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Provisional Peer-Reviewed Toxicity Values for

3-Methylphenol
(CASRN 108-39-4)

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 3-METHYLPHENOL (CASRN 108-39-4)

BACKGROUND

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

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

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to use the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

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

Other U.S. Environmental Protection Agency (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. Environmental Protection Agency 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

3-Methylphenol, CASRN 108-39-4, also known as *meta*-cresol, is obtained by chemical synthesis or by distillation from petroleum or coal tar. It can be isolated and used as a pure compound, but it is also used in a mixture with either or both the *ortho*- and *para*-isomers, or just the *para*-isomer (ATSDR, 2008). Mixtures of *o*-, *m*-, and *p*-cresols are often used as solvents, especially for wire enameling and metal degreasers, and as wood preservatives (Fiege, 2000). They are also used in ore flotation and fiber treatments and to make phenolic resins via condensation with formaldehyde (ATSDR, 2008; Fiege, 2000). Mixtures of *m*- and *p*-cresol are used to manufacture contact herbicides, such as fenitrothion and fenthion, and the flame-retardant plasticizers, tricresyl phosphate and diphenyl cresyl phosphate (ATSDR, 2008). Pure 3-methylphenol is an important chemical intermediate and is used to make pyrethroid insecticides, fragrance compounds, and the explosive, 2,4,6-trinitro-*m*-cresol (ATSDR, 2008). 3-Methylphenol is a registered pesticide active ingredient under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), although only one product containing 3-methylphenol, the agricultural microbiocide Gallex, is currently used in the United States, of which 3-methylphenol constitutes 0.47% (Kegley et al., 2014). Cresols, including 3-methylphenol, occur naturally and are found in various plants and trees (HSDB, 2010). 3-Methylphenol has also been identified in the particulate phase of tobacco smoke (HSDB, 2010).

The empirical formula for 3-methylphenol is C_7H_8O (see Figure 1). Table 1 summarizes the physicochemical properties of 3-methylphenol. 3-Methylphenol is a liquid with a moderate vapor pressure and a moderate measured Henry's law constant (HSDB, 2010). These properties indicate that some volatilization from both dry and moist surfaces is expected to occur. Once in the atmosphere, 3-methylphenol will react with photochemically generated hydroxy radicals; its estimated atmospheric half-life is 6 hours (HSDB, 2010). 3-Methylphenol has high water solubility and a relatively low soil adsorption coefficient (ATSDR, 2008), indicating that it is likely to leach to groundwater or undergo runoff after a rain event. As a result, removal of 3-methylphenol from soil by leaching with water will likely compete with volatilization, depending on the local conditions (wet, dry, etc.).

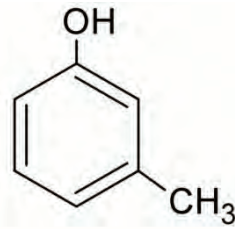

Figure 1. 3-Methylphenol Structure

Table 1. Physicochemical Properties of 3-Methylphenol (CASRN 108-39-4)

Property (unit)	Value
Physical state	Liquid[a]
Boiling point (°C)	202.32[a]
Melting point (°C)	12.22[a]
Density (g/cm^3)	1.034[a]
Vapor pressure (mm Hg at 25°C)	0.138[a]
pH (unitless)	NV
pKa (unitless)	10.09[b]
Solubility in water (mg/L at 25°C)	22,700[a]
Octanol-water partition coefficient (log K_{ow})	1.96[a]
Henry's law constant (atm-m^3/mol at 25°C)	8.65×10^{-7} [c]
Soil adsorption coefficient K_{oc} (mL/g)	34.7[a]
Atmospheric OH rate constant (cm^3/molecule-second at 25°C)	6.4×10^{-11} [d]
Atmospheric half-life (hours)	6[d]
Relative vapor density (air = 1)	3.72[a]
Molecular weight (g/mol)	108.1[a]
Flash point (closed cup in °C)	85[a]

[a]ATSDR (2008).
[b]Fiege (2000).
[c]Estimated from vapor pressure and water solubility.
[d]HSDB (2010).

NV = not available.

A summary of available toxicity values for 3-methylphenol from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for 3-Methylphenol (CASRN 108-39-4)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference(s)
Noncancer			
IRIS (RfD)	5×10^{-2} mg/kg-d (*m*-cresol)	Based on decreased body weight and neurotoxicity in a 90-d oral rat study.	U.S. EPA (1988a)
HEAST (sRfD)	5×10^{-1} mg/kg-d (*m*-cresol)	Based on decreased body weight and neurotoxicity in a 90-d oral rat study.	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR (MRL, chronic oral)	0.1 mg/kg-d (*m/p*-cresol)	Based on bronchiole hyperplasia of the lung and follicular degeneration of the thyroid gland in female mice following chronic oral exposure to *m*/*p*-cresol (60% *m*- and 40% *p*-cresol).	ATSDR (2008)
ATSDR (MRL, intermediate oral)	0.1 mg/kg-d (*m/p*-cresol)	Based on nasal lesions in male rats following oral exposure to *m*/*p*-cresol (60% *m*- and 40% *p*-cresol) for 13 wk.	ATSDR (2016)
WHO (ADI)	0.17 mg/kg-d (cresols, all isomers)	Based on subchronic-duration studies that identified a NOAEL of 50 mg/kg-d for all 3 isomers, and a UF of 300.	IPCS (1996); IPCS (1995)
Cal/EPA (REL, chronic inhalation)	600 µg/m^3 (cresol mixtures)	Based on decreased body weights and neurotoxicity in a 90-d gavage study in rats.	Cal/EPA (2000); Cal/EPA (2014)
OSHA (PEL)	5 ppm or 22 mg/m^3 (cresols, all isomers)	8-hr TWA for general industry, construction, and shipyard employment; skin designation.	OSHA (2011); OSHA (2006a); OSHA (2006b)
NIOSH (REL)	2.3 ppm or 10 mg/m^3 (*m*-cresol)	TWA concentration for up to a 10-hr workday during a 40-hr workweek.	NIOSH (2015)
ACGIH (TLV-TWA)	20 mg/m^3 (cresols, all isomers)	Measured as inhalable fraction and vapor. Skin notation because it has been shown that systemic toxicity can result from skin exposure. Based on upper respiratory tract irritation.	ACGIH (2010); ACGIH (2014)
Cancer			
IRIS (WOE)	Group C, possible human carcinogen (*m*-cresol)	Based on an increased incidence of skin papillomas in mice in an initiation-promotion study. The 3 cresol isomers produced positive results in genetic toxicity studies both alone and in combination.	U.S. EPA (1990)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2015)
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2016a); Cal/EPA (2016b)

Table 2. Summary of Available Toxicity Values for 3-Methylphenol (CASRN 108-39-4)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference(s)
ACGIH (WOE)	Category A4, not classifiable as a human carcinogen (cresols, all isomers)	There is some evidence that cresols are mutagenic and have tumor-promoting properties, but the evidence is contradictory.	ACGIH (2010); ACGIH (2014)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Research; Cal/EPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.
[b]Parameters: ADI = acceptable daily intake; MRL = minimum risk level; PEL = permissible exposure level; REL (Cal/EPA) = reference exposure level; REL (NIOSH) = recommended exposure limit; sRfD = subchronic reference dose; TLV = threshold limit value; TWA = time-weighted average; WOE = weight of evidence.

NA = not applicable; NOAEL = no-observed-adverse-effect level; NV = not available; UF = uncertainty factor.

Non-date-limited literature searches were conducted in March 2015 and June 2016 for studies relevant to the derivation of provisional toxicity values for 3-methylphenol (CASRN 108-39-4). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, ToxLine (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related values: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, NIOSH, NTP, OSHA, and WHO.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide an overview of the relevant noncancer and cancer databases for 3-methylphenol, respectively, and include all potentially relevant short-term-, subchronic-, and chronic-duration studies, as well as developmental and reproductive toxicity studies. Principal studies are identified in bold. No cancer studies for 3-methylphenol alone were identified. The phrase "statistical significance" and term "significant(ly)," used throughout the document, indicate a p-value of < 0.05 unless otherwise noted.

Table 3A. Summary of Potentially Relevant Noncancer Data for 3-Methylphenol (CASRN 108-39-4)

Category[a]	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[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)[b]								
Short-term	5 M/5 F, F344/N rat, diet, 7 d/wk, 28 d	0, 300, 1,000, 3000,10,000, or 30,000 ppm ADD (M): 0, 25, 85, 252, 870, 2,470 ADD (F): 0, 25, 82, 252, 862, 2,310	Increased absolute liver weight in males and relative liver weight in males and females	252	NDr	862	NTP (1992b)	PR
Short-term	5 M/5 F, B6C3F$_1$ mouse, diet, 7 d/wk, 28 d	0, 300, 1,000, 3000, 10,000, or 30,000 ppm ADD (M): 0, 53, 193, 521, 1,730, 4,710 ADD (F): 0, 66, 210, 651, 2,080, 4,940	Increased relative liver weight in females; clinical signs of toxicity (e.g., hunched posture, labored respiration, lethargy, tremors) in both sexes in the two high-dose groups	66	178	210	NTP (1992b)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for 3-Methylphenol (CASRN 108-39-4)

Category[a]	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Short-term	5 M/5 F, neonatal S-D rat, gavage in olive oil, daily from PNDs 4−21 (18 d)	0, 100, 300, 1,000	Deep respiration, tremors, increased bilirubin, body-weight depression (females only), and increased relative liver weight at 300 (all animals of the high-dose group died after 2 d of exposure)	100	NDr	300	Koizumi et al. (2003)	PR
Short-term	12 M/12 F, neonatal S-D rat, gavage in olive oil, daily from PNDs 4−21 (18 d) 6 animals/sex/dose sacrificed at PND 22; remaining animals sacrificed 9 wk post exposure	0, 30, 100, 300	Decreased body weight in males, increased relative liver weight in males and females (≥10%), and clinical signs of toxicity (deep respiration, increased motor activity, and contact stimulus tremors and hypersensitivity)	100	NDr	300	Koizumi et al. (2003)	PR
Short-term	5 M/5 F, young S-D rat, gavage in olive oil, PNWs 5−7 (14 d)	0, 125, 250, 500, 1,000	Increased relative liver weight in both sexes	250	NDr	500	Koizumi et al. (2003)	PR
Short-term	7 M/7 F, young S-D rat, gavage in olive oil, PNWs 5−9 (28 d) An additional 7 rats/sex in the high-dose group were treated for 28 d and allowed to recover for 2 wk	0, 100, 300, 1,000	Increased relative liver weight in females	100	NDr	300	Koizumi et al. (2003)	PR
Subchronic	**30 M/30 F, S-D rat, gavage in corn oil, 7 d/wk, 13 wk**	**0, 50, 150, 450**	**Decreased body weight in males; clinical signs of toxicity (e.g., lethargy, tremors, hunched posture) in both sexes in the high-dose group**	**50**	**106**	**150**	**Dietz and Mulligan (1988)**	**NPR, IRIS, PS, Co-principal study**

Table 3A. Summary of Potentially Relevant Noncancer Data for 3-Methylphenol (CASRN 108-39-4)

Category[a]	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Subchronic	**10 M/10 F, S-D rat, gavage in corn oil, 7 d/wk, 90 d**	**0, 50, 150, 450**	**Clinical signs of neurotoxicity (tremors, myoclonus, labored respiration, and salivation)**	**50**	**DU**	**150**	**TRL (1986)**	**NPR, IRIS, PS, Co-principal study**
Reproductive/ developmental	25 M/25 F, S-D rat, gavage in corn oil, 2 generations (5 d/wk premating, 7 d/wk during mating, gestation, and lactation)	F0 (M): 0, 23, 137, 350 F0 (F): 0, 25, 149, 380 F1 (M): 0, 23, 136, 350 F1 (F): 0, 27, 155, 400	Increased mortality in F0 males and females and F1 females and increased postnatal mortality in F2 pups	137	NDr	350 (FEL)	BushyRun (1989)	NPR
Reproductive/ developmental	0 M/25 F (50 F for control), S-D rat, gavage in corn oil, GDs 6−15, animals sacrificed on GD 21	0, 30, 175, 450	Maternal: decreased body-weight gain, clinical signs of toxicity Fetal: no adverse effects	Maternal: 175 Fetal: 450	Maternal: NDr Fetal: NDr	Maternal: 450 Fetal: NDr	BushyRun (1988); Hazleton Laboratories (1988f)	NPR
Reproductive/ developmental (dose range finding)	0 M/8 F (15 F for control), NZW rabbit, gavage in corn oil, GDs 6−18, animals sacrificed on GD 29	0, 50, 150, 300, 500	Increased preimplantation loss, fetal death, external malformations	150	NDr	300	Hazleton Laboratories (1988f); BushyRun (1987b)	NPR
Reproductive/ developmental	0 M/14 F (28 F for controls), NZW rabbit, gavage in corn oil, GDs 6−18, animals sacrificed on GD 29	0, 5, 50, 100	No adverse maternal or fetal effects	100	NDr	NDr	BushyRun (1987a)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for 3-Methylphenol (CASRN 108-39-4)								
Category[a]	**Number of Male/Female, Strain Species, Study Type, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
2. Inhalation (mg/m^3)[b]								
ND								

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long-term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (more than approximately 90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: Doses are presented as adjusted daily dose (ADD in mg/kg-day). Values from all studies except gestational exposure studies are converted, if applicable, from a discontinuous to a continuous exposure.
[c]Notes: IRIS = used by IRIS, date of last update; PR = peer reviewed; PS = principal study; NPR = not peer reviewed.

ADD = adjusted daily dose; BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; DU = data unsuitable to BMD modeling; F = female(s); FEL = frank effect level; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = male(s); NA = not applicable; ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; NZW = New Zealand white; PND = postnatal day; PNW = postnatal week; S-D = Sprague-Dawley.

Table 3B. Summary of Potentially Relevant Cancer Data for 3-Methylphenol (CASRN 108-39-4)								
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**BMDL/ BMCL**	**LOAEL**	**Reference (comments)**	**Notes**
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)								
ND								

BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; LOAEL = lowest-observed-adverse-effect level; ND = no data; NOAEL = no-observed-adverse-effect level.

HUMAN STUDIES

No studies of humans exposed to 3-methylphenol through oral or inhalation routes have been located in the available literature.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure to 3-methylphenol on animals have been evaluated in an National Toxicology Program (NTP)-sponsored short-term-duration study in rats and mice (NTP, 1992b), a short-term-duration study in neonatal and young rats and associated dose range-finding studies (Koizumi et al., 2003), a subchronic-duration study in rats (Dietz and Mulligan, 1988), a neurotoxicity study in rats (TRL, 1986), a two-generation reproductive study in rats (BushyRun, 1989), and two developmental studies in rats and rabbits and the companion dose range-finding study in rabbits (BushyRun, 1988; Hazleton Laboratories, 1988a; BushyRun, 1987a, b).

Short-Term-Duration Studies

NTP (1992b) − Rat study

Groups of F344/N rats (five/sex/group) were administered 3-methylphenol (98% pure) at dietary concentrations of 0, 300, 1,000, 3,000, 10,000, or 30,000 ppm for 28 days. Based on body weight (BW) and food consumption, the study authors' calculated daily doses of 0, 25, 85, 252, 870, or 2,470 mg/kg-day for males and 0, 25, 82, 252, 862, or 2,310 mg/kg-day for females. Animals were observed twice daily for clinical signs of toxicity. Animals were weighed weekly, during study initiation, and at termination of the study. Food was available ad libitum and consumption was recorded twice weekly. Gross necropsies were performed on all animals, and the weights of the brain, heart, right kidney, liver, lungs, thymus, and testes were recorded. All tissues were preserved and evaluated microscopically. A histopathological examination was conducted on a complete set of 41 tissues from all control animals, all animals in the highest-dose group, and all animals that died early in the higher dose groups. Appropriate statistical tests were conducted.

There were no treatment-related mortalities or clinical signs of toxicity in rats at any dose. Terminal body weights and body-weight gains were significantly decreased by 14−16 and 31−34%, respectively, in the 30,000-ppm dose male and female rats (see Table B-1). Food consumption was decreased by up to 38−47% in males and females during the first week of 3-methylphenol administration, but was comparable to controls for the remainder of the study. At study termination, relative liver weights were significantly increased by 12−31% in male and female rats in the 10,000 and 30,000-ppm dose groups, compared with controls; absolute liver weight was also statistically significantly increased by 16% in males at 10,000 ppm, but not at 30,000 ppm (although it was biologically significant at 12%), apparently reflecting the decrease in body weight at that dose level (see Table B-2). Relative (but not absolute) brain and kidney weights were also significantly elevated by 13−16% in males and females in the 30,000-ppm dose group (see Table B-2) secondary to the decrease in body weight. All other organ weights in exposed rats were comparable to controls. No gross lesions were found during necropsy. The only histopathological lesion attributed to 3-methylphenol exposure was mild uterine atrophy in 80% (4/5) of the female rats in the 30,000-ppm dose group (see Table B-3). Atrophy was characterized by reduced cross-sectional diameter of the uterine horns and decreased size of stromal and smooth muscle cells.

A no-observed-adverse-effect level (NOAEL) of 252 mg/kg-day (3,000 ppm) and a lowest-observed-adverse-effect level (LOAEL) of 862 mg/kg-day (10,000 ppm) are determined based on increased (>15%) absolute and relative liver weight in male rats and increased (>10%) relative liver weight in female rats. Uterine lesions in females and decreased body weight in both sexes were observed at higher doses.

NTP (1992b) − Mouse study

NTP (1992b) conducted and published a 28-day, peer-reviewed study examining the effects of exposure to 3-methylphenol on mice. Groups of $B6C3F_1$ mice (five/sex/dose) were administered 3-methylphenol (98% pure) at dietary concentrations of 0, 300, 1,000, 3,000, 10,000, or 30,000 ppm for 28 days. Based on body weight and food consumption, the study authors calculated daily doses of 0, 53, 193, 521, 1,730, or 4,710 mg/kg-day for males and 0, 66, 210, 651, 2,080, or 4,940 mg/kg-day for females. The study design and endpoints examined were identical to the NTP (1992b) rat study described above.

There were two male and two female mortalities at 30,000 ppm, one female mortality at 10,000 ppm, and one control male mortality over the course of the study (see Table B-4); cause(s) of death were not reported. Clinical signs of toxicity were observed at ≥10,000 ppm. In males, hunched posture and rough appearance of coats was observed at ≥10,000 ppm, with thin appearance, lethargy, and tremors at 30,000 ppm only. In females, labored respiration, lethargy, sunken eyes, hunched posture, and rough appearance of coats was observed at ≥10,000 ppm, with thin appearance and tremors at 30,000 ppm only. Terminal body weights were significantly decreased 20−22% at the highest dose in both sexes, compared with controls (see Table B-4). Food consumption decreased in males administered the highest dose during the first week and in females administered the highest dose during the first and third weeks (quantitative data not reported). At study termination, relative liver weights were significantly increased by 4−19% in females from all dose groups and by 6−23% in males at ≥3,000 ppm, compared with controls; absolute liver weights were not statistically significantly increased (see Table B-5), although they were biologically significant in females at ≥1,000 ppm. Other significant organ-weight changes included a 9% increase in relative kidney weight in males at 3,000 ppm, an 11% increase in relative kidney weight in females at 30,000 ppm, and a 20% increase in relative brain weight in males at 30,000 ppm (see Table B-5). No gross lesions were found during necropsy. The only histopathological lesions attributed to 3-methylpheonol exposure were atrophy of the mammary glands, ovaries, and uterus in all surviving females (3/3) in the highest-dose group; these lesions were not observed in the two high-dose females that died prior to study termination (see Table B-3).

A NOAEL of 66 mg/kg-day (300 ppm) and a LOAEL of 210 mg/kg-day (1,000 ppm) are identified based on increased relative liver weight (≥~10%) in female mice. Clinical signs of toxicity (e.g., hunched posture, labored respiration, lethargy, and tremors) were observed in both sexes in the two highest-dose groups. Frank effect levels (FELs) of 4,710 and 4,940 mg/kg-day (30,000 ppm) are identified in males and females, respectively, for 40% mortality. Decreased body weight and atrophy of the mammary glands, ovaries, and uterus were also observed at this dose level.

Koizumi et al. (2003) − Neonatal rat study

In a dose-range-finding study, neonatal Sprague-Dawley (S-D) rats (five/sex/group) were exposed to 3-methylphenol at doses of 0, 100, 300, or 1,000 mg/kg-day via gavage in olive oil on

Postnatal Days (PNDs) 4−21. Body weight was recorded and observations for general behavior were taken during the exposure period. Pups were sacrificed on PND 22 and blood was collected for hematology and clinical chemistry. Organ weights were collected and the pups were examined macroscopically.

