evaluated included mortality, clinical signs, body weight, gross pathology, and histopathological examinations.	No mortality was observed. An increase in activity occurred at 16,700 mg/m^3; hyperactivity, slight loss of coordination, and prostration were observed at 26,300 mg/m^3. No effects on body weight or gross or histopathological lesions were observed.	The rat LC_0 (1 h) was >26,300 mg/m^3. Clinical signs indicative of CNS effects were seen at 26,300 mg/m^3.	Kinkead et al. (1979)
Acute (inhalation)	ICR mice (20 females/group) were exposed, whole-body, to methylcyclohexane vapor concentrations of 0, 4,758, or 6,564 ppm (0, 19,110, or 26,360 mg/m^3, respectively) for 1 h. Half of the animals (10/group) were euthanized at the end of the exposure period; the remaining animals were necropsied after a 28-d observation period. Endpoints evaluated included mortality, clinical signs, body weight, gross pathology, and limited histopathological examinations (control and low-exposure animals only).	No mortality was observed. At 19,100 mg/m^3, hyperactivity was observed during the exposure period. At 26,300 mg/m^3, hyperactivity occurred along with coordination loss and prostration. One mouse showed tono-clonic spasms. Minimal-to-mild cytoplasmic changes were found in the liver of 1/10 controls and 5/10 exposed animals. No other effects were observed.	The mouse LC_0 (1 h) was >26,300 mg/m^3. Clinical signs indicative of CNS effects and slight liver changes were seen at 26,300 mg/m^3.	Kinkead et al. (1979)
Acute (inhalation)	Mice (number, strain, and sex not available) were exposed to methylcyclohexane vapors for 2 h.	ND	The mouse LC_{50} (2 h) was 41,000 mg/m^3	ECHA (1982a)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute (inhalation)	Mice (strain, sex, and number per group not reported) were exposed to methylcyclohexane at concentrations ranging from 30,000 to 50,000 mg/m^3 for up to 2 h. Animals were monitored for mortality and clinical signs. The duration of observations was not specified. Necropsies were performed.	Mortality occurred at 50,000 mg/m^3 (number of deaths not reported); some deaths occurred within 1−2 min after the start of exposure. Clinical signs in animals that died included lethargy, narcosis, prostration, clonic convulsions, and labored breathing. The minimum narcotic concentration was 40,000 mg/m^3.	The mouse LC_0 (2 h) and LC_{Lo} were 40,000 and 50,000 mg/m^3, respectively.	ECHA (1929)
Acute (inhalation)	Rabbits (four per group; strain and sex not reported) were exposed to a methylcyclohexane vapor concentration of 59,900 mg/m^3 for 70 min.	There was 100% mortality in animals exposed to 59,900 mg/m^3. Severe convulsions, narcosis, labored breathing, salivation, conjunctival congestion with mucoid secretion and lacrimation, and diarrhea were observed.	The rabbit LC_{100} (70 min) was 59,900 mg/m^3.	Treon et al. (1943a)
Acute (inhalation)	Beagle dogs (four per group, sex not specified) were exposed, whole-body, to methylcyclohexane concentrations of 0 or 16,300 mg/m^3 for 1 h. Animals were observed for 28 d. Endpoints evaluated included mortality, clinical signs, and body weights. Field trial evaluations were performed prior to and after exposure. Neurological examinations (flexor reflex, extensor thrust, tonic neck, tonic eye, righting, and placing reflexes) were performed after exposure. Hematology and clinical chemistry were done at 2 and 4 wk postexposure. Necropsies and complete histology were performed after the 28-d observation period.	No mortality was observed. There were no exposure-related effects on any of the endpoints tested.	The dog LC_0 (1 h) was >16,300 mg/m^3. There was no evidence of CNS effects.	Kinkead et al. (1979)
Short-term (inhalation)	Rabbits (four per group; strain and sex not reported) were exposed 6 h/d, 5 d/wk to methylcyclohexane vapor concentrations of 0, 28,750, or 39,550 mg/m^3 for 2 wk, 11,350 mg/m^3 for 3 wk, or 21,900 mg/m^3 for 4 wk. Endpoints included mortality, clinical sings, rectal temperature, body weight, and hematology. Histology was performed following a 2-mo recovery period.	Effects were mortality (in four of four rabbits), convulsions, light narcosis, labored breathing, salivation, conjunctival congestion, and weight loss at 39,600 mg/m^3; mortality (in one of four rabbits), lethargy, impaired coordination, and decreased body weight at ≥28,750 mg/m^3; only slight lethargy at 21,900 mg/m^3; and only minimal liver and kidney lesions at 11,350 mg/m^3.	The rabbit LC_0 and LC_{Lo} were 21,900 and 28,750 mg/m^3, respectively, with repeated exposure.	Treon et al. (1943a)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Subchronic (inhalation)	Rabbits (four per group; strain and sex not reported) were exposed to methylcyclohexane vapor for 6 h/d, 5 d/wk at concentrations of 948 or 4,570 mg/m^3 for 10 wk. Rabbits exposed to clean air served as controls. Endpoints included mortality, clinical sings, rectal temperature, body weight, and hematology. Histology (limited details) was performed following a 2-mo recovery period.	No effects were observed.	No effects were observed in rabbits at concentrations up to 4,570 mg/m^3 for 10 wk.	Treon et al. (1943a)
Subchronic (inhalation)	A single Rhesus monkey (sex not specified) was exposed to 1,460 mg/m^3 methylcyclohexane for 6 h/d, 5 d/wk for 10 wk. Endpoints included mortality, clinical signs, rectal temperature, body weight, and hematology. Histology was performed following a 2-mo recovery period.	The monkey survived with no signs of intoxication. There was a slight fall in the daily rectal temperature during exposure. The monkey gained weight during the exposure period, but a control was not included for comparison. No microscopic lesions were observed.	No effects were observed in a monkey exposed to 1,460 mg/m^3 for 10 wk in a limited study (single animal tested, no control).	Treon et al. (1943a)
Supporting evidence−noncancer effects in animals following other routes of exposure				
Acute (dermal)	A single white rabbit (sex, strain, age, and body weight not provided) had 60 mL of methylcyclohexane applied for 1 h (12;5-mL portions at 5-min intervals) to a clipped 24-square-inch area of skin (under a hood to prevent inhalation) for 6 successive days. The corresponding dose provided by the study authors was 86,700 mg/kg. Endpoints included mortality, clinical signs, body weight, and gross observations at the site of application.	The animal survived treatment. Skin irritation at the site appeared on the 2nd day and increased somewhat with successive treatments. Hardening of the skin, thickening, and ulceration appeared later, and the experiment was terminated on the 6th day. In contrast to the other chemicals tested, it was reported that there was only slight hypothermia and weight loss (weight was regained within 2 d).	The lethal dose was >86,700 mg/kg. There was evidence of injury to the skin.	Treon et al. (1943b)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Subchronic (subcutaneous injection)	Sprague Dawley rats (five/sex/group) were administered daily subcutaneous injections of methylcyclohexane at 0, 10, 100, or 1,000 mg/kg-d in olive oil 5 d/wk for 13 wk. Endpoints evaluated included mortality, clinical signs, FOB (including motility, fall landing test, activity count, heart rate and blood pressure, and serotonin levels), body weight, hematology, serum chemistry, sperm counts, measurements of sex hormones, estrous cyclicity, organ weights, and histopathology.	In the 1,000 mg/kg-d group, 4/5 males and 4/5 females died, all between the 5th and 60th day of the study. No deaths occurred at ≤100 mg/kg-d. Body weights were significantly decreased relative to controls in the 1,000-mg/kg-d males, starting on the 2nd week of the study. Smaller, transitory body-weight decreases were also seen in the 1,000-mg/kg-d females. Body weights in the lower dose groups did not differ from controls. Animals in the 1,000-mg/kg-d group showed a variety of lesions in the liver (microgranuloma, bile-duct proliferation), kidney (hyperemia, protein casts), and heart (hyperemia, myocardial necrosis). Incidences were not reported. Few lesions were seen in the lower dose groups. Testing results in the 10 and 100 mg/kg-d groups for hematology, serum chemistry, organ weights, neurobehavioral endpoints, blood pressure, serotonin levels, estrous cyclicity in females, testes and sperm in males, and hormone levels in both sexes were generally unremarkable, although some statistically significant results were found.	The high dose of 1,000 mg/kg-d was a FEL, based on high mortality. The mid dose of 100 mg/kg-d was a NOAEL.	Kim et al. (2011b); Kim et al. (2011c) This study is published in Korean, with abstract and data tables in English.)

α2u-g = alpha 2u-globulin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CNS = central nervous system; FEL = frank-effect level; FOB = functional observation battery; GGT = γ-glutamyl transferase; IFN-γ = interferon-gamma; IL-2 = interleukin 2; IL-4 = interleukin 4; LC_0 = highest concentration showing no mortality; LC_{Lo} = lowest concentration that caused death; LC_{50} = median lethal concentration; LC_{100} = lethal concentration causing 100% mortality; LD_0 = highest dose showing no mortality; LD_{Lo} = lowest dose that caused death; LD_{50} = median lethal dose; ND = no data; NOAEL = no-observed-adverse-effect level; NS = not statistically significant; OR = odds ratio; RR = relative risk; TNF-α = tumor necrosis factor-alpha; U.K. = United Kingdom; VOC = volatile organic compound.

2.3.3. Supporting Animal Studies

The acute effects of oral and inhalation methylcyclohexane exposure are reported in Table 4B along with short-term and subchronic studies that evaluated limited endpoints, were inadequately reported, or were performed via alternate routes of exposure (e.g., dermal or subcutaneous injection).

Acute lethality studies on methylcyclohexane indicate relatively low lethality via oral and inhalation routes. In rats, a median lethal dose (LD_{50}) of >3,200 mg/kg was reported in one study (Eastman Kodak, 1994) and an LD_0 (highest dose showing no mortality) of >5,000 mg/kg was reported in another (Kim et al., 2011c). An LD_{50} of 2,250 mg/kg was reported in mice (ECHA, 1982b). In rabbits, no deaths occurred at doses up to 4,000 mg/kg, and the minimum lethal dose was 4,500 mg/kg (Treon et al., 1943b). In inhalation studies, rats survived exposures up to 26,300 mg/m^3 for 1 hour (Kinkead et al., 1979) and 11,000 mg/m^3 for 6 hours (ECHA, 1965); a 4-hour median lethal concentration (LC_{50}) of 15,054 mg/m^3 was reported (Kim et al., 2006). Mice survived inhalation exposures up to 26,300 mg/m^3 for 1 hour (Kinkead et al., 1979) and 40,000 mg/m^3 for 2 hours (ECHA, 1929), with a reported 2-hour LC_{50} of 41,000 mg/m^3 (ECHA, 1982a). Mortality was 100% (4/4) in rabbits exposed to methylcyclohexane vapor concentrations of 59,900 mg/m^3 for 70 minutes (Treon et al., 1943a). With repeated exposure for 2−10 weeks, mortality in rabbits occurred at concentrations of 28,750 mg/m^3, but not at concentrations ≤21,900 mg/m^3 (Treon et al., 1943a). Sublethal effects in the available studies included clinical signs indicative of central nervous system (CNS) effects, such as narcosis, ataxia, lethargy, prostration, labored breathing, and convulsions (Shell Chemical, 1999; ECHA, 1965; Treon et al., 1943a). Effects on liver and kidney, including increases in organ weight and minimal-to-mild lesions, were found in some studies (Kim et al., 2011c; Kinkead et al., 1979; Treon et al., 1943a). One study included specific histopathological examination for renal lesions characteristic of α2u-g nephropathy in male rats treated with 400 mg/kg-day for 14 days but found only "very slight traces of nephropathy" (Parnell et al., 1988). In studies by other routes, dermal exposure did not cause death in rabbits at a dose of 86,700 mg/kg (Treon et al., 1943b), while repeated subcutaneous injection was lethal at 1,000 mg/kg-day, but not at 100 mg/kg-day, in rats in a 13-week study (Kim et al., 2011b; Kim et al., 2011a).

2.3.4. Metabolism/Toxicokinetic Studies

Methylcyclohexane is absorbed following oral or inhalation exposure. Absorption following oral exposure was >89% in rabbits administered single doses of 2.1−2.4 mmol/kg (equivalent to 200−230 mg/kg) [U-^{14}C]methylcyclohexane by gavage in water, based on total and fecal radioactivity recoveries of 89.6−93.9 and 0.4−0.7%, respectively, through approximately 60 hours postdosing (Elliott et al., 1965). Methylcyclohexane is primarily absorbed in the lung based on the blood-air partition coefficient ($\log K_{blood}$). Based on indirect assays in F344 rats measuring the rate of loss of methylcyclohexane in closed-battery jar chambers, the maximum first-order rate constant for gas uptake in rats exposed to ≤50 ppm was 0.32 hour^{-1} kg^{-1} (Andersen, 1981). Rats exposed to 100 ppm (402 mg/m^3) for 12 hours had steady-state blood levels of 5.8 µmol/kg immediately following the end of exposure (Zahlsen et al., 1992). Based on these data, a $\log K_{blood}$ of 0.79 was calculated for rats (Abraham et al., 2005). A $\log K_{blood}$ of 0.61 was calculated separately for methylcyclohexane in humans (Abraham et al., 2005; Imbriani et al., 1985).

Upon absorption, methylcyclohexane is distributed throughout the body. Methylcyclohexane was found primarily in fat (356 µmol/kg), with lesser amounts in kidney

(94.7 µmol/kg), brain (45.7 µmol/kg), liver (30.1 µmol/kg), and blood (5.8 µmol/kg), immediately following a 12-hour inhalation exposure to 100 ppm (402 mg/m^3) methylcyclohexane vapor (Zahlsen et al., 1992). Levels in tissues other than fat were similar when the exposures were repeated on 2 additional days, suggesting that steady-state was achieved within the daily 12-hour exposure period in these tissues. Levels in fat increased from 356 ± 41 µmol/kg after Day 1 to 460 ± 79 µmol/kg after Day 2 and 550 ± 99 µmol/kg after Day 3, suggesting some accumulation in fat. Twelve hours after the end of the last exposure period, levels (of parent compound; metabolites were not monitored) had dropped close to 0 µmol/kg in all monitored tissues (2.9, 0.5, 0.5, and 0.1 µmol/kg left in kidney, liver, brain, and blood, respectively) except fat, which still contained 231 µmol/kg. Based on these data, a fat-blood partition coefficient (log P_{fat}) of 1.95 was calculated for rats (Abraham and Ibrahim, 2006).

Methylcyclohexane is metabolized primarily via hydroxylation of the ring structure, followed by conjugation with glucuronic acid (Parnell et al., 1988; Frommer et al., 1970; Elliott et al., 1965). In rabbits administered single doses of 2.1−2.4 mmol/kg (equivalent to 206−236 mg/kg) [U-^{14}C]methylcyclohexane by gavage in water and monitored for approximately 60 hours, most of the metabolites identified were glucuronide conjugates of the following methylcyclohexanols in the urine: *trans*-4-, *cis*-3-, *trans*-3-, *cis*-4-, *trans*-2-, and *cis*-2-, accounting for 14.7, 11.5, 10.5, 2.4, 1.3, and 0.6% of the administered radiolabel, respectively (Elliott et al., 1965). Small amounts of benzoic acid and cyclohexylmethanol were also observed in the urine, which the study authors suggested may have resulted from hydroxylation of the methyl group on the cyclohexane ring and subsequent aromatization. In male F344 rats orally dosed once with 800 mg/kg methylcyclohexane, metabolites identified in urine collected over the ensuing 48 hours were glucuronide conjugates of the following methylcyclohexanols: *trans*-2-hydroxy-*cis*-4, *cis*-2-hydroxy-*trans*-4, *cis*-2-hydroxy-*cis*-4-, *trans*-3, *trans*-4, and cyclohexylmethanol; relative abundances in the gas chromatograph tracing were 23.4, 15.7, ≤10, ≤10, ≤10, and ≤10%, respectively (Parnell et al., 1988)[11]. Deichman and Thomas (1943) and Treon et al. (1943b) also reported glucuronic acid conjugates in the urine of rabbits dosed orally with methylcyclohexane. Using rat liver microsomes in vitro, Frommer et al. (1970) demonstrated that hydroxylation of methylcyclohexane in the liver is mediated by cytochrome P450 (CYP450) monooxygenases and that metabolism can be induced by using liver microsomes from rats pretreated with phenobarbital.

