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Provisional Peer-Reviewed Toxicity Values for

2-Methylphenol
(CASRN 95-48-7)

Superfund Health Risk Technical Support Center
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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
FEV1	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 2-METHYLPHENOL (CASRN 95-48-7)

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 utilize 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.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

2-Methylphenol, also called *ortho*-cresol or *o*-cresol, is widely used alone or with other methylphenols (cresols) as general disinfectants, preservatives, solvents, and chemical intermediates for pharmaceuticals, fragrances, and dyes. Methylphenols (2-methylphenol, 3-methylphenol, and 4-methylphenol) can occur naturally as components in food, and are released into the environment during the burning of wood, coal, fossil fuels, and waste products (HSDB, 2010; ATSDR, 2008). The empirical formula for 2-methylphenol is C_7H_8O and its chemical structure is presented in Figure 1. A summary of the physicochemical properties for 2-methylphenol is provided in Table 1.

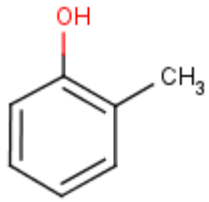

Figure 1. Structure of 2-Methylphenol

Table 1. Physicochemical Properties of 2-Methylphenol[a] (CASRN 95-48-7)

Property (unit)	Value
Boiling point (°C)	191
Melting point (C)	31
Density (g/cm^3)	1.05
Vapor pressure (Pa at 25°C)	33
pH	Data not available
Solubility in water (g/100 mL at 25°C)	2.5 (moderate)
Relative vapor density (air = 1)	3.7
Molecular weight (g/mol)	108.14

[a]IPCS/CEC (1994).

A summary of available toxicity values for 2-methylphenol (CASRN 95-48-7) from U.S. EPA and other agencies/organizations is provided in Table 2. Please note that values for mixtures of methylphenols are not included in Table 2.

Table 2. Summary of Available Toxicity Values for 2-Methylphenol (CASRN 95-48-7)

Source/Parameter[a,b]	Value (Applicability)	Notes	Reference	Date Accessed
Noncancer				
ACGIH	NV	NA	ACGIH (2013)	NA
ATSDR	NV	NA	ATSDR (2013)	NA
Cal/EPA	NV	NA	Cal/EPA (2014a, b, 2000)	NA
NIOSH	REL = 2.3 ppm (10 mg/m^3)	For 2-methylphenol as a TWA for up to a 10-hour workday.	NIOSH (2010)	NA
OSHA	8-hour PEL-TWA = 22 mg/m^3 (5 ppm)	For all isomers of 2-methylphenol (*o*-cresol).	OSHA (2011, 2006)	NA
IRIS	Chronic RfD = 5 × 10^{-2} mg/kg-day	Based on decreased body weight and significant neurological effects (increased salivation, urination, tremors, lacrimation, and rapid respiration) observed in S-D rats administered daily doses of 2-methylphenol by gavage for 90 days.	U.S. EPA (1990)	NA
Drinking water	NV	NA	U.S. EPA (2012a)	NA
HEAST	Subchronic RfD = 0.5 mg/kg-day	Based on the same study used by IRIS to set the chronic RfD. UF of 100 applied to NOAEL.	U.S. EPA (2011)	NA
CARA HEEP	NV	NA	U.S. EPA (1994)	NA
WHO	NC	NA	(WHO)	8-26-2014
Cancer				
ACGIH	Group A4, *"Not Classifiable as a Human Carcinogen"*	NA	ACGIH (2013)	NA
IRIS	Group C, *"Possible Human Carcinogen"*	Based on an increased incidence of skin papilloma in mice in a dermal initiation-promotion study.	U.S. EPA (1990)	NA
HEAST	NV	NA	U.S. EPA (2011)	NA
IARC	NV	NA	IARC (2013)	NA
NTP	NV	NA	NTP (2011)	NA

Table 2. Summary of Available Toxicity Values for 2-Methylphenol (CASRN 95-48-7)

Source/Parameter[a,b]	Value (Applicability)	Notes	Reference	Date Accessed
Cal/EPA	NV	NA	(Cal/EPA, 2014b, 2011)	NA

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; CARA = Chemical Assessments and Related Activities; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profile; 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; AIC = Acceptable Intake Chronic (Inhalation); MRL = Minimal Risk Level; NSRL = no significant risk level; PEL = permissible exposure level; REL = recommended exposure level; RfD = oral reference dose; TLV = threshold limit value; TWA = time-weighted average; UF = uncertainty factor.