All newborns in the 1,000-mg/kg-day group died after 2 days of treatment and exhibited pale skin, decreased spontaneous activity, and deep respiration. Deep respiration and tremors under contact stimulus were observed in all neonatal rats (5/5) at 300 mg/kg-day. No clinical signs of toxicity were observed in the 100-mg/kg-day group. Slight (<15%) increases in serum total bilirubin levels were observed in both males and females at 300 mg/kg-day (statistical analysis not reported). No other clinical chemistry or hematological parameters differed between exposed and control rats. Terminal body weights were significantly reduced by 16% in females and relative liver weights were significantly elevated by 13% in males and females in the 300-mg/kg-day group. Body weights and organ weights were similar between rats in the 100-mg/kg-day group and controls. No abnormal gross findings were observed.

Based on the results of the dose range-finding study, Koizumi et al. (2003) administered 3-methylphenol (99.13% pure) at doses of 0, 30, 100, or 300 mg/kg-day via gavage in olive oil to newborn S-D rats (12/sex/dose) from PNDs 4−21 (18 days). The newborn rats were obtained from 21 female pregnant rats, which delivered the pups and nursed them for 2 days. The pups were separated from dams on PND 3, randomly assigned to a dose group, and suckled by foster mothers (four/sex/dam) until weaning. Following treatment, six rats/sex/group were selected for sacrifice on PND 22. The remaining animals were maintained without exposure for a 9-week observation period and sacrificed. The behavior of the newborns and foster dams was recorded at least once per day, and body weights were measured on PNDs 4, 7, 10, 13, 16, 19, and 21 of the dosing period. During the 9-week recovery period, body weights and food consumption were measured weekly. The investigators examined animals for abnormal gait, pupillary reflex, auricular reflex, corneal reflex, visual placing reflex, surface and mid-air righting reflexes, and ipsilateral flexor reflex on PND 20 (males) and PND 21 (females). On PNDs 7, 9, and 11, animals were examined for fur appearance, incisor eruption, and eye-opening ability. On PND 17, males were examined for testes descent, and at PND 29, females were examined for vaginal opening.

Investigators measured urine at the end of the recovery-maintenance period for abnormalities in color, pH, occult blood, protein, glucose, ketone bodies, bilirubin, urobilirubin, sediment, specific gravity, and volume. Two samples of blood were obtained at sacrifice from each of the animals examined, either on PND 22 or at the end of the recovery period. One blood sample was used to determine red blood cell (RBC) count, hemoglobin (Hb), hematocrit, mean corpuscular volume, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell (WBC) count, platelet count, reticulocyte count, and leukocytes (percentage), prothrombin time, and activated thromboplastin time. The second blood sample was analyzed for the following biochemical parameters: total protein, albumin, albumin-globulin (A/G) ratio, glucose, total cholesterol, triglycerides, phospholipid, total bilirubin, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), lactate dehydrogenase (LDH), cholinesterase, calcium, inorganic phosphorus, sodium, potassium, and chlorine. The investigators completed histopathological examinations of the following tissues from the control and high-dose groups: brain, pituitary gland, thymus, thyroid, heart, lungs, liver,

spleen, kidneys, adrenals, testes, epididymides, prostate, seminal vesicles, ovaries, uterus, trachea, stomach, intestine, pancreas, lymph glands, urinary bladder, spinal cord, bone marrow, and sciatic nerve. Histopathological exams were only conducted on other dose groups when macroscopic examinations revealed abnormalities in a specific group, or microscopic examination of the highest-dose group indicated dose-related effects in a particular organ or tissue. Appropriate statistical tests were conducted.

There were no mortalities during the study. Various clinical signs of toxicity were observed in all neonates exposed to 300 mg/kg-day throughout the treatment period, including deep respiration, increased motor activity, and/or tremors and hypersensitivity under contact stimulus (see Table B-6). A few males in the 100-mg/kg-day group showed tremors and hypersensitivity under contact stimulus on specific dosing days; no clinical signs were observed at 30 mg/kg-day. Incidence of clinical signs in control neonates was not reported. In males, body weights were significantly decreased in the high-dose group starting on PND 7 (data presented graphically), with a significant 12% decrease in terminal body weights, compared with controls (see Table B-6). In females, body weights were significantly decreased on PND 13 and 15 (data presented graphically); however, terminal body weights (at PND 22) were not significantly different than controls (see Table B-6). Body weights at lower doses were comparable to controls. Statistically significant increases in GGT (42%), total bilirubin (18%), and BUN (33%) levels were reported only in males in the 300-mg/kg-day dose group (see Table B-7). Statistically significant organ-weight changes observed in male and female neonates at PND 22 included a 10−14% increase in relative liver weight and a 5−7% decrease in absolute brain weight at 300 mg/kg-day, compared with controls (see Table B-6). The only histopathological lesion potentially related to 3-methylphenol exposure was an increased severity of basophilic tubules in the kidneys of males; slight and moderate changes were observed in 2/6 and 3/6 males, respectively, in the 300-mg/kg-day group, while other groups showed only slight basophilic changes in 5−6/6 males per group.

In the recovery group, no changes in body weight, food consumption, blood hematology, clinical chemistry, urinalysis, gross examination, or histopathology were observed in treated animals sacrificed after the recovery period, compared with controls. The only persistent organ-weight effect was a 9% decrease in absolute brain weight in "treated" males of the recovery group (dose group not reported), compared with controls.

A NOAEL of 100 mg/kg-day and a LOAEL of 300 mg/kg-day are identified in neonatal rats based on the decreased body weight in males, increased relative liver weight in males and females (≥10%), and clinical signs of toxicity (deep respiration, increased motor activity, and contact stimulus tremors and hypersensitivity) in males and females.

Koizumi et al. (2003) − Young rat study

In a dose-range-finding study (Koizumi et al., 2003), young S-D rats (five/sex/group) were administered 3-methylphenol at doses of 0, 125, 250, 500, or 1,000 mg/kg-day via gavage in olive oil from Postnatal Weeks (PNWs) 5−7 (14 days). Body weight and food consumption were recorded and observations for general behavior were taken during the exposure period. Animals were sacrificed on Day 15 of the study, and blood was collected for hematology and clinical chemistry. Organ weights were collected and the animals were examined macroscopically.

All animals survived until necropsy. At 1,000 mg/kg-day, salivation, tremors, and prone/lateral position were observed in both sexes during the dosing period. Males of the high-dose group had decreased body weight and food consumption. Total cholesterol was increased by 30% in females of the high-dose group. Both sexes showed an 8−16% increase in relative liver weights at 500 and 1,000 mg/kg-day, compared with controls. Relative kidney weights in males were also increased by 9% at 1,000 mg/kg-day. Hematological parameters were not affected by treatment, and there were no abnormal gross findings.

Based on the results of the dose range-finding study, Koizumi et al. (2003) administered 3-methylphenol (99.13% pure) to young S-D rats (seven/sex/dose) at doses of 0, 100, 300, or 1,000 mg/kg-day via gavage in olive oil from PNWs 5−9 (28 days). A concurrent recovery group of control and high-dose animals (seven/sex/group) were treated from PNWs 5−9 and observed for 2 weeks following treatment. Observations and endpoints evaluated are as described in the study of neonatal rats above. Animals in the main study group were sacrificed on the day immediately following the last treatment.

There were no mortalities during the study period. Males and females in the 1,000-mg/kg-day dose group showed clinical signs of toxicity during the dosing period, including salivation and tremors (incidence not reported). Body weights in males and females from the high-dose group were lower than control body weights during the dosing period and transient decreases in food consumption were observed during the early dosing period (data not reported). At study termination, however, only females showed a significant 11% decrease in body weight in the 1,000-mg/kg-day dose group (see Table B-8). No hematological differences between treated and control rats were observed. Increases in water consumption and urine volume were seen in males at dosing Week 4 (data not reported). Lower urine pH values were observed in both sexes at the highest dose (data not shown). Statistically significant changes in AST (−13%), total cholesterol (+31%), and BUN levels (+17%) were reported only in males in the 1,000-mg/kg-day dose group, compared with control (see Table B-9). Statistically significant organ-weight changes observed in young rats in the high-dose group included a 13−15% increase in relative liver weights in males and females, a 16% increase in relative kidney weight in females, and a 10% increase in relative brain weight in males (see Table B-8). Relative liver weight was also increased 10% in females at 300 mg/kg-day. No histopathological findings attributable to treatment were observed. No significant changes to any parameter were found in the high-dose recovery group, compared with control (data not provided).

A NOAEL of 100 mg/kg-day and a LOAEL of 300 mg/kg-day are identified based on increased relative liver weights (≥10%) in young female rats; this effect was noted in young male rats at 1,000 mg/kg-day. Decreases in body weight and clinical signs of toxicity were also observed in both sexes at 1,000 mg/kg-day.

Subchronic-Duration Studies

Dietz and Mulligan (1988)

Groups of S-D rats (30/sex/group) were administered 3-methylphenol (99.5% pure) at doses of 0, 50, 150, or 450 mg/kg-day via gavage in corn oil once daily for 13 weeks. Animals were inspected for mortality and moribundity twice daily. Detailed physical examinations, body weights, and food consumption were recorded weekly. Animals found dead or sacrificed moribund were subjected to gross necropsy. Ten animals/sex/dose were sacrificed at Week 7 (interim sacrifice) and the remaining animals were sacrificed at Week 14 (terminal sacrifice).

Prior to the initiation of the study and at Week 13, animals were examined for ophthalmological lesions by indirect ophthalmoscopy. Blood was collected from 10 rats/sex for baseline hematology and clinical chemistry analysis and from 10 animals/sex/dose at Week 7 and 10 animals/sex/dose at Week 14. Hematological parameters examined included: Hb, hematocrit, erythrocyte count, total and differential leukocyte count, prothrombin time, activated partial thromboplastin time, and reticulocyte count. Blood clinical chemistry parameters examined included: sodium, chloride, potassium, calcium, carbon dioxide (CO_2), AST, ALT, ALP, glucose, BUN, direct and total bilirubin, total cholesterol, albumin, globulin (calculated), total protein, and A/G ratio (calculated). Urine samples were also collected from 10 animals/sex/dose at Weeks 7 and 14. Urinalysis parameters examined included: appearance, volume, color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, and Hb, and microscopic examinations were also performed. The following tissues were collected for histopathological evaluation in control and high-dose animals at interim and terminal sacrifices: all gross lesions, brain (three levels), spleen, bone (with marrow), skeletal muscle, ovaries, corpus and cervix uteri, eye, pituitary, mandibular lymph nodes, salivary gland, heart, thymus, thyroid (with parathyroid), lungs (with mainstem bronchi), trachea, liver, stomach, small and large intestine, adrenals, spinal cord, mammary gland, aorta, sciatic nerve, pancreas, esophagus, kidneys, urinary bladder, testes, and prostate. At terminal sacrifice, body, heart, liver, spleen, brain, kidney (individual), gonads (individual), adrenal, and thyroid weights were recorded. Appropriate statistical tests were conducted.

One male in the high-dose group was found dead during Week 1, but the cause of death could not be determined. Lung congestion, red lungs, and blood in the thoracic cavity were found at necropsy. No other mortalities were observed. Clinical signs of toxicity were observed throughout the exposure period in males and females in the high-dose group, including lethargy, tremors, and/or hunched posture (see Table B-10). Significant reductions in male body weight were observed at 450 mg/kg-day from Weeks 2−5 and at ≥150 mg/kg-day from Weeks 6−14. The reduction in male body weights at ≥150 mg/kg-day was 6−10% at the interim sacrifice and 9−13% at the terminal sacrifice (see Table B-10). In females, body weights did not differ significantly between exposed and control rats. Statistically significant decreases in food consumption were observed in males from the 150-mg/kg-day dose group during Weeks 3, 6, 8, 12, and 13 and males from the 450-mg/kg-day dose group during Weeks 1−4, 6−9, and 11. Increased food consumption was observed in females from the 150-mg/kg-day dose group during Weeks 1, 2, 9, 11, and 12 and females from the 450-mg/kg-day dose group during Weeks 4 and 6. However, these changes in food intake were not dose-dependent and occurred sporadically; therefore, they are not considered biologically significant. Clinical chemistry, hematology, ophthalmologic analyses, organ weight, and histopathology were unaffected by treatment with 3-methylphenol.

A NOAEL of 50 mg/kg-day and a LOAEL of 150 mg/kg-day are identified based on significant body-weight decreases (~10%) in male rats. Clinical signs of toxicity (lethargy, tremors, hunched posture) were observed in both sexes at 450 mg/kg-day.

TRL (1986)

In an unpublished neurotoxicity study, groups of CD rats (10/sex/group) were administered 50, 150, or 450 mg/kg-day 3-methylphenol via gavage in corn oil for 90 days (7 days/week). A control group consisting of 20 rats/sex was administered corn oil only. Animals were observed twice daily for mortality and were observed for clinical signs for an hour

after dosing while in the cage, at the end of the hour after dosing outside of the cage, and 4 hours after dosing outside of the cage. Weekly determinations of body weights and food consumption were conducted. Four rats/sex from the control group and two rats/sex/group were assigned to behavioral testing groups. Neurobehavioral toxicity observations occurred once prior to initiation of treatment, 1 and 6 hours after dosing on study Day 1, and before dosing on Days 2, 7, 14, 30, 60, and 90 by an individual blind to treatment groups. The parameters assessed included: respiration, salivation, urination, tremors, piloerection, diarrhea, pupil size and response, lacrimation, hypothermia, vocalization, exophthalmos, palpebral closure, and convulsions. In an arena, impaired gait, locomotor activity, stereotypy, startle response, and righting reflex were assessed. Positional passivity, wire maneuver, forelimb grip strength, positive geotropism, extensor thrust, limb rotation, tail pinch, toe pinch, and hind limb splay were tested outside of an arena. At necropsy, animals were randomly selected for perfusion for neuropathology and included 11 males and 12 females from the control group and 19 males and 25 females from the treated groups. The remaining animals were euthanized. The brains and spinal cords were removed from the first 10/sex of the control group and the first 5/sex of the treated groups, and the length, width, depth, and weight of the brain were recorded. Neuropathology was conducted on the following tissues: forebrain, center of cerebrum, midbrain, cerebellum, pons, medulla oblongata, cervical spinal cord, lumbar spinal cord, Gasserian ganglia, dorsal root ganglia, ventral root fibers, proximal sciatic nerve, sural nerve, tibial nerve, eye, and optic nerve. Animals found dead were examined macroscopically and the following tissues were collected for histopathology: esophagus, stomach, lungs with trachea, and gross lesions. Appropriate statistical analyses were conducted; however, quantitative data were not included in the available copy of the report.

The only mortality was one female in the high-dose group; death was attributed to pulmonary edema or pneumonia from aspiration of the test substance. The study authors reported clinical signs of toxicity shortly after dosing in all exposed rats, such as salivation, low body posture, labored respiration, and urine-wet abdomens; however, incidences at low doses were low and sporadic. Tremors were observed in both sexes at ≥150 mg/kg-day with peak incidences occurring during Week 8. Myoclonus was observed at ≥150 mg/kg-day in males and at 450 mg/kg-day in females. Rapid respiration, myotonus, hypoactivity, and clonic convulsions were observed at 450 mg/kg-day in both sexes. The incidence of rales at 6 hours after treatment was significantly increased in females of the high-dose group. Body weights did not differ in exposed rats compared with controls. In the high-dose group, significantly decreased food consumption was observed in males during Week 3 and females during Week 1. The only significant changes observed during neurobehavioral observations were increased urination in high-dose females and decreased diarrhea in high-dose males, compared with controls. No differences in brain weight were observed between exposed and control animals and no abnormal gross or microscopic findings were observed.

A NOAEL of 50 mg/kg-day and a LOAEL of 150 mg/kg-day are identified for increases in the incidence of multiple clinical signs of neurotoxicity (tremors, myoclonus, labored respiration, and salivation).

Chronic-Duration Studies

No animal studies could be located describing the effects of chronic oral exposure to 3-methylphenol alone. However, NTP (2008) investigated the toxicity of chronic dietary

exposure to a mixture of 3-methylphenol and 4-methylphenol. Findings from this study are summarized in the "Other Data" section of this document and Table 4B.

Reproductive/Developmental Studies

BushyRun (1989)

In an unpublished two-generation reproductive study, groups of weanling S-D rats (25/sex/group) were exposed to 3-methylphenol (99.4% pure) at doses of 0, 30, 175, or 450 mg/kg-day via gavage in corn oil, 5 days/week for 10 weeks. After the initial 10-week exposure period, animals were randomly paired for a 3-week mating period. During the mating period, the dosing regimen was changed from 5 days/week to 7 days/week. Gestation Day (GD) 0 was considered the first day a copulation plug or vaginal sperm was seen. For females, dosing continued 7 days/week during gestation and lactation. Males were euthanized at the end of the 3-week mating period. F0 females were sacrificed and necropsied after weaning of the offspring on PND 21. Twenty-five F1 offspring/sex/group were randomly selected to continue exposure and were mated to produce an F2 generation. Dosing began between PNDs 28 and 40. The nonmated F1 pups were sacrificed and examined externally. Tissues from control and high-dose parental animals were examined histologically. F1 parental animals were dosed under the same schedule as the F0 generation parental animals for an 11-week premating period, 3-week mating period, during gestation, and through lactation. F2 pups were sacrificed and examined at weaning.

During premating, all animals were examined twice per day for mortality and clinical signs. During mating, dams were observed twice daily for signs of successful mating. Body weights were recorded weekly. Food consumption was determined weekly during premating and visually monitored throughout the rest of the study. Mated females were weighed on GDs 0, 7, 13, and 20 and on PNDs 4, 6, 14, and 21. Pups were sexed, weighed, and examined on Days 1, 4, 6, and 14 and upon weaning (PND 21), and examined twice daily for survival. On PND 4, pups were culled to four males and four females per litter (as possible). At weaning of the F2 generation, all animals were necropsied.

All animals were subjected to gross necropsy. The following tissues of animals in the high-dose and control groups of both parental generations (F0 and F1) were examined microscopically: pituitary gland, vagina, uterus, ovaries, testes, epididymides, seminal vesicles, prostate, and gross lesions of each animal. Complete necropsies and histopathological examinations were performed on any animal that died during the dosing period. Investigators examined the following in females failing to produce litters: implantation sites; external surfaces; all orifices; cranial cavity; carcass; external and cut surfaces of the brain and spinal cord; the thoracic, abdominal, and pelvic cavities; and cervical tissues and organs. Abnormal or dead pups were also necropsied and grossly examined. The calculated reproductive indices included the following: mating, fertility, gestation, live birth, survival (4-, 7-, 14-, and 21-day), and lactation. Appropriate statistical tests were conducted.

In the F0 generation, survival was significantly decreased in high-dose males (18/25) and females (18/25) compared with control males (25/25) and females (25/25), respectively; mortality was similar to controls in other exposure groups (see Table B-11). Clinical signs of toxicity observed in the high-dose group included hypoactivity, ataxia, twitches, tremors, prostration, unkempt appearance, urine stains, audible respiration, perinasal encrustation, perioral wetness, and red perioral wetness (see Table B-12). Body weights were significantly decreased

in F0 males exposed to 450 mg/kg-day throughout the entire premating and mating periods, with a significant 15% decrease at Week 13, compared with controls (see Table B-11). Body weights were also significantly decreased in female F0 rats exposed to 450 mg/kg-day at many time-points during the exposure period (premating through lactation); however, body weights remained within 10% of controls throughout the experiment (see Table B-11). No significant differences in body weights were observed between rats exposed to 30 or 175 mg/kg-day and controls. F0 males in the 175- or 450-mg/kg-day groups showed intermittent decreases in food consumption during early treatment, compared with control, with levels returning to normal after Week 7 of treatment. Food consumption was only decreased in females at 450 mg/kg-day during the first week of treatment, compared with controls. No gross lesions were reported in F0 males or females that survived until scheduled sacrifice. Animals in the 450-mg/kg-day group that died prior to scheduled sacrifice showed brain hemorrhage, intestinal dilation and distention, diffuse or multifocal color changes in the lungs, and crust on the skin at necropsy. Males also had decreased numbers of sperm, atrophied seminal vesicles, congestion and rhinitis in the nasal cavity, and lung congestion. Females also showed lung congestion and congestion of the meningeal vessels.

Gestational length, mating, fertility and gestational indices, litter size, sex ratio, and pup survival in the F0 mating to produce the F1 generation were not significantly different in exposed animals, compared with controls. Male F1 pups in the 450-mg/kg-day group showed a significant 7−9% reduction in litter body-weight means on PNDs 14 and 21, compared with controls (see Table B-13). Female F1 pups in the 30-mg/kg-day group (but not in the 175 or 450-mg/kg-day groups) showed a statistically significant 8% decrease in litter body-weight means on PND 21, compared with controls (see Table B-13).