The rapid loss from tissues (other than fat) of parent methylcyclohexane following inhalation exposure in rats (Zahlsen et al., 1992) suggests that metabolism and elimination of methylcyclohexane are rapid (on the order of days). Data from Elliott et al. (1965) also support rapid metabolism and elimination of methylcyclohexane, with elimination occurring primarily as metabolites in the urine following oral dosing in rabbits. The percentages of administered radioactivity recovered were 54.2−77.4% in urine, 5.0−8.6% in expired air as CO_2, 4.4−15.9% in expired air as parent compound, 0.4−0.7% in feces, and only 2.8−5.9% remaining in body tissues approximately 60 hours after dosing, meaning that the vast majority of administered radioactivity was eliminated from the body within 60 hours, mostly as metabolites in the urine.

[11]The study authors reported specific values for each of the metabolites, but the numbers for the less-abundant metabolites differed between the text and Table 1 of Parnell et al. (1988), necessitating the presentation here of each as ≤10%.

2.3.5. Mode-of-Action/Mechanistic Studies

The liver and kidney are primary target organs following methylcyclohexane exposures. No mode-of-action or mechanistic studies on methylcyclohexane-induced effects on the liver were identified. Methylcyclohexane effects on the kidney, seen in male rats in repeated-exposure oral and inhalation studies (JECDB, 2013; ECHA, 2011a, 2001c; AFRL, 1985), were attributed by the study authors to α2u-g nephropathy, a male-rat-specific effect that is not relevant to humans (U.S. EPA, 1991). However, none of these studies (nor any other in the database for methylcyclohexane) provided a rigorous demonstration that the observed renal lesions were in fact associated with accumulation of α2u-g, and not all findings in these studies were consistent with this hypothesis. No specific mechanistic investigations of this endpoint were located for methylcyclohexane.

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF ORAL REFERENCE DOSES

The database of relevant studies for derivation of provisional reference doses (p-RfDs) for methylcyclohexane is limited. No adequate human studies were identified. Animal studies available via the oral route include an unpublished, non-peer-reviewed OECD 407 guideline study as summarized in secondary sources (the primary study was not available for review) and an unpublished, non-peer-reviewed OECD 422 guideline study published primarily in Japanese (JECDB, 2013). Due to the limitations of the available reports for these studies, p-RfDs cannot be confidently derived. However, the available reports for the two studies provide sufficient data to develop a screening subchronic p-RfD value for methylcyclohexane (see Appendix A).

3.2. DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Limited data are available for derivation of provisional reference concentrations (p-RfCs) for methylcyclohexane. No adequate human studies were identified. Animal inhalation studies include a study published primarily in Korean with data tables in English for a limited number of endpoints (Kim et al., 2006) and a study that was not published or peer-reviewed (AFRL, 1985). Due to the limitations of the available studies, p-RfCs cannot be confidently derived. However, the 12-month AFRL (1985) study provides sufficient data to develop a screening chronic p-RfC value for methylcyclohexane (see Appendix A).

3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

Table 5 presents a summary of noncancer provisional reference values.

Table 5. Summary of Noncancer Reference Values for Methylcyclohexane (CASRN 108-87-2)

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 incidence of renal tubule hyaline droplet degeneration	1×10^{-2}	$BMDL_{10}$	3.37	300	ECHA (2001c)
Chronic p-RfD (mg/kg-d)	NDr						
Subchronic p-RfC (mg/m^3)	NDr						
Screening chronic p-RfC (mg/m^3) (see Appendix A)	Hamster/M	Decreased body weight	9.5×10^{-2}	LOAEL	287		AFRL (1985)

BMD = benchmark dose; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = extra risk 10%); BMR = benchmark response; HEC = human equivalent concentration; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; M = male(s); NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

3.4. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Following the U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment*, methylcyclohexane has *inadequate information to assess carcinogenic potential* by oral or inhalation exposure (see Table 6). There are no human studies to indicate cancer risk. The database of information regarding carcinogenicity of methylcyclohexane in animals is limited to a single study in which CDF F344/CrlBR rats (65/sex/group), C57BL/6J mice (200 females/group), Syrian golden hamsters (100 males/group), and purebred beagle dogs (4/sex/group) were exposed to measured concentrations of 0, 1,607, or 8,048 mg/m^3 methylcyclohexane (~99% pure) vapors for 6 hours/day, 5 days/week for 1 year (AFRL, 1985). Most rodents were held for another year and all dogs were held for another 5 years prior to histopathological examination. No exposure-related tumors were observed in any species, but there were serious limitations in the design, conduct, and reporting of results of the study that may have impacted its ability to detect an effect, including the short (1-year) exposure duration, small group sizes for dogs, and insufficient exposure levels (the noncancer findings indicate that the maximum tolerated dose [MTD] was not achieved in any species). Genotoxicity studies, including two Ames tests for mutation in bacteria and two assays for chromosome aberrations in Chinese hamster lung cells, were negative (JECDB, 2011a, b; ECHA, 2001a, b).

Table 6. Cancer WOE Descriptor for Methylcyclohexane (CASRN 108-87-2)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	No human carcinogenicity data are available.
"Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	The available data do not support this descriptor.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**Selected based on lack of evidence for carcinogenicity of methylcyclohexane in a limited inhalation study and no information by oral 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.

3.5. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES

Due to a lack of carcinogenicity data, derivation of cancer risk estimates is precluded for methylcyclohexane (see Table 7).

Table 7. Summary of Cancer Risk Estimates for Methylcyclohexane (CASRN 108-87-2)

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

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

APPENDIX A. SCREENING PROVISIONAL VALUES

Due to limitations of the studies described in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment, it is inappropriate to derive provisional toxicity values for methylcyclohexane. 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 assessment. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there could be more uncertainty associated with deriving an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the CPHEA.

A screening subchronic provisional reference dose (p-RfD) and a screening chronic provisional reference concentration (p-RfC) were derived for methylcyclohexane. These screening assessments are presented below.

DERIVATION OF SCREENING ORAL PROVISIONAL REFERENCE DOSES

As discussed in the main body of this assessment, the available reports of the Organisation for Economic Co-operation and Development (OECD) guideline 407 repeated-dose 28-day gavage rat study (ECHA, 2001c) and the OECD guideline 422 combined repeated-dose with reproductive/developmental screening study (JECDB, 2013) have limitations precluding their use in deriving provisional toxicity values (unpublished, not peer-reviewed, available only in a secondary source, and/or published primarily in a foreign language). While limited by these shortcomings, the available reports for both studies provide sufficient information to suggest that the studies were otherwise adequately designed and conducted and include dose-response information on multiple endpoints suitable for quantitative toxicity assessment and derivation of screening provisional toxicity values.

Treatment-related effects of methylcyclohexane in both studies were seen in the liver and kidney, including lesions and organ weight increases. The renal effects were dismissed as being largely consistent with alpha 2u-globulin (α2u-g) nephropathy by the study authors of the secondary European Chemicals Agency (ECHA) reports in both studies (ECHA, 2011a, 2001c). Although ECHA considered hyaline droplet formation related to α2u-g accumulation and therefore not relevant to humans, the U.S. Environmental Protection Agency (U.S. EPA) has specific guidance for the establishment of an α2u-g mode of action by which the default position is to assume that renal effects in male rats are relevant to humans. According to the U.S. EPA guidance, "a chemical can be described as inducing α2u-g accumulation with certainty only when there is a positive identification of α2u-g in the hyaline droplets" (U.S. EPA, 1991). Neither study (nor any other study in the database for methylcyclohexane) provided a rigorous demonstration that the renal effects observed in male rats were, in fact, due to α2u-g nephropathy, and both studies also reported limited renal changes in female rats. Because the available data failed to provide sufficient evidence that the α2u-g process was operative, renal

effects in the male rats are considered a human health-relevant endpoint for this assessment, as outlined in the U.S. EPA α2u-g guidance (U.S. EPA, 1991) (see Section 2.2.1).

The data for increased absolute and relative liver and kidney weights and increased incidence of hepatocellular hypertrophy and hyaline droplet lesions from the two available oral short-term studies (JECDB, 2013; ECHA, 2001c) are shown in Tables A-1 and A-2. For the organ weight data, relative weights were modeled preferentially over absolute weights. For organs such as liver and kidney, whose weights are correlated with body weight, relative weights provide the more reliable, inclusive measure of effect (Nirogi et al., 2014; Bailey et al., 2004). Absolute weights were only modeled when modeling was unsuccessful for the relative weights and the absolute weights showed a biologically significant change (>10%).

Table A-1. Data for Endpoints Considered for Derivation in Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days[a]

	Males: ADD [HED] in mg/kg-d[b]			
Endpoint	**0**	**100 [24.9]**	**300 [74.6]**	**1,000 [249]**
Liver weight[c,d]				
Absolute (g)	9.65 ± 0.97	9.28 ± 1.89 (−4%)	11.22 ± 1.02 (+16%)	**11.75 ± 0.93 (+22%)***
Relative (%)	3.385 ± 0.16	3.225 ± 0.339 (−5%)	3.572 ± 0.1 (+6%)	**4.13 ± 0.137 (+22%)****
Liver cell hypertrophy[e]	0/5 (0%)	0/5 (0%)	0/5 (0%)	**5/5 (100%)****
Kidney tubule hyaline droplet degeneration[e]	0/5 (0%)	1/5 (20%)	**5/5 (100%)****	**5/5 (100%)****
	Females: ADD [HED] in mg/kg-d			
Endpoint	**0**	**100 [23.2]**	**300 [69.7]**	**1,000 [232]**
Liver weight[c,d]				
Absolute (g)	6.01 ± 0.55	6.81 ± 0.79 (+13%)	6.29 ± 0.49 (+5%)	6.6 ± 0.77 (+10%)
Relative (%)	3.17 ± 0.071	3.368 ± 0.213 (+6%)	3.231 ± 0.09 (+2%)	**3.577 ± 0.25 (+13%)****

[a]ECHA (2001c).
[b]The ADDs were converted to HEDs [appearing in brackets] of 24.9, 74.6, and 249 mg/kg-day in low-, mid-, and high-dose males, respectively, and 23.2, 69.7, and 232 mg/kg-day in low-, mid-, and high-dose females, respectively, using DAFs of 0.249 (males) and 0.232 (females), where HED = ADD × DAF. The DAFs were calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$). In the absence of body-weight data in the study, reference body weight of 0.267 kg for male and 0.204 kg for female Sprague Dawley rats in a subchronic study were used (U.S. EPA, 1988). For humans, the reference body-weight value of 70 kg was used (U.S. EPA, 1988).
[c]Data are mean ± SD from five animals.
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[e]Values denote number of animals showing changes/total number of animals examined (% incidence).
*Significantly different from control ($p < 0.05$) as reported by the study authors.
**Significantly different from control ($p < 0.01$) as reported by the study authors.

ADD = adjusted daily dose; BW_a = animal body weight; BW_h = human body weight; DAF = dosimetric adjustment factor; HED = human equivalent dose; SD = standard deviation.

Table A-2. Data for Endpoints Considered for Derivation in Crl:CD Sprague Dawley Rats Exposed to Methylcyclohexane via Gavage for 28 Days (Including Premating and Mating for Males)[a]

Endpoint	Males: ADD [HED] in mg/kg-d[b]			
	0	**62.5 [17.1]**	**250 [68.6]**	**1,000 [273]**
Liver weight[c,d]				
Absolute (g)	11 ± 0.32	10.95 ± 0.98 (+0%)	11.65 ± 0.57 (+6%)	**15.18 ± 0.94 (+38%)****
Relative (g %)	2.59 ± 0.08	2.64 ± 0.18 (+2%)	**2.81 ± 0.13 (+8%)***	**3.82 ± 0.13 (+47%)****
Kidney weight[c,d]				
Absolute (g)	2.75 ± 0.16	2.99 ± 0.31 (+9%)	2.92 ± 0.14 (+6%)	**3.14 ± 0.20 (+14%)***
Relative (g %)	0.65 ± 0.03	**0.72 ± 0.07 (+11%)***	0.70 ± 0.03 (+8%)	**0.79 ± 0.04 (+22%)****
Kidney tubule hyaline droplets[e]	0/6 (0%)	0/6 (0%)	4/6 (67%)	**6/6 (100%)****
Endpoint	**Unmated females: ADD [HED] in mg/kg-d**			
	0	**62.5 [15.7]**	**250 [63.0]**	**1,000 [251.3]**
Liver weight[c,d]				
Absolute (g)	7.58 ± 0.6	7.84 ± 0.47 (+3%)	7.77 ± 0.48 (+3%)	8.29 ± 0.88 (+9%)
Relative (g %)	2.63 ± 0.19	2.75 ± 0.14 (+5%)	2.71 ± 0.12 (+3%)	**3.02 ± 0.28 (+15%)***
Kidney weight[c,d]				
Absolute (g)	1.83 ± 0.11	1.87 ± 0.09 (+2%)	1.95 ± 0.08 (+7%)	2.04 ± 0.25 (+11%)
Relative (g %)	0.64 ± 0.04	0.66 ± 0.03 (+3%)	0.68 ± 0.03 (+6%)	**0.74 ± 0.09 (+16%)***

[a] JECDB (2013).
[b] The ADDs were converted to HEDs [appearing in brackets] of 17.1, 68.6, and 273.4 mg/kg-day in low-, mid-, and high-dose males, respectively, and 15.7, 63.0, and 251.3 mg/kg-day in low-, mid-, and high-dose females, respectively, using DAFs of 0.27 (males) and 0.25 (females), where HED = ADD × DAF. The DAFs were calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$). Individual animal body weights were provided in the study; group TWA body weights determined for this review were 0.395, 0.398, and 0.391 kg (for low-, mid-, and high-dose males, respectively) and 0.282, 0.283, 0.279 kg (for low-, mid-, and high-dose unmated females, respectively). For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).
[c] Values are expressed as mean ± SD from n = 6 (males), n = 5 (unmated females).
[d] Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[e] Values denote the number of animals showing changes/total number of animals examined (% incidence).
*Significantly different from control ($p < 0.05$), as reported by the study authors (Dunnett's test).
**Significantly different from control ($p < 0.01$), as reported by the study authors (Dunnett's test).

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

Benchmark dose (BMD) modeling of these endpoints was performed using all available continuous or dichotomous models in the U.S. EPA's Benchmark Dose Software (BMDS; Version 3.2), as appropriate. Human equivalent dose (HED) values in mg/kg-day were used as the dose metric. A benchmark response (BMR) of 10% relative deviation (0.1RD) was used for the continuous liver and kidney weight data because a 10% change in these organ weights was considered to be biologically significant. Dichotomous data were modeled using a BMR of 10% extra risk.

Tables A-3 and A-4 summarize the BMD modeling results and provide candidate points of departure (PODs) for the modeled endpoints from the two studies. Details of model fit for each data set are presented in Appendix C.

Table A-3. BMD and BMDL Values from Best Fitting Models in Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days[a]

Endpoints	Best Fitting Model	BMR	BMD (HED) (mg/kg-d)	BMDL (HED) (mg/kg-d)
Increased relative liver weight (males)	No selected model[b]	10% RD from control (0.1RD)	NA	NA
Increased absolute liver weight (males)	Exponential 4 (constant variance)	10% RD from control (0.1RD)	39.86	13.47
Increased relative liver weight (females)	No selected model[b]	10% RD from control (0.1RD)	NA	NA
Increased liver cell hypertrophy (males)	Log-logistic	10% extra risk	120.51	59.86
Increased kidney tubule hyaline droplet degeneration (males)	Multistage 2-degree	10% extra risk	13.35	3.37

[a]ECHA (2001c).
[b]No model provided adequate fit to the data.