NA = not applicable; NV = not available; NR = not relevant.

Literature searches were conducted on sources published from 1900 through August 2014 for studies relevant to the derivation of provisional toxicity values for 2-methylphenol (CASRN 95-48-7). The synonym o-cresol was also used in the search. The following databases were searched by chemical name, synonyms, or CASRN: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal/EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for relevant health information: ACGIH, Agency for Toxic Substances and Disease Registry (ATSDR), Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Table 3 provides an overview of the relevant database for 2-methylphenol and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. Principal studies are identified in Table 3 and bolded. The phrase "statistical significance," as used throughout the document, indicates a *p*-value of <0.05 unless otherwise noted.

Table 3. Summary of Potentially Relevant Data for 2-Methylphenol (CASRN 95-48-7)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration (Concentration)	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
1. Oral (mg/kg-d)[a]								
None								
2. Inhalation (mg/m^3)[a]								
Short-term[c]	10 human volunteers (sex unspecified), case study, duration unspecified (6 mg/m^3)	6	8/10 reported dryness, constriction in the nose, irritation of the throat, and taste in the mouth.	NI	NC	6	Uzhdavini et al. (1972)	PR status unknown
Animal								
1. Oral (mg/kg-d)[a]								
Short-term[c]	Rat (number of animals/sex/strain unknown), dietary, 28 d	0, 0.91, 6.96, 22.6	Significantly increased adrenal weight gain.	6.96	NC	22.6	BioFax (1969) (as cited in ECB, 2000; WHO, 1995)	PR status unknown
	5/5, F344/N rat, dietary, 7 d/wk, 28 d (0, 300, 1,000, 3,000, 10,000, or 30,000 ppm)	M (Adj): 0, 27, 87, 266, 861, 2,610 F (Adj): 0, 27, 89, 271, 881, 2,510	Significantly increased absolute and relative liver and kidney weights in males; significantly increased absolute and relative liver weights in females.	266 (M) 271 (F)	NC	861 (M) 881 (F)	NTP (1992)	PR

Table 3. Summary of Potentially Relevant Data for 2-Methylphenol (CASRN 95-48-7)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration (Concentration)	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Short-term[c]	5/5, B6C3F$_1$ mouse, dietary, 7 d/wk, 28 d (0, 300, 1,000, 3,000, 10,000, and 30,000 ppm)	M (Adj): 0, 66, 193, 558, 1,650, 4,480 F (Adj): 0, 82, 280, 763, 1,670, 5,000	Increased relative liver weight in male and female mice.	193 (M) 280 (F)	NC	558 (M) 763 (F)	NTP (1992)	PR
	5/5, standard dark mink, dietary, 7 d/wk, 28 d (0, 214, 473, 862, 1,534, and 3,680 ppm)	M(Adj):0, 33, 66, 113, 175, 301 F(Adj):0, 55, 120, 179, 294, 524	Increased liver-to-body-weight ratios in males and females.	33 (M) 55 (F)	NC	66 (M) 120 (F)	Hornshaw et al. (1986)	PR
	5/5, European agouti-colored ferret, dietary, 7 d/wk, 28 d (0, 473, 862, 1,534, 3,680, and 5,189 ppm)	M(Adj):0, 44, 82, 132, 263, 393 F(Adj):0, 79, 146, 244, 494, 755	Increased liver-to-brain weight in males and females.	82 (M) 146 (F)	NC	132 (M) 244 (F)	Hornshaw et al. (1986)	PR
Subchronic[d]	30/30, S-D rat, gavage, 7 d/wk, 13 wk	0, 50, 175, 600	Central nervous system depression (i.e., tremors, coma, lethargy) in females.	50	NC	175	Dietz and Mulligan (1988). These results are also reported in U.S. EPA (1986b).	NPR IRIS