In the F1 parental animals, survival was significantly decreased in high-dose females (15/25) compared with control females (24/25); a nonsignificant decrease in survival was observed in high-dose males (22/25) compared with control males (25/25). Mortality was similar to controls in other exposure groups (see Table B-11). Clinical signs of toxicity observed in high-dose animals included hypoactivity, ataxia, twitches, tremors, prostration, urine stains, labored and audible respiration, perinasal encrustation, and perioral wetness (see Table B-14). Body weight was statistically significantly reduced by 6−13% at the beginning of the pre-exposure period in all exposed F1 males and females (see Table B-11). In high-dose males, this reduction continued to be significant throughout premating and mating exposure, with a significant 15% reduction at terminal sacrifice, compared with controls (see Table B-11). In high-dose females, body-weight reductions also continued to be significant at many time-points during premating, mating, gestation, and lactation; however, body weights remained within 10% of controls (see Table B-11). F1 males in the 450-mg/kg-day group showed reduced food consumption in the first 3 weeks of treatment, and males dosed at 175 mg/kg-day showed reduced food consumption during the first 2 weeks of treatment. Food consumption levels were comparable to controls for all dose groups following the first 3 weeks of treatment. There were no lesions or histological findings attributable to treatment in F1 parental animals that survived until scheduled sacrifice. In high-dose animals that died prior to sacrifice, gross findings included focal or multifocal color changes in the lungs; congestion of the nares, nasal cavity, and lungs; crusting around the nose; stained skin; and alopecia.

Gestational length, mating, fertility and gestational indices, litter size, or sex ratio in the F1 mating to produce the F2 generation were not significantly different in exposed animals,

compared with controls. At the highest dose, pup survival on PND 14 was significantly decreased (see Table B-13). The number of dead F2 pups at the highest dose was also increased on PND 21, relative to controls; however, this was not considered treatment-related because half of the dead pups did not die on their own but were sacrificed following the death of their mother (see Table B-13). The litter body-weight means for F2 male and female pups were significantly decreased by 9−12% on PNDs 14 and 21 in the high-dose group, compared with controls (see Table B-13).

A NOAEL of 175 mg/kg-day and a LOAEL (FEL) of 450 mg/kg-day are identified for increased mortality in F0 males and females and F1 females and increased postnatal mortality in F2 pups. Additional effects observed at this dose included significantly reduced body weight (>10%) in F0 and F1 males, clinical signs of toxicity in F0 and F1 males and females, and significantly reduced postnatal body weights in F1 male pups and F2 male and female pups; effects were more severe in dosed adults than pups. Gavage doses of 30, 175, or 450 mg/kg-day were converted to the following time-weighted adjusted daily doses (ADDs): 23, 137, or 350 mg/kg-day in F0 males; 23, 136, or 350 mg/kg-day in F1 males; 25, 149, or 380 mg/kg-day in F0 females; and 27, 155, or 400 mg/kg-day in F1 females.[1]

BushyRun (1988); Hazleton Laboratories (1988a)

In an unpublished developmental study, groups of timed-pregnant S-D rats (25/group) were administered 3-methylphenol (99.4% pure) at doses of 30, 175, or 450 mg/kg-day via gavage in corn oil from GDs 6−15. A control group consisting of 50 timed-pregnant females was administered corn oil only. The animals were examined twice daily for morbidity and mortality and once daily for clinical signs of toxicity. Females were weighed on GDs 0, 6, 11, 15, and 21, and food consumption was measured over the following time periods: GDs 0−6, 6−9, 9−11, 11−13, 13−15, 15−18, and 18−21. Females were sacrificed on GD 21, and gross examinations of the uterus, ovaries (including corpora lutea), cervix, vagina, and abdominal and thoracic cavities were conducted in all animals. Corpora lutea were counted, and the uteri and livers of all dams were weighed. Uteri were examined externally before dissection; live and dead fetuses and resorption sites were counted. All fetuses were examined for external malformations. Half of all fetuses in each litter were examined for thoracic and abdominal visceral abnormalities; the remaining fetuses were examined for skeletal malformations and anomalies. Appropriate statistical tests were conducted, using the pregnant dam or the litter as the statistical unit of comparison.

No mortalities occurred during the study. High-dose dams showed increased clinical signs of toxicity including hypoactivity, ataxia, twitches, tremors, urogenital area wetness, audible respiration, and perioral wetness and encrustation (see Table B-15). In the high-dose group, maternal body weights were significantly decreased by 5−6% on GDs 11 and 15 and maternal body-weight gain during exposure was significantly decreased by up to 85% (GDs 6−11), compared with controls (see Table B-16). Gestational-weight change (GDs 0−21)

[1]Time-weighted ADD doses in males = [(premating dose × (5 days ÷ 7 days) × premating length) + (mating dose × (7 days ÷ 7 days) × mating length)] ÷ total length of exposure; premating length was 10 weeks for F0 rats and 11 weeks for F1 rats, mating length was up to 3 weeks for both generations.

Time-weighted ADD doses in females = [(premating dose × (5 days ÷ 7 days) × premating length) + (mating-lactation dose × (7 days ÷ 7 days) × mating-lactation length); premating length was 10 weeks for F0 rats and 11 weeks for F1 rats, mating-lactation length was up to 9 weeks for both generations.

corrected for uterine weight was also significantly decreased by 25% in high-dose dams, compared with controls (see Table B-16). Food consumption was significantly decreased by 14% in high-dose dams during the entire dosing period (GDs 6−15) (see Table B-16). Relative, but not absolute, liver weights were statistically significantly increased by 8% in high-dose dams, compared with controls (see Table B-16). No gross lesions attributable to treatment were reported in any of the dose groups.

There were no significant changes in resorption or pregnancy rates in treated dams compared with controls. There were also no significant increases in malformations or skeletal variations in fetuses from treated dams, compared with controls.

A maternal NOAEL of 175 mg/kg-day and LOAEL of 450 mg/kg-day are identified based on decreased maternal body-weight gain and clinical signs of toxicity. A fetal NOAEL of 450 mg/kg-day is identified based on a lack of adverse fetal effects. These findings suggest that the fetus is not a sensitive target of 3-methylphenol toxicity.

Hazleton Laboratories (1988a); BushyRun (1987b)

In an unpublished maternal dose range-finding study, groups of mated New Zealand white (NZW) rabbits (eight/group) were exposed to 3-methylphenol (purity not reported) at doses of 50, 150, 300, or 500 mg/kg-day via gavage in corn oil from GDs 6−18. A control group consisting of 16 mated females was administered corn oil only. Animals were observed daily for clinical signs of toxicity. Does were weighed on GDs 0, 6, 12, 18, and 29. Food consumption was monitored throughout gestation. Does were sacrificed on GD 29, and gross evaluation of the thoracic and abdominal cavities and reproductive organs was conducted. Body, liver, and gravid uterine weights, the number of corpora lutea and the number implantation sites, the number and type of resorptions, and the number of live and dead fetuses were recorded. Live fetuses were examined for external malformations. Visceral and skeletal examinations were not conducted. Statistical results were reported, but methods were not provided.

All high-dose does (8/8) died prior to scheduled sacrifice. Other mortalities included 1/8 does at 300 mg/kg-day and 2/8 does at 150 mg/kg-day (cause of death was not determined). Significant increases in the incidences of labored, audible, and rapid respiration were observed at ≥300 mg/kg-day. Additional clinical signs of toxicity observed at 500 mg/kg-day included hypoactivity, twitches, gasping, decreased respiration, cyanosis, and perioral wetness. Maternal body weight was significantly decreased on GD 12 by 10% in does exposed to 300 mg/kg-day; body weights measured at other time-points during and after the exposure period were not significantly different from control (see Table B-17). Maternal body-weight gain was also significantly decreased by 678 and 1,474% from GDs 6−12 in does exposed to 150 and 300 mg/kg-day, respectively (see Table B-17). Food consumption was significantly decreased from GDs 6−10 at ≥300 mg/kg-day and from GDs 7−9 at 150 mg/kg-day. Absolute and relative uterine weights and absolute liver weights did not differ significantly in exposed does, compared with controls. Relative liver weights were significantly elevated by 21% at 50 mg/kg-day, but not ≥150 mg/kg-day. No changes attributable to treatment were observed at gross necropsy of does.

There were no significant differences in the number of corpora lutea, implants or resorptions, or the percent live fetuses per litter in surviving does from exposed groups, compared with controls. Preimplantation loss was significantly increased at 50 and

300 mg/kg-day, compared with controls; no significant change was observed at 150 mg/kg-day (see Table B-17). The number of dead fetuses per litter was significantly increased in surviving does exposed to 300 mg/kg-day (see Table B-17). Mean litter weights were comparable among exposure groups. The percent of litters with external malformations was increased at 300 mg/kg-day (66.7%) compared with controls (26.7%), with significant increases in the incidence of bony protrusion of the ventral chest above the forelimbs, inverted forelimbs, and tight skin around the elbows (see Table B-18). However, due to the very small number of litters in the 300-mg/kg-day group, the biological significance of these findings is unclear.

A NOAEL of 150 mg/kg-day and a LOAEL of 300 mg/kg-day are identified for increased preimplantation loss, fetal death, and external malformations. A FEL of 500 mg/kg-day is identified for maternal death. It is unclear if the few deaths in the lower dose groups were compound-related because cause of death was not reported.

BushyRun (1987a)

In an unpublished developmental study, groups of mated NZW rabbits (14/group) were exposed to 3-methylphenol (99.4% pure) at doses of 5, 50, or 100 mg/kg-day via gavage in corn oil from GDs 6−18. A control group consisting of 28 mated females was administered corn oil only. The animals were observed for mortality, morbidity, and clinical effects twice daily, and body weights were measured on GDs 0, 6, 12, 18, 24, and 29. Food intake was measured on GDs 0−29. Animals were sacrificed on GD 29, and gross evaluation of the thoracic and abdominal cavities and reproductive organs was conducted. Body, liver, and gravid uterine weights, the number of corpora lutea and the number implantation sites, the number and type of resorptions, and the number of live and dead fetuses were recorded. Live fetuses were examined for external, visceral, and skeletal malformations and visceral and skeletal variations. The fetuses were also weighed and sexed internally. The heads of half of the live fetuses were examined for craniofacial malformations. Appropriate statistical tests were conducted, using the pregnant female or litter as the unit of comparison.

One doe died in the 5-mg/kg-day group (cause of death was not reported); no other mortalities were observed. A number of clinical toxicity signs (audible respiration, ocular and nasal discharge) were noted during the study in exposed animals; however, incidences were not statistically significantly different from controls. No changes were observed in maternal body weights or weight gains relative to the control group. Food consumption was similar in all groups. Upon necropsy, no lesions or differences in maternal organ weights were reported in exposed groups compared with controls.

There were no significant differences in the gestational parameters examined, including the number of early or late resorptions, dead or live fetuses, sex ratio, or fetal body weights. No significant increases in the incidences of external malformations, visceral malformations, or skeletal malformations or variations were observed in fetuses from exposed litters, compared to controls. The only significantly increased visceral variation was pale gallbladder in the 5-mg/kg-day group, but not higher dose groups, compared with controls. Based on lack of dose response, this variation is not attributed to treatment.

A free-standing NOAEL of 100 mg/kg-day is identified based on a lack of maternal or fetal effects.

Inhalation Exposures

No studies of laboratory animals exposed to 3-methylphenol via inhalation have been identified in the available literature.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Genotoxicity

The potential genotoxicity of 3-methylphenol has been evaluated in numerous in vitro studies and two in vivo mammalian studies. Available studies are summarized below (see Table 4A for more details). The majority of studies indicate that 3-methylphenol is not mutagenic. Evidence from some in vitro studies suggests that 3-methylphenol has the ability to react with deoxyribonucleic acid (DNA) and may be clastogenic in certain conditions; however, limited evidence from rats and mice exposed via gavage or injection do not indicate that 3-methylphenol is clastogenic in vivo.

Table 4A. Summary of 3-Methylphenol (CASRN 108-39-4) Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results Without Activation[a]**	**Results With Activation[a]**	**Comments**	**References**
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100	0, 0.5, 5, 50, 500, 5,000 µg/plate	−	−	Plate incorporation assay.	Pool and Lin (1982)
Mutation	*S. typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100	Up to 2 mg/plate	−	−	Plate incorporation assay.	Nestmann et al. (1980)
Mutation	*S. typhimurium* strains TAl535, TA1537, TA98, TA100	0, 3.3, 10.0, 33.0, 100.0, 333.0 µg/plate	−	−	Preincubation assay.	Haworth et al. (1983)
Mutation	*S. typhimurium* strains TAl535, TA1537, TA98, TA100	0.005−50 µL/plate	−	−	Plate incorporation assay with a mixture of 2-, 3-, and 4-methylphenol (33.3% each). Toxicity was seen in all strains at ≥10 µL/plate, with slight toxicity seen in strains TA100 and TA1537 at 5.0 µL/plate.	Litton Bionetics (1980c); Litton Bionetics (1980d)
Mutation	*S. typhimurium* strains TAl535, TA1537, TA98, TA100	3 µM/plate	−	−	Spot test.	Florin et al. (1980)
Genotoxicity studies in mammalian cells in vitro						
Mutation	L5178Y TK ± mouse lymphoma cells	0, 52.0, 104, 156, 260, 312, 416, 520 µg/mL	−	−	*m*-Cresol was soluble up to concentrations of 312 µg/mL; toxicity was seen at 520 µg/mL.	Hazleton Laboratories (1988b)

Table 4A. Summary of 3-Methylphenol (CASRN 108-39-4) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results Without Activation[a]	Results With Activation[a]	Comments	References
Mutation	L5178Y mouse lymphoma cells	Without activation: 0.977−750 nL/mL With activation: 0.488−31.3 nL/mL	−	+	Test substance was a mixture of 2-, 3-, and 4-methylphenol (33.3% each). Dose-related increases in the mutant frequency at the TK locus in L5178Y mouse lymphoma cells were observed with activation at ≥3.9 nL/mL; toxicity was observed at 31.3 nL/mL. Without activation, concentrations ≥750 nL/mL became highly toxic and yielded equivocal results only suggestive of weak mutagenic activity.	Litton Bionetics (1980a); Litton Bionetics (1980d)
UDS	Cultured rat hepatocytes from adult male F344 rats	0, 0.251, 0.502, 1.00, 2.51, 5.02, 10.0, 25.1, 50.2, 100, 251, 502 µg/mL	−	NT	3-Methylphenol did not induce significant changes in the nuclear labeling of rat primary hepatocytes for an applied concentration range of 0.251−10.0 µg/mL. Concentrations ≥25.1 µg/mL were highly toxic.	Hazleton Laboratories (1988e)
UDS	SHE cells	0, 1, 3, 10 µM	−	+	3-Methylphenol induced UDS at doses of ≥1 µM in the presence of exogenous metabolic activation.	Hamaguchi and Tsutui (2000)
CAs	SHE cells	Without activation: 0, 200, 400, 800, 1,000 µM With activation: 0, 100, 300, 1,000 µM	+	+	A statistically significant increase in the frequency of CAs was induced in SHE cells at ≥400 µM without activation and at ≥100 µM with activation.	Hikiba et al. (2005)
CAs	CHO cells	Without activation: 0, 198, 297, 396, 495 µg/mL With activation: 250, 500, 699, 749, 799, 898, 998, 999, 1,100 µg/mL	−	−	Concentrations ≥898 µg/mL were toxic under activation conditions.	Hazleton Laboratories (1988g)

Table 4A. Summary of 3-Methylphenol (CASRN 108-39-4) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results Without Activation[a]	Results With Activation[a]	Comments	References
SCEs	Human diploid fibroblasts	0, 0.08, 0.8, 4, 8, 10, 30 mM	−	NT	3-Methylphenol was cytotoxic at concentrations ≥10 mM. A slight increase in SCE frequency at 8 mM was observed, but the study authors concluded that it was likely to be indicative of a small cytotoxic response.	Cheng and Kligerman (1984); CIIT (1983)
SCEs	SHE cells	0, 100, 300, 1,000 µM	+	NT	A statistically significant increase in the frequency of SCEs in SHE cells was observed at doses ≥100 µM.	Miyachi and Tsutsui (2005)
SCEs	CHO cells	Without activation: 0.5−125.0 nL/mL With activation: 0.625−500.0 nL/mL	+	+	Test substance was a mixture of 2-, 3-, and 4-methylphenol (33.3% each). Significant increases in SCEs were observed without metabolic activation at ≥50 nL/mL with marked cell cycle delay and with metabolic activation at ≥400 nL/mL with little toxicity or cell cycle delay.	Litton Bionetics (1980a); Litton Bionetics (1980d)
Cell transformation assay	BALB/c-3T3 cells	0, 6, 12, 24, 48, 72 nL/mL	NA	−	Cytotoxicity was observed at ≥24 nL/mL.	Hazleton Laboratories (1988c)
Cell transformation assay	BALB/c-3T3 cells	Trial 1: 0, 0.57, 3.4, 8.5, 17, 34 nL/mL Trials 2 and 3: 0, 8.0, 12, 24, 48 nL/mL	−	NT	In Trial 1, there was a significant increase in the number of transformed foci at 3.4 and 8.5 nL/mL in the absence of cytotoxicity, but not at higher concentrations. No significant increase in the number of transformed foci were observed in Trials 2 or 3; cytotoxicity (<50% of control survival) was observed at ≥24 nL/mL in Trial 2 and ≥12 nL/mL in Trial 3. The study authors considered two negative trials out of three trials to indicate a negative result.	Hazleton Laboratories (1988d)

Table 4A. Summary of 3-Methylphenol (CASRN 108-39-4) Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results Without Activation[a]**	**Results With Activation[a]**	**Comments**	**References**
Cell transformations	BALB/3T3 cells	0.01−8.0 nL/mL	NA	+	Test substance was a mixture of 2-, 3-, and 4-methylphenol (33.3% each). The total number of transformed foci was increased in a dose-related manner, with a significant increase at 8.0 nL/mL.	Litton Bionetics (1980a); Litton Bionetics (1980d)
Cell transformation assay	SHE cells	0, 10, 30, 100 µM	+	NA	3-Methylphenol significantly increased the frequency of morphological transformation at ≥10 µM.	Yamaguchi and Tsutsui (2003)
Genotoxicity studies—in vivo						
CAs	Male and female ICR mice (15/sex/group) were administered 3-methylphenol via gavage in corn oil. Five rats/sex/group were sacrificed 6, 24, and 48 hr after dosing. Negative controls (five/sex) were included at each time point. Bone marrow was extracted and examined for chromosome damage.	0, 96, 320, 960 mg/kg	−	−	3-Methylphenol did not induce significant increases in CAs in bone marrow at doses that produced observable animal toxicity, including clinical signs (e.g., rapid breathing, mild tonic convulsions, difficulty breathing) and death (3/15 males) at 960 mg/kg.	Hazleton Laboratories (1989)

Table 4A. Summary of 3-Methylphenol (CASRN 108-39-4) Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results Without Activation[a]**	**Results With Activation[a]**	**Comments**	**References**
SCE	Male DBA/2NCrlBR mice (6−9/group) were given a single i.p. injection of 3-methylpheonol dissolved in sunflower oil. Half of the animals (3−5/group) were partially hepatectomized.	0, 200 mg/kg	−	−	3-Methylphenol did not induce significant increases in SCE frequencies in bone marrow, alveolar macrophages, or regenerating liver cells at doses that produced observable animal toxicity (e.g., lethargy, piloerection, and lacrimation).	Cheng and Kligerman (1984); CIIT (1983)

[a]+ = positive; − = negative; NA = not applicable.

CA = chromosomal aberration; CHO = Chinese hamster ovary; i.p. = intraperitoneal; NA = not applicable; NT = not tested; SCE = sister chromatid exchange; SHE = Syrian hamster embryo; UDS = unscheduled DNA synthesis.

Exposure to 3-methylphenol alone or a mixture of 2-, 3-, and 4-methylphenol was not mutagenic in various *Salmonella typhimurium* strains with or without metabolic activation (Haworth et al., 1983; Pool and Lin, 1982; Florin et al., 1980; Litton Bionetics, 1980c, d; Nestmann et al., 1980). Results were also negative for 3-methylphenol in L5178Y TK ± mouse lymphoma cells with or without metabolic activation (Hazleton Laboratories, 1988b; Litton Bionetics, 1980d; Nestmann et al., 1980). However, a mixture of 2-, 3-, and 4-methylphenol was mutagenic with metabolic activation in mouse L5178Y TK ± lymphoma cells; the mixture was not mutagenic in the absence of metabolic activation (Litton Bionetics, 1980a, d).

3-Methylphenol induced unscheduled DNA synthesis (UDS) in Syrian hamster embryo (SHE) cells with metabolic activation, but not without metabolic activation (Hamaguchi and Tsutui, 2000). UDS was not induced by 3-methylphenol in cultured rat hepatocytes in the absence of metabolic activation (not tested with activation) (Hazleton Laboratories, 1988e).