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

Table A-4. BMD and BMDL Values from Best Fitting Models for Endpoints Considered for Derivation in Male and Female Crl:CD Sprague Dawley Rats Exposed to Methylcyclohexane During Premating and Mating (Males Only) or for 28 Days[a]

Endpoints	Best Fitting Model	BMR	BMD (HED) (mg/kg-d)	BMDL (HED) (mg/kg-d)
Increased relative liver weight (males)	Exponential 2 (constant variance)	10% RD from control (0.1RD)	66.03	61.05
Increased relative liver weight (females)	Polynomial 3-degree (constant variance)	10% RD from control (0.1RD)	218.90	126.60
Increased relative kidney weight (males)	No selected model[b]	10% RD from control (0.1RD)	NA	NA
Increased relative kidney weight (females)	Polynomial 3-degree (nonconstant variance)	10% RD from control (0.1RD)	161.67	97.08
Increased kidney tubule hyaline droplets (males)	Multistage 1-degree	10% extra risk	8.12	4.25

[a]JECDB (2013).
[b]No model provided adequate fit to the data.

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

Derivation of a Screening Subchronic Provisional Reference Dose

The 10% benchmark dose lower confidence limit ($BMDL_{10}$) (HED) of 3.37 mg/kg-day based on increased incidence of renal tubule hyaline droplet degeneration in male rats in the ECHA (2001c) study is the most sensitive POD identified and is selected as the POD for derivation of the screening subchronic p-RfD for methylcyclohexane.

The screening subchronic p-RfD of 1×10^{-2} mg/kg-day for methylcyclohexane 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 3.37 mg/kg-day, as follows:

Screening Subchronic p-RfD = POD (HED) ÷ UF_C
= 3.37 mg/kg-day ÷ 300
= **1×10^{-2} mg/kg-day**

Table A-5 summarizes the uncertainty factors for the screening subchronic p-RfD for methylcyclohexane.

Table A-5. Uncertainty Factors for the Screening Subchronic p-RfD for Methylcyclohexane (CASRN 108-97-2)

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	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The repeated-dose oral database for methylcyclohexane includes only two studies, both of which have significant limitations. Reproductive/developmental endpoints were included in one study and no effects were found, but only a limited screening-level assessment was performed.
UF_H	10	A UF_H of 10 is applied for interindividual variability in the absence of information to assess the toxicokinetic and toxicodynamic variability of methylcyclohexane in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because the POD was derived from a study of suitable duration (28 days) for a subchronic value.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

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 a Screening Chronic Provisional Reference Dose

The POD used for derivation of the screening subchronic p-RfD, the $BMDL_{10}$ (HED) for increased incidence of renal tubule hyaline droplet degeneration in the 28-day study (ECHA, 2001c) cannot be used directly for derivation of the screening chronic p-RfD, due to the short duration of the critical study. Therefore, derivation of a screening chronic p-RfD is not supported by the available database.

DERIVATION OF SCREENING INHALATION PROVISIONAL REFERENCE CONCENTRATIONS

As discussed in the main body of this PPRTV assessment, the available inhalation studies have limitations precluding their use in deriving provisional toxicity values (unpublished, not peer-reviewed, written primarily in a foreign language). In order to account for the uncertainty associated with deriving toxicity values from these limited study reports, the assessment is considered a screening-level assessment**.**

AFRL (1985) exposed rats of both sexes, female mice, male hamsters, and dogs of both sexes to methylcyclohexane vapor for 1 year and observed them for an additional 1 year (rodents) or 5 years (dogs) prior to sacrifice. No effects clearly related to exposure were observed in mice or dogs.

In rats, renal lesions (medullary mineralization and papillary hyperplasia) were increased in the high-exposure males after the 1-year recovery at 24 months. The study authors considered these lesions to be related to α2u-g nephropathy, but neither this study nor any other in the database for methylcyclohexane provided a rigorous demonstration that the renal effects observed in male rats were, in fact, due to α2u-g nephropathy. Based on the available data, only

one of three criteria (the presence of lesions observed in the latter stages of α2u-g) were fulfilled to satisfy the involvement of α2u-g as outlined by the U.S. EPA (1991) guidance. Because the available data fail to provide sufficient evidence that the α2u-g process was operative, renal effects in the male rats are considered a human health-relevant endpoint for this assessment. The data for increased incidences of renal medullary mineralization and papillary hyperplasia in male rats reported in AFRL (1985) are shown in Table A-6.

Table A-6. Renal Lesions in Male CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year[a]

Endpoint	Time of Sacrifice	Exposure Concentration [HEC_{ER}][b] in mg/m^3		
		0	1,607 [287.0]	8,048 [1,437]
Medullary mineralization	24 months	1/53 (2%)[c]	2/55 (4%)	**19/52 (37%)****
Papillary hyperplasia	24 months	1/53 (2%)	1/55 (2%)	**23/52 (44%)****

[a]AFRL (1985).
[b]Reported concentrations; calculated HEC_{ER} values appear in brackets. HEC values based on extrarespiratory effects were calculated by treating methylcyclohexane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure concentration (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 since the hamster blood-air partition coefficient (logK_{blood}) is unknown; the human logK_{blood} is 0.61.

[c]Values denote number of animals showing changes/total number of animals examined (% incidence).
*Significantly different from control ($p < 0.05$) as reported by the study authors.
**Significantly different from control ($p < 0.01$) as reported by the study authors.

HEC_{ER} = human equivalent concentration based on extrarespiratory effects.

BMD modeling of these endpoints was performed using all available dichotomous models in the U.S. EPA's BMDS (Version 3.2). HEC values in mg/m^3 were used as the dose metric. The data were modeled using a BMR of 10% extra risk.

Table A-7 summarizes the BMD modeling results and provides candidate PODs for the modeled endpoints. Details of model fit for each data set are presented in Appendix C.

Table A-7. BMC and BMCL Values from Best Fitting Models for Increased Renal Lesions in Male CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year[a]

Endpoints	Best Fitting Model	BMR	BMC (HEC) (mg/m^3)	BMCL (HEC) (mg/m^3)
Medullary mineralization	Logistic	10% extra risk	816.3	660.1
Papillary hyperplasia	Logistic	10% extra risk	804.4	641.6

[a]AFRL (1985).

BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; BMR = benchmark response; HEC = human equivalent concentration.

In hamsters exposed to either 1,607 or 8,048 mg/m^3 methylcyclohexane for 1 year, mean body weight was decreased as early as 1 month and persisted throughout the exposure period. Estimated data for decreased body weight in male hamsters are shown in Table A-8. The LOAEL of 1,607 mg/m^3 was selected as the POD for methylcyclohexane based on a biologically significant decrease in body weight relative to control animals. In the absence of variance reported by the study authors, these data were not amendable to BMD modeling with BMDS (version 3.2). Instead, a $LOAEL_{HEC}$ of 297 mg/m^3 was calculated based on body weight data presented in Figure 3 of the study report (AFRL, 1985).

Table A-8. Body Weight in Male Syrian Golden Hamsters Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year[a]

Endpoint	Time of Sacrifice	Exposure Concentration [HEC_{ER}][b] in mg/m^3		
		0	1,607 [287.0]	8,048 [1,437]
Body weight (g)[c]	12 mo	127	112 (−12%)	107 (−15%)

[a]AFRL (1985).
[b]Reported concentrations; calculated HEC_{ER} values appear in brackets. HEC values based on extrarespiratory effects were calculated by treating methylcyclohexane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure concentration (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 since the hamster blood-air partition coefficient ($\log K_{blood}$) is unknown; the human $\log K_{blood}$ is 0.61.
[c]Values denote estimated body weight based on Figure 3 of the study report (AFRL, 1985).

HEC_{ER} = human equivalent concentration based on extrarespiratory effects.

Derivation of a Screening Subchronic Provisional Reference Concentration

There are no suitable human or animal data available to derive a subchronic provisional reference concentration (p-RfC) for methylcyclohexane. (Kim et al., 2006), an inhalation study in rats study written in Korean with some data tables written in English, reported on a limited number of endpoints that were not deemed suitable to identify and derive a POD. Therefore, derivation of a screening chronic p-RfC is not supported by the available database.

Derivation of a Screening Chronic Provisional RfC

The $LOAEL_{HEC}$ value of 287 mg/m^3, based on decreased body weight >10% in male Syrian golden hamsters exposed to methylcyclohexane for 1 year, is the most sensitive of the three PODs identified from the AFRL (1985) study and is selected as the POD for derivation of the screening chronic p-RfC.

The screening chronic p-RfC of 9.5×10^{-2} mg/m^3 for methylcyclohexane is derived by applying a UFc of 3,000 (reflecting a UF_A of 3, a UF_D of 10, a UF_H of 10, and a UF_L of 10) to the selected POD of 287 mg/m^3, as follows:

$$\begin{aligned} \textbf{Screening Chronic p-RfC} &= \text{POD (HEC)} \div UF_C \\ &= 287 \text{ mg/m}^3 \div 3{,}000 \\ &= \mathbf{9.5 \times 10^{-2} \text{ mg/m}^3} \end{aligned}$$

Table A-9 summarizes the uncertainty factors for the screening chronic p-RfC for methylcyclohexane.

Table A-9. Uncertainty Factors for the Screening Chronic p-RfC for Methylcyclohexane (CASRN 108-87-2)

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 repeated-dose inhalation database for methylcyclohexane includes only two studies, both of which have significant limitations. No inhalation studies evaluating reproductive or developmental endpoints are available.
UF_H	10	A UF_H of 10 is applied for interindividual variability in the absence of information to assess the toxicokinetic and toxicodynamic variability of methylcyclohexane in humans.
UF_L	10	A UF_L of 10 is applied for LOAEL to NOAEL extrapolation because the POD is a LOAEL.
UF_S	1	A UF_S of 1 is applied because the POD was derived from a study of suitable duration (1 yr) for a chronic value.
UF_C	3,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

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.

APPENDIX B. DATA TABLES

Table B-1. Body Weight Gain and Food Consumption in Male and Female Crj:CD (Sprague Dawley) Rats Treated with Methylcyclohexane via Gavage for 28 Days[a]

Endpoint	Males: ADD [HED] in mg/kg-d[b]			
	0	**100 [24.9]**	**300 [74.6]**	**1,000 [249]**
Body-weight gain (g) (Days 0−27)	167 ± 32[c]	176 ± 33 (+5%)[d]	**210 ± 24 (+26%)***	**200 ± 26 (+20%)***
Total food consumption (g)				
Males (Days 0−27)	515 ± 31	541 ± 60 (+5%)	**577 ± 36 (+12%)***	**598 ± 42(+16%)****
Recovery males (Days 29−41)	294 ± 29	ND	ND	**356 ± 35 (+21%)***
Endpoint	**Females: ADD [HED] in mg/kg-d[b]**			
	0	**100 [23.2]**	**300 [69.7]**	**1,000 [232]**
Body-weight gain (g) (Days 0−27)	87 ± 18	102 ± 24 (+17%)	91 ± 12 (+5%)	85 ± 13 (−2%)

[a]ECHA (2001c).
[b]ADD (mg/kg-day) values were reported in the secondary source; calculated HEDs appear in brackets.
[c]Data are mean ± SD, from 10 animals (control and high-dose groups) or five animals (low- and mid-dose groups).
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$) as reported by the study authors.
**Significantly different from control ($p < 0.01$) as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; ND = not determined; SD = standard deviation.

Table B-2. Select Blood Biochemistry in Male and Female Crj:CD (Sprague Dawley) Rats Treated with Methylcyclohexane via Gavage for 28 Days[a]

Endpoint	Males: ADD [HED] in mg/kg-d[b]			
	0	**100 [24.9]**	**300 [74.6]**	**1,000 [249]**
	After Dosing (Day 28)			
ALP (U/L)	789 ± 101[c]	787 ± 214 (+0%)[d]	672 ± 172 (−15%)	**523 ± 90 (−34%)***
AST (U/L)	69 ± 7	63 ± 6 (−9%)	69 ± 16 (+0%)	72 ± 17 (+4%)
TBIL (mg/dL)	0.02 ± 0.01	0.02 ± 0.01 (+0%)	**0.04 ± 0.01 (+100%)***	0.02 ± 0.01 (+0%)
TC (mg/dL)	53 ± 16	55 ± 7 (+4%)	62 ± 9 (+17%)	64 ± 5 (+21%)
TP (g/dL)	5.5 ± 0.1	5.39 ± 0.13 (−2%)	5.61 ± 0.18 (+2%)	**5.89 ± 0.16 (+7%)****
A/G	1.71 ± 0.15	1.76 ± 0.14 (+3%)	1.76 ± 0.08 (+3%)	1.6 ± 0.07 (−6%)
	After Recovery (Day 42)			
ALP (U/L)	654 ± 93	NA	NA	**520 ± 75 (−20%)***
TC (mg/dL)	46 ± 5	NA	NA	**72 ± 12 (+57%)****
TP (g/dL)	5.63 ± 0.18	NA	NA	**5.95 ± 0.14 (+6%)***
GLU (mg/dL)	165 ± 20	NA	NA	163 ± 15 (−1%)
A/G	1.7 ± 0.07	NA	NA	**1.52 ± 0.12 (−11%)***
K (mmol/L)	4.97 ± 0.06	NA	NA	**4.54 ± 0.12 (−9%)****
Endpoint	**Females: ADD [HED] in mg/kg-d**			
	0	**100 [23.2]**	**300 [69.7]**	**1,000 [232]**
	After Dosing (Day 28)			
ALP (U/L)	450 ± 203	448 ± 97 (+0%)	548 ± 88 (+22%)	351 ± 109 (−22%)
AST (U/L)	79 ± 7	70 ± 9 (−11%)	70 ± 11 (−11%)	**62 ± 8 (−22%)***
TBIL (mg/dL)	0.03 ± 0.01	0.03 ± 0.01 (+0%)	0.03 ± 0.01 (+0%)	0.02 ± 0.01 (−33%)
TC (mg/dL)	50 ± 7	56 ± 7 (+12%)	59 ± 10 (+18%)	**73 ± 13 (+46%)****
TP (g/dL)	5.78 ± 0.23	5.71 ± 0.24 (−1%)	5.71 ± 0.34 (−1%)	5.85 ± 0.19 (+1%)
A/G	1.85 ± 0.04	**2.11 ± 0.07 (+14%)***	2 ± 0.31 (+8%)	1.96 ± 0.2 (+6%)

Table B-2. Select Blood Biochemistry in Male and Female Crj:CD (Sprague Dawley) Rats Treated with Methylcyclohexane via Gavage for 28 Days[a]

	After Recovery (Day 42)			
ALP (U/L)	295 ± 44	NA	NA	301 ± 56 (+2%)
TC (mg/dL)	67 ± 7	NA	NA	64 ± 11 (−4%)
TP (g/dL)	6.09 ± 0.43	NA	NA	6.01 ± 0.23 (−1%)
GLU (mg/dL)	121 ± 11	NA	NA	**139 ± 14 (+15%)***
A/G	1.84 ± 0.12	NA	NA	1.87 ± 0.19 (+2%)
K (mmol/L)	4.72 ± 0.25	NA	NA	4.45 ± 0.44 (−6%)

[a]ECHA (2001c).
[b]ADD (mg/kg-day) values were reported in the secondary source; calculated HEDs appear in brackets.
[c]Data are mean ± SD from five animals.
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$) as reported by the study authors.
**Significantly different from control ($p < 0.01$) as reported by the study authors.

ADD = adjusted daily dose; A/G = albumin:globulin ratio; ALP = alkaline phosphatase; AST = aspartate aminotransferase; GLU = glucose; HED = human equivalent dose; K = potassium NA = not applicable; SD = standard deviation; TBIL = total bilirubin; TC = total cholesterol; TP = total protein.