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Category	Number of Male/Female, Strain Species, Study Type, Study Duration (Concentration)	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Subchronic[d]	20/20, F344/N rat, dietary, 7 d/wk, 13 wk (0, 1,880, 3,750, 7,500, 15,000, and 30,000 ppm)	M(Adj): 0, 126, 247, 510, 1,017, 2,028 F(Adj): 0, 129, 256, 513, 1,021, 2,004	Increased relative liver weight in males and females.	247 (M) 256 (F)	NC	510 (M) 513 (F)	NTP (1992)	PR
	10/10, B6C3F$_1$ mouse, dietary, 7 d/wk, 13 wk (0, 1,250, 2,500, 5,000, 10,000, and 20,000 ppm)	M(Adj): 0, 199, 400, 794, 1,460, and 2,723 F(Adj): 0, 237, 469, 935, 1,663, and 3,205	Increased relative liver weight in males.	199	NC	400	NTP (1992)	PR
	10/10, S-D rat, gavage, 7 d/wk, 13 wk	0, 50, 175, 450, 600	Neurotoxicity (hypoactivity, rapid labored respiration, excessive salivation, and tremors) and decreased body weight.	NI	NC	50	TRL (1986). Study results are also reported in U.S. EPA (1987). This is a neurotoxicity study.	PR status unknown IRIS
	10/0, Wistar rat, drinking water, 5, 10, 15, or 20 wk (0 and 300 mg/L)	0, 30	Increased 2',3'-cyclic nucleotide 3'-phosphohydrolase (a marker of demyelination) activity after 10 wk.	NI	NC	30	Savolainen (1979)	PR
Chronic[e]	None							

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Category	Number of Male/Female, Strain Species, Study Type, Study Duration (Concentration)	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Developmental	0/25, S-D rat, gavage, GDs 6−15	0, 30, 175, 450	Maternal: death and neurotoxicity (i.e., hypoactivity, twitching and ataxia). Developmental: visceral variations (dilated lateral ventricles of the brain with no tissue compression).	175 (maternal) 175 (developmental)	NC	450 (maternal); note this is a frank effect level (FEL) 450 (developmental)	Tyl (1988b)	NPR
	0/14, New Zealand white rabbit, gavage, GDs 6−18	0, 5, 50, 100	Maternal: no statistically significant effects. Developmental: increased external and skeletal variations (ecchymosis on the head and poorly ossified sternebra number six).	100 (maternal) 50 (developmental)	NC	NI (maternal) 100 (developmental)	Tyl (1988a)	NPR
Reproductive	Males/females (number not reported), F344 rat, dietary, 90 d (0, 0.188%, 0.75%, or 3.0%)	M(Adj): 0, 188, 750, 3,000 F(Adj): 0, 212, 847, 3,387	Decreased terminal body weight (>10%) in males and females; no reproductive effects observed in either sex.	750 (M) 847 (F)	NC	3,000 (M) 3,387 (F)	Gulati et al. (1988) (as cited in Andersen, 2006)	NPR

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Category	Number of Male/Female, Strain Species, Study Type, Study Duration (Concentration)	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Reproductive	Males/females (number not reported), B6C3F$_1$ mouse, dietary, 90 d (0, 0.188%, 0.75%, or 3.0%)	M(Adj): 0, 226, 902, 3,608 F(Adj): 0, 244, 976, 3,902	Decreased body weights in males and females. Significantly increased estrous cycle length in females.	902 (M) 976 (F)	NC	3,608 (M) 3,902 (F)	Gulati et al. (1988). Results of decreased caudal and epididymal weights in males not clearly understood.	NPR
	25/25, S-D rat, gavage, 2-generation reproductive toxicity study, F0 and F1: 5 d/wk, 20 wk	**0, 30, 175, 450**	**Hypoactivity and ataxia in adult F1 female rats.** **Decreased body weight in F1 male offspring**	**30 [parental]** **175 [offspring]**	**28.8 (based on hypoactivity in adult F1 females)**	**175 [parental]** **450 [offspring]**	**Tyl and Neeper-Bradley (1989). This study was not available for review at the time of the IRIS assessment.**	**NPR PS**
	20/20, CD1 Swiss mouse, dietary, 7 d/wk, 14 wk (F0: 0%, 0.05%, 0.2%, and 0.5%) (F1: 0% and 0.5%)	F0: 0, 60, 660 in (Task 2) F1: 0 and 773 (M) or 1,128 (F) (Task 4)	No reproductive or general toxicity observed in either generation.	660 [F0] 773 (M) or 1,128 (F) [F1]	NC	NI [F0] NI [F1]	George et al. (1992); Heindel et al. (1997).	PR