3-Methylphenol induced chromosomal aberrations (CAs) in SHE cells both with and without metabolic activation (Hikiba et al., 2005); however, CAs were not induced in Chinese Hamster ovary (cell line cells) (CHO) cells (Hazleton Laboratories, 1988g). Sister chromatid exchanges (SCEs) were induced in SHE cells following exposure to 3-methylphenol without metabolic activation (not tested with activation) (Miyachi and Tsutsui, 2005) and in CHO cells following exposure to a mixture of 2-, 3-, and 4-methylphenol with or without metabolic activation (Litton Bionetics, 1980b, d). In contrast, 3-methylphenol did not induce SCEs in human diploid fibroblasts without metabolic activation (not tested with activation) (Cheng and Kligerman, 1984; CIIT, 1983). In vivo, CAs were not induced in the bone marrow of ICR mice exposed once to 3-methylphenol at gavage doses up to 960 mg/kg (Hazleton Laboratories, 1989), and SCEs were not induced in the bone marrow, alveolar macrophages, or regenerating liver cells of healthy or partially hepatectomized BDA/2NCrlBR mice injected intraperitoneally with a single 3-methylphenol dose of 200 mg/kg (Cheng and Kligerman, 1984; CIIT, 1983).

Cell transformation was induced by 3-methylphenol in SHE cells in the absence of metabolic activation (Yamaguchi and Tsutsui, 2003). Cell transformation was also induced by a mixture of 2-, 3-, and 4-methylphenol in BALB/c-3T3 cells in the presence of a rat liver cell activation system (Litton Bionetics, 1980d). However, 3-methylphenol alone did not induce cell transformation in BALB/c-3T3 in the presence or absence of a rat liver cell activation system (Hazleton Laboratories, 1988c, d).

Supporting Human Studies

Human health effects data are limited to case reports, which generally lack exposure level data. Numerous case reports of accidental or intentional ingestion of cleaning products containing methylphenol mixtures have reported severe toxic effects and death [reviewed by IPCS (1995), ATSDR (2008), and ACGIH (2010)]. Based on these reports, the main targets of methylphenol toxicity are the gastrointestinal (GI) tract (severe burning), the central nervous system (CNS) (loss of consciousness, coma), kidney (acute renal failure), and blood (hemolysis, methemoglobinemia). Additionally, damage to the lungs, pancreas, heart, and liver has been reported after high oral exposure. Case reports of accidental dermal exposure to methylphenol mixtures report severe corrosive damage to exposed skin, and, at high enough exposures, systemic toxicity and death [reviewed by IPCS (1995)]. Workers exposed to unknown levels of methylphenol vapor for 1.5−3 years reported frequent headaches, nausea, vomiting, elevated blood pressure, impaired kidney function, blood calcium imbalance, and tremors [reviewed by ACGIH (2010)].

Several case studies attributed adverse reactions to insulin treatment in diabetic patients to the 3-methylphenol used as an excipient in the insulin formulation, including localized itching, erythema, lesions, and pain (Wheeler and Taylor, 2012; Kim and Baraniuk, 2007; Rajpar et al., 2006; Clerx et al., 2003). In another case report, a generalized systemic allergy to two insulin excipients (protamine and 3-methylphenol) was observed in a type-1 diabetic male; symptoms included tremor, tachycardia, vertigo, shortness of breath, and brief period of unconsciousness (Malaise et al., 2005).

Supporting Animal Toxicity Studies

A number of supporting animal toxicity studies were identified that exposed animals to 3-methylphenol in a ~60:40 ratio mixture with 4-methylphenol (see Table 4B for study details). The most sensitive effect in short-term- and subchronic-duration mixture studies was increased relative liver weight; NOAELs (27−472 mg/kg-day) and LOAELs (95−923 mg/kg-day) are similar to those identified for this effect in studies evaluating exposure to 3-methylphenol alone (NTP, 1992b). Other effects generally observed at higher doses include body-weight loss, clinical signs of toxicity, hyperplastic lesions of the nose, esophagus, and stomach, and bone marrow hypocellularity (NTP, 1992a, b). In chronic-duration mixture studies, the most sensitive targets were the nasal epithelium in rats and the lung and thyroid in mice, with LOAELs of 70−100 mg/kg-day (Sanders et al., 2009; NTP, 2008). There was no clear evidence of carcinogenicity in rats or mice in the chronic-duration mixture studies (Sanders et al., 2009; NTP, 2008). In a two-generation mixture study, mild reproductive and developmental effects (increased time between litters, decreased pup weight, and decreased reproductive organ weights) were only observed at doses >1,650 mg/kg-day, which also caused systemic toxicity in parental F0 and F1 animals (body-weight decreases, increased liver and kidney weights) (NTP, 1992a).

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Oral mixture studies				
Short-term	F344/N rats (five/sex/dose) were exposed to a mixture of 58.5% 3-methylphenol and 40.9% 4-methylphenol at dietary concentrations of 0, 300, 1,000, 3,000, 10,000, or 30,000 ppm for 28 d. The study authors calculated estimated daily doses of 0, 26, 90, 261, 877, and 2,600 mg/kg-d and 0, 27, 95, 268, 886, and 2,570 mg/kg-d for males and females, respectively. Animals were observed twice daily for signs of toxicity, food consumption was measured twice weekly, and weights were taken before dosing, weekly during dosing, and at study termination. Necropsy was performed on all animals, organs were weighed, and tissues were collected and preserved for histopathology.	All rats survived the study. Clinical signs of toxicity included thin appearance in high-dose rats by D 6, but not beyond D 7. Decreased body weight (M), body-weight gain (M and F), and food consumption (M and F) were observed at 30,000 ppm. Relative kidney weights were significantly higher at ≥10,000 ppm, compared with controls. Relative liver weights were significantly elevated at ≥3,000 ppm in males and ≥1,000 ppm in females. Histopathological lesions attributable to treatment included respiratory epithelium hyperplasia in the nasal cavity of males at ≥3,000 ppm and females at ≥1,000 ppm, hyperkeratosis and hyperplasia of esophagus of both sexes at ≥3,000 ppm, increased colloid content of thyroid gland follicular cells of both sexes at ≥3,000 ppm, forestomach epithelial hyperplasia in males at 5,000 ppm and females at ≥3,000 ppm, and bone marrow hypocellularity in both sexes at 5,000 ppm.	A NOAEL of 300 ppm and a LOAEL of 1,000 ppm are identified based on increased relative liver weight and nasal lesions in female rats.	NTP (1992b)
Short-term	CD-1 (Swiss) mice (eight/sex/group) were exposed to a 60:40 dietary mixture of 3- and 4-methylphenol at 0, 0.25, 0.5, 1.0, 2.0, or 3.0% in feed for 2 wk. The study authors reported average daily intakes of 386 and 465 mg/kg-d for males and females, respectively, in the 0.25% group and 4,014 and 4,265 mg/kg-d for males and females, respectively, in the 3.0% group. Based on the doses reported for the 0.25% group, respective estimated doses in the 0.5, 1.0, and 2.0% groups are 772, 1,544, and 3,088 mg/kg-d in males and 930, 1,860, and 3,720 mg/kg-d in females. Endpoints evaluated included clinical signs of toxicity, body weight, feed and water consumption 2 times/wk, and mortality data.	One male and one female from the high-dose group died (cause of death not determined). Clinical signs observed in the 3.0% group included lethargy, hunch back, squinted eyes, and rough coat. These were observed occasionally at 1.0 and 2.0%. Body weights were significantly decreased at 3.0%. Feed and water consumption was decreased at ≥1.0% during Wk 1 only.	A NOAEL of 2.0% and a LOAEL of 3.0% are identified based on decreased body weight and clinical signs of toxicity in male and female mice.	NTP (1992a)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term	$B6C3F_1$ mice (five/sex/dose) were exposed to a mixture of 58.5% 3-methylphenol and 40.9% 4-methylphenol at dietary concentrations of 0, 300, 1,000, 3,000, 10,000, or 30,000 ppm for 28 d. The study authors calculated estimated daily doses of 0, 50, 161, 471, 1,490, and 4,530 mg/kg-d and 0, 65, 200, 604, 1,880, and 4,730 mg/kg-d for males and females, respectively. Animals were observed twice daily for signs of toxicity, food consumption was measured twice weekly, and weights were taken before dosing, weekly during dosing, and at study termination. Necropsy was performed on all animals, organs were weighed, and tissues were collected and preserved for histopathology.	All mice survived the study. Clinical signs of toxicity were seen at 30,000 ppm in both sexes (alopecia, dehydration, hunched posture, hypothermia, lethargy, rough hair coat, thin appearance). Body weight, body-weight gain, and food consumption were significantly decreased at 30,000 ppm in both sexes; body-weight gain in males was also significantly decreased at ≥300 ppm. Relative liver weights were significantly elevated in males at ≥1,000 ppm and females at ≥3,000 ppm. Relative brain weight and relative testis weight were increased in high-dose males. Relative brain weight and relative kidney weight were increased in high-dose females, while absolute brain weight in high-dose females was decreased. Histopathological changes attributable to exposure in the high-dose group included epithelial hyperplasia in the nasal cavity, respiratory metaplasia of the olfactory epithelium, and minimal to mild bronchiolar epithelial hyperplasia. Uterine and ovarian atrophy were observed in one female at the high dose.	A NOAEL of 300 ppm and a LOAEL of 1,000 ppm are identified based on increased relative liver weight in male mice.	NTP (1992b)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Subchronic-duration	F344/N rats (20/sex/dose) were administered a mixture of 58.5% 3-methylphenol and 40.9% 4-methylphenol at dietary concentrations of 0, 1,880, 3,750, 7,500, 15,000, or 30,000 ppm for 13 wk. The study authors calculated estimated daily doses of 0, 123, 241, 486, 991, and 2,014 mg/kg-d and 0, 131, 254, 509, 1,024, and 2,050 mg/kg-d for males and females, respectively. Animals were observed twice daily for signs of toxicity; body weights were recorded before and after study and weekly during the course of study. Clinical pathology, hematologic analyses, and serum chemistry analyses were performed at the end of the study. Reproductive toxicity evaluation included sperm motility, sperm density, and vaginal cytology. Necropsy was performed on all animals, organs were weighed, and tissues were collected and preserved for histopathology.	All rats survived the study. Clinical signs of toxicity were observed at the highest dose (rough hair coat, urine staining, thin appearance). Body weights were decreased in males and females at doses ≥15,000 ppm. Body-weight gain was decreased at 30,000 ppm in males and at ≥15,000 ppm in females. Feed consumption was depressed in all high-dose animals during the first week of study. Hematological analyses were mostly insignificant, with some evidence of hemoconcentration observed early in the study in high-dose animals. Exposed males showed increased serum ALT and SDH at Day 5, but resolved later in the study. Total bile acids were decreased in both sexes at ≥15,000 ppm. Relative kidney weights were increased in males at doses ≥7,500 ppm and in females at 30,000 ppm. Relative liver weights were increased in both sexes at doses ≥7,500 ppm. Relative testis weights in males receiving doses ≥15,000 ppm were elevated. The estrous cycle length was significantly lengthened at ≥7,500 ppm. The incidence of nasal respiratory epithelial hyperplasia and glandular hyperplasia was increased at ≥3,750 ppm in both sexes, compared with controls.	A NOAEL of 1,880 ppm and a LOAEL of 3,750 ppm are identified based on nasal lesions in male and female rats.	NTP (1992b)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Subchronic-duration	$B6C3F_1$ mice (10/sex/dose) were administered a mixture of 58.5% 3-methylphenol and 40.9% 4-methylphenol at dietary concentrations of 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm for 13 wk. The study authors calculated estimated daily doses of 0, 96, 194, 402, 776, and 1,513 mg/kg-d, and 0, 116, 239, 472, 923, and 1,693 mg/kg-d for males and females, respectively. Animals were observed twice daily for signs of toxicity; body weights were recorded before and after study and weekly during the course of study. Clinical pathology, hematologic analyses, and serum chemistry analyses were performed at the end of the study. Reproductive toxicity evaluation included sperm motility, sperm density, and vaginal cytology. Necropsy was performed on all animals, organs were weighed, and tissues were collected and preserved for histopathology.	All mice survived to the end of the study. Clinical signs of toxicity included rough hair coat in high-dose females. Mean final body weights were decreased in high-dose males and females. Mean body-weight gain for high-dose males was significantly decreased compared to controls. Serum SDH levels were slightly increased in high-dose males, while high-dose females had elevated levels of 5'-nucleotidase. Absolute and relative liver weights were significantly increased in males at ≥5,000 ppm and relative liver weights were significantly increased in females at 10,000 ppm. Increased incidence of hyperplasia in nasal respiratory epithelium was seen at the highest dose in both sexes; however, findings were only statistically significant in males (2-tailed Fisher's exact test conducted for this review).	A NOAEL of 2,500 ppm and a LOAEL of 5,000 ppm are identified based on increased liver weights in male mice.	NTP (1992b)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Chronic-duration/ carcinogenicity	Male F344/N rats (50/dose) were administered a mixture of 60% 3-methylphenol and 40% 4-methylphenol at dietary concentrations of 0, 1,500, 5,000, or 15,000 ppm for 105 wk. The study authors calculated estimated daily doses of 0, 70, 230, and 720 mg/kg-d, respectively. All animals were examined twice daily for clinical signs of toxicity. Body weights were recorded at the beginning and end of the study, weekly for the first 13 wk, and then at 4-wk intervals. Necropsy was performed on all animals, organs were weighed, and tissues collected and preserved for histopathology.	Mortality occurred in all exposure groups, but survival rates were similar to controls. No clinical signs of toxicity were recorded. Mean body weights and body-weight gains were decreased at 15,000 ppm throughout the study when compared to controls. Feed consumption in the 15,000-ppm group was decreased during the first wk of study, but this resolved by the second wk. Non-neoplastic lesions attributed to treatment included hyperplasia of goblet cells and respiratory epithelium of the nose at all doses, hyperplasia of the renal transition epithelium and increased severity of nephropathy at 15,000 ppm, and increased liver eosinophilic foci at 15,000 ppm. The incidence of renal tube adenoma at 15,000 ppm (4/50, 8%) exceeded the historical incidence of 0−2%, but did not differ significantly from concurrent control incidence. No other tumors were attributable to 3-methylphenol treatment.	A LOAEL of 1,500 ppm is identified for nasal lesions. No NOAEL was identified. There was no clear evidence of carcinogenicity in male rats under the conditions of this study.	Sanders et al. (2009); NTP (2008)
Chronic-duration/ carcinogenicity	Female B6C3F$_1$ mice were administered a mixture of 60% 3-methylphenol and 40% 4-methylphenol at dietary concentrations of 0, 1,000, 3,000, or 10,000 ppm for 104−105 wk. The study authors calculated estimated daily doses of 0, 100, 300, and 1,040 mg/kg-d, respectively. All animals were examined twice daily for clinical signs of toxicity. Body weights were recorded at the beginning and end of the study, weekly for the first 13 wk, and then at 4-wk intervals. Necropsy was performed on all animals, organs were weighed, and tissues collected and preserved for histopathology.	Mortality occurred in all exposure groups, but survival rates were similar to controls. No clinical signs of toxicity were recorded. Mean body weights were decreased at doses ≥3,000 ppm. Feed consumption was decreased by 13% at 10,000 ppm. Non-neoplastic lesions attributed to treatment included increased bronchiolar hyperplasia in the lung and thyroid gland follicular degeneration at all doses, increased nasal respiratory epithelial hyperplasia at ≥3,000 ppm, and increased eosinophilic foci in the liver and forestomach squamous cell papilloma at 10,000 ppm.	A LOAEL of 1,000 ppm is identified based on lung and thyroid lesions. No NOAEL was identified. There was no clear evidence of carcinogenicity in female rats under the conditions of this study.	Sanders et al. (2009); NTP (2008)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Reproductive/ developmental	In a two-generation study with continuous and crossover breeding, CD-1 Swiss mice (20 breeding pairs/dose/generation; 40 control breeding pairs/generation) were exposed to a 60:40 dietary mixture of 3- and 4-methylphenol at 0, 0.25, 1.0, or 1.5% in feed. Based on reported dietary intakes, respective estimated daily doses were calculated to be 0, 355, 1,397, or 1,755 mg/kg-d in F0 males, 0, 368, 1,382, or 1,699 mg/kg-d in F0 females, 0, 439, 1,781, or 2,595 mg/kg-d in F1 males, and 0, 432, 1,672, or 2,606 mg/kg-d in F1 females. Endpoints assessed included clinical signs, parental body weight, parental food and water consumption, reproductive and developmental indices for both generations, sperm parameters, estrous cyclicity, reproductive organ weights and histology for both generations, and reproductive hormone levels.	F0: Parental body weight was decreased at 1.5%. The interval between litters was significantly increased at 1.5%. The number of live pups/litter and adjusted live pup weights (adjusted for average litter size) were significantly decreased at 1.5%. Significant organ-weight changes observed included decreased absolute epididymal weight at 1.5%, decreased absolute and relative seminal vesicle weight at 1.5%, increased absolute and relative liver weight at 1.5% in males and ≥0.25% in females, and increased relative kidney weight at 1.5% in males. No other changes were observed. F1: Clinical signs of toxicity observed primarily at 1.5% included lethargy, hunched back, rough coat, reduced size, and dehydration. F1 parental body weights were significantly decreased at ≥1%. There were no treatment-related changes in reproductive function of F1 mice. F2 litters has significantly decreased actual and adjusted live pup weights at 1.5%. Significant organ-weight changes observed included decreased absolute prostate weight at ≥1% and relative prostate weight at 1.5%, decreased absolute and relative seminal vesicle weight at ≥1%, decreased absolute testicular weight at ≥1%, decreased absolute ovary weight at ≥0.25%, increased absolute liver weight at ≥0.25% in females, increased relative liver weight at ≥1% in males and ≥0.25% in females, and increased relative kidney weight at 1.5% in males and ≥0.25% in females. No other changes were observed.	A NOAEL of 0.25% and a LOAEL of 1.0% are identified for decreased body weight and decreased reproductive organ weights in F1 parental animals.	NTP (1992a)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Dermal studies				
Initiation/ promotion tumor assay	Female Sutter mice (29 exposed, 12 control) were given a single dermal application of 0.3% DMBA in acetone (initiator) followed by twice weekly applications of 0 or 20% (v/v) 3-methylphenol in chrysene for 12 wk.	15 mice from the exposed group died. Of surviving mice, 7/14 developed skin papillomas compared with 0/12 benzene controls. No carcinomas were observed.	3-Methylphenol was a tumor promotor in this assay.	Boutwell and Bosch (1959)
Initiation/ promotion tumor assay	Mice (20/group) of unspecified strain and sex were given a single dermal application of 0.3% DMBA in acetone (initiator) followed by twice weekly applications of 0 or 5.7% 3-methylphenol in benzene for 20 wk.	Three exposed and two control mice died. Of the surviving mice, 4/17 exposed mice developed skin papillomas compared with 0/18 benzene controls. No carcinomas were observed.	3-Methylphenol was a weak tumor promotor in this assay.	Boutwell and Bosch (1959)

ALT = alanine aminotransferase; DMBA = 7,12-dimethylbenz-[a]anthracene; F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; SDH = sorbitol dehydrogenase.

Two dermal initiation-promotion studies were identified that evaluated the potential of 3-methylphenol to act as a tumor promotor following initiation with 7,12-dimethylbenz-[a]anthracene (DMBA) (see Table 4B for details). 3-Methylphenol was a tumor promotor at a concentration of 20% and a weak tumor promotor at a concentration of 5.7% (Boutwell and Bosch, 1959).

Reported acute toxicity values for 3-methylphenol include oral median lethal dose (LD_{50}) values of 242−2,020 mg/kg in rats, an inhalation median lethal concentration (LC_{50}) value of 58 mg/m^3 in rats, and dermal LD_{50} values of 1.80 mL/kg and 2,830 mg/kg in rabbits [reviewed by Andersen (2006)]. A 10% dilution of 3-methylphenol caused severe erythema and moderate edema when applied to the skin (graded 6/10); undiluted 3-methylphenol caused severe skin necrosis (Mellon Institute of Industrial Research, 1949). A 5% dilution of 3-methylphenol caused severe ocular damage in rabbits (graded 9/10); no ocular effects were observed at 1% (Mellon Institute of Industrial Research, 1949).

Metabolism/Toxicokinetic Studies

The absorption, distribution, metabolism, and elimination of methylphenols (in general) are summarized below based on reviews by Andersen (2006), OECD (2005), ATSDR (2008), and IPCS (1995). Limited data are available on 3-methylphenol specifically.