Table B-3. Select Organ Weights in Male and Female Crj:CD (Sprague Dawley) Rats Treated with Methylcyclohexane via Gavage for 28 Days[a]

Endpoint	Males: ADD [HED] in mg/kg-d[b]			
	0	**100 [24.9]**	**300 [74.6]**	**1,000 [249]**
	After Dosing (Day 28)			
Liver weight				
Absolute (g)	9.65 ± 0.97[c]	9.28 ± 1.89 (−4%)[d]	11.22 ± 1.02 (+16%)	**11.75 ± 0.93 (+22%)***
Relative (%)	3.385 ± 0.16	3.225 ± 0.339 (−5%)	3.572 ± 0.1 (+6%)	**4.13 ± 0.137 (+22%)****
	After Recovery (Day 42)			
Liver weight				
Absolute (g)	9.99 ± 1.52	NA	NA	**13.11 ± 1.20 (+31%)****
Relative (%)	3.119 ± 0.131	NA	NA	**3.406 ± 0.169 (+9%)****
Endpoint	**Females: ADD [HED] in mg/kg-d**			
	0	**100 [23.2]**	**300 [69.7]**	**1,000 [232]**
	After Dosing (Day 28)			
Liver weight				
Absolute (g)	6.01 ± 0.55	6.81 ± 0.79 (+13%)	6.29 ± 0.49 (+5%)	6.6 ± 0.77 (+10%)
Relative (%)	3.17 ± 0.071	3.368 ± 0.213 (+6%)	3.231 ± 0.09 (+2%)	**3.577 ± 0.25 (+13%)****
	After Recovery (Day 42)			
Liver weight				
Absolute (g)	6.11 ± 0.71	NA	NA	6.61 ± 0.54 (+8%)
Relative (%)	2.861 ± 0.168	NA	NA	3.113 ± 0.239 (+9%)

[a]ECHA (2001c).
[b]ADD (mg/kg-day) values were reported in the secondary source; calculated HEDs appear in brackets.
[c]Data are mean ± SD from five animals.
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$) as reported by the study authors.
**Significantly different from control ($p < 0.01$) as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; NA = not applicable; SD = standard deviation.

Table B-4. Select Histological Findings in Male and Female Crj:CD (Sprague Dawley) Rats Treated with Methylcyclohexane via Gavage for 28 Days[a]

Endpoint	Males: ADD [HED] in mg/kg-d[b]			
	0	**100 [24.9]**	**300 [74.6]**	**1,000 [249]**
	After Dosing (Day 28)			
Liver				
Hypertrophy, hepatocytes	0/5 (0%)[c]	0/5 (0%)	0/5 (0%)	**5/5 (100%)****
Kidney				
Hyaline droplet formation	0/5 (0%) 0/5 (0%)	1/5 (20%) 0/5 (0%)	**5/5 (100%)**** 0/5 (0%)	**5/5 (100%)**** 0/5 (0%)
	After Recovery (Day 42)			
Kidney				
Degeneration, hyaline droplet Hyaline droplet formation	0/5 (0%) 0/5 (0%)	NA NA	NA NA	1/5 (20%) 0/5 (0%)
Endpoint	**Females: ADD [HED] in mg/kg-d**			
	0	**100 [23.2]**	**300 [69.7]**	**1,000 [232]**
	After Dosing (Day 28)			
Liver				
Hypertrophy, hepatocytes	0/5 (0%)	0/5 (0%)	0/5 (0%)	1/5 (20%)
Kidney				
Degeneration, hyaline droplet Hyaline droplet formation	0/5 (0%) 0/5 (0%)	0/5 (0%) 0/5 (0%)	0/5 (0%) 0/5 (0%)	0/5 (0%) 2/5 (40%)
	After Recovery (Day 42)			
Kidney				
Degeneration, hyaline droplet Hyaline droplet formation	0/5 (0%) 0/5 (0%)	NA NA	NA NA	0/5 (0%) **5/5 (100%)****

[a]ECHA (2001c).
[b]ADD (mg/kg-day) values were reported in the secondary source; calculated HEDs appear in brackets.
[c]Values denote number of animals showing changes/total number of animals examined (% incidence).
**Significantly different from control ($p < 0.01$) as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; NA = not applicable.

Table B-5. Select Serum Biochemistry Results in Male and Female Crl:CD Sprague Dawley Rats Treated with Methylcyclohexane via Gavage for 28 Days (Including Premating and Mating for Males)[a]

Endpoint	Males: ADD [HED] in mg/kg-d[b]			
	0	**62.5 [17.1]**	**250 [68.6]**	**1,000 [273.4]**
	After Dosing (Day 28)			
ALT (IU/L)	25.5 ± 1.1[c]	28.4 ± 3.9 (+11%)[d]	35.6 ± 16.2 (+40%)	**44.3 ± 17.6 (+74%)***
AST (IU/L)	85.4 ± 11.4	80.0 ± 8.4 (−6%)	94.7 ± 37.8 (+11%)	90.8 ± 25.1 (+6%)
ALP (IU/L)	426.4 ± 113.3	369.5 ± 92.3 (−13%)	359.7 ± 43.8 (−16%)	364.2 ± 137.7 (−15%)
GGT (IU/L)	0.61 ± 0.08	0.51 ± 0.11 (−16%)	0.65 ± 0.17 (+7%)	**1.18 ± 0.33 (+93%)***
TP (g/dL)	5.59 ± 0.22	5.48 ± 0.18 (−2%)	5.55 ± 0.15 (−1%)	**6.25 ± 0.28 (+12%)****
TC (mg/dL)	45.1 ± 5.9	**60.8 ± 8.4 (+35%)***	**60.5 ± 9.3 (+34%)***	**81.2 ± 12.6 (+80%)****
TG (mg/dL)	39 ± 11	31.1 ± 8.3 (−20%)	30.8 ± 8.8 (−21%)	28.9 ± 11.4 (−26%)
GLU (mg/dL)	107.9 ± 7.5	112.1 ± 9.2 (+4%)	103.2 ± 6.7 (−4%)	97.9 ± 10.1 (−9%)
Cl (mEq/L)	108.6 ± 1	108.2 ± 1 (+0%)	**107.2 ± 1.1 (−1%)***	**105.7 ± 0.5 (−3%)****
Ca (mg/dL)	9.6 ± 0.2	9.5 ± 0.2 (−1%)	9.5 ± 0.2 (−1%)	**10 ± 0.2 (+4%)****
	After Recovery (Day 42)			
ALT (IU/L)	29.5 ± 6.2	27.6 ± 2.9 (−6%)	30.7 ± 6.4 (+4%)	**39.6 ± 8.8 (+34%)***
AST (IU/L)	85.3 ± 16.4	85.5 ± 13 (+0%)	74.8 ± 8.8 (−12%)	90.8 ± 25 (+6%)
ALP (IU/L)	301.2 ± 46.7	267 ± 17.1 (−11%)	308.3 ± 39.3 (+2%)	326.4 ± 40 (+8%)
GGT (IU/L)	0.44 ± 0.11	0.41 ± 0.06 (−7%)	0.43 ± 0.06 (−2%)	0.47 ± 0.12 (+7%)
TP (g/dL)	5.64 ± 0.13	5.65 ± 0.33 (+0%)	5.62 ± 0.19 (+0%)	5.87 ± 0.47 (+4%)
TC (mg/dL)	45.3 ± 6.3	51.6 ± 15.4 (+14%)	52.8 ± 10.4 (+17%)	**73.1 ± 13.5 (+61%)****
TG (mg/dL)	25.6 ± 11.4	31.6 ± 7.1 (+23%)	37.4 ± 22.1 (+46%)	33.7 ± 12.6 (+32%)
GLU (mg/dL)	116.1 ± 7.6	109.9 ± 8.2 (−5%)	**103.3 ± 8.8 (−11%)***	109.5 ± 9.4 (−6%)
Cl (mEq/L)	107.5 ± 1.1	108 ± 1.4 (+0%)	108.7 ± 1.3 (+1%)	106.8 ± 1.1 (−1%)
Ca (mg/dL)	9.5 ± 0.4	9.4 ± 0.2 (−1%)	9.6 ± 0.2 (+1%)	9.7 ± 0.2 (+2%)
Endpoint	**Unmated Females: ADD [HED] in mg/kg-d**			
	0	**62.5 [15.7]**	**250 [63.0]**	**1,000 [251.3]**
	After Dosing (Day 28)			
ALT (IU/L)	21.8 ± 2	27.0 ± 7.5 (+24%)	25.0 ± 1.8 (+15%)	25.0 ± 6.6 (+15%)
AST (IU/L)	71.9 ± 12	76.5 ± 6.5 (+6%)	76.2 ± 12.0 (+6%)	73.0 ± 11.0 (+2%)
ALP (IU/L)	198.3 ± 23.5	164 ± 31.2 (−17%)	191.8 ± 45.5 (−3%)	178.1 ± 42 (−10%)
GGT (IU/L)	0.7 ± 0.18	0.75 ± 0.12 (+7%)	0.74 ± 0.17 (+6%)	0.72 ± 0.18 (+3%)
TP (g/dL)	6.04 ± 0.4	5.94 ± 0.37 (−2%)	6.04 ± 0.07 (+0%)	6.35 ± 0.48 (+5%)
TC (mg/dL)	63.5 ± 11.8	57 ± 11.2 (−10%)	63.6 ± 13.8 (+0%)	76.7 ± 18.2 (+21%)
TG (mg/dL)	25.4 ± 14.3	23.9 ± 12.1 (−6%)	18.7 ± 4.8 (−26%)	27.4 ± 16.9 (+8%)
GLU (mg/dL)	119.2 ± 10.6	110.1 ± 2.7 (−8%)	110.2 ± 9.0 (−8%)	**105.9 ± 7.2 (−11%)***
Cl (mEq/L)	108.4 ± 0.9	107.1 ± 1.8 (−1%)	108.3 ± 1.2 (+0%)	108 ± 2.4 (+0%)

Table B-5. Select Serum Biochemistry Results in Male and Female Crl:CD Sprague Dawley Rats Treated with Methylcyclohexane via Gavage for 28 Days (Including Premating and Mating for Males)[a]

Ca (mg/dL)	9.7 ± 0.3	9.8 ± 0.3 (+1%)	9.6 ± 0.1 (−1%)	9.9 ± 0.5 (+2%)
	After Recovery (Day 42)			
ALT (IU/L)	25.2 ± 3.8	NA	NA	39 ± 37.2 (+55%)
AST (IU/L)	65.4 ± 4.1	NA	NA	92.7 ± 69.1 (+42%)
ALP (IU/L)	134.3 ± 30.4	NA	NA	137.2 ± 34 (+2%)
GGT (IU/L)	0.53 ± 0.16	NA	NA	0.48 ± 0.07 (−9%)
TP (g/dL)	6.65 ± 0.14	NA	NA	6.53 ± 0.25 (−2%)
TC (mg/dL)	78.8 ± 12.3	NA	NA	71.1 ± 16.7 (−10%)
TG (mg/dL)	25 ± 3.4	NA	NA	24 ± 1.4 (−4%)
GLU (mg/dL)	118.3 ± 9.2	NA	NA	120.5 ± 8.3 (+2%)
Cl (mEq/L)	105.7 ± 0.8	NA	NA	106.8 ± 1.3 (+1%)
Ca (mg/dL)	10.1 ± 0.2	NA	NA	10.2 ± 0.3 (+1%)

[a]JECDB (2013).
[b]ADD (mg/kg-day) values were reported by the study authors; calculated HEDs appear in brackets.
[c]Values are expressed as mean ± SD from n = 6 (males), n = 5 (unmated females).
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$), as reported by the study authors (Steel's test or Dunnett's test).
**Significantly different from control ($p < 0.01$), as reported by the study authors (Dunnett's test).

ADD = adjusted daily dose; ALT = alanine transaminase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; Ca = calcium; Cl = chloride; GGT = γ-glutamyl transferase; GLU = glucose; HED = human equivalent dose; NA = not applicable; SD = standard deviation; TC = total cholesterol; TG = triglyceride; TP = total protein.

Table B-6. Select Organ Weights of Male and Female Crl:CD Sprague Dawley Rats Treated with Methylcyclohexane During Premating, Mating, and Lactation or for 28 Days[a]

Endpoint	Males: ADD [HED] in mg/kg-d[b]			
	0	**62.5 [17.1]**	**250 [68.6]**	**1,000 [273.4]**
	After Dosing (Day 28)			
Body weight (g)	425 ± 12[c]	415 ± 29 (−2%)[d]	416 ± 9 (−2%)	398 ± 29 (−6%)
Liver weight				
Absolute (g)	11 ± 0.32	10.95 ± 0.98 (+0%)	11.65 ± 0.57 (+6%)	**15.18 ± 0.94 (+38%)****
Relative (g %)	2.59 ± 0.08	2.64 ± 0.18 (+2%)	**2.81 ± 0.13 (+8%)***	**3.82 ± 0.13 (+47%)****
Kidney weight				
Absolute (g)	2.75 ± 0.16	2.99 ± 0.31 (+9%)	2.92 ± 0.14 (+6%)	**3.14 ± 0.20 (+14%)***
Relative (g %)	0.65 ± 0.03	**0.72 ± 0.07 (+11%)***	0.70 ± 0.03 (+8%)	**0.79 ± 0.04 (+22%)****
Adrenal weight				
Absolute (mg)	61.7 ± 8.8	66.1 ± 6 (+7%)	55.9 ± 6.8 (−9%)	68.9 ± 11.9 (+12%)
Relative (mg %)	14.6 ± 2.2	16 ± 2 (+10%)	13.4 ± 1.5 (−8%)	17.3 ± 2.8 (+18%)
	After Recovery (Day 42)			
Body weight (g)	446 ± 20	442 ± 13 (−1%)	448 ± 30 (+0%)	433 ± 41(−3%)
Liver weight				
Absolute (g)	11.16 ± 1.42	10.97 ± 0.38 (−2%)	11.55 ± 0.97 (+3%)	12.25 ± 1.52 (+10%)
Relative (g %)	2.5 ± 0.26	2.49 ± 0.07 (+0%)	2.57 ± 0.1 (+3%)	2.83 ± 0.17 (+13%)
Kidney weight				
Absolute (g)	3.04 ± 0.18	3.02 ± 0.25 (−1%)	2.96 ± 0.38 (−3%)	3.15 ± 0.22 (+4%)
Relative (g %)	0.68 ± 0.01	0.69 ± 0.05 (+1%)	0.66 ± 0.08 (−3%)	0.73 ± 0.05 (+7%)
Adrenal weight				
Absolute (mg)	64.5 ± 8.6	59.5 ± 14.6 (−8%)	58.8 ± 11 (−9%)	56.4 ± 5.2 (−13%)
Relative (mg %)	14.5 ± 1.7	13.4 ± 3 (−8%)	13.1 ± 2.1 (−10%)	13.1 ± 0.8 (−10%)
Endpoint	**Unmated Females: ADD [HED] in mg/kg-d**			
	0	**62.5 [15.7]**	**250 [63.0]**	**1,000 [251.3]**
	After Dosing (Day 28)			
Body weight (g)	289 ± 16	285 ± 9 (−1%)	286 ± 7 (−1%)	274 ± 7 (−5%)
Liver weight				
Absolute (g)	7.58 ± 0.6	7.84 ± 0.47 (+3%)	7.77 ± 0.48 (+3%)	8.29 ± 0.88 (+9%)
Relative (g %)	2.63 ± 0.19	2.75 ± 0.14 (+5%)	2.71 ± 0.12 (+3%)	**3.02 ± 0.28 (+15%)***
Kidney weight				
Absolute (g)	1.83 ± 0.11	1.87 ± 0.09 (+2%)	1.95 ± 0.08 (+7%)	2.04 ± 0.25 (+11%)
Relative (g %)	0.64 ± 0.04	0.66 ± 0.03 (+3%)	0.68 ± 0.03 (+6%)	**0.74 ± 0.09 (+16%)***
Adrenal weight				
Absolute (mg)	65.3 ± 5.6	75.3 ± 8.7 (+15%)	74.7 ± 6.5 (+14%)	**84.1 ± 8.5 (+29%)****
Relative (mg %)	22.7 ± 2.6	26.5 ± 3.5 (+17%)	26.1 ± 2.7 (+15%)	**30.6 ± 2.4 (+35%)****

Table B-6. Select Organ Weights of Male and Female Crl:CD Sprague Dawley Rats Treated with Methylcyclohexane During Premating, Mating, and Lactation or for 28 Days[a]

Uterus weight				
Absolute (mg)	499 ± 69	542 ± 87 (+9%)	568 ± 148 (+14%)	665 ± 108 (+33%)
Relative (mg %)	173 ± 23	190 ± 33 (+10%)	199 ± 54 (+15%)	**243 ± 38 (+40%)***
	After Recovery (Day 42)			
Body weight (g)	295 ± 5	NA	NA	293 ± 18 (−1%)
Liver weight				
Absolute (g)	7.41 ± 0.18	NA	NA	**7.86 ± 0.37 (+6%)†**
Relative (g %)	2.51 ± 0.07	NA	NA	2.69 ± 0.23 (+7%)
Kidney weight				
Absolute (g)	1.94 ± 0.12	NA	NA	1.92 ± 0.18 (−1%)
Relative (g %)	0.66 ± 0.04	NA	NA	0.66 ± 0.06 (+0%)
Adrenal weight				
Absolute (mg)	78.2 ± 6.5	NA	NA	80.5 ± 10 (+3%)
Relative (mg %)	26.5 ± 2.3	NA	NA	27.7 ± 4.5 (+5%)
Uterus weight				
Absolute (mg)	581 ± 165	NA	NA	595 ± 109 (+2%)
Relative (mg %)	196 ± 56	NA	NA	203 ± 36 (+4%)
Endpoint	**Mated Females: ADD [HED] in mg/kg-d**			
	0	**62.5 [16.0]**	**250 [63.9]**	**1,000 [253.9]**
	Day 5 of Lactation			
Body weight (g)	309 ± 19	320 ± 21	314 ± 18	297 ± 35
Uterus weight				
Absolute (mg)	625 ± 92	647 ± 88 (+4%)	634 ± 95 (+1%)	657 ± 146 (+5%)
Relative (mg %)	202 ± 30	203 ± 29 (+0%)	202 ± 33 (+0%)	221 ± 39 (+9%)

[a]JECDB (2013).
[b]ADD (mg/kg-day) values were reported by the study authors; calculated HEDs appear in brackets.
[c]Values are expressed as mean ± SD from n = 6 (males), n = 5 (unmated females), and n = 11 (mated females).
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$), as reported by the study authors (Dunnett's test).
**Significantly different from control ($p < 0.01$), as reported by the study authors (Dunnett's test).
†Significantly different from control ($p < 0.05$), as reported by the study authors (Student's *t*-test).