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Category	Number of Male/Female, Strain Species, Study Type, Study Duration (Concentration)	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Reproductive	4/12, mink, dietary, 7 d/wk, 2 mo (0, 100, 400, 1,600 ppm)	0, 100, 400, 1,600 ppm	No birth defects and no reproductive parameters differed from controls.	1,600 ppm (not adjusted, mink)	NC	NI	Hornshaw et al. (1986). Adjusted doses could not be calculated because complete feed consumption data was not provided by the study authors.	PR
Carcinogenic	None							
2. Inhalation (mg/m^3)[a]								
Short-term[c]	Mouse (sex, number and strain unknown), vapor/aerosol, 2 hr/d, 6 d/wk, 1 mo (0, 26−76 mg/m^3)	0, 50	Decreased weight gain in dosed animals, irritation in respiratory tract, and small hemorrhages in lungs. Dystrophic changes of nerve cells, glial elements, and changes to the muscle fibers of heart. Degeneration of liver and kidneys observed.	NI	NC	50	Uzhdavini et al. (1972) Concentrations not converted to HECs.	PR status unknown
	Cat (sex, number and strain not reported), vapor, 2−6 hr/d, 1 mo or longer, duration unspecified (9−50 mg/m^3)	9−50	Inflammation and irritation of upper respiratory tract, pulmonary edema, hemorrhage, and perivascular sclerosis in lungs observed.	NI	NC	9	ATSDR (1992) (as cited in HSDB, 2010). Concentrations not converted to HECs.	PR

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Category	Number of Male/Female, Strain Species, Study Type, Study Duration (Concentration)	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Subchronic[d]	Male/female, rat (number and strain not reported), vapor, 6 hr/d, 5 d/wk for 2 mo, and 4 hr/d, 5 d/wk for 2 mo (0, 9 mg/m^3)	0, 3.2	Accelerated loss of elementary conditioned defensive reflex. Irritation and inflammation in respiratory tract. Decreased ratio of leukocytes: erythrocytes in red bone marrow. Impaired liver function.	NI	NC	3.2	Uzhdavini et al. (1972). This study was noted to contain flaws.	PR status unknown
	Guinea pig (sex, number and strain not reported), vapor, 6 hr/d, 5 d/wk for 2 mo, and 4 hr/d, 5 d/wk, 2 mo (0, 9 mg/m^3)	0, 0.68	Increased number of eosinophils in white portion of bone marrow. Changes observed in hemoglobin concentrations and electrocardiogram readings (EKGs).	NI	NC	0.68	Uzhdavini et al. (1972)	PR status unknown
	6, Rat (sex, strain not reported), mixed methylphenol vapor, 3 mo (frequency of exposure not stated) (0, 0.0052 and 0.05 mg/m^3)	0, 0.0052, 0.05	Central nervous system excitation, denaturation of lung protein, and decreased body-weight gain.	0.0052	NC	0.05	Kurlyandskiy et al. (1975) (as cited in Andersen, 2006; Cal/EPA, 2000; NIOSH, 1978). Results are stated for mixed methylphenols only. Concentrations not converted to HECs.	PR status unknown