Methylphenols can be absorbed through the skin, respiratory tract, and digestive tract; however, little is known regarding the distribution of methylphenols after absorption. Human findings from accidental fatal overdoses report the presence of methylphenol in the brain and liver. In animals exposed via gavage, methylphenols are distributed rapidly to many organs and tissues. After absorption and distribution, methylphenols are metabolized in the liver. The predominant metabolic pathway is oxidation and conjugation with glucuronic acid and inorganic sulfate, although 3-methylphenol hydroxylation to 2,5- or 3,4-dihydroxytoluene occurs to a small extent. Methylphenols are excreted into the bile, and can undergo enterohepatic recirculation. In animals, methylphenols are rapidly eliminated, predominantly in the urine, as sulfate or glucuronide conjugates.

Mode-of-Action/Mechanistic Studies

The limited data available regarding the mechanistic pathways underlying the toxic actions of 3-methylphenol are summarized below based on reviews by Andersen (2006) and ATSDR (2008).

Clinical signs of neurotoxicity were described in several studies summarized above. The mechanism of neurotoxicity is unknown; however, methylphenols have been shown to alter neurotransmitter levels and enzyme activity in the brain. Additionally, methylphenols may change membrane fluidity in the brain via lipid peroxidation.

Toxicity in the liver appears to be mediated via metabolites, as toxicity in rat liver slices (measured via LDH leakage or intracellular potassium) is dependent upon an exogenous metabolic system. Additionally, of the methylphenol isomers, toxicity of 4-methylphenol is 5 to 10-fold higher than 2- or 3-methylphenol, and only 4-methylphenol depleted intracellular levels of glutathione (GSH). Isomeric differences are thought to be due to the formation of a reactive quinone metabolite during the metabolism of 4-methylphenol. Mitochondrial respiration in the liver has also been shown to be disrupted by methylphenols. However, the relevance of these

findings are unclear, as liver lesions have not been observed in animals following oral exposure to 3-methylphenol alone.

While 3-methylphenol has been shown to promote skin tumor formation in tumor-promotion assays, available data are inadequate to determine the underlying mechanism. Available genotoxicity data indicate that 3-methyphenol is not mutagenic, but may interact with DNA and cause clastogenic effects under certain circumstances (see "Genotoxicity" section and Table 4A above).

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer references values, respectively.

Table 5. Summary of Noncancer Reference Values for 3-Methylphenol (CASRN 108-39-4)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD (HED)	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Rat/M and F	Reduced body weight in males, clinical signs of neurotoxicity in both sexes	4×10^{-1}	NOAEL (HED)	12	30	Dietz and Mulligan (1988); TRL (1986)
Chronic p-RfD (mg/kg-d)	Oral RfD value of 5×10^{-2} mg/kg-day is available on IRIS						
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

F = female(s); HED = human equivalent dose; IRIS = Integrated Risk Information System; M = male(s); NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

Table 6. Summary of Cancer Reference Values for 3-Methylphenol (CASRN 108-39-4)

Toxicity Type (units)	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.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of a Subchronic Provisional Reference Dose (p-RfD)

The database of potentially relevant studies for derivation of oral reference values for 3-methylphenol includes 28-day studies in rats and mice sponsored by the NTP (1992b), 18- and

28-day studies in neonatal and young rats, respectively, and associated dose range-finding studies (Koizumi et al., 2003), a 13-week subchronic-duration study in rats (Dietz and Mulligan, 1988), a 13-week neurotoxicity study in rats (TRL, 1986), a two-generation reproductive study in rats (BushyRun, 1989), and two developmental studies in rats and rabbits and the companion dose range-finding study in rabbits (BushyRun, 1988; Hazleton Laboratories, 1988a; BushyRun, 1987a, b). The 13-week toxicity and neurotoxicity studies in rats by Dietz and Mulligan (1988) and TRL (1986), respectively, were selected as co-principal studies for derivation of the p-RfD. Critical effects were decreased body weight in male rats and clinical signs of neurotoxicity (e.g., tremors, myoclonus, labored respiration, and salivation) in male and female rats.

Justification of the Critical Effect

All potential 3-methylphenol-induced effects observed in the studies listed above were evaluated to determine the most sensitive response. The most sensitive effects included decreased body weight, increased relative liver weight, and clinical signs of neurotoxicity:

- A NOAEL of 50 mg/kg-day and a LOAEL of 150 mg/kg-day for decreased body weight in male rats exposed to 3-methylphenol via gavage for 13 weeks (Dietz and Mulligan, 1988)

- A NOAEL of 50 mg/kg-day and a LOAEL of 150 mg/kg-day for clinical signs of neurotoxicity in male rats exposed to 3-methylphenol via gavage for 13 weeks (TRL, 1986)

- A NOAEL of 66 mg/kg-day and a LOAEL of 210 mg/kg-day based on increased relative liver weight in female mice exposed to dietary 3-methylphenol for 28 days (NTP, 1992b)

Benchmark dose (BMD) modeling was performed on the male rat body weight and female mouse relative liver weight data sets (see Appendix C). Ten percent relative deviation benchmark dose lower confidence limit ($BMDL_{10}$) values of 106 and 178 mg/kg-day were derived for the body-weight data in male rats and relative liver-weight data in female mice, respectively (see Appendix Tables C-2 and C-4, respectively). Clinical signs of neurotoxicity data could not be modeled due to lack of quantitative reporting (TRL, 1986), so the NOAEL of 50 mg/kg-day is the point of departure (POD) for this endpoint. The neurotoxicity data from TRL (1986) provided the lowest candidate POD (NOAEL = 50 mg/kg-day).

Justification of the Principal Study

The unpublished studies by Dietz and Mulligan (1988) and TRL (1986) are selected as co-principal studies; these studies were also used as co-principal studies in the derivation of the chronic RfD by IRIS (U.S. EPA, 1988b). The studies have an adequate number of dose groups and dose spacing, sufficient group sizes, and comprehensive endpoint assessment. Data reported by Dietz and Mulligan (1988) have sufficient quantitation of results to describe dose-response relationships for the critical effects in rats associated with exposure to 3-methylphenol for 13 weeks; quantitative data were not provided in the available copy of the TRL (1986) report, however the textual summaries provided substantial information that facilitated identification of effect levels (e.g., NOAEL). Among the available candidate endpoints, neurotoxicity data from TRL (1986) provided the lowest candidate POD for deriving a subchronic p-RfD (NOAEL of 50 mg/kg-day).

Approach for Deriving the Subchronic p-RfD

The NOAEL of 50 mg/kg-day for clinical signs of toxicity in male and female rats is the selected POD for derivation of the subchronic p-RfD. In *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information, without a complete physiologically based toxicokinetic model. In lieu of chemical-specific models or data to inform the derivation of human equivalent oral exposures, EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite, but not for portal-of-entry effects or developmental endpoints.

A validated human physiologically based pharmacokinetic (PBPK) model for 3-methylphenol is not available for use in extrapolating doses from animals to humans. In addition, the selected POD of 50 mg/kg-day is not a portal-of-entry. Therefore, scaling by $BW^{3/4}$ is relevant for deriving human equivalent doses (HEDs) for this effect.

Following U.S. EPA (2011b) guidance, the POD for the 13-week study in rats is converted to an HED through the application of a dosimetric adjustment factor (DAF) derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where:

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a reference BW_a of 0.25 kg for rats and a reference BW_h of 70 kg for humans (U.S. EPA, 1988c), the resulting DAF is 0.24. Applying this DAF to the NOAEL identified in the 13-week rat study yields a NOAEL (HED) as follows:

$$\begin{aligned} \text{POD (HED)} &= \text{NOAEL (mg/kg-day)} \times \text{DAF} \\ &= 50 \text{ mg/kg-day} \times 0.24 \\ &= 12 \text{ mg/kg-day} \end{aligned}$$

$$\begin{aligned} \textbf{Subchronic p-RfD} &= \text{POD (HED)} \div UF_C \\ &= 12 \text{ mg/kg-day} \div 30 \\ &= 4 \times 10^{-1} \text{ mg/kg-day} \end{aligned}$$

Table 7 summarizes the uncertainty factors for the subchronic p-RfD for 3-methylphenol.

Table 7. Uncertainty Factors for the Subchronic p-RfD for 3-Methylphenol (CASRN 108-39-4)

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_H	10	A UF_H of 10 is applied to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 3-methylphenol in humans.
UF_D	1	A UF_D of 1 is applied because there is a relatively complete database, including short-term-duration studies in rats and mice sponsored by the NTP (1992b), a short-term-duration study in neonatal and young rats (Koizumi et al., 2003), a 13-wk subchronic-duration study in rats (Dietz and Mulligan, 1988), a 13-wk neurotoxicity study in rats (TRL, 1986), a two-generation reproductive study in rats (BushyRun, 1989), and developmental studies in rats and rabbits (BushyRun, 1988; Hazleton Laboratories, 1988a; BushyRun, 1987a, b). Although most of these studies are unpublished, they appear to be adequate and to rule out reproductive/developmental effects as potentially critical endpoints.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study was used.
UF_C	30	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

HED = human equivalent dose; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor.

The confidence in the subchronic p-RfD for 3-methylphenol is medium, as explained in Table 8 below.

Table 8. Confidence Descriptors for the Subchronic p-RfD for 3-Methylphenol (CASRN 108-39-4)

Confidence Categories	Designation	Discussion
Confidence in study	M	The confidence in the co-principal studies is medium. Dietz and Mulligan (1988) and TRL (1986) examined appropriate subchronic endpoints, included multiple effect levels, and both a NOAEL and LOAEL were identified. They were performed according to GLP standards and were used by IRIS (U.S. EPA, 1988b) to derive a chronic RfD. However, these studies are unpublished.
Confidence in database	M	Confidence in the database is medium. The database includes short-term-duration studies in 2 species (rats and mice), subchronic-duration studies (including evaluation of neurotoxicity) in 1 species (rats), a 2-generation study in rats, and developmental studies in 2 species (rats and rabbits). However, the majority of these studies are unpublished.
Confidence in subchronic p-RfD[a]	M	The overall confidence in the subchronic p-RfD for 3-methylphenol is medium.

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

GLP = good laboratory practice; IRIS = Integrated Risk Information System; LOAEL = lowest-observed-adverse-effect level; M = medium; NOAEL = no-observed-adverse-effect level; p-RfD = provisional reference dose.

Derivation of a Chronic Provisional Reference Dose (p-RfD)

A chronic p-RfD value is not derived because an oral RfD value is available on EPA's IRIS database.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Human and animal data are inadequate to derive subchronic or chronic provisional reference concentrations (p-RfCs) for 3-methylphenol because no quantitative studies examining the effects of subchronic or chronic inhalation exposure to 3-methylphenol have been identified.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

A cancer weight-of-evidence (WOE) descriptor is not determined because a cancer WOE descriptor is available on EPA's IRIS database.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of data on the carcinogenicity of 3-methylphenol alone following oral or inhalation exposure precludes the derivation of quantitative estimates for provisional oral slope factor (p-OSF) or provisional inhalation unit risk (p-IUR) exposure.

APPENDIX A. SCREENING PROVISIONAL VALUES

No provisional screening values for 3-methylphenol are derived.

APPENDIX B. DATA TABLES

Table B-1. Survival and Body Weights of Male and Female F344/N Rats Following Dietary Exposure to 3-Methylphenol (CASRN 108-39-4) for 28 Days[a]

Parameter	Exposure Group, ppm (mg/kg-d)[b]					
Male	**0**	**300 (25)**	**1,000 (85)**	**3,000 (252)**	**10,000 (870)**	**30,000 (2,470)**
Survival	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)
Terminal body weight (g)[c]	258 ± 7	262 ± 5 (+2%)	256 ± 6 (−1%)	264 ± 6 (+2%)	257 ± 5 (0%)	222 ± 12* (−14%)
Body-weight gain (g)[c]	141 ± 2	137 ± 2 (−3%)	135 ± 3 (−4%)	142 ± 3 (+1%)	136 ± 2 (−4%)	97 ± 3** (−31%)
Female	**0**	**300 (25)**	**1,000 (82)**	**3,000 (252)**	**10,000 (862)**	**30,000 (2,310)**
Survival	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)
Terminal body weight (g)[c]	174 ± 3	160 ± 6 (−8%)	167 ± 2 (−4%)	166 ± 4 (−5%)	165 ± 3 (−5%)	146 ± 2** (−16%)
Body-weight gain (g)[c]	68 ± 3	58 ± 4 (−15%)	65 ± 4 (−4%)	62 ± 2 (−9%)	62 ± 3 (−9%)	45 ± 3** (−34%)

[a]NTP (1992b).
[b]Daily doses in mg/kg-day were calculated by the study authors based on measured food consumption and body weights.
[c]Data reported as mean ± SEM (percent change compared with control); % change control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p \leq 0.01$), as reported by the study authors.

SEM = standard error of the mean.

Table B-2. Selected Organ Weights in Male and Female F344/N Rats Following Dietary Exposure to 3-Methylphenol (CASRN 108-39-4) for 28 Days[a]

Parameter[b]	Exposure Group, ppm (mg/kg-d)[c]					
Male	**0**	**300 (25)**	**1,000 (85)**	**3,000 (252)**	**10,000 (870)**	**30,000 (2,470)**
Brain:						
Absolute (g)	1.83 ± 0.02	1.81 ± 0.03 (−1%)	1.82 ± 0.03 (−1%)	1.86 ± 0.03 (+2%)	1.83 ± 0.02 (0%)	1.82 ± 0.04 (−1%)
Relative (mg/g body weight)	7.13 ± 0.23	6.92 ± 0.13 (−3%)	7.12 ± 0.15 (0%)	7.07 ± 0.08 (−1%)	7.14 ± 0.12 (0%)	8.27 ± 0.26* (+16%)
Right kidney:						
Absolute (g)	1.12 ± 0.03	1.09 ± 0.03 (−3%)	1.11 ± 0.05 (−1%)	1.12 ± 0.03 (0%)	1.19 ± 0.03 (+6%)	1.11 ± 0.05 (−1%)
Relative (mg/g body weight)	4.36 ± 0.09	4.14 ± 0.08 (−5%)	4.31 ± 0.13 (−1%)	4.26 ± 0.04 (−2%)	4.64 ± 0.10 (+6%)	5.04 ± 0.10* (+16%)
Liver:						
Absolute (g)	11.64 ± 0.53	11.66 ± 0.40 (0%)	11.87 ± 0.33 (+2%)	12.55 ± 0.40 (+8%)	13.54 ± 0.36** (+16%)	13.04 ± 0.79 (+12%)
Relative (mg/g body weight)	45.0 ± 1.0	44.5 ± 1.0 (−1%)	46.3 ± 0.5 (+3%)	47.5 ± 0.8 (+6%)	52.8 ± 0.8** (+17%)	58.8 ± 1.1** (+31%)
Female	**0**	**300 (25)**	**1,000 (82)**	**3,000 (252)**	**10,000 (862)**	**30,000 (2,310)**
Brain:						
Absolute (g)	1.80 ± 0.01	1.68 ± 0.05* (−7%)	1.75 ± 0.03 (−3%)	1.74 ± 0.04 (−3%)	1.73 ± 0.01 (−4%)	1.70 ± 0.03* (−6%)
Relative (mg/g body weight)	10.3 ± 0.1	10.5 ± 0.2 (+2%)	10.5 ± 0.1 (+2%)	10.5 ± 0.2 (+2%)	10.5 ± 0.2 (+2%)	11.6 ± 0.2** (+13%)
Right kidney:						
Absolute (g)	0.75 ± 0.02	0.67 ± 0.02* (−11%)	0.71 ± 0.01 (−5%)	0.71 ± 0.04 (−5%)	0.71 ± 0.02 (−5%)	0.73 ± 0.02 (−3%)
Relative (mg/g body weight)	4.34 ± 0.08	4.20 ± 0.07 (−5%)	4.25 ± 0.06 (−4%)	4.27 ± 0.14 (−4%)	4.31 ± 0.03 (−3%)	5.00 ± 0.08* (+13%)
Liver:						
Absolute (g)	7.11 ± 0.23	6.29 ± 0.24 (−12%)	6.90 ± 0.11 (−3%)	7.02 ± 0.17 (−1%)	7.55 ± 0.23 (+6%)	7.16 ± 0.09 (+1%)
Relative (mg/g body weight)	40.9 ± 1.0	39.3 ± 0.4 (−4%)	41.5 ± 0.9 (+1%)	42.3 ± 0.9 (+3%)	45.7 ± 1.0* (+12%)	49.0 ± 0.6** (+20%)

[a]NTP (1992b).
[b]Data reported as mean ± SEM (percent change compared with control); % change control = [(treatment mean − control mean) ÷ control mean] × 100.
[c]Daily doses in mg/kg-day were calculated by the study authors based on measured food consumption and body weights.
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p \leq 0.01$), as reported by the study authors.

SEM = standard error of the mean.

Table B-3. Selected Histopathology in Female F344/N Rats and B6C3F$_1$ Mice Following Dietary Exposure to 3-Methylphenol (CASRN 108-39-4) for 28 Days[a]

Parameter[b]	Exposure Group, ppm (mg/kg-d)[c]					
Rat	**0**	**300 (25)**	**1,000 (82)**	**3,000 (252)**	**10,000 (862)**	**30,000 (2,310)**
Uterine atrophy Severity[d]	0/5 (0%)	NE	NE	NE	0/5 (0%)	4/5 (80%) 1.5
Mouse	**0**	**300 (66)**	**1,000 (210)**	**3,000 (651)**	**10,000 (2,080)**	**30,000 (4,940)**
Mammary gland atrophy Severity[d]	0/5 (0%)	NE	NE	NE	0/4 (0%)	3/5 (60%) 2.7
Ovarian atrophy Severity[d]	0/5 (0%)	NE	NE	NE	0/5 (0%)	3/5 (60%) 2.0
Uterine atrophy Severity[d]	0/5 (0%)	NE	NE	NE	0/5 (0%)	3/5 (60%) 3.0

[a]NTP (1992b).
[b]Results are expressed as the number of animals with lesions/number of animals examined (%).
[c]Daily doses in mg/kg-day were calculated by the study authors based on measured food consumption and body weights.
[d]Average severity score based on scale of 1−4: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

NE = not examined.

Table B-4. Survival and Mean Body Weights of Male and Female B6C3F$_1$ Mice Following Dietary Exposure to 3-Methylphenol (CASRN 108-39-4) for 28 Days[a]

Parameter	Exposure Group, ppm (mg/kg-d)[b]					
Male	**0**	**300 (53)**	**1,000 (193)**	**3,000 (521)**	**10,000 (1,730)**	**30,000 (4,710)**
Survival	4/5 (80%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	3/5 (60%)
Terminal body weight (g)[c]	25.4 ± 0.7	25.5 ± 0.8 (0%)	25.0 ± 0.4 (−2%)	25.7 ± 0.2 (+1%)	23.5 ± 0.7 (−7%)	20.4 ± 1.3** (−20%)
Body-weight gain (g)[c]	3.8 ± 0.4	3.8 ± 0.4 (0%)	2.6 ± 0.5 (−32%)	3.6 ± 0.3 (−5%)	2.9 ± 0.7 (−24%)	−2.8 ± 0.6** (−174%)
Female	**0**	**300 (66)**	**1,000 (210)**	**3,000 (651)**	**10,000 (2,080)**	**30,000 (4,940)**
Survival	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	4/5 (80%)	3/5 (60%)
Terminal body weight (g)[c]	22.6 ± 1.1	22.9 ± 0.9 (+1%)	23.9 ± 0.6 (+6%)	23.0 ± 0.7 (+2%)	21.9 ± 0.8 (−3%)	17.6 ± 1.2* (−22%)
Body-weight gain (g)[c]	3.9 ± 0.2	4.4 ± 0.4 (+13%)	4.9 ± 0.5 (+25%)	4.3 ± 0.4 (+10%)	3.2 ± 0.4 (−18%)	−1.2 ± 0.9 (−131%)

[a]NTP (1992b).
[b]Daily doses in mg/kg-day were calculated by the study authors based on measured food consumption and body weights.
[c]Data reported as mean ± SEM (percent change compared with control) for mice surviving to 28 days; % change control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p \leq 0.01$), as reported by the study authors.

SEM = standard error of the mean.