ADD = adjusted daily dose; HED = human equivalent dose; NA = not applicable; SD = standard deviation.

Table B-7. Select Hematology in Male and Female CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year[a]

Endpoint	Exposure Concentration [HEC_{ER}][b] in mg/m^3		
	0	**1,607 [287.0]**	**8,048 [1,437]**
	Males		
WBC (10^3)	6.7[c]	**5.4 (−19%)[d,*]**	**5.3 (−21%)***
RBC (10^6)	9.7	9.8 (+1%)	9.7 (+0%)
HCT (%)	47.7	**48.9 (+3%)***	47.0 (−1%)
HGB (g/dL)	15.2	15.4 (+1%)	**14.7 (−3%)****
	Females		
WBC (10^3)	5.4	4.8 (−11%)	**3.6 (−33%)***
RBC (10^6)	7.8	7.8 (+0%)	7.9 (+1%)
HCT (%)	44.1	43.1 (−2%)	44.0 (+0%)
HGB (g/dL)	14.5	14.4 (−1%)	14.3 (−1%)

[a]AFRL (1985).
[b]Reported concentrations; calculated HEC_{ER} values appear in brackets.
[c]Data are means from 9 or 10 animals; measures of variance were not provided.
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$) as reported by the study authors.
**Significantly different from control ($p < 0.01$) as reported by the study authors.

HCT = hematocrit; HGB = hemoglobin; HEC_{ER} = human equivalent concentration based on extrarespiratory effects; RBC = red blood cell; WBC = white blood cell.

Table B-8. Renal Lesions in Male and Female CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year[a]

Endpoint	Time of Sacrifice	Exposure Concentration [HEC_{ER}][b] in mg/m^3		
		0	1,607 [287.0]	8,048 [1,437]
		Males		
Renal tubular dilatation	12 mo	1/11 (9%)[c]	2/10 (20%)	4/11 (36%)
CPN	24 mo	49/53 (92%)	52/55 (95%)	52/52 (100%)
Medullary mineralization		1/53 (2%)	2/55 (4%)	**19/52 (37%)****
Papillary hyperplasia		1/53 (2%)	1/55 (2%)	**23/52 (44%)****
Tubular degeneration		1/53 (2%)	0/55 (0%)	2/52 (4%)
		Females		
CPN	24 mo	15/52 (29%)	7/51 (14%)	15/54 (28%)
Medullary mineralization		4/52 (8%)	0/51 (0%)	1/54 (2%)

[a]AFRL (1985).
[b]Reported concentrations; calculated HEC_{ER} values appear in brackets.
[c]Values denote number of animals showing changes/total number of animals examined (% incidence).
*Significantly different from control ($p < 0.05$) as reported by the study authors.
**Significantly different from control ($p < 0.01$) as reported by the study authors.

CPN = chronic progressive nephropathy; HEC_{ER} = human equivalent concentration based on extrarespiratory effects.

Table B-9. Select Neoplastic Lesions in Male and Female CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year[a]

Endpoint	Time of Sacrifice	Exposure Concentration [HEC_{ER}][b] in mg/m^3		
		0	1,607 [287.0]	8,048 [1,437]
		Males		
Testicular tumor (unspecified)	12 mo	0/11 (0%)[c]	**5/10 (50%)***	2/10 (20%)
Testis (interstitial cell tumor)	24 mo	49/54 (91%)	49/55 (89%)	50/52 (96%)
Renal cell adenoma	24 mo	0/54 (0%)	0/55 (0%)	1/52 (2%)
Renal cell carcinoma		0/54 (0%)	1/55 (2%)	0/52 (0%)
		Females		
Mammary gland fibroadenoma	24 mo	0/47 (0%)	4/50 (8%)	6/48 (13%)

[a]AFRL (1985).
[b]Reported concentrations; calculated HEC_{ER} values appear in brackets.
[c]Values denote number of animals showing changes/total number of animals examined (% incidence).
*Significantly different from control ($p < 0.05$) as reported by the study authors.

HEC_{ER} = human equivalent concentration based on extrarespiratory effects.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE FOR DICHOTOMOUS DATA

Benchmark dose (BMD) modeling of dichotomous data was conducted with the U.S. Environmental Protection Agency (U.S. EPA) Benchmark Dose Software (BMDS; Version 3.2). For the dichotomous data, the Gamma, Logistic, Log-Logistic, Log-Probit, Multistage, Probit, and Weibull dichotomous models available within the software were 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, 2012a). 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 was 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), BMDL that is not 10 times lower than the lowest nonzero dose, 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) was selected as a potential POD if the BMDLs were sufficiently close (less than threefold); if the BMDLs were not sufficiently close (greater than threefold), model-dependence was indicated, and the model with the lowest reliable BMDL was selected.

MODELING PROCEDURE FOR CONTINUOUS DATA

BMD modeling of continuous data was conducted with the U.S. EPA's BMDS (Version 3.2). For the continuous 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, 2012a). 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 was 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 was selected if the BMDLs estimated from different models varied by greater than threefold; otherwise, the BMDL from the model with the lowest AIC was 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 Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (ECHA, 2001c)

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in male Crj:CD (Sprague Dawley) rats orally exposed to methylcyclohexane for 28 days (ECHA, 2001c). The constant variance model did not provide an adequate fit to the variance data (Test 2; *p*-value <0.01). The nonconstant variance model did provide an adequate fit to the variance data (Test 3; *p*-value >0.1); however, with the nonconstant variance model applied, none of the models provided adequate fits to the means (Test 4; *p*-value <0.1). The results of the BMD modeling are summarized in Table C-1. Because none of the models provided adequate fit to the data, this endpoint was not considered further.

Table C-1. BMD Modeling Results (Nonconstant Variance) for Increased Relative Liver Weight in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 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]	0.11	0.06	0.55	−1.76	104.15	87.81
Exponential (model 3)[c]	0.11	0.02	0.67	0.20	112.39	87.92
Exponential (model 4)[c]	0.11	0.02	0.40	0.20	94.17	39.07
Exponential (model 5)[c]	0.11	NA	−0.25	−0.78	75.59	58.52
Polynomial (3-degree)[d]	0.11	0.06	0.43	−1.80	95.70	78.95
Polynomial (2-degree)[d]	0.11	0.06	0.43	−1.80	95.70	78.68
Power[c]	0.11	0.02	0.64	0.07	109.64	79.05
Linear[d]	0.11	0.06	0.43	−1.80	95.70	78.68

[a]ECHA (2001c).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Coefficients restricted to be positive.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 0.1RD = relative deviation of 10%); BMR = benchmark response; HED = human equivalent dose; NA = not applicable (computation failed).

Increased Absolute Liver Weight in Male Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (ECHA, 2001c)

The procedure outlined above for continuous data was applied to the data for increased absolute liver weight in male Crj:CD (Sprague Dawley) rats orally exposed to methylcyclohexane for 28 days (ECHA, 2001c). The constant variance model provided adequate fit to the variance data (Test 2 *p*-value >0.1). With the constant 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, BMDLs were not 10 times lower than the lowest nonzero dose, and scaled residuals did not exceed ±2 units at the data point closest to the BMD. BMDLs for models providing adequate fit were not sufficiently close (differed by greater than threefold), so the model with the lowest BMDL was selected (Exponential 4). The Exponential 4 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 39.9 and 13.5 mg/kg-day, respectively. The results of the BMD modeling are summarized in Table C-2 and plotted in Figure C-1.

Table C-2. BMD Modeling Results (Constant Variance) for Increased Absolute Liver Weight in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 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]	0.27	0.12	1.568173	72.04	115.74	75.78
Exponential (model 3)[c]	0.27	0.12	1.568171	72.04	115.74	76.54
Exponential (model 4)[c,*]	**0.27**	**0.10**	**−1.234229**	**72.44**	**39.9**	**13.5**
Exponential (model 5)[c]	0.27	NA	−0.000001	72.02	70.41	25.65
Polynomial (3-degree)[d]	0.27	0.13	1.527652	71.86	106.43	65.78
Polynomial (2-degree)[d]	0.27	0.13	1.527652	71.86	106.43	65.78
Power[c]	0.27	0.13	1.527651	71.86	106.43	65.78
Linear[d]	0.27	0.13	1.527651	71.86	106.43	65.78

[a]ECHA (2001c).
[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 provided an adequate fit to the variance data. All models, except the Exponential 5 model provided adequate fit to the means. BMDLs for models providing adequate fit were not sufficiently close (differed by greater than threefold), so the model with the lowest BMDL was selected (Exponential 4).

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 0.1RD = relative deviation of 10%); BMR = benchmark response; HED = human equivalent dose; NA = not applicable (computation failed).

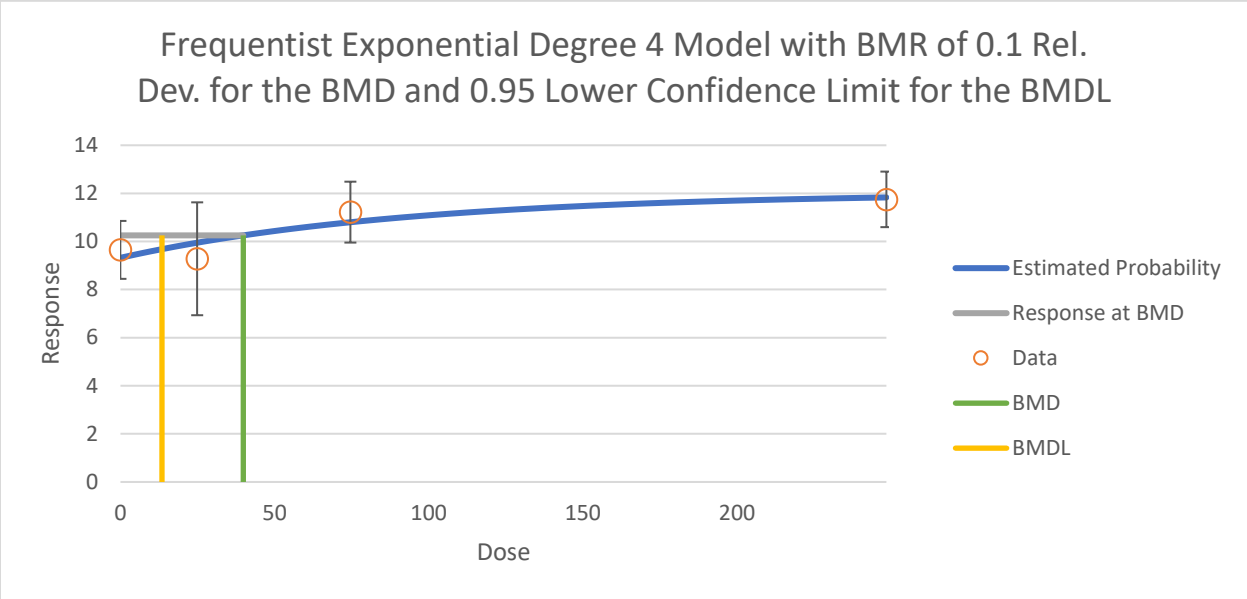

Figure C-1. Fit of Exponential 4-Degree Model to the Data for Increased Absolute Liver Weight in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (ECHA, 2001c)

BMD Model Output of Exponential 4-Degree Model for Increased Absolute Liver Weight in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (ECHA, 2001c)

Frequentist Exponential Degree 4 Restricted

User Input

Info	
Model	frequentist Exponential degree 4 v1.1
Dataset Name	Abs_liv_Wt_M_R
User notes	[Add user notes here]
Dose-Response Model	M[dose] = a * [c-(c-1) * exp(-b * dose)]
Variance Model	Var[i] = alpha

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

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

Model Results

Benchmark Dose	
BMD	39.85902309
BMDL	13.46632275
BMDU	173.0784801
AIC	72.44059703
Test 4 P-value	0.101059176
D.O.F.	1

Model Parameters	
# of Parameters	4
Variable	Estimate
a	9.32129997
b	0.01061126
c	1.289946148
log-alpha	0.384152652

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	9.32129997	9.65	9.65	1.211763	0.97	0.97	0.606550629
24.9	5	9.948849455	9.28	9.28	1.211763	1.89	1.89	-1.23422884
74.6	5	10.799341	11.22	11.22	1.211763	1.02	1.02	0.776242649
248.5	5	11.8305095	11.75	11.75	1.211763	0.93	0.93	-0.1485643

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-30.87592439	5	71.7518488
A2	-28.91408293	8	73.8281659
A3	-30.87592439	5	71.7518488
fitted	-32.22029852	4	72.440597
R	-36.94835965	2	77.8967193

* Includes additive constant of -18.37877. 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	16.06855345	6	0.01339071
2	3.92368292	3	0.26982379
3	3.92368292	3	0.26982379
4	2.688748248	1	0.10105918

Increased Relative Liver Weight in Female Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (ECHA, 2001c)

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in female Crj:CD (Sprague Dawley) rats orally exposed to methylcyclohexane for 28 days (ECHA, 2001c). The constant variance model did not provide an adequate fit to the variance data (Test 2 *p*-value <0.1). The nonconstant variance model did provide an adequate fit to the variance data (Test 3 *p*-value >0.1); however, with the nonconstant variance model applied, none of the models provided adequate fits to the means (Test 4 *p*-value <0.1). The results of the BMD modeling are summarized in Table C-3. Because none of the models provided adequate fit to the data, this endpoint was not considered further.

Table C-3. BMD Modeling Results (Nonconstant Variance) for Increased Relative Liver Weight in Female Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 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]	0.64	0.0022	0.21	−6.42	222.34	142.28
Exponential (model 3)[c]	0.64	0.0022	0.21	−6.42	222.24	142.28
Exponential (model 4)[c]	0.64	0.0005	0.24	−4.38	223.94	0.00
Exponential (model 5)[c]	0.64	0.0005	0.23	−4.38	222.37	0.00
Polynomial (3-degree)[d]	0.64	0.0029	0.01	−7.01	232.02	145.96
Polynomial (2-degree)[d]	0.64	0.0005	0.07	−4.70	231.30	141.86
Power[c]	0.64	0.0021	0.23	−6.39	222.33	138.21
Linear[d]	0.64	0.0021	0.23	−6.39	222.34	138.21

[a]ECHA (2001c).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Coefficients restricted to be positive.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 0.1RD = relative deviation of 10%); BMR = benchmark response; HED = human equivalent dose; NA = not applicable (computation failed).