Table 3. Summary of Potentially Relevant Data for 2-Methylphenol (CASRN 95-48-7)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration (Concentration)	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Subchronic[d]	Rat (sex, number and strain not reported), vapor, (frequency not reported), 40 d	0, 0.01 mg/L	Increasing amounts of 2-methylphenol observed in lung homogenates; concentrations decreased during the recovery period.	NI	NC	NI	Pereyma (1977) (as cited in ECB, 2000). Units reported unclear. Concentrations not converted to HECs.	PR status unknown
	Rat (sex, number and strain not reported), vapor, (frequency not reported), 16 wk	0, 0.01 mg/L	Initial increase of dehydrogenase activity in the lung followed by a decrease.	NI	NC	NI	Pereyma (1977). Units reported unclear. Concentrations not converted to HECs.	PR status unknown
Chronic[e]	None							
Developmental	None							
Reproductive	White rat (sex, number and strain not reported), vapor, (frequency not reported), 4 mo (0, 0.6 and 4.0 mg/m^3)	0, 0.6, 4.0	Decreased number of primary follicles in ovaries and enhanced process of follicular atresia.	NI	NC	0.6	Pashkova (1973, 1972) (as cited in WHO, 1995). Results are stated for mixed methylphenols *only*. Concentrations not converted to HECs.	PR status unknown

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Category	Number of Male/Female, Strain Species, Study Type, Study Duration (Concentration)	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Carcinogenic	None							

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (Adj in mg/kg-d) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer effects, unless otherwise noted. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous exposure. Values from animal developmental studies are not adjusted to a continuous exposure. Adj = adjusted daily dose [Adjusted daily dose = dose in ppm × (daily food consumption ÷ body weight)]. Note that adjusted daily doses were calculated using study-specific data whenever available. When study-specific data were not available, default values were used (U.S. EPA, 1988).

[b]Notes: IRIS = utilized by IRIS; PS = principal study; NPR = not peer reviewed.

[c]Short-term = repeated exposure for >24 hr ≤ 30 d.

[d]Subchronic= repeated exposure for >90 d ≤ 10% lifespan (based on 70-yr typical lifespan).

[e]Chronic = repeated exposure for >10% lifespan.

F = female; GD = Gestational Day; M = male; NI = not identified; NC = not calculated; S-D = Sprague-Dawley.

HUMAN STUDIES

Oral Exposures

No studies by the oral route of exposure were identified for 2-methylphenol in humans.

Inhalation Exposures

The effects of inhalation exposure of humans to 2-methylphenol have not been evaluated in any subchronic-duration, chronic-duration, developmental, reproductive, or carcinogenic studies. A French dissertation (Corcos, 1939) examined exposure of workers to mixed methylphenols in air in a manufacturing plant for synthetic resins, but there were concomitant exposures to formaldehyde and ammonia in the plant. Due to combined effects from mixed methylphenols and other chemicals present in air, this study will not be discussed in detail. In an acute study, Uzhdavini et al. (1972) administered 6 mg/m^3 2-methylphenol to 10 test subjects, 8 of whom reported symptoms such as dryness, nasal constriction, and irritation of the throat. The duration of exposure, the purity of the test compound, and whether a control group was used were not reported; no additional details on research ethics were available.

Other Studies

A number of case studies have been published regarding acute oral poisonings with the cleaning solution Lysol®, which is composed of 50% mixed methylphenols (Hayakawa, 2002; Hashimoto et al., 1998; Isaacs, 1992; NIOSH, 1978; Chan et al., 1971). Due to combined effects from mixed methylphenols and other active ingredients present during the exposures, these studies will not be discussed in detail.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to 2-methylphenol have been evaluated in five short-term-duration studies (NTP, 1992; Hornshaw et al., 1986; BioFax, 1969), seven subchronic-duration studies (NTP, 1992; Dietz and Mulligan, 1988 [referenced as principal study for chronic reference dose (RfD) in the IRIS summary as U.S. EPA, 1986a]; TRL, 1986 [referenced as co-principal study for the chronic RfD in the IRIS summary as U.S. EPA, 1987]; Savolainen, 1979) two developmental toxicity studies in rats (Tyl, 1988b) and one in rabbits (Tyl, 1988a), and five reproductive toxicity studies (Heindel et al., 1997; George et al., 1992; NTP, 1992; Tyl and Neeper-Bradley, 1989; Gulati et al., 1988; Hornshaw et al., 1986).