Table B-5. Selected Organ Weights in Male and Female B6C3F$_1$ Mice Following Dietary Exposure to 3-Methylphenol (CASRN 108-39-4) for 28 Days[a]

Parameter[b]	Exposure Group, ppm (mg/kg-d)[c]					
Male	**0**	**300 (53)**	**1,000 (193)**	**3,000 (521)**	**10,000 (1,730)**	**30,000 (4,710)**
Brain:						
Absolute (g)	0.455 ± 0.007	0.459 ± 0.006 (+1%)	0.465 ± 0.005 (+2%)	0.463 ± 0.005 (+2%)	0.442 ± 0.006 (−3%)	0.435 ± 0.008 (−4%)
Relative (mg/g body weight)	17.9 ± 0.5	18.0 ± 0.4 (+1%)	18.6 ± 0.2 (+4%)	18.0 ± 0.3 (+1%)	18.9 ± 0.4 (+6%)	21.5 ± 1.3** (+20%)
Right kidney:						
Absolute (g)	0.250 ± 0.009	0.261 ± 0.015 (+4%)	0.254 ± 0.008 (+2%)	0.274 ± 0.001 (+10%)	0.242 ± 0.009 (−3%)	0.194 ± 0.022 (−22%)
Relative (mg/g body weight)	9.8 ± 0.1	10.2 ± 0.4 (+4%)	10.2 ± 0.2 (+4%)	10.7 ± 0.1* (+9%)	10.3 ± 0.1 (+5%)	9.5 ± 0.7 (−3%)
Liver:						
Absolute (g)	1.28 ± 0.05	1.27 ± 0.06 (−1%)	1.27 ± 0.02 (−1%)	1.36 ± 0.02 (+6%)	1.39 ± 0.08 (+9%)	1.27 ± 0.14 (−1%)
Relative (mg/g body weight)	50.1 ± 0.9	49.6 ± 1.2 (−1%)	50.7 ± 0.5 (+1%)	53.0 ± 0.9 (+6%)*	58.8 ± 1.6** (+17%)	61.7 ± 3.2** (+23%)
Female	**0**	**300 (66)**	**1,000 (210)**	**3,000 (651)**	**10,000 (2,080)**	**30,000 (4,940)**
Brain:						
Absolute (g)	0.460 ± 0.010	0.463 ± 0.011 (+1%)	0.468 ± 0.004 (+2%)	0.471 ± 0.004 (+2%)	0.466 ± 0.006 (+1%)	0.432 ± 0.004 (−6%)
Relative (mg/g body weight)	20.6 ± 0.9	20.3 ± 0.4 (−1%)	19.7 ± 0.4 (−4%)	20.6 ± 0.6 (0%)	21.3 ± 0.8 (+3%)	24.8 ± 1.6 (+20%)
Right kidney:						
Absolute (g)	0.189 ± 0.010	0.196 ± 0.012 (+4%)	0.186 ± 0.006 (−2%)	0.201 ± 0.007 (+6%)	0.193 ± 0.007 (+2%)	0.164 ± 0.013 (−13%)
Relative (mg/g body weight)	8.4 ± 0.2	8.6 ± 0.2 (+2%)	7.8 ± 0.1 (−7%)	8.7 ± 0.1 (+4%)	8.8 ± 0.1 (+5%)	9.3 ± 0.2* (+11%)
Liver:						
Absolute (g)	1.158 ± 0.058	1.216 ± 0.041 (+5%)	1.338 ± 0.053 (+16%)	1.315 ± 0.032 (+14%)	1.333 ± 0.063 (+15%)	0.985 ± 0.064 (−15%)
Relative (mg/g body weight)	51.3 ± 0.4	53.2 ± 0.7* (+4%)	56.0 ± 1.1** (+9%)	57.3 ± 1.1** (+12%)	60.8 ± 1.1** (+19%)	56.4 ± 4.3** (+10%)

[a]NTP (1992b).
[b]Data reported as mean ± SEM (percent change compared with control) for mice surviving until 28 days (n = 3−5/sex/group; see Table B-4); % change control = [(treatment mean − control mean) ÷ control mean] × 100.
[c]Daily doses in mg/kg-day were calculated by the study authors based on measured food consumption and body weights.
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p \leq 0.01$), as reported by the study authors.

SEM = standard error of the mean.

Table B-6. Clinical Signs, Body Weight, and Selected Organ Weights of Neonatal S-D Rats Following Exposure to 3-Methylphenol (CASRN 108-39-4) via Gavage from PNDs 4–21[a]

Parameter	Exposure Group, mg/kg-d			
Male	**0**	**30**	**100**	**300**
Clinical signs of toxicity[b]				
Deep respiration	NR	0/12 (0%)	0/12 (0%)	5/12 (42%)
Increase in motor activity	NR	0/12 (0%)	0/12 (0%)	12/12 (100%)
Hypersensitivity on handling	NR	0/12 (0%)	1/12 (8%)	7/12 (58%)
Tremors with contact stimulus	NR	0/12 (0%)	3/12 (25%)	12/12 (100%)
Body weight at PND 22[c] (g)	53.1 ± 3.3	52.7 ± 3.5 (−1%)	51.4 ± 3.5 (−3%)	46.7 ± 4.3* (−12%)
Brain weight at PND 22[c]				
Absolute (g)	1.55 ± 0.04	1.58 ± 0.06 (+2%)	1.51 ± 0.06 (−3%)	1.47 ± 0.02* (−5%)
Relative (mg/100 g body weight)	2.93 ± 0.18	3.00 ± 0.11 (+2%)	2.94 ± 0.13 (0%)	3.16 ± 0.28 (+8%)
Liver weight at PND 22[c]				
Absolute (g)	1.74 ± 0.15	1.71 ± 0.13 (−2%)	1.75 ± 0.24 (+1%)	1.75 ± 0.20 (+1%)
Relative (mg/100 g body weight)	3.27 ± 0.12	3.24 ± 0.14 (−1%)	3.39 ± 0.25 (+4%)	3.74 ± 0.13** (+14%)
Female	**0**	**30**	**100**	**300**
Clinical signs of toxicity[b]				
Deep respiration	NR	0/12 (0%)	0/12 (0%)	3/12 (25%)
Increase in motor activity	NR	0/12 (0%)	0/12 (0%)	12/12 (100%)
Hypersensitivity on handling	NR	0/12 (0%)	0/12 (0%)	10/12 (83%)
Tremors with contact stimulus	NR	0/12 (0%)	0/12 (0%)	12/12 (100%)
Body weight at PND 22[c] (g)	49.4 ± 3.8	50.5 ± 4.1 (+2%)	51.6 ± 3.3 (+4%)	45.5 ± 1.4 (−8%)
Brain weight at PND 22[c]				
Absolute (g)	1.52 ± 0.05	1.48 ± 0.06 (−3%	1.48 ± 0.05 (−3%)	1.42 ± 0.05* (−7%)
Relative (mg/100 g body weight)	3.09 ± 0.27	2.94 ± 0.27 (−5%)	2.88 ± 0.13 (−7%)	3.13 ± 0.10 (+1%)
Liver weight at PND 22[c]				
Absolute (g)	1.59 ± 0.18	1.59 ± 0.13 (0%)	1.72 ± 0.08 (+8%)	1.61 ± 0.05 (+1%)
Relative (mg/100 g body weight)	3.21 ± 0.13	3.16 ± 0.04 (−2%)	3.34 ± 0.11 (+4%)	3.54 ± 0.12** (+10%)

[a]Koizumi et al. (2003).
[b]Results are expressed as the number of animals showing clinical signs/number of animals examined (%).
[c]Data reported as mean ± SD (percent change compared with control) for the six neonates sacrificed 24 hours after final dose; % change control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.

NR = not reported; PND = postnatal day; SD = standard deviation; S-D = Sprague-Dawley.

Table B-7. Selected Blood Chemistry Values of Neonatal S-D Rats on PND 22 Following Exposure to 3-Methylphenol (CASRN 108-39-4) via Gavage from PNDs 4–21[a]

Parameter[b]	Exposure Group, mg/kg-d			
Male	**0**	**30**	**100**	**300**
AST (IU/L)	127 ± 13	121 ± 7 (−5%)	121 ± 11 (−5%)	132 ± 22 (+4%)
GGT (IU/L)	0.84 ± 0.24	0.90 ± 0.15 (+7%)	1.07 ± 0.11 (+27%)	1.19 ± 0.15* (+42%)
Total cholesterol (mg/dL)	74 ± 11	78 ± 9 (+5%)	81 ± 7 (+9%)	85 ± 9 (+15%)
Total bilirubin (mg/dL)	0.40 ± 0.03	0.41 ± 0.04 (+2%)	0.41 ± 0.03 (+2%)	0.47 ± 0.02** (+18%)
BUN (mg/dL)	13.5 ± 1.8	11.8 ± 2.1 (−13%)	13.0 ± 2.1 (−4%)	17.9 ± 3.6* (+33%)
Female	**0**	**30**	**100**	**300**
AST (IU/L)	122 ± 15	119 ± 12 (−2%)	131 ± 9 (+7%)	116 ± 10 (−5%)
GGT (IU/L)	0.93 ± 0.21	0.85 ± 0.10 (−9%)	0.98 ± 0.26 (+5%)	1.20 ± 0.14 (+29%)
Total cholesterol (mg/dL)	77 ± 11	77 ± 10 (0%)	75 ± 8 (−3%)	78 ± 12 (+1%)
Total bilirubin (mg/dL)	0.41 ± 0.04	0.40 ± 0.03 (−2%)	0.40 ± 0.02 (−2%)	0.45 ± 0.03 (+10%)
BUN (mg/dL)	13.5 ± 2.3	13.5 ± 2.5 (0%)	13.2 ± 2.3 (−2%)	14.2 ± 2.8 (+5%)

[a]Koizumi et al. (2003).
[b]Data reported as mean ± SD (percent change compared with control) for the six neonates sacrificed 24 hours after final dose; % change control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.

AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = γ-glutamyl transferase; IU = International Unit; PND = postnatal day; SD = standard deviation; S-D = Sprague-Dawley.

Table B-8. Selected Body and Organ Weights of Young S-D Rats Following Exposure to 3-Methylphenol (CASRN 108-39-4) via Gavage from PNWs 5–9[a]

Parameter	Exposure Group, mg/kg-d			
Male	**0**	**100**	**300**	**1,000**
Terminal body weight (g)	325 ± 23.5	345.6 ± 23.5 (+6%)	335.9 ± 16.7 (+3%)	298.3 ± 31.8 (−8%)
Brain weight: Absolute (g) Relative (mg/100 g body weight)	 2.04 ± 0.06 0.63 ± 0.05	 2.11 ± 0.09 (+3%) 0.61 ± 0.03 (−3%)	 2.03 ± 0.08 (0%) 0.60 ± 0.02 (−5%)	 2.05 ± 0.06 (0%) 0.69 ± 0.06* (+10%)
Liver weight: Absolute (g) Relative (mg/100 g body weight)	 10.55 ± 1.30 3.24 ± 0.22	 11.28 ± 1.08 (+7%) 3.26 ± 0.19 (+1%)	 11.29 ± 0.68 (+7%) 3.36 ± 0.11 (+4%)	 10.94 ± 2.01 (+4%) 3.65 ± 0.34** (+13%)
Kidney weight: Absolute (g) Relative (mg/100 g body weight)	 2.65 ±0.24 0.82 ± 0.04	 2.82 ± 0.24 (+6%) 0.82 ± 0.03 (0%)	 2.78 ± 0.19 (+5%) 0.83 ± 0.06 (+1%)	 2.61 ±0.23 (−2%) 0.88 ± 0.05 (+7%)
Female	**0**	**100**	**300**	**1,000**
Terminal body weight (g)	210.1 ± 15.4	207.6 ± 13.0 (−1%)	197.3 ± 19.3 (−6%)	186.4 ± 17.4* (−11%)
Brain weight: Absolute (g) Relative (mg/100 g body weight)	 1.96 ± 0.06 0.93 ± 0.06	 1.90 ± 0.07 (−3%) 0.92 ± 0.05 (−1%)	 1.89 ± 0.07 (−4%) 0.96 ± 0.08 (+3%)	 1.88 ± 0.06 (−4%) 1.01 ± 0.09 (+9%)
Liver weight: Absolute (g) Relative (mg/100 g body weight)	 6.39 ± 0.68 3.04 ± 0.17	 6.59 ± 0.56 (+3%) 3.17 ± 0.08 (+4%)	 6.60 ± 0.67 (+3%) 3.35 ± 0.13** (+10%)	 6.51 ± 0.45 (+2%) 3.50 ± 0.20** (+15%)
Kidney weight: Absolute (g) Relative (mg/100 g body weight)	 1.66 ± 0.18 0.79 ± 0.06	 1.73 ± 0.11 (+4%) 0.84 ± 0.05 (+6%)	 1.65 ± 0.17 (−1%) 0.84 ± 0.06 (+6%)	 1.72 ± 0.14 (+4%) 0.92 ± 0.03** (+16%)

[a]Koizumi et al. (2003).
[b]Data reported as mean ± SD (percent change compared with control) for seven rats/sex/group; % change control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.

PNW = postnatal week; SD = standard deviation; S-D = Sprague-Dawley.

Table B-9. Selected Blood Chemistry Values of Young S-D Rats Following Exposure to 3-Methylphenol (CASRN 108-39-4) via Gavage from PNWs 5–9[a]

Parameter[b]	Exposure Group, mg/kg-d			
Male	**0**	**100**	**300**	**1,000**
AST (IU/L)	68.6 ± 4.8	65.4 ± 5.4 (−5%)	62.7 ± 3.2 (−9%)	59.4 ± 5.4** (−13%)
GGT (IU/L)	0.17 ± 0.24	0.21 ± 0.13 (+24%)	0.60 ± 1.15 (+253%)	0.36 ± 0.23 (+112%)
Total cholesterol (mg/dL)	52.7 ± 15.1	58.1 ± 11.8 (+10%)	58.3 ± 5.8 (+11%)	69.0 ± 9.4* (+31%)
Total bilirubin (mg/dL)	0.056 ± 0.005	0.049 ± 0.007 (−13%)	0.054 ± 0.010 (−4%)	0.050 ± 0.008 (−11%)
BUN (mg/dL)	13.89 ± 1.46	14.10 ± 0.85 (+2%)	14.56 ± 1.17 (+5%)	16.23 ± 2.14* (17%)
Female	**0**	**100**	**300**	**1,000**
AST (IU/L)	57.1 ± 4.3	65.9 ± 3.6 (+15%)	62.0 ± 5.7 (+9%)	59.1 ± 3.1 (+4%)
GGT (IU/L)	0.83 ± 0.20	0.90 ± 0.16 (+8%)	1.00 ± 0.29 (+20%)	1.06 ± 0.10 (+28%)
Total cholesterol (mg/dL)	63.4 ± 14.0	58.7 ± 10.6 (−7%)	61.4 ± 10.3 (−3%)	78.7 ± 13.7 (24%)
Total bilirubin (mg/dL)	0.053 ± 0.011	0.056 ± 0.011 (+6%)	0.043 ± 0.008 (−19%)	0.054 ± 0.008 (+2%)
BUN (mg/dL)	17.71 ± 1.96	16.63 ± 1.11 (−6%)	17.30 ± 2.14 (−2%)	18.03 ± 2.00 (+2%)

[a]Koizumi et al. (2003).
[b]Data reported as mean ± SD (percent change compared with control) for seven rats/sex/group; % change control = [(treatment mean − control mean)/control mean] × 100.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.

AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = γ-glutamyl transferase; IU = International Unit; PNW = postnatal week; SD = standard deviation; S-D = Sprague-Dawley.

Table B-10. Clinical Signs of Toxicity and Body Weights of Male and Female S-D Rats Following Exposure to 3-Methylphenol (CASRN 108-39-4) via Gavage for 13 Weeks[a]

Parameter[b]	Exposure Group, mg/kg-d[d]			
	0	50	150	450
Male				
Clinical signs of toxicity[b]	No signs observed at any time	No signs observed at any time	No signs observed at any time	
Lethargy:				
Wk 2				5/29 (17%)
Wk 12				8/19 (42%)
Wk 13				9/19 (47%)
Tremors:				
Wk 12				4/19 (21%)
Wk 13				4/19 (21%)
Body weight (g)[c]				
Wk 1	220 ± 12	217 ± 14 (−1%)	220 ± 10 (0%)	215 ± 14 (−2%)
Wk 7	468 ± 38	460 ± 33 (−2%)	439 ± 30* (−6%)	423 ± 39* (−10%)
Wk 14	580 ± 57	578 ± 36 (0%)	529 ± 47* (−9%)	502 ± 51* (−13%)
Female				
Clinical signs of toxicity[b]	No signs observed at any time	No signs observed at any time	No signs observed at any time	
Lethargy:				
Wk 1				9/30 (30%)
Wk 2				9/30 (30%)
Wk 12				7/20 (35%)
Wk 13				7/20 (35%)
Tremors:				
Wk 1				2/30 (7%)
Wk 2				2/30 (7%)
Wk 12				5/20 (25%)
Wk 13				2/20 (10%)
Hunched posture:				
Wk 2				30/30 (100%)
Body weight (g)[c]				
Wk 1	146 ± 11	151 ± 10 (+3%)	149 ± 9 (+2%)	146 ± 10 (0%)
Wk 7	251 ± 16	250 ± 18 (0%)	249 ± 16 (−1%)	245 ± 23 (−2%)
Wk 14	291 ± 19	287 ± 22 (−1%)	287 ± 26 (−1%)	271 ± 39 (−7%)

[a]Dietz and Mulligan (1988).
[b]Data reported as the number of animals showing clinical sign/number of animals observed (% incidence).
[c]Data reported as mean ± SD (percent change compared with control) for the 29−30/group at Week 1 and 19−20/group at Weeks 7 and 14; % change control = [(treatment mean − control mean) ÷ control mean] × 100.
[d]No clinical signs were observed in rats treated at the mid- and low-dose groups (50 and 150 mg/kg-day).
*Statistically significantly different from control ($p \leq 0.05$), as reported by study authors.

SD = standard deviation; S-D = Sprague-Dawley.

Table B-11. Survival and Body Weights of F0 and F1 Parental S-D Rats Following Exposure to 3-Methylphenol (CASRN 108-39-4) via Gavage for 13−17 Weeks in a 2-Generation Reproductive Study[a]

	Exposure Group, mg/kg-d (ADD male/female)			
F0 parental rats	**0**	**30 (23/25)**	**175 (137/149)**	**450 (350/380)**
Survival[b]				
Males	25/25 (100%)	25/25 (100%)	25/25 (100%)	18/25** (72%)
Females	25/25 (100%)	25/25 (100%)	24/25 (95%)	18/25** (72%)
Body weight (g)[c]				
Males:				
Wk 13	550.2 ± 39.65	547.8 ± 52.41 (0%)	532.9 ± 39.48 (−3%)	469.6 ± 38.01** (−15%)
Females:				
Wk 10 (mating)	269.5 ± 19.55	269.5 ± 18.89 (0%)	262.0 ± 20.55(−3%)	253.0 ± 15.16** (−6%)
Wk 13 (GD 20)	388.61 ± 29.600	386.05 ±33.698 (−1%)	382.54 ± 28.426 (−2%)	363.03 ± 35.922 (−7%)
Wk 16 (PND 21)	311.45 ± 20.199	316.81 ± 19.208 (+2%)	307.85 ± 13.889 (−1%)	296.67 ± 19.072* (−5%)
	Exposure group, mg/kg-d (ADD male/female)			
F1 parental rats	**0**	**30 (23/27)**	**175 (136/155)**	**450 (349/400)**
Survival[b]				
Males	25/25 (100%)	25/25 (100%)	25/25 (100%)	22/25 (88%)
Females	24/25 (95%)	23/25 (92%)	24/25 (95%)	15/25** (60%)
Body weight (g)[c]				
Males:				
Wk 0	173.6 ± 15.82	157.3 ± 18.69** (−9%)	157.5 ± 26.22** (−9%)	151.0 ± 21.12** (−13%)
Wk 14	557.9 ± 55.74	518.0 ± 55.54* (−7%)	526.1 ± 47.88* (−6%)	472.9 ± 58.79** (−15%)
Females:				
Wk 0	140.9 ± 11.32	132.2 ± 14.82* (−6%)	132.9 ± 17.72* (−6%)	126.2 ± 11.62** (−10%)
Wk 11 (mating)	281.1 ± 31.14	265.0 ± 28.84* (−6%)	270.7 ± 25.80 (−4%)	257.4 ± 27.21** (−8%)
Wk 14 (GD 20)	399.01 ± 26.600	382.91 ± 35.953 (−4%)	383.55 ± 31.948 (−4%)	365.14 ± 42.433* (−8%)
Wk 17 (PND 21)	321.32 ± 16.111	311.61 ± 26.517 (−3%)	308.44 ± 20.005 (−4%)	300.58 ± 23.560 (−6%)

[a]BushyRun (1989).

[b]Data reported as number of animals alive at scheduled sacrifice/total number of animals (%); F0 and F1 parental males were sacrificed at Weeks 13 and 14, respectively. F0 and F1 parental females were sacrificed at Weeks 16 and 17, respectively.

[c]Data reported as mean ± SD (percent change compared with control) for 15−25/sex/group/generation; % change control = [(treatment mean − control mean) ÷ control mean] × 100. Data from females with no live pups were not included in the mean for Week 17.

*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.

**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.

GD = gestation day; PND = postnatal day; SD = standard deviation; S-D = Sprague-Dawley.