Increased Incidence of Liver Cell Hypertrophy in Male Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (ECHA, 2001c)

Incidences of liver cell hypertrophy in male Crj:CD (Sprague Dawley) rats exposed to methylcyclohexane via gavage for 28 days were fit to the dichotomous models in the BMDS (Version 3.2) using the procedure described above for dichotomous data. 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 BMD (see Table C-4). The BMDL computation failed when the Weibull model was applied to the data; therefore, this model was not considered for selection. BMDLs for the remaining models were not sufficiently close (differed by greater than threefold), so the model with the lowest BMDL (Multistage 1-degree) was considered. However, fit of this model to the data was particularly poor. This is the least flexible model applied, and visual inspection showed that the model shape was not representative of the observed data at any point. For this reason, the Multistage 1-degree was rejected. Among the remaining models, BMDLs were sufficiently close, so the model with the lowest AIC was selected (Log-Logistic). Figure C-2 shows the fit of the Log-Logistic model to the data. Based on HEDs, the 10% benchmark dose (BMD_{10}) and 10% benchmark dose lower confidence limit ($BMDL_{10}$) values for increased incidence of liver hypertrophy in male Crj:CD (Sprague Dawley) rats were 121 and 59.9 mg/kg-day, respectively.

Table C-4. BMD Modeling Results for Increased Incidence of Liver Cell Hypertrophy in Male Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days[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
Gamma[c]	0.996	2.12	−0.1908	102.96	55.69
Log-logistic[d,]*	**1.0**	**2.00**	**−0.0100**	**121**	**59.9**
Multistage (degree = 3)[e]	0.88	3.29	−0.7153	76.57	33.51
Multistage (degree = 2)[e]	0.61	5.35	−1.0979	52.11	24.57
Multistage (degree = 1)[e]	0.18	10.38	−0.8175	20.91	10.19
Weibull[c]	1.0	2.00	0.0002	186.52	0.00
Logistic	1.0	2.00	−0.0202	137.25	57.44
Log-probit[d]	1.0	4.00	−0.0003	133.84	59.91
Probit	1.0	4.00	0.0000	147.00	54.88

[a]ECHA (2001c).
[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, although the BMDL computation failed for the Weibull model. BMDLs for the remaining models were not sufficiently close (differed by greater than threefold), so the model with the lowest BMDL (Multistage 1-degree) was considered. However, fit of this model to the data was particularly poor. This is the least flexible model applied, and visual inspection showed that the model shape was not representative of the observed data at any point. For this reason, the Multistage 1-degree was rejected. Among the remaining models, BMDLs were sufficiently close, so the model with the lowest AIC was selected (Log-Logistic).

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = exposure concentration associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose; NA = not applicable (computation failed).

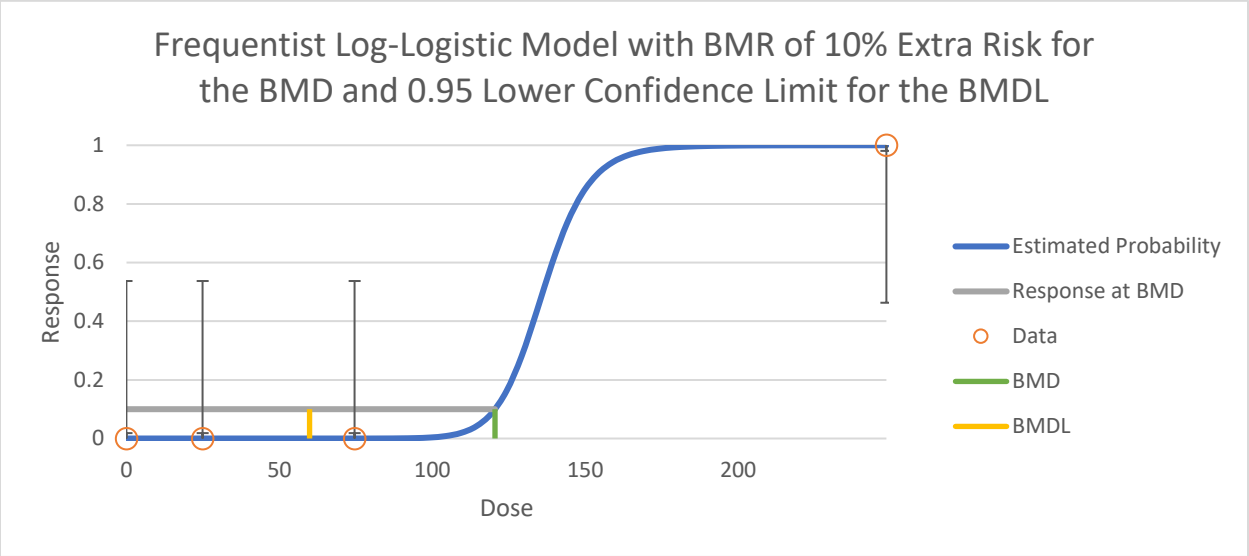

Figure C-2. Fit of Log-Logistic Model to the Data for Increased Incidence of Liver Cell Hypertrophy in Male Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (ECHA, 2001c)

BMD Model Output of Log-Logistic Model for Increased Incidence of Liver Cell Hypertrophy in Male Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (ECHA, 2001c)

User Input

Info	
Model	frequentist Log-Logistic v1.1
Dataset Name	liv_hypertroph_M_R
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	HED
Independent Variable	Incidence
Total # of Observations	4

Model Results

Benchmark Dose	
BMD	120.5089082
BMDL	59.86096088
BMDU	206.1051687
AIC	2.000396496
P-value	0.999999258
D.O.F.	3
Chi^2	0.00019825

Model Parameters	
# of Parameters	3
Variable	Estimate
g	Bounded
a	-88.44825077
b	Bounded

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-08	0	5	-0.000276
24.9	1.523E-08	7.61502E-08	0	5	-0.000276
74.6	1.9817E-05	9.90848E-05	0	5	-0.0099542
248.5	0.999980198	4.999900991	5	5	0.0099504

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	0	4	-	-	NA
Fitted Model	-0.000198248	1	0.0003965	3	0.9999979
Reduced Model	-11.24670289	1	22.4934058	3	<0.0001

Increased Incidence of Kidney Tubule Hyaline Droplet Degeneration in Male Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (ECHA, 2001c)

Incidences of kidney tubule hyaline droplet degeneration in male Crj:CD (Sprague Dawley) rats exposed to methylcyclohexane via gavage for 28 days were fit to the dichotomous models in the BMDS (Version 3.2) using the procedure described above for dichotomous data. 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 BMD (see Table C-5). The Multistage 1-degree model was considered questionable because the BMDL was more than 10 times lower than the lowest nonzero dose; therefore, this model was not considered for selection. BMDLs for the remaining models were not sufficiently close (differed by greater than threefold), so the model with the lowest BMDL (Multistage 2-degree) was selected. Figure C-3 shows the fit of the Multistage 2-degree model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ values for increased incidence of kidney tubule hyaline droplet degeneration in male Crj:CD (Sprague Dawley) rats were 13.35 and 3.37 mg/kg-day, respectively.

Table C-5. BMD Modeling Results for Increased Incidence of Kidney Tubule Hyaline Droplet Degeneration in Male Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days[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
Gamma[c]	1.00	7.01	−0.00186	21.73	5.70
Log-logistic[d]	1.00	9.01	−0.00113	22.61	9.35
Multistage (degree = 3)[e]	1.00	7.02	−0.05486	19.04	3.61
Multistage (degree = 2)[e,*]	**0.93**	**7.67**	**−0.51755**	**13.4**	**3.4**
Multistage (degree = 1)[e]	0.31	12.22	−0.00028	4.21	2.10
Weibull[c]	0.99	7.15	−0.13495	17.71	16.71
Logistic	1.00	7.00	0.00006	22.89	9.05
Log-probit[d]	1.00	9.00	0.00000	23.38	9.26
Probit	1.00	7.07	0.00918	19.19	8.14

[a]ECHA (2001c).
[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. The Multistage 1-degree model was considered questionable because the BMDL was more than ten times lower than the lowest nonzero dose; therefore, this model was not considered for selection. BMDLs for the remaining models were not sufficiently close (differed by greater than threefold), so the model with the lowest BMDL (Multistage 2-degree) was selected.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = exposure concentration associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose; NA = not applicable (computation failed).

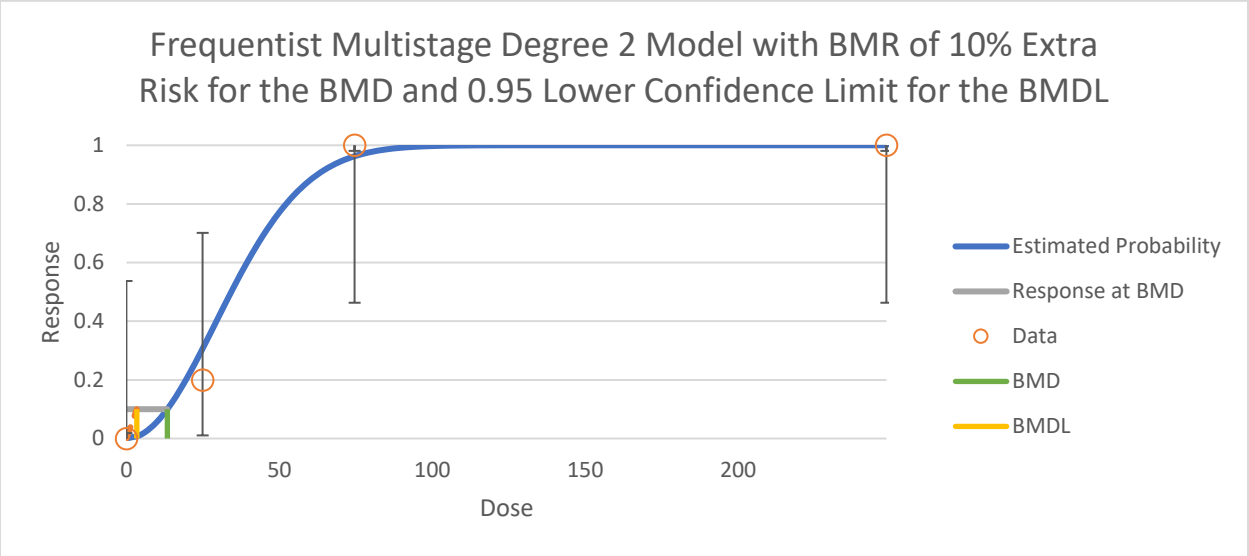

Figure C-3. Fit of Multistage 2-Degree Model to the Data for Increased Incidence of Kidney Tubule Hyaline Droplet Degeneration in Male Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (ECHA, 2001c)

BMD Model Output of Multistage 2-Degree Model for Increased Incidence of Kidney Tubule Hyaline Droplet Degeneration in Male Crj:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (ECHA, 2001c)

Frequentist Multistage Degree 2 Restricted

User Input

Info	
Model	frequentist Multistage degree 2 v1.1
Dataset Name	Hyaline_drop_degen_M_rat
User notes	
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	4

Model Results

Benchmark Dose	
BMD	13.35354628
BMDL	3.374676462
BMDU	21.29793115
AIC	7.674613074
P-value	0.92722381
D.O.F.	3
Chi^2	0.461689187
Slope Factor	0.02963247

Model Parameters	
# of Parameters	3
Variable	Estimate
g	Bounded
b1	Bounded
b2	0.00059086

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-08	0	5	-0.000276
24.9	0.306732356	1.533661781	1	5	-0.5175482
74.6	0.962680177	4.813400883	5	5	0.44026461
248.5	1	5	5	5	3.7697E-08

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-2.502012118	4	-	-	NA
Fitted Model	-2.837306537	1	0.670588839	3	0.88009896
Reduced Model	-13.76277627	1	22.52152831	3	<0.0001

Increased Relative Liver Weights in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days During Premating and Mating (JECDB, 2013)

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in male Crl:CD (Sprague Dawley) rats orally exposed to methylcyclohexane for 28 days during premating and mating (JECDB, 2013). The constant variance model provided adequate fit to the variance data (Test 2 *p*-value >0.1). With the constant 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, BMDLs were not 10 times lower than the lowest nonzero dose, and scaled residuals did not exceed ±2 units at the data point closest to the BMD. BMDLs for models providing adequate fit were sufficiently close (differed by less than threefold), so the model with the lowest AIC was selected (Exponential 2). The Exponential 2 model estimated human equivalent $BMD_{0.1RD}$ and $BMDL_{0.1RD}$ values of 66.03 and 61.05 mg/kg-day, respectively. The results of the BMD modeling are summarized in Table C-6 and plotted in Figure C-4.

Table C-6. BMD Modeling Results (Constant Variance) for Increased Relative Liver Weight in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days During Premating and Mating[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,*]	**0.30**	**0.79**	**−0.562989**	**−26.00**	**66.0**	**61.1**
Exponential (model 3)[c]	0.30	0.93	−0.028174	−24.48	79.09	61.50
Exponential (model 4)[c]	0.30	0.17	−1.123355	−22.59	55.70	45.23
Exponential (model 5)[c]	0.30	NA	−0.048939	−22.45	78.93	51.51
Polynomial (3-degree)[d]	0.30	1.00	0.000004	−24.48	79.26	52.76
Polynomial (2-degree)[d]	0.30	0.99	−0.002791	−24.48	79.18	52.76
Power[c]	0.30	0.86	−0.050385	−24.45	78.88	52.78
Linear[d]	0.30	0.39	−1.111341	−24.60	55.77	50.42

[a]JECDB (2013).
[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 provided an adequate fit to the variance data. All models, except the Exponential 5 model, provided adequate fit to the means. BMDLs for models providing adequate fit were sufficiently close (differed by less than threefold), so the model with the lowest AIC was selected (Exponential 2).

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 0.1RD = relative deviation of 10%); BMR = benchmark response; HED = human equivalent dose; NA = not applicable (computation failed).

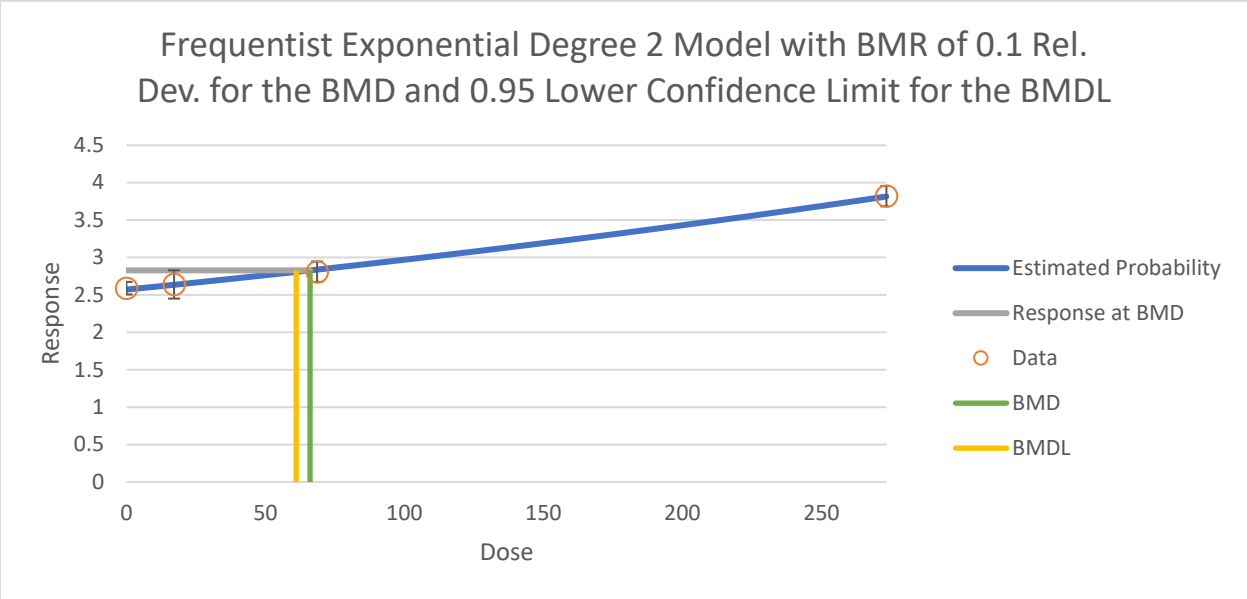

Figure C-4. Fit of Exponential 2-Degree Model to the Data for Increased Relative Liver Weight in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days During Premating and Mating (JECDB, 2013)

BMD Model Output of Exponential 2-Degree Model for Increased Relative Liver Weight in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days During Premating and Mating (JECDB, 2013)

Frequentist Exponential Degree 2 Restricted

User Input

Info	
Model	frequentist Exponential degree 2 v1.1
Dataset Name	rel_liv_wt_M_R
User notes	JECB (2013) HERO 6982772
Dose-Response Model	M[dose] = a * exp(±1 * b * dose)
Variance Model	Var[i] = alpha

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

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

Model Results

Benchmark Dose	
BMD	66.03011427
BMDL	61.05298636
BMDU	71.92354647
AIC	-26.00262795
Test 4 P-value	0.785812921
D.O.F.	2

Model Parameters	
# of Parameters	3
Variable	Estimate
a	2.570948485
b	0.001443434
log-alpha	-4.171223687

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	6	2.570948485	2.59	2.59	0.12423109	0.08	0.08	0.375642618
17.1	6	2.635196141	2.64	2.64	0.12423109	0.18	0.18	0.09471868
68.6	6	2.838553175	2.81	2.81	0.12423109	0.13	0.13	-0.56298879
273.4	6	3.814882254	3.82	3.82	0.12423109	0.13	0.13	0.100907652

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	16.2423505	5	-22.484701
A2	18.05914626	8	-20.118293
A3	16.2423505	5	-22.484701
fitted	16.00131397	3	-26.002628
R	-18.13857944	2	40.2771589

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

Tests of Interest

Test	2*Log(Likelihood Ratio)	Test df	p-value
1	72.3954514	6	<0.0001
2	3.633591515	3	0.30384458
3	3.633591515	3	0.30384458
4	0.482073059	2	0.78581292

Increased Relative Liver Weights in Unmated Female Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (JECDB, 2013)

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in unmated female Crl:CD (Sprague Dawley) rats orally exposed to methylcyclohexane for 28 days (JECDB, 2013). The constant variance model provided adequate fit to the variance data (Test 2 *p*-value >0.1). With the constant 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, BMDLs were not 10 times lower than the lowest nonzero dose, and scaled residuals did not exceed ±2 units at the data point closest to the 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 218.90 and 126.60 mg/kg-day, respectively. The results of the BMD modeling are summarized in Table C-7 and plotted in Figure C-5.