Short-Term-Duration Studies

BioFax (1969)

In a 28-day oral feeding study in rats (strain, number, and sex unknown) were fed 0, 0.91, 6.96, or 22.6 mg/kg-day of 2-methylphenol (purity unknown) as a 2%-corn oil solution blended in the diet (BioFax, 1969). Peer-review and good-laboratory-practice (GLP) status were not discussed, and additional details are unknown because the original source (BioFax, 1969) was not available for review during the preparation of this document. The study authors found no mortality or unusual behavioral reactions. At autopsy, statistically significantly increased adrenal weight gain was observed in the highest dose group. Few other details regarding toxicity were available for this study. Based on increased adrenal weight gain, the LOAEL is identified as 22.6 mg/kg-day, and the NOAEL is identified as 6.96 mg/kg-day. However, because of inadequate reporting and the fact that no other studies in the database indicate effects on adrenal weight, this short-term-duration study is deemed inadequate for risk assessment purposes.

NTP (1992)

As part of a larger peer-reviewed subchronic-duration study of methylphenols, NTP (1992) carried out short-term-duration feed studies in rats and mice. Groups of five F344/N rats per sex were given 0-, 300-, 1,000-, 3,000-, 10,000-, or 30,000-ppm 2-methylphenol (>99% purity) in feed ad libitum for 28 days. Concentrations of 2-methylphenol were converted to adjusted daily doses by EPA utilizing the average body weight and food consumption data provided in the study report. The resulting adjusted daily doses were 0, 27, 87, 266, 861, and 2,610 mg/kg-day for males and 0, 27, 89, 271, 881, and 2,510 mg/kg-day for females. This study was performed in accordance with GLP. Feed consumption was recorded twice weekly, and animals were observed twice per day for signs of toxicity. Body weights were obtained weekly. At study termination, necropsy was performed, and organ weights were obtained for brain, heart, right kidney, liver, lungs, and thymus. A complete histopathological examination was conducted on all the control animals, all the animals in the highest dose group with at least 60% survivors at the end of the study, and all the animals in the higher dose groups inclusive of early deaths. Target organs and gross lesions were examined at lower doses until a no-observed chemical effect was determined. Nonparametric multiple comparison tests were used to compare dosed groups to control groups, and Jonckheere's test was used to assess the significance of dose-response trends.

No mortality or clinical signs of toxicity were observed in the rats (NTP, 1992). In the first week, feed consumption was depressed by as much as 58% in males and 53% in females at the highest dose (30,000-ppm), although feed consumption was similar for the remainder of the study. At the end of the study, terminal body weights for females treated with the highest dose were lower (>10%) than that of the controls. Mean body-weight gains in both males and females receiving 30,000-ppm were significantly lower (>10%) than controls as well. Reduced body weights in higher dose groups and decreased feed consumption early in the study were observed in both the 28-day and the subsequent 13-week rodent studies, which the study authors attributed to poor palatability of the compound.

Absolute and relative liver weights were statistically significantly increased (>10%) in males and females at 10,000- and 30,000-ppm (NTP, 1992). Absolute and relative kidney weights were statistically significantly increased (>10%) at 10,000- and 30,000-ppm in males only. Relative brain weight was increased in females at 30,000-ppm (10%), but the study authors indicated that this was likely a result of the reduced body-weight gain in this group. No gross lesions were observed, nor were any treatment-related lesions found based on the microscopic evaluation of tissues. Based on increased absolute and relative liver weight and increased absolute and relative kidney weight in males, a LOAEL of 861 mg/kg-day is identified. The corresponding NOAEL is 266 mg/kg-day.

In the same short-term-duration, peer-reviewed NTP (1992) study, groups of five $B6C3F_1$ mice per sex were given 0-, 300-, 1,000-, 3,000-, 10,000-, or 30,000-ppm 2-methylphenol (greater than 99% purity)—calculated by EPA to be equivalent to adjusted daily doses of 0, 66, 193, 558, 1,650, and 4,480 mg/kg-day for males and 0, 82, 280, 763, 1,670, and 5,000 mg/kg-day for females—in feed ad libitum for 28 days. The study was performed in accordance with GLP. The study protocol was the same as discussed above in the rat portion of the study.