Table B-12. Clinical Signs of Toxicity in F0 Parental S-D Rats Following Exposure to 3-Methylphenol (CASRN 108-39-4) via Gavage for 13−17 Weeks in a 2-Generation Reproductive Study[a]

Parameter[b]	Exposure Group, mg/kg-d (ADD male/female)			
	0	30 (23/25)	175 (137/149)	450 (350/380)
Males:				
Hypoactivity	0/25 (0%)	0/25 (0%)	0/25 (0%)	16/25** (64%)
Ataxia	0/25 (0%)	0/25 (0%)	0/25 (0%)	13/25** (52%)
Twitch	0/25 (0%)	0/25 (0%)	0/25 (0%)	21/25** (84%)
Tremor	0/25 (0%)	0/25 (0%)	0/25 (0%)	11/25** (44%)
Prostration	0/25 (0%)	0/25 (0%)	0/25 (0%)	9/25** (36%)
Unkempt	0/25 (0%)	0/25 (0%)	0/25 (0%)	10/25** (40%)
Urine stains	0/25 (0%)	0/25 (0%)	0/25 (0%)	10/25** (40%)
Audible respiration	0/25 (0%)	0/25 (0%)	1/25 (4%)	13/25** (52%)
Perinasal encrustation	1/25 (4%)	2/25 (8%)	1/25 (4%)	9/25** (36%)
Perioral wetness	0/25 (0%)	1/25 (4%)	2/25 (8%)	23/25** (92%)
Red perioral wetness	0/25 (0%)	0/25 (0%)	0/25 (0%)	6/25* (24%)
Females:				
Hypoactivity	0/25 (0%)	0/25 (0%)	1/25 (4%)	20/25** (80%)
Ataxia	0/25 (0%)	0/25 (0%)	0/25 (0%)	15/25** (60%)
Twitch	0/25 (0%)	0/25 (0%)	0/25 (0%)	20/25** (80%)
Tremor	0/25 (0%)	0/25 (0%)	0/25 (0%)	11/25** (44%)
Prostration	0/25 (0%)	0/25 (0%)	0/25 (0%)	8/25** (32%)
Unkempt	0/25 (0%)	0/25 (0%)	1/25 (4%)	3/25 (12%)
Urine stains	0/25 (0%)	0/25 (0%)	0/25 (0%)	17/25** (68%)
Audible respiration	0/25 (0%)	0/25 (0%)	0/25 (0%)	10/25** (40%)
Perinasal encrustation	0/25 (0%)	0/25 (0%)	0/25 (0%)	7/25** (28%)
Perioral wetness	0/25 (0%)	0/25 (0%)	4/25 (16%)	24/25** (96%)
Red perioral wetness	0/25 (0%)	0/25 (0%)	0/25 (0%)	3/25 (12%)

[a]BushyRun (1989).
[b]Data reported as number of animals displaying sign on at least one exposure day/total number of animals (%).
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; S-D = Sprague-Dawley.

Table B-13. Survival and Body Weights of F1 and F2 S-D Rat Pups Following Exposure to 3-Methylphenol via Gavage in a 2-Generation Reproductive Study[a]

	Exposure Group, mg/kg-d (ADD male/female)			
F1 pups	**0**	**30 (23/25)**	**175 (137/149)**	**450 (350/380)**
Survival[b]				
PND 0	298/301 (99%)	279/281 (99%)	308/310 (99%)	236/239 (99%)
PNDs 0−4 (precull)	294/298 (99%)	271/279 (97%)	307/308 (100%)	215/236[c] (91%)
PNDs 4 (postcull) to 7	180/182 (99%)	161/162 (99%)	184/184 (100%)	128/131 (98%)
PNDs 7−14	180/180 (100%)	161/161 (100%)	181/184 (98%)	128/128 (100%)
PNDs 14−21	180/180 (100%)	161/161 (100%)	181/181 (100%)	128/128 (100%)
Body weight (g)[d]				
Males:				
PND 14	35.00 ± 2.676	32.32 ± 5.466 (−8%)	34.38 ± 2.673 (−2%)	32.70 ± 2.399* (−7%)
PND 21	56.03 ± 5.131	52.16 ± 8.430 (−7%)	54.80 ± 4.593 (−2%)	51.09 ± 3.555* (−9%)
Females:				
PND 14	33.76 ± 2.643	30.86 ± 5.572 (−9%)	33.15 ± 2.751 (−2%)	32.04 ± 1.997 (−5%)
PND 21	53.56 ± 4.866	49.38 ± 8.517* (−8%)	52.57 ± 4.452 (−2%)	49.69 ± 2.393 (−7%)
	Exposure Group, mg/kg-d (ADD male/female)			
F2 pups	**0**	**30 (23/27)**	**175 (136/155)**	**450 (349/400)**
Survival[b]				
PND 0	267/278[e] (96%)	284/286 (99%)	264/266 (99%)	221/222 (100%)
PNDs 0−4 (precull)	260/267 (97%)	280/284 (99%)	257/264 (98%)	212/221(96%)
PNDs 4 (postcull) to 7	155/160 (97%)	173/173 (100%)	158/160 (99%)	135/139 (97%)
PNDs 7−14	152/155 (98%)	170/173 (98%)	155/158 (98%)	124/135** (92%)
PNDs 14−21	152/152 (100%)	170/170 (100%)	155/155 (100%)	107/124[f] (86%)
F2 pups				
Males:				
PND 14	34.50 ± 2.879	35.60 ± 3.635 (+3%)	33.03 ± 2.608 (−4%)	31.29 ± 4.143* (−9%)
PND 21	54.21 ± 5.024	56.35 ± 5.812 (+4%)	51.81 ± 5.080 (−4%)	47.81 ± 6.631** (−12%)
Females:				
PND 14	33.21 ± 3.093	33.87 ± 3.139 (+2%)	31.91 ± 3.248 (−4%)	29.90 ± 3.912* (−10%)
PND 21	52.29 ± 5.204	52.87 ± 5.026 (+1%)	49.35 ± 5.649 (−6%)	47.16 ± 6.949* (−10%)

[a]BushyRun (1989).
[b]Data reported as number alive/total number (%).
[c]One dam was found dead on PND 2. All pups from this litter (n = 13) were euthanized.
[d]Data reported as litter mean ± SD (percent change compared with control) for 15−23 litters/group/generation;
% change control = [(treatment mean − control mean) ÷ control mean] × 100.
[e]One female delivered nine dead and macerated pups on GD 33.
[f]Two dams died prior to PND 21. All pups from these litters (n = 16) were euthanized.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; GD = gestation day; PND = postnatal day; S-D = Sprague-Dawley.

Table B-14. Clinical Signs of Toxicity in F1 Parental S-D Rats Following Exposure to 3-Methylphenol (CASRN 108-39-4) via Gavage for 13−17 Weeks in a 2-Generation Reproductive Study[a]

Parameter[b]	Exposure Group, mg/kg-d (ADD male/female)			
	0	30 (23/27)	175 (136/155)	450 (349/400)
Males:				
Hypoactivity	0/25 (0%)	0/25 (0%)	1/25 (4%)	20/25** (80%)
Ataxia	1/25 (4%)	0/25 (0%)	0/25 (0%)	8/25* (32%)
Twitch	0/25 (0%)	0/25 (0%)	0/25 (0%)	18/25** (72%)
Tremor	1/25 (4%)	0/25 (0%)	0/25 (0%)	9/25** (36%)
Prostration	0/25 (0%)	0/25 (0%)	0/25 (0%)	7/25** (28%)
Urine stains	0/25 (0%)	0/25 (0%)	0/25 (0%)	8/25** (32%)
Labored respiration	0/25 (0%)	0/25 (0%)	0/25 (0%)	5/25 (20%)
Audible respiration	0/25 (0%)	0/25 (0%)	0/25 (0%)	10/25** (40%)
Perinasal encrustation	2/25 (8%)	2/25 (8%)	2/25 (8%)	8/25 (0%)
Perioral wetness	0/25 (0%)	0/25 (0%)	5/25 (20%)	24/25** (96%)
Females:				
Hypoactivity	0/25 (0%)	0/25 (0%)	0/25 (0%)	23/25** (92%)
Ataxia	0/25 (0%)	0/25 (0%)	0/25 (0%)	18/25** (72%)
Twitch	0/25 (0%)	0/25 (0%)	1/25 (4%)	21/25** (84%)
Tremor	0/25 (0%)	0/25 (0%)	1/25 (4%)	15/25** (60%)
Prostration	0/25 (0%)	0/25 (0%)	1/25 (4%)	15/25** (60%)
Urine stains	0/25 (0%)	1/25 (4%)	4/25 (16%)	13/25** (52%)
Labored respiration	0/25 (0%)	0/25 (0%)	1/25 (4%)	8/25** (32%)
Audible respiration	0/25 (0%)	1/25 (4%)	0/25 (0%)	8/25** (32%)
Perinasal encrustation	0/25 (0%)	1/25 (4%)	2/25 (8%)	7/25** (28%)
Perioral wetness	0/25 (0%)	1/25 (4%)	6/25* (24%)	24/25** (96%)

[a]BushyRun (1989).
[b]Data reported as number of animals displaying sign on at least one exposure day/total number of animals (%).
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; S-D = Sprague-Dawley.

Table B-15. Clinical Signs Observed in S-D Rat Dams Exposed to 3-Methylphenol (CASRN 108-39-4) via Gavage from GDs 6–15[a]

Parameter	Exposure Group, mg/kg-d			
	0	30	175	450
Clinical signs, GDs 6−15[b]				
Hypoactivity	0/46	0/24	0/23	10/21**
Ataxia	0/46	0/24	0/23	6/21**
Twitch	0/46	0/24	0/23	6/21**
Tremor	0/46	0/24	0/23	4/21*
Audible respiration	0/46	1/24	0/23	7/21***
Perioral wetness	0/46	0/24	1/23	14/21***
Perioral encrustations	0/46	0/24	0/23	5/21**
Urogenital area wetness	0/46	0/24	0/23	8/21**

[a]BushyRun (1988); Hazleton Laboratories (1988a).
[b]Results are expressed as the number of animals showing clinical signs/number of animals examined (%). Clinical signs were reported only for dams with confirmed pregnancies.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.
*** Statistically significantly different from control ($p < 0.001$), as reported by the study authors.

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

Table B-16. Food Consumption, Body Weight, and Liver Weight of S-D Rat Dams Exposed to 3-Methylphenol (CASRN 108-39-4) via Gavage from GDs 6−15[a]

Parameter[b]	Exposure Group, mg/kg-d			
	0	30	175	450
Food consumption, GDs 6−15 (g/animal/day)	22.44 ± 2.705	22.67 ± 2.043 (+1%)	22.51 ± 2.434 (0%)	19.37 ± 2.171*** (−14%)
Body weight (g):				
GD 6	259.27 ± 12.434	254.05 ± 12.479 (−2%)	256.74 ± 13.438 (−1%)	259.26 ± 14.781 (0%)
GD 11	276.94 ± 15.500	273.95 ± 13.496 (−1%)	272.98 ± 14.259 (−1%)	261.90± 12.419*** (−5%)
GD 15	300.69 ± 16.193	297.08 ± 18.189 (−1%)	294.47 ± 15.824 (−2%)	281.33 ± 16.257*** (−6%)
GD 21	391.17 ± 26.157	386.89 ± 30.793 (−1%)	388.06 ± 25.579 (−1%)	376.56 ± 23.116 (−4%)
GD 21 (corrected)[c]	291.41 ± 20.555	290.46 ± 21.071 (0%)	288.09 ± 17.495 (−1%)	278.69 ± 17.415 (−4%)
Body-weight gain (g):				
GDs 6−11	17.67 ± 7.214	19.90 ± 8.927 (+13%)	16.23 ± 5.238 (−8%)	2.64 ± 7.309*** (−85%)
GDs 11−15	23.74 ± 7.795	23.12 ± 7.146 (−3%)	21.49 ± 4.386 (−9%)	19.43 ± 7.287 (−18%)
GDs 6−15	41.42 ± 8.307	43.02 ± 10.535 (+4%)	37.73 ± 6.214 (−9%)	22.07 ± 7.959*** (−47%)
GDs 0−21	163.09 ± 20.695	159.45 ± 26.160 (−2%)	160.61 ±18.356 (−2%)	145.40 ± 22.638** (−11%)
GDs 0−21 (corrected)[c]	63.33 ± 14.822	63.02 ± 17.999 (0%)	60.65 ± 12.731 (−4%)	47.52 ± 21.160** (−25%)
Liver weight:				
Absolute (g)	13.16 ± 2.004	13.66 ± 1.415 (+4%)	13.70 ± 1.780 (+4%)	13.69 ± 1.662 (+4%)
Relative (% body weight)	4.52 ± 0.565	4.70 ± 0.346 (+4%)	4.74 ± 0.462 (+5%)	4.90 ± 0.436** (+8%)

[a]BushyRun (1988); Hazleton Laboratories (1988a).
[b]Data reported as mean ± SD (percent change compared with control) for pregnant dams (21−24/exposure group, 46 controls; % change control = [(treatment mean − control mean) ÷ control mean] × 100.
[c]Corrected body weight = body weight at sacrifice − gravid uterine weight.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.
***Statistically significantly different from control ($p < 0.001$), as reported by the study authors.

GD = gestation day; SD = standard deviation; S-D = Sprague-Dawley.

Table B-17. Survival, Body Weight, Preimplantation Loss, and Fetal Death in Pregnant NZW Rabbits Exposed in Range-Finding Study to 3-Methylphenol (CASRN 108-39-4) via Gavage from GD 6–18[a]

Parameter	Exposure Group, mg/kg-d				
	0	**50**	**150**	**300**	**500**
Survival[b]	16/16 (100%)	8/8 (100%)	6/8 (75%)	7/8 (88%)	0/8*** (0%)
Body weight (g)[c]					
GD 6	3,791.49 ± 173.68	3,750.49 ± 304.23 (−1%)	3,741.37 ±157.59 (−1%)	3,743.34 ± 279.70 (−1%)	3,738.41 ± 275.23 (−1%)
GD 12	3,811.80 ± 185.99	3,767.10 ± 268.99 (−1%)	3,620.80 ± 130.91 (−5%)	3,428.03 ± 429.10* (−10%)	2,883.80 ± NA[d] (−24%)
GD 18	3,822.02 ± 228.05	3,737.45 ± 258.03 (−2%)	3,655.13 ± 217.02 (−4%)	3,466.05 ± 442.607 (−9%)	NA
GD 29	3,924.51 ± 316.88	3,903.26 ± 321.57 (−1%)	3,942.52 ±125.55 (0%)	3,838.62 ± 339.53 (−2%)	NA
Body-weight gain (g)[c]					
GDs 6−12	20.31 ± 84.75	16.61 ± 89.43 (−18%)	−117.43 ± 151.35* (−678%)	−279.13 ± 200.43*** (−1,474%)	−1,071.20 ± NA (−5,374%)
GDs 12−18	10.22 ± 102.97	−29.65 ± 107.95 (−390%)	5.45 ± 160.89 (−47%)	38.02 ± 237.15 (+270%)	NA
GDs 6−18	30.53 ± 170.41	−13.04 ± 183.70 (−143%)	−82.85 ± 239.07 (−371%)	−241.10 ± 226.92 (−890%)	NA
Percent preimplantation loss[e]	6.0 ± 11.0	18.1 ± 14.5* (+12.1%)	6.7 ± 10.5 (+0.7%)	21.6 ± 0.2* (+15.6%)	NA
Dead fetuses/litter[f]	0.1 ± 0.4	0.1 ± 0.4 (1-fold)	0.2 ± 0.4 (+2-fold)	1.3 ± 1.2* (+13-fold)	NA

[a]BushyRun (1987b); Hazleton Laboratories (1988a).
[b]Data reported as number alive/total number (%).
[c]Data reported as mean ± SD (percent change compared with control) for pregnant does (3−8/exposure group, 15 controls; % change control = [(treatment mean − control mean) ÷ control mean] × 100.
[d]NA = not applicable; only one doe in the 500 mg/kg-day survived until GD 12 and all does died prior to GD 18.
[e]Data reported as mean ± SD (change in percent compared with control) for 3−8 litters/exposure group and 15 control litters; change in % compared with control = treatment % preimplantation loss − control % preimplantation loss.
[f]Data reported as mean ± SD (fold-change compared with control) for pregnant does (3−8/exposure group, 15 controls); fold-change = treatment mean ÷ control mean.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.
***Statistically significantly different from control ($p < 0.001$), as reported by the study authors.

GD = gestation day; NA = not applicable; NZW = New Zealand White; SD = standard deviation.

Table B-18. Selected External Fetal Malformations in Offspring of Pregnant NZW Rabbits Exposed in Range-Finding Study to 3-Methylphenol (CASRN 108-39-4) via Gavage from GDs 6–18[a]

Parameter[b]	Exposure Group, mg/kg-d				
	0	50	150	300	500[c]
Dome-shaped head:					
Litter incidence	0/15 (0%)	0/7 (0%)	0/6 (0%)	1/3 (33%)	0/0
Fetal incidence	0/119 (0%)	0/45 (0%)	0/44 (0%)	3/16 (19%)	0/0
Low set ears:					
Litter incidence	4/15 (27%)	0/7 (0%)	0/6 (0%)	2/3 (67%)	0/0
Fetal incidence	7/119 (6%)	0/45 (0%)	0/44 (0%)	4/16 (25%)	0/0
Bony protrusion of ventral chest:					
Litter incidence	0/15 (0%)	0/7 (0%)	0/6 (0%)	2/3* (67%)	0/0
Fetal incidence	0/119 (0%)	0/45 (0%)	0/44 (0%)	4/16 (25%)	0/0
Bony protrusion of midline chest:					
Litter incidence	0/15 (0%)	1/7 (14%)	0/6 (0%)	1/3 (33%)	0/0
Fetal incidence	0/119 (0%)	1/45 (2%)	0/44 (0%)	1/16 (6%)	0/0
Inverted forelimbs:					
Litter incidence	0/15 (0%)	0/7 (0%)	0/6 (0%)	2/3* (67%)	0/0
Fetal incidence	0/119 (0%)	0/45 (0%)	0/44 (0%)	4/16 (25%)	0/0
Spina bifida:					
Litter incidence	0/15 (0%)	1/7 (14%)	0/6 (0%)	0/3 (0%)	0/0
Fetal incidence	0/119 (0%)	1/45 (2%)	0/44 (0%)	0/16 (0%)	0/0
Tight skin around elbow:					
Litter incidence	0/15 (0%)	0/7 (0%)	0/6 (0%)	2/3* (67%)	0/0
Fetal incidence	0/119 (0%)	0/45 (0%)	0/44 (0%)	4/16 (25%)	0/0
Hindlimb digits curled:					
Litter incidence	0/15 (0%)	0/7 (0%)	0/6 (0%)	1/3 (33%)	0/0
Fetal incidence	0/119 (0%)	0/45 (0%)	0/44 (0%)	1/16 (6%)	0/0
Cleft palate:					
Litter incidence	0/15 (0%)	0/7 (0%)	1/6 (17%)	1/3 (33%)	0/0
Fetal incidence	0/119 (0%)	0/45 (0%)	1/44 (2%)	1/16 (6%)	0/0
Any external malformation:					
Litter incidence	4/15 (27%)	2/7 (29%)	1/6 (17%)	2/3 (67%)	0/0
Fetal incidence	7/119 (6%)	2/45 (4%)	1/44 (2%)	4/16 (25%)	0/0

[a]Hazleton Laboratories (1988a); BushyRun (1987b).
[b]Data reported as number of litters or fetuses with malformation/total number of litters or fetuses (%).
[c]All dams in the 500-mg/kg-day group died prior to delivery.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.

GD = gestation day; NZW = New Zealand white.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE FOR CONTINUOUS DATA

The benchmark dose (BMD) modeling of continuous data was conducted with EPA's Benchmark Dose Software (BMDS, Version 2.5). For these data, all continuous models available within the software were fit using a default benchmark response (BMR) of 1 standard deviation (SD) relative risk unless a biologically determined BMR was available (e.g., BMR 10% relative risk for body, liver, or kidney weight based on a biologically significant weight loss of 10%), as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b). An adequate fit was judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was homogeneous. If a homogeneous variance model was deemed appropriate based on the statistical test provided by BMDS (i.e., Test 2), the final BMD results were estimated from a homogeneous variance model. If the test for homogeneity of variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous 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 benchmark dose lower confidence limit/benchmark concentration lower confidence limit (BMDL/BMCL) was selected if the BMDL/BMCL estimates from different models varied less than threefold; otherwise, the BMDL/BMCL from the model with the lowest Akaike's information criterion (AIC) was selected as a potential point of departure (POD) from which to derive the oral reference dose/inhalation reference concentration (RfD/RfC).