Table C-7. BMD Modeling Results (Constant Variance) for Increased Relative Liver Weight in Unmated Female Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 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]	0.23	0.57	0.06169	−6.45	193.07	131.72
Exponential (model 3)[c]	0.23	0.29	0.02343	−4.47	207.50	131.88
Exponential (model 4)[c]	0.23	0.28	0.07442	−4.42	189.79	65.31
Exponential (model 5)[c]	0.23	NA	−0.00006	−2.36	243.00	64.73
Polynomial (3-degree)[d,*]	**0.23**	**0.60**	**0.00288**	**−6.55**	**219.0**	**126.60**
Polynomial (2-degree)[d]	0.23	0.30	0.01260	−4.52	211.42	126.32
Power[c]	0.23	0.29	0.02201	−4.46	208.27	125.77
Linear[d]	0.23	0.56	0.07489	−6.42	189.94	125.47

[a]JECDB (2013).
[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 provided an adequate fit to the variance data. All models, except the Exponential 5 model provided adequate fit to the means. 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).

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 0.1RD = relative deviation of 10%); BMR = benchmark response; HED = human equivalent dose; NA = not applicable (computation failed).

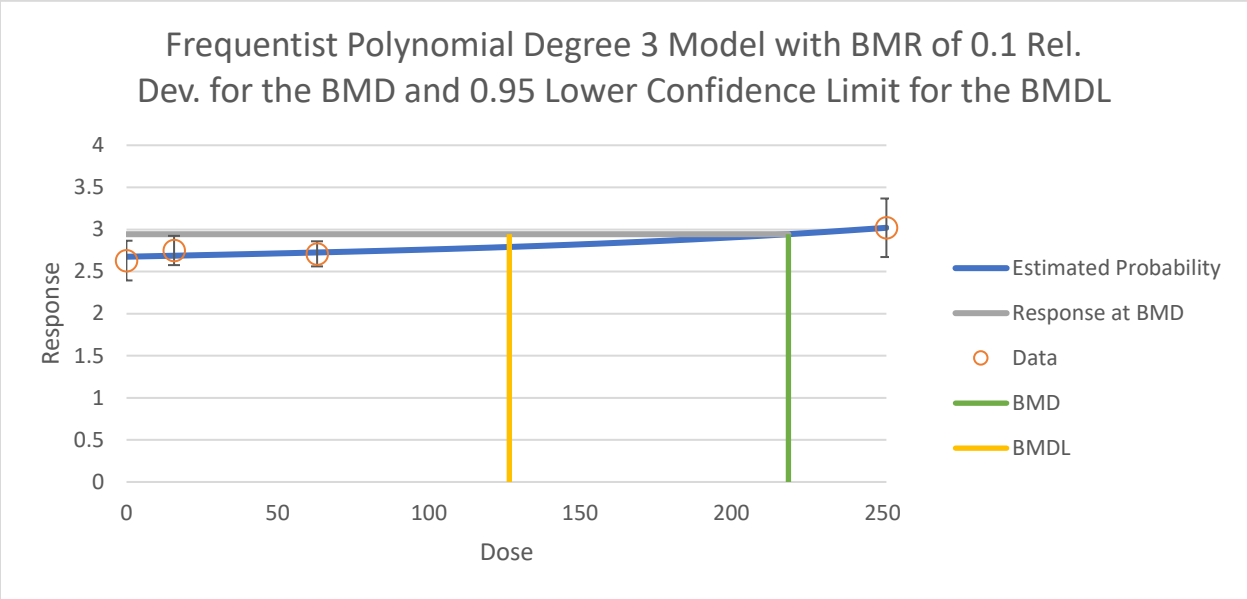

Figure C-5. Fit of Polynomial 3-Degree Model to the Data for Increased Relative Liver Weight in Unmated Female Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (JECDB, 2013)

BMD Model Output of Polynomial 3-Degree Model for Increased Relative Liver Weight in Unmated Female Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (JECDB, 2013)

Frequentist Polynomial Degree 3 Restricted

User Input

Info	
Model	frequentist Polynomial degree 3 v1.1
Dataset Name	rel_liv_wt_unmated_F_R
User notes	JECB (2013) HERO 6982772
Dose-Response Model	M[dose] = g + b1*dose + b2*dose^2 + ...
Variance Model	Var[i] = alpha

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

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

Model Results

Benchmark Dose	
BMD	218.9001076
BMDL	126.5996693
BMDU	364.7746736
AIC	-6.552506626
Test 4 P-value	0.599860378
D.O.F.	2

Model Parameters	
# of Parameters	5
Variable	Estimate
g	2.675879076
beta1	0.000763083
beta2	Bounded
beta3	Bounded
alpha	0.031293475

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	2.675879076	2.63	2.63	0.17689962	0.19	0.19	-0.57992624
15.7	5	2.687896573	2.75	2.75	0.17689962	0.14	0.14	0.785007254
63	5	2.726350255	2.71	2.71	0.17689962	0.12	0.12	-0.20667247
251.3	5	3.019772512	3.02	3.02	0.17689962	0.28	0.28	0.002875518

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	6.787311668	5	-3.5746233
A2	8.953031225	8	-1.9060624
A3	6.787311668	5	-3.5746233
fitted	6.276253313	3	-6.5525066
R	1.347492184	2	1.30501563

* Includes additive constant of -18.37877. 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	15.21107808	6	0.01867703
2	4.331439114	3	0.22782739
3	4.331439114	3	0.22782739
4	1.02211671	2	0.59986038

Increased Relative Kidney Weights in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days During Premating and Mating (JECDB, 2013)

The procedure outlined above for continuous data was applied to the data for increased relative kidney weight in male Crl:CD (Sprague Dawley) rats orally exposed to methylcyclohexane for 28 days (JECDB, 2013). The constant variance model did not provide an adequate fit to the variance data (Test 2 *p*-value <0.1). The nonconstant variance model also did not provide an adequate fit to the variance data (Test 3 *p*-value <0.1). Because none of the models provided adequate fit to the data, this endpoint was not considered further.

Increased Relative Kidney Weights in Unmated Female Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (JECDB, 2013)

The procedure outlined above for continuous data was applied to the data for increased relative kidney weight in unmated female Crl:CD (Sprague Dawley) rats orally exposed to methylcyclohexane for 28 days (JECDB, 2013). 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. Visual inspection of the dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest nonzero dose, and scaled residuals did not exceed ±2 units at the data point closest to the 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 161.67 and 97.08 mg/kg-day, respectively. The results of the BMD modeling are summarized in Table C-8 and plotted in Figure C-6.

Table C-8. BMD Modeling Results (Nonconstant Variance) for Increased Relative Kidney Weight in Unmated Female Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 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]	0.32	0.94	−0.26	−63.68	166.13	103.26
Exponential (model 3)[c]	0.32	0.94	−0.26	−63.68	166.15	103.26
Exponential (model 4)[c]	0.32	0.77	0.33	−61.72	156.02	58.33
Exponential (model 5)[c]	0.32	0.76	−0.24	−61.72	157.40	58.41
Polynomial (3-degree)[d,*]	**0.32**	**0.95**	**−0.25**	**−63.70**	**162.0**	**97.1**
Polynomial (2-degree)[d]	0.32	0.95	−0.25	−63.70	161.67	97.03
Power[c]	0.32	0.95	−0.25	−63.70	161.67	97.08
Linear[d]	0.32	0.95	−0.25	−63.70	161.67	97.03

[a]JECDB (2013).
[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 an adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, all models provided adequate fit to the means. 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).

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 0.1RD = relative deviation of 10%); BMR = benchmark response; HED = human equivalent dose.

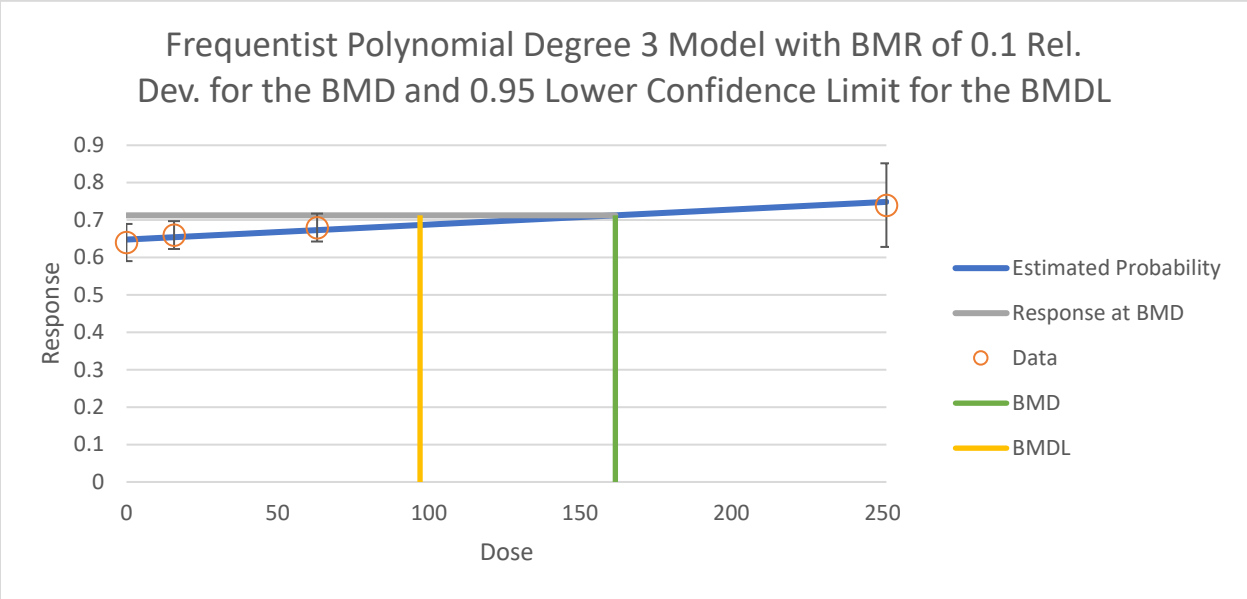

Figure C-6. Fit of Polynomial 3-Degree Model to the Data for Increased Relative Kidney Weight in Unmated Female Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (JECDB, 2013)

BMD Model Output of Polynomial 3-Degree Model for Increased Relative Kidney Weight in Unmated Female Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days (JECDB, 2013)

Frequentist Polynomial Degree 3 Restricted

User Input

Info	
Model	frequentist Polynomial degree 3 v1.1
Dataset Name	rel_kid_wt_unmated_F_R
User notes	JECB (2013) HERO 6982772
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	161.6689733
BMDL	97.07765358
BMDU	397.9418582
AIC	-63.70461899
Test 4 P-value	0.949195135
D.O.F.	2

Model Parameters	
# of Parameters	6
Variable	Estimate
g	0.647930091
beta1	0.000400776
beta2	Bounded
beta3	Bounded
rho	13.1378527
alpha	-1.353486086

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	0.647930091	0.64	0.64	0.029379	0.04	0.04	-0.6035686
15.7	5	0.654222273	0.66	0.66	0.031305	0.03	0.03	0.4127001
63	5	0.673178974	0.68	0.68	0.037766	0.03	0.03	0.4038669
251.3	5	0.748645079	0.74	0.74	0.075897	0.09	0.09	-0.2547016

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	32.3696909	5	-54.73938
A2	37.05235099	8	-58.1047
A3	35.90445037	6	-59.8089
fitted	35.85230949	4	-63.70462
R	27.61545393	2	-51.23091

* Includes additive constant of -18.37877. 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	18.87379412	6	0.004382
2	9.365320186	3	0.024808
3	2.295801233	2	0.317302
4	0.104281759	2	0.949195

Increased Incidence of Kidney Tubule Hyaline Droplets in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days During Premating and Mating (JECDB, 2013)

Incidences of kidney tubule hyaline droplets in male Crl:CD (Sprague Dawley) rats exposed to methylcyclohexane via gavage for 28 days during premating and mating were fit to the dichotomous models in the BMDS (Version 3.2) using the procedure described above for dichotomous data. 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 BMD (see Table C-9). BMDLs for the models were not sufficiently close (differed by greater than threefold), so the model with the lowest BMDL (Multistage 1-degree) was selected. Figure C-7 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 hyaline droplets in male Crl:CD (Sprague Dawley) rats were 8.12 and 4.25 mg/kg-day, respectively.

Table C-9. BMD Modeling Results for Increased Incidence of Kidney Tubule Hyaline Droplets in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days During Premating and Mating[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
Gamma[c]	1.00	13.64	6.8×10^{-5}	45.02	9.26
Log-logistic[d]	1.00	9.64	5.8×10^{-7}	54.46	12.09
Multistage (degree = 3)[e]	0.99	9.84	−0.32	31.69	7.49
Multistage (degree = 2)[e]	0.81	12.41	−0.62	22.40	6.40
Multistage (degree = 1)[e,*]	**0.40**	**14.80**	**−0.00031**	**8.12**	**4.25**
Weibull[c]	1.00	9.77	−0.26	34.02	8.47
Logistic	1.00	11.64	8.5×10^{-6}	57.99	18.96
Log-probit[d]	1.00	11.64	3.0×10^{-10}	50.32	12.05
Probit	1.00	9.66	−0.095	42.72	17.21

[a]JECDB (2013).
[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. BMDLs were not sufficiently close (differed by greater than threefold), so the model with the lowest BMDL (Multistage 1-degree) was selected.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = exposure concentration associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose; NA = not applicable (computation failed).