Two male mice and one female mouse dosed with 30,000-ppm died or were sacrificed moribund between Days 5 and 9 of the study (NTP, 1992). At 30,000-ppm, clinical signs of toxicity in both males and females included hunched posture, lethargy, rough hair coat, and thin appearance. In males in the 30,000-ppm dose group, hypothermia, rapid breathing, and tremors were also observed. Mean terminal body weights for the seven surviving male and female mice in the 30,000-ppm group were significantly lower (>10%) than those observed for controls. Similar to rats in the first week of the study, feed consumption in mice was depressed at 30,000-ppm in both sexes. A reduction in feed consumption for males in the 3,000- and 10,000-ppm dose groups was also observed in the first 3 days of the study. Mean body-weight gains at 10,000- and 30,000-ppm in both sexes were also significantly lower (>10%) than that of controls. Additionally, female body-weight gains were decreased (>10%) at 300- and 3,000-ppm but were not found to be statistically significant.

At study termination, relative liver weights for males and females in the 3,000-, 10,000-, and 30,000-ppm groups were statistically significantly increased (≥10%) compared to controls (NTP, 1992). Relative kidney weights were statistically increased for females at 10,000-ppm (9.4%) and 30,000-ppm (19%) and for males at 10,000-ppm (11%). Statistically significantly increased relative brain weight was noted in 30,000-ppm females (37%). No gross lesions were noted at necropsy in either sex. However, histopathologic evaluation revealed ovarian atrophy at 30,000-ppm and uterine atrophy at 10,000- and 30,000- ppm in females. Mice that died early did not show notable histopathological changes.

According to the study authors, the lowest "minimum effective doses" were 3,000-ppm for transient decreased feed consumption during Week 1 in males, and 3,000-ppm for increased relative liver weights in male and female mice (NTP, 1992). Based on increased relative liver weight in male mice, the LOAEL is identified as 558 mg/kg-day, and the NOAEL is identified as 193 mg/kg-day.

Hornshaw et al. (1986)

Hornshaw et al. (1986) conducted a peer-reviewed, 28-day toxicity study in minks. Groups of five male and five female standard dark minks (*Mustela vison*) were randomly assigned to test groups of 0-, 240-, 432-, 778-, 1,400-, or 2,520-ppm 2-methylphenol (purity unknown) administered in corn oil to the basal diet. It was not reported whether the study was performed in accordance with GLP. The study authors reported actual concentrations after mixing in the diet to be closer to 0-, 214-, 473-, 862-, 1,534-, and 3,680-ppm (calculated by EPA to be equivalent to adjusted daily doses[1] of 0, 33, 66, 113, 175, and 301 mg/kg-day in males and 0, 55, 120, 179, 294, and 524 mg/kg-day in females). Feed and water were provided ad libitum, and body weights and feed consumption were measured weekly. Animals were observed clinically, and necropsies were performed on all animals with organ weights of brain, liver, spleen, kidneys, lungs, heart, and testes recorded. Hematological parameters were measured at study termination. Microscopic examination and complete histopathology were not discussed. Statistical analyses were performed by two-way (dose and sex) analysis of variance (ANOVA) with statistically significant differences determined by Dunnett's test.

[1]Adjusted dose = dose in ppm × (daily food consumption ÷ body weight), where food consumption and mink body weights were obtained from Hornshaw et al. (1986).

No clinical signs of toxicity were observed and no mortalities occurred (Hornshaw et al., 1986). Feed consumption was initially decreased at the highest dose of 2,520-ppm but returned to normal levels by the second week. Body-weight gain in males was statistically significantly decreased at 2,520-ppm using two-way ANOVA. The terminal body weight of males and females at the highest dose, body-weight gain in males at 240-, 778-, and 1,400-ppm, and body-weight gain in females at dietary concentrations of ≥240-ppm were decreased by >10% compared to controls, but these decreases were not statistically significant. Hematological data were analyzed with no sex-specific differences observed; therefore, data from male and females were pooled. There were significant decreases in red blood cell (RBC) counts at 1,400- and 2,520-ppm and in hemoglobin at 2,520-ppm. The study authors did not differentiate between male and female results when reporting organ weights. Relative liver-to-body weights in minks were significantly increased in all groups except at the lowest dietary concentration of 240-ppm, and relative heart weight was increased at 2,520-ppm (data not presented in original study report). Relative liver-to-brain weights were not elevated. No gross lesions were noted at necropsy in the organs of either sex.