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

BMD MODELING TO IDENTIFY POTENTIAL PODs FOR THE DERIVATION OF A SUBCHRONIC p-RfD

The following data sets were selected for BMD modeling:

- Continuous data for decreased body weight in male rats exposed to 3-methylphenol via gavage 7 days/week for 13 weeks (Dietz and Mulligan, 1988)

- Continuous data for increased relative liver weight in female $B6C3F_1$ mice administered dietary 3-methylphenol for 28 days (NTP, 1992b)

Decreased Body Weight in Male Rats Exposed to 3-Methylphenol via Gavage for 13 Weeks

The procedure outlined above was applied to the data for decreased body weight (BW) in male Sprague-Dawley (S-D) rats exposed to 3-methylphenol via gavage 7 days/week for 13 weeks (Dietz and Mulligan, 1988) (see Table C-1). Table C-2 summarizes the BMD modeling results. Only the Exponential Model 4 with constant variance provided adequate fit to the means. Thus, the $BMDL_{10}$ of 106 mg/kg-day from this model is selected for this endpoint (see Figure C-1 and the BMD text output for details).

Table C-1. Body Weight in Male S-D Rats Exposed to 3-Methylphenol (CASRN 108-39-4) via Gavage 5 Days/Week for 13 Weeks[a]

	Dose (mg/kg-d)			
	0	**50**	**150**	**450**
Sample size	20	20	20	19
Mean	580	578	529	502
SD	57	36	47	51

[a]Dietz and Mulligan (1988).

SD = standard deviation; S-D = Sprague-Dawley.

Table C-2. Benchmark Dose Modeling Results for BW in Male S-D Exposed to 3-Methylphenol (CASRN 108-39-4) via Gavage 5 Days/Week for 13 Weeks[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residual: Dose Below BMD[d]	Scaled Residual: Dose Above BMD[d]	Scaled Residual: Overall Largest[d]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Constant variance									
Exponential (Model 2)[e]	<0.0001	0.24	0.09	−1.80	0.55	−1.80	698.35	312.97	239.75
Exponential (Model 3)[e]	<0.0001	0.24	0.09	−1.80	0.55	−1.80	698.35	312.97	239.75
Exponential (Model 4)[e,f]	**<0.0001**	**0.24**	**0.13**	**−0.72**	**0.14**	**1.16**	**697.85**	**194.88**	**105.66**
Exponential (Model 5)[e]	<0.0001	0.24	NA	1.39×10^{-7}	2.10×10^{-8}	-2.66×10^{-7}	697.61	161.48	113.40
Hill[e]	<0.0001	0.24	NA	4.24×10^{-7}	6.66×10^{-8}	4.24×10^{-7}	697.61	167.21	104.91
Linear[g]	<0.0001	0.24	0.08	−1.88	0.53	−1.88	698.69	324.31	253.72
Polynomial (2-degree)[g]	<0.0001	0.24	0.08	−1.88	0.53	−1.88	698.69	324.31	253.72
Polynomial (3-degree)[g]	<0.0001	0.24	0.08	−1.88	0.53	−1.88	698.69	324.31	253.72
Power[e]	<0.0001	0.24	0.08	−1.88	0.53	−1.88	698.69	324.31	253.72

[a]Dietz and Mulligan (1988).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[d]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[e]Power restricted to ≥1.
[f]Selected model.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); BW = body weight; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); S-D = Sprague-Dawley.

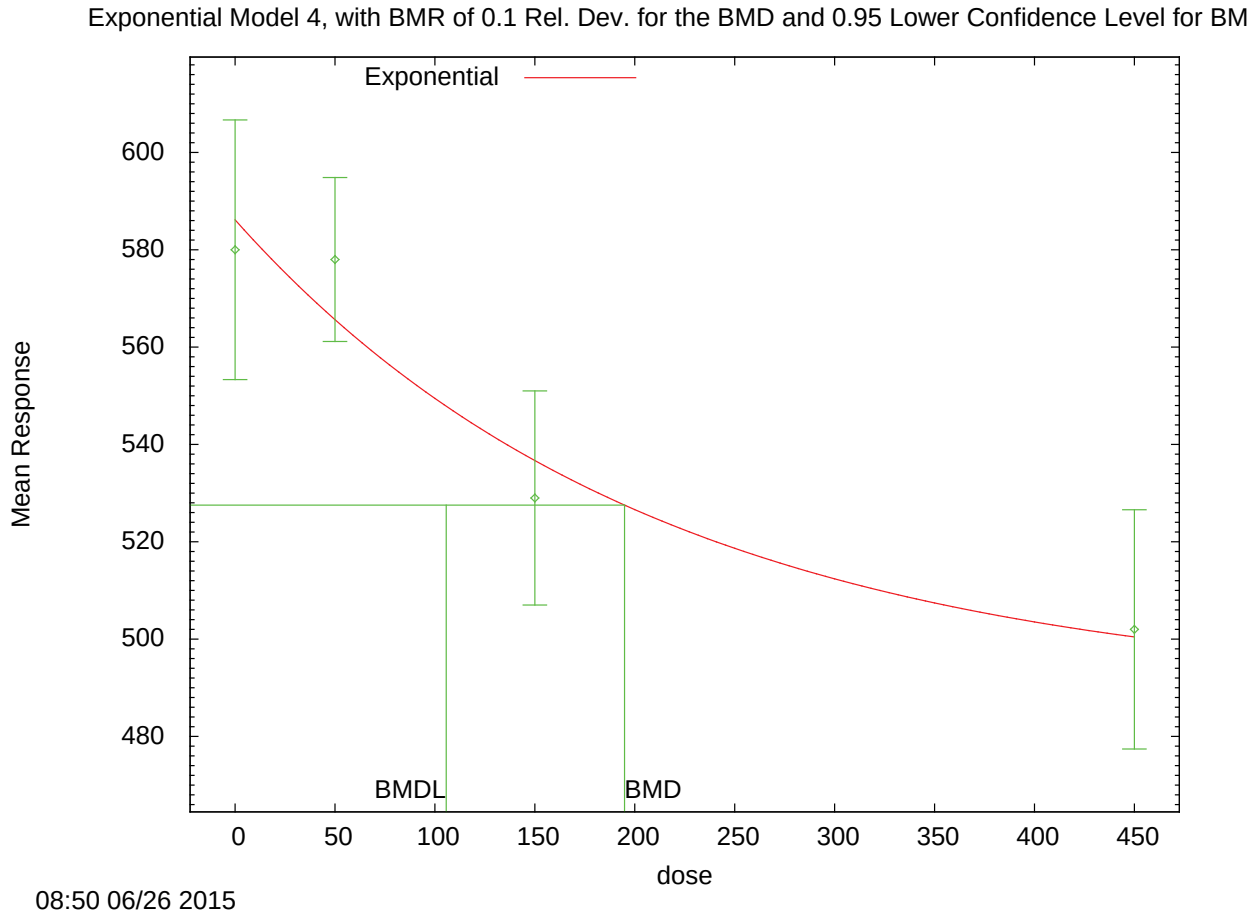

Figure C-1. Exponential Model 4 for Body Weight in Male S-D Exposed to 3-Methylphenol via Gavage 5 Days/Week for 13 Weeks (Dietz and Mulligan, 1988)

Text Output for Exponential Model 4 for Body Weight in Male S-D Exposed to 3-Methylphenol via Gavage 5 Days/Week for 13 Weeks (Dietz and Mulligan, 1988)

```
================================================================
        Exponential Model. (Version: 1.9;  Date: 01/29/2013)
        Input Data File:
C:/BMDS250_2014/Data/3-Methylphenol_PTV/exp_TermBW_mrat_Exp-ConstantVariance-BMR1Std-D
own.(d)
        Gnuplot Plotting File:
                                              Fri Jun 26 08:50:11 2015
 ================================================================

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

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

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

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

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

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

MLE solution provided: Exact

               Initial Parameter Values

               Variable          Model 4
               --------          --------
                 lnalpha             7.70392
                     rho(S)                0
                       a                 609
                       b           0.00404557
                       c              0.78505
                       d                     1

  (S) = Specified

                 Parameter Estimates

                Variable          Model 4
                --------          -------
                 lnalpha            7.73228
                     rho                  0
                       a            586.151
                       b          0.00473749
                       c            0.834101
                       d                  1

        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
     0     20          580           57
    50     20          578           36
   150     20          529           47
   450     19          502           51

              Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         586.2        47.76          -0.5759
     50         565.6        47.76            1.157
    150         536.7        47.76          -0.7199
    450         500.4        47.76           0.1421

Other models for which likelihoods are calculated:
```

```
  Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

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

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-343.8047	5	697.6094
A2	-341.6866	8	699.3732
A3	-343.8047	5	697.6094
R	-359.5686	2	723.1372
4	-344.9251	4	697.8503

Additive constant for all log-likelihoods = -72.6. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

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

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

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	35.76	6	< 0.0001
Test 2	4.236	3	0.2371
Test 3	4.236	3	0.2371
Test 6a	2.241	1	0.1344

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

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

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

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 0.100000

Risk Type = Relative deviation

```
Confidence Level = 0.950000

             BMD =      194.883

            BMDL =      105.664
```

Increased Relative Liver Weight in Female Mice Exposed to Dietary 3-Methylphenol 28 Days

The procedure outlined above was applied to the data for increased relative liver weight in female $B6C3F_1$ mice exposed to dietary 3-methylphenol for 28 days (NTP, 1992b) (see Table C-3). Table C-4 summarizes the BMD modeling results. Neither the constant nor the nonconstant variance models provide adequate fit to the variance data using the full data set. After dropping the highest dose, neither the constant nor the nonconstant variance models provided adequate fit to the means. After dropping the two highest doses, only the Exponential Model 4 with constant variance provided adequate fit to the means. Thus, the $BMDL_{10}$ of 178 mg/kg-day from this model is selected for this endpoint (see Figure C-2 and the BMD text output for details).

Table C-3. Relative Liver Weight in Female $B6C3F_1$ Mice Exposed to Dietary 3-Methylphenol (CASRN 108-39-4) for 28 Days[a]

	Dose (mg/kg-d)					
	0	**66**	**210**	**651**	**2,080**	**4,940**
Sample size	5	5	5	5	4	3
Mean	51.3	53.2	56.0	57.3	60.8	56.4
SD	0.4	0.7	1.1	1.1	1.1	4.3

[a]NTP (1992b).

SD = standard deviation.

Table C-4. Benchmark Dose Modeling Results for Relative Liver Weight in Female B6C3F$_1$ Mice Exposed to 3-Methylphenol (CASRN 108-39-4) via the Diet for 28 Days[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residual: Dose Below BMD[d]	Scaled Residual: Dose Above BMD[d]	Scaled Residual: Overall Largest[d]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Constant variance									
Linear[e]	<0.0001	<0.0001	<0.0001	−1.65	NA	2.80	92.36	5,849.38	3,447.22
Nonconstant variance									
Linear[e]	<0.0001	0.003069	<0.0001	1.73	−0.04	−2.89	80.61	1,462.74	776.71
Constant variance, high dose dropped									
Exponential (Model 2)[f]	<0.0001	0.21	<0.0001	1.91	−0.82	−2.86	55.23	1,417.09	1,181.87
Exponential (Model 3)[f]	<0.0001	0.21	<0.0001	1.91	−0.82	−2.86	55.23	1,417.09	1,181.87
Exponential (Model 4)[f]	<0.0001	0.21	0.000754	2.16	−1.98	2.16	36.51	447.18	284.49
Exponential (Model 5)[f]	<0.0001	0.21	0.000754	2.16	−1.98	2.16	36.51	447.18	284.49
Hill[f]	<0.0001	0.21	0.01119	1.42	−2.06	−2.06	31.12	346.27	221.54
Linear[e]	<0.0001	0.21	<0.0001	1.83	−0.89	−2.82	54.33	1,364.01	1,125.72
Polynomial (2-degree)[e]	<0.0001	0.21	<0.0001	1.83	−0.89	−2.82	54.33	1,364.01	1,125.72
Polynomial (3-degree)[e]	<0.0001	0.21	<0.0001	1.83	−0.89	−2.82	54.33	1,364.01	1,125.72
Polynomial (4-degree)[e]	<0.0001	0.21	<0.0001	1.83	−0.89	−2.82	54.33	1,364.01	1,125.72
Power[f]	<0.0001	0.21	<0.0001	1.83	−0.89	−2.82	54.33	1,364.01	1,125.72
Nonconstant variance, high dose dropped									
Exponential (Model 2)[f]	<0.0001	0.60	<0.0001	1.96	−0.49	−2.77	55.76	1,549.35	1,249.29
Exponential (Model 3)[f]	<0.0001	0.60	<0.0001	1.96	−0.49	−2.77	55.76	1,549.35	1,249.29
Exponential (Model 4)[f]	<0.0001	0.60	0.008985	0.47	−2.14	−2.14	29.62	262.41	203.81
Exponential (Model 5)[f]	<0.0001	0.60	<0.0001	0.14	−2.46	2.96	46.68	71.91	69.71
Hill[f]	<0.0001	0.60	0.06001	0.85	−1.57	−1.57	25.82	286.69	215.91
Linear[e]	<0.0001	0.60	<0.0001	1.91	−0.55	−2.74	55.03	1,501.61	1,178.17
Polynomial (2-degree)[e]	<0.0001	0.60	<0.0001	1.91	−0.55	−2.74	55.03	1,501.61	1,178.17

Table C-4. Benchmark Dose Modeling Results for Relative Liver Weight in Female B6C3F$_1$ Mice Exposed to 3-Methylphenol (CASRN 108-39-4) via the Diet for 28 Days[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residual: Dose Below BMD[d]	Scaled Residual: Dose Above BMD[d]	Scaled Residual: Overall Largest[d]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Polynomial (3-degree)[e]	<0.0001	0.60	<0.0001	1.91	−0.55	−2.74	55.03	1,501.61	1,178.17
Polynomial (4-degree)[e]	<0.0001	0.60	<0.0001	1.91	−0.55	−2.74	55.03	1,501.61	1,178.17
Power[f]	<0.0001	0.60	<0.0001	1.91	−0.55	−2.74	55.03	1,501.61	1,178.17
Constant variance, 2 highest doses dropped									
Exponential (Model 2)[f]	<0.0001	0.14	<0.0001	−0.88	NA	2.86	38.72	654.18	523.38
Exponential (Model 3)[f]	<0.0001	0.14	<0.0001	−0.88	NA	2.86	38.72	654.18	523.38
Exponential (Model 4)[f,g]	**<0.0001**	**0.14**	**0.46**	**0.44**	**−0.15**	**−0.52**	**18.78**	**267.51**	**177.90**
Exponential (Model 5)[f]	<0.0001	0.14	NA	-3.50×10^{-8}	-6.45×10^{-8}	-3.91×10^{-7}	20.24	254.70	174.05
Hill[f]	<0.0001	0.14	NA	1.30×10^{-6}	1.80×10^{-6}	7.18×10^{-6}	20.24	266.98	166.54
Linear[e]	<0.0001	0.14	<0.0001	2.85	−0.94	2.85	38.20	644.82	511.23
Polynomial (2-degree)[e]	<0.0001	0.14	<0.0001	2.85	−0.94	2.85	38.20	644.82	511.23
Polynomial (3-degree)[e]	<0.0001	0.14	<0.0001	2.85	−0.94	2.85	38.20	644.82	511.23
Power[f]	<0.0001	0.14	<0.0001	2.85	−0.94	2.85	38.20	644.82	511.23

[a]NTP (1992b).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[e]Coefficients restricted to be positive.
[f]Power restricted to ≥1.
[g]Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested).

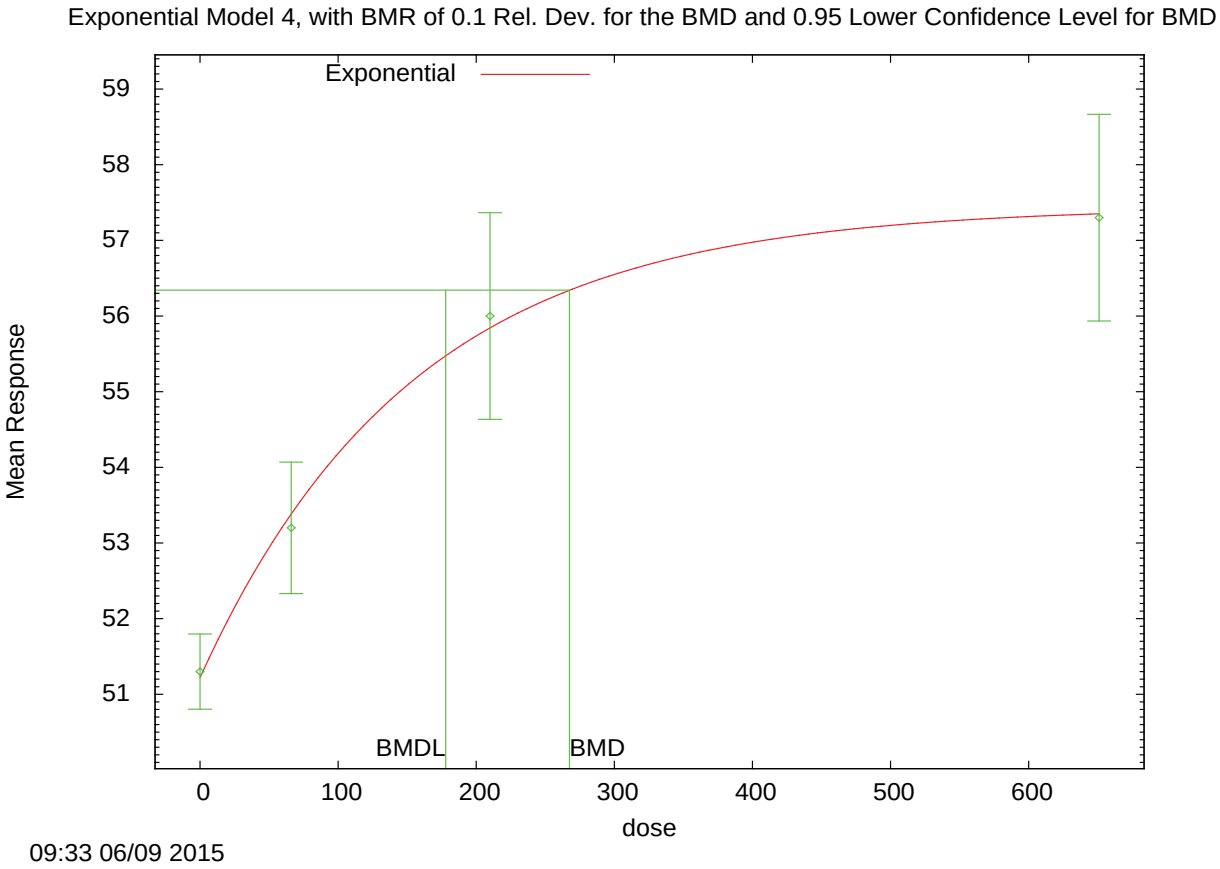

Figure C-2. Exponential Model 4 for Relative Liver Weight in Female B6C3F$_1$ Mice Exposed to 3-Methylphenol via the Diet for 28 Days, Two Highest Doses Dropped (NTP, 1992b)

Text Output for Exponential Model 4 for Relative Liver Weight in Female B6C3F$_1$ Mice Exposed to 3-Methylphenol via the Diet for 28 Days, Two Highest Doses Dropped (NTP, 1992b)

```
 ================================================================
        Exponential Model. (Version: 1.9;  Date: 01/29/2013)
        Input Data File:
C:/BMDS250_2014/Data/3-Methylphenol_PTV/NTP1992/exp_RelLvrWt_fm_2hdd_Exp-ConstantVaria
nce-BMR10_RelDev-Up.(d)
        Gnuplot Plotting File:
                                              Tue Jun 09 09:33:11 2015
 ================================================================

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

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

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

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

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

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

MLE solution provided: Exact

               Initial Parameter Values

               Variable          Model 4
               --------          --------
                 lnalpha            -0.48776
                     rho(S)                0
                       a               48.735
                       b           0.00242551
                       c              1.23453
                       d                    1

  (S) = Specified

                 Parameter Estimates

                Variable          Model 4
                --------          -------
                 lnalpha           -0.460919
                     rho                   0
                       a             51.2198
                       b           0.00646858
                       c             1.12154
                       d                    1

        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      5         51.3          0.4
     66      5         53.2          0.7
    210      5           56          1.1
    651      5         57.3          1.1

              Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         51.22       0.7942           0.2259
     66         53.38       0.7942          -0.5151
    210         55.84       0.7942           0.4374
    651         57.35       0.7942          -0.148


Other models for which likelihoods are calculated:
```

```
  Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

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

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-5.122396	5	20.24479
A2	-2.356838	8	20.71368
A3	-5.122396	5	20.24479
R	-28.1099	2	60.2198
4	-5.390807	4	18.78161

Additive constant for all log-likelihoods = -18.38. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

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

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

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	51.51	6	< 0.0001
Test 2	5.531	3	0.1368
Test 3	5.531	3	0.1368
Test 6a	0.5368	1	0.4638

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

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

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

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 0.100000

Risk Type = Relative deviation

Confidence Level = 0.950000

```
 BMD =      267.507

BMDL =      177.899
```

APPENDIX D. REFERENCES

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