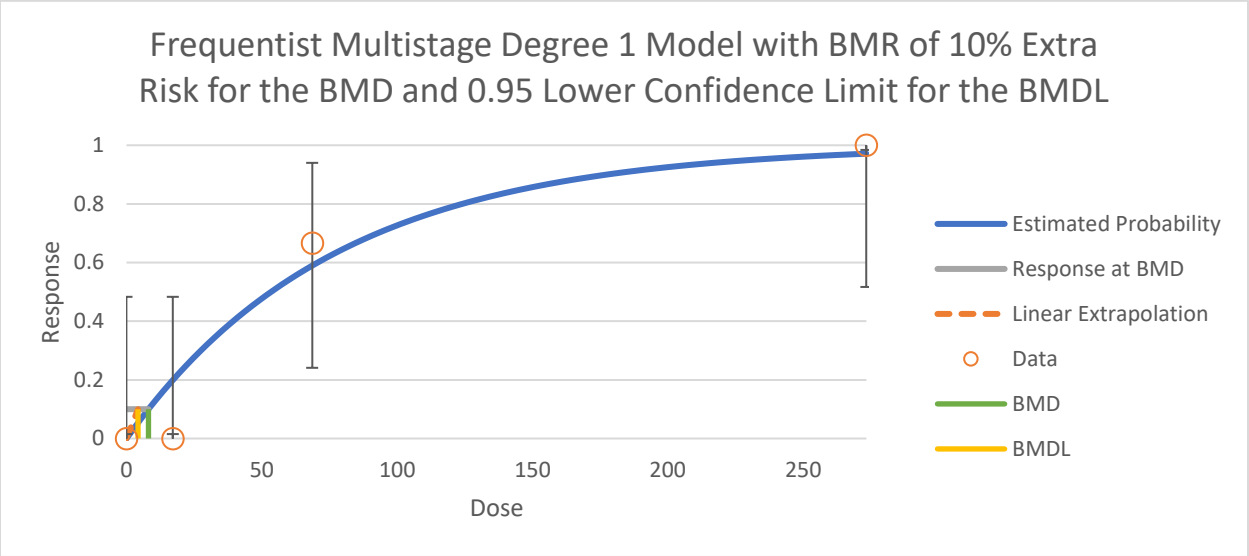

Figure C-7. Fit of Multistage 1-Degree Model to the Data for Increased Incidence of Kidney Tubule Hyaline Droplets in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days During Premating and Mating (JECDB, 2013)

BMD Model Output of Multistage 1-Degree Model for Increased Incidence of Kidney Tubule Hyaline Droplets in Male Crl:CD (Sprague Dawley) Rats Exposed to Methylcyclohexane via Gavage for 28 Days During Premating and Mating (JECDB, 2013)

Frequentist Multistage 1 Degree Restricted

User Input

Info	
Model	frequentist Multistage degree 1 v1.1
Dataset Name	Hyaline_Droplet_M_rat
User notes	
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	4

Model Results

Benchmark Dose	
BMD	8.119923939
BMDL	4.253517746
BMDU	16.18663929
AIC	14.8029746
P-value	0.403233628
D.O.F.	2
Chi^2	1.816478324
Slope Factor	0.023509952

Model Parameters	
# of Parameters	2
Variable	Estimate
g	1.58233E-08
b1	0.012975553

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.58233E-08	9.49395E-08	0	6	-0.0003081
17.1	0.198990104	1.193940622	0	6	-1.2208784
68.6	0.589394743	3.536368459	4	6	0.38475296
273.4	0.971203928	5.827223567	6	6	0.42178102

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-3.81908501	4	-	-	NA
Fitted Model	-5.401487298	2	3.164804576	2	0.20548088
Reduced Model	-16.30063838	1	24.96310675	3	<0.0001

BMD MODELING TO IDENTIFY POTENTIAL PODS FOR DERIVATION OF A SCREENING CHRONIC PROVISIONAL REFERENCE CONCENTRATION (p-RfC) Increased Incidence of Renal Medullary Mineralization in Male CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year (AFRL, 1985)

Incidences of renal medullary mineralization in male CDF F344/CrlBr rats exposed to methylcyclohexane vapors for 6 hours/day, 5 days/week for 1 year were fit to the dichotomous models in the BMDS (Version 3.2) using the procedure described above for dichotomous data. Three models (Multistage 1-degree, Logistic, and Probit) provided an adequate fit according to the χ^2 goodness-of-fit *p*-value ($p > 0.1$) and had scaled residuals that did not exceed ±2 units at the data point closest to the benchmark concentration (BMC) (see Table C-10). The χ^2 goodness-of-fit *p*-values could not be calculated for the other models because they were saturated (i.e., degrees of freedom [*df*] = 0); therefore, these models were not considered for selection. Among the models that provided adequate fit, benchmark concentration lower confidence limits (BMCLs) were sufficiently close (differed by less than threefold), so the model with the lowest AIC (Logistic) was selected. Figure C-8 shows the fit of the Logistic model to

the data. Based on human equivalent concentrations (HECs), the 10% benchmark concentration (BMC_{10}) and 10% benchmark concentration lower confidence limit ($BMCL_{10}$) values for increased incidence of renal medullary mineralization in male CDF F344/CrlBr rats were 816.27 and 660.05 mg/m^3, respectively.

Table C-10. BMD Modeling Results for Increased Incidence of Renal Medullary Mineralization in Male CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year[a]

Model	χ^2 Goodness-of-fit *p*-value[b]	AIC	Scaled Residual at Dose Nearest BMC	BMC_{10} (mg/m^3) HEC_{ER}	$BMCL_{10}$ (mg/m^3) HEC_{ER}
Gamma[c]	NA	101.38	-6.40×10^{-7}	671.80	358.35
Log-logistic[d]	NA	101.38	−0.000249	676.34	353.97
Multistage (degree = 2)[e]	NA	101.38	-1.29×10^{-5}	703.43	360.73
Multistage (degree = 1)[e]	0.14	101.98	−1.30	396.82	277.61
Weibull[c]	NA	101.38	−0.000296	701.05	358.72
Logistic*	**1.00**	**99.38**	**−0.00293**	**816.27**	**660.05**
Log-probit[d]	NA	101.38	4.47×10^{-5}	617.03	346.46
Probit	0.89	99.40	−0.0938	745.92	600.58

[a]AFRL (1985).
[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. The Multistage 1-degree, Logistic, and Probit models provided an adequate fit to the data. The χ^2 goodness-of-fit *p*-values could not be calculated for the other models. Among the models providing adequate fit, BMCLs were sufficiently close (differed by less than threefold), so the model with the lowest AIC was selected (Logistic).

AIC = Akaike's information criterion; BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% benchmark concentration lower confidence limit on the BMC (subscripts denote BMR: i.e., 10 = exposure concentration associated with 10% extra risk); BMR = benchmark response; HEC = human equivalent concentration; NA = not applicable (computation failed).

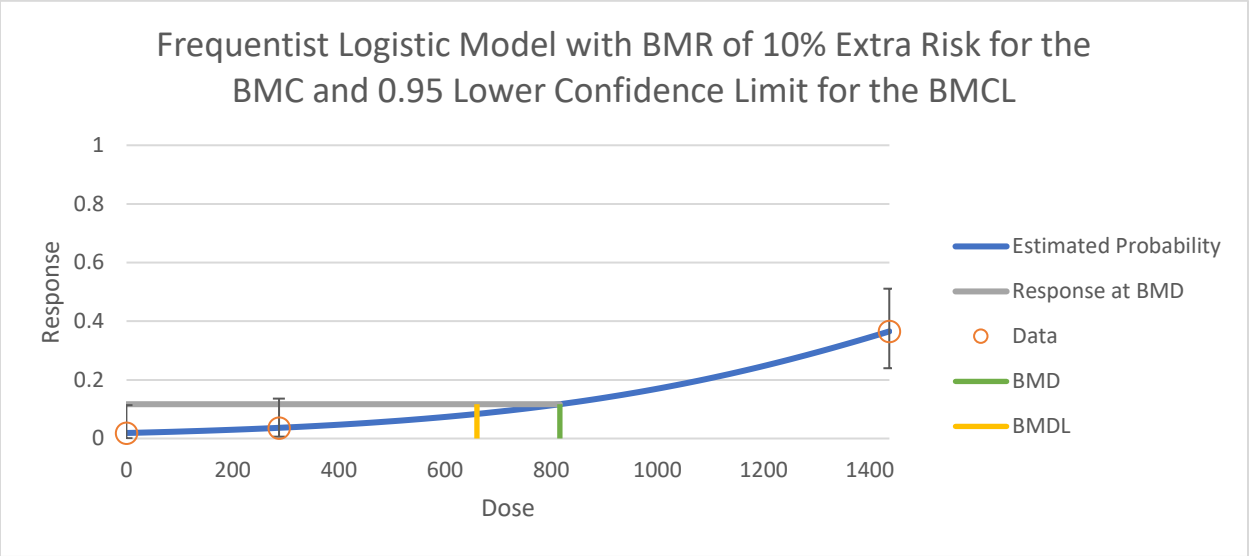

Figure C-8. Fit of Logistic Model to the Data for Increased Incidence of Renal Medullary Mineralization in Male CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year (AFRL, 1985)

BMD Model Output of Logistic Model for Increased Incidence of Renal Medullary Mineralization in Male CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year (AFRL, 1985)

User Input

Info	
Model	frequentist Logistic v1.1
Dataset Name	med_min_kid_M_rat
User notes	
Dose-Response Model	P[dose] = 1/[1+exp(-a-b*dose)]

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

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

Model Results

Benchmark Dose	
BMD	816.2660672
BMDL	660.0483152
BMDU	984.6848764
AIC	99.37590091
P-value	0.996474229
D.O.F.	1
Chi^2	1.95268E-05

Model Parameters	
# of Parameters	2
Variable	Estimate
a	-3.954572712
b	0.002367736

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.018806397	0.996739043	1	53	0.00329744
287	0.036437726	2.004074919	2	55	-0.0029324
1437	0.36536899	18.99918748	19	52	0.00023399

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-47.68794069	3	-	-	NA
Fitted Model	-47.68795045	2	1.95196E-05	1	0.99647487
Reduced Model	-64.06386791	1	32.75185443	2	<0.0001

Increased Incidence of Renal Papillary Hyperplasia in Male CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year (AFRL, 1985)

Incidences of renal papillary hyperplasia in male CDF F344/CrlBr rats exposed to methylcyclohexane vapors for 6 hours/day, 5 days/week for 1 year were fit to the dichotomous models in the BMDS (Version 3.2) using the procedure described above for dichotomous data. Three models (Multistage 2-degree, Logistic, and Probit) provided an adequate fit according to the χ^2 goodness-of-fit *p*-value ($p > 0.1$) and had scaled residuals that did not exceed ±2 units at the data point closest to the BMC (see Table C-11). The Multistage 1-degree model did not provide adequate fit. The χ^2 goodness-of-fit *p*-values could not be calculated for the other models because they were saturated (i.e., $df = 0$); therefore, these models were not considered for selection. Among the models that provided adequate fit, BMCLs were sufficiently close (differed by less than threefold), so the model with the lowest AIC (Logistic) was selected. Figure C-9 shows the fit of the Logistic model to the data. Based on HECs, the BMC_{10} and $BMCL_{10}$ values for increased incidence of renal papillary hyperplasia in male CDF F344/CrlBr rats were 804.35 and 641.61 mg/m^3, respectively.

Table C-11. BMD Modeling Results for Increased Incidence of Renal Papillary Hyperplasia in Male CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year[a]

Model	χ^2 Goodness-of-fit *p*-value[b]	AIC	Scaled Residual at Dose Nearest BMC	BMC_{10} (mg/m^3) HEC_{ER}	$BMCL_{10}$ (mg/m^3) HEC_{ER}
Gamma[c]	NA	97.31	0.00051	1,030.29	447.22
Log-logistic[d]	NA	97.31	-1.7×10^{-5}	1,291.40	441.65
Multistage (degree = 2)[e]	0.44	95.99	−0.66	625.74	440.87
Multistage (degree = 1)[e]	0.02	102.29	−2.0	327.43	235.26
Weibull[c]	NA	97.31	-1.3×10^{-5}	1,308.92	456.47
Logistic*	**0.53**	**95.68**	**−0.39**	**804.35**	**642.0**
Log-probit[d]	NA	97.31	4.9×10^{-6}	1,278.74	419.05
Probit	0.42	95.92	−0.51	720.86	575.77

[a]AFRL (1985).
[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. The Multistage 2-degree, Logistic, and Probit models provided an adequate fit to the data. The Multistage 1-degree model did not provide adequate fit. The χ^2 goodness-of-fit *p*-values could not be calculated for the other models. Among the models providing adequate fit, BMCLs were sufficiently close (differed by less than threefold), so the model with the lowest AIC was selected (Logistic).

AIC = Akaike's information criterion; BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% benchmark concentration lower confidence limit on the BMC (subscripts denote BMR: i.e., 10 = exposure concentration associated with 10% extra risk); BMR = benchmark response; HEC = human equivalent concentration; NA = not applicable (computation failed).

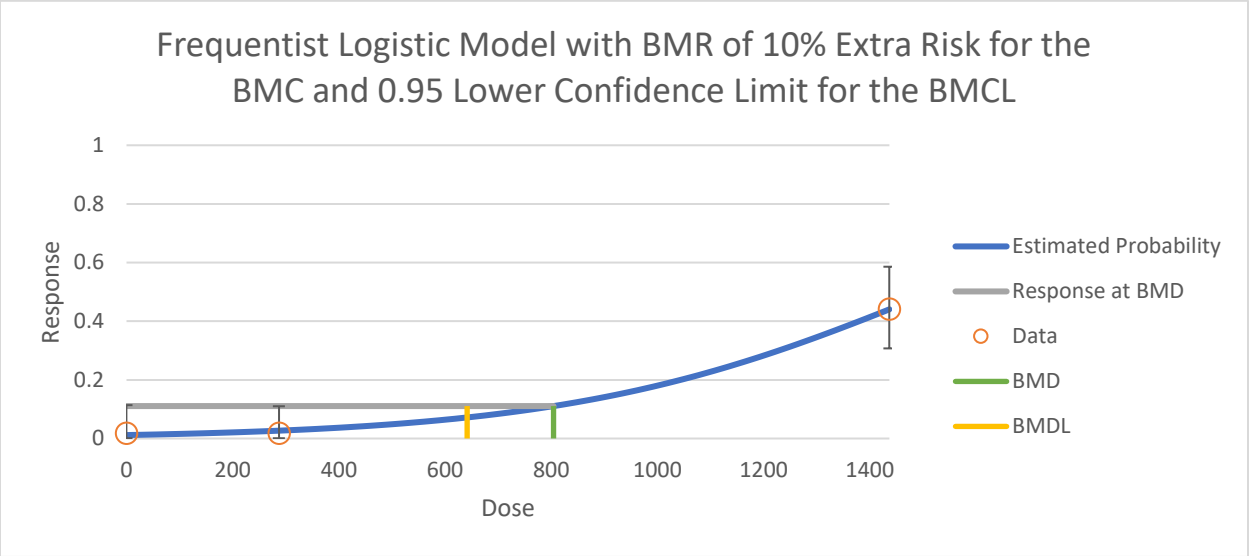

Figure C-9. Fit of Logistic Model to the Data for Increased Incidence of Renal Papillary Hyperplasia in Male CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year (AFRL, 1985)

BMD Model Output of Logistic Model for Increased Incidence of Renal Papillary Hyperplasia in Male CDF F344/CrlBr Rats Exposed to Methylcyclohexane Vapors for 6 Hours/Day, 5 Days/Week for 1 Year (AFRL, 1985)

Frequentist Logistic Restricted

User Input

Info	
Model	frequentist Logistic v1.1
Dataset Name	pappilary_hyperplas_kid_M_rat
User notes	
Dose-Response Model	P[dose] = 1/[1+exp(-a-b*dose)]

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

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

Model Results

Benchmark Dose	
BMD	804.3477117
BMDL	641.6145639
BMDU	976.5547886
AIC	95.68144797
P-value	0.534235207
D.O.F.	1
Chi^2	0.386329316

Model Parameters	
# of Parameters	2
Variable	Estimate
a	-4.431318473
b	0.002917294

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.011758875	0.623220359	1	53	0.48010381
287	0.026751337	1.471323508	1	55	-0.3938702
1437	0.44049154	22.90556007	23	52	0.02638043

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-45.65571206	3	-	-	NA
Fitted Model	-45.84072398	2	0.370023856	1	0.54299126
Reduced Model	-69.34381973	1	47.37621534	2	<0.0001

APPENDIX D. REFERENCES

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