The LOAEL for this study is identified at 66 mg/kg-day based on increased relative liver-to-body weights in male minks. The corresponding NOAEL is 33 mg/kg-day (Hornshaw et al., 1986).

In the same peer-reviewed study previously summarized for minks, European agouti-colored ferrets (*Mustela putorius furo*) were exposed to 2-methylphenol (purity unknown) in the diet for 28-days (Hornshaw et al., 1986). Groups of five ferrets per sex per dose were exposed to dietary concentrations of 0-, 432-, 778-, 1,400-, 2,520-, and 4,536-ppm 2-methylphenol. However, actual concentrations after mixing were reported to be closer to 0-, 473-, 862-, 1,534-, 3,680-, and 5,189-ppm (as calculated by EPA, these concentrations are equivalent to adjusted daily doses[2] of 0, 44, 82, 132, 263, and 393 mg/kg-day in males and 0, 79, 146, 244, 494, and 755 mg/kg-day in females). It was not reported whether the study was performed in accordance with GLP. Feed and water were provided ad libitum, and body weights and feed consumption were measured weekly. Animals were observed clinically and necropsies were performed on all animals, as discussed above for minks. Microscopic examination and complete histopathology were not discussed.

No clinical signs of toxicity were observed and no mortalities occurred in male ferrets (Hornshaw et al., 1986). A slight reduction in overall feed consumption (results not differentiated by sex) was observed at 4,536-ppm, but no statistically significant effects on body weight were seen. However, body weight gains in males at 778-, 1,400-, and 4,536-ppm and in females at 432- and 1,400-ppm were decreased by >10% compared to controls, but these endpoints were not statistically significant. Pooled hematological data revealed reduced RBC counts at 4,536-ppm for the ferrets. Statistically significant increases were seen in liver-to-brain weights at the three highest dietary concentrations (1,400-, 2,520-, and 4,536-ppm), but were not reported as liver-to-body weight data. Kidney-to-brain weights in females were also increased at

[2]Adjusted dose = dose in ppm × (daily food consumption ÷ body weight), where food consumption and ferret body weights were obtained from Hornshaw et al. (1986).

4,536-ppm ($p \leq 0.05$). The rationale for reporting organ-to-brain weights was not discussed, and the study authors did not differentiate between male and female organ results. No gross lesions were noted at necropsy in organs of either sex.

Based on increased relative liver-to-brain weight in male ferrets, a LOAEL of 132 mg/kg-day is identified, with a corresponding NOAEL of 82 mg/kg-day. The study authors stated that minks appeared to be more sensitive than ferrets based on male body-weight changes, feed consumption, and hematological parameters (Hornshaw et al., 1986).

Subchronic-Duration Studies

Dietz and Mulligan (1988)

In this 13-week gavage study in rats (Dietz and Mulligan, 1988), groups of 30 Sprague-Dawley rats per sex per dose were administered 2-methylphenol (99.5% purity) at doses of 0, 50, 175, and 600 mg/kg-day. This study is identified as a co-principal study and cited as U.S. EPA (1986b) in the IRIS summary for the derivation of an RfD for 2-methylphenol. This study has not been peer reviewed, but it was conducted in accordance with GLP. Analyses of hematology, clinical chemistry, and urine were performed for 10 rats per sex per dose at interim sacrifice (Week 7) and at study termination. Food consumption, body weights, and clinical toxicity were recorded weekly, and morbidity/mortality checks were performed twice daily. Ophthalmology examinations were performed at the start of the experiment and at study termination. Complete gross necropsy was performed on all tissues and organs of the rats, and the heart, liver, spleen, brain, individual kidneys, individual gonads, adrenals, and thyroid/parathyroid were weighed. Histopathological examination was performed on the control group and rats in the 175- and 600-mg/kg-day dose groups. Statistical analyses were performed using one-way (by sex) ANOVA tests, with significant differences determined using Dunnett's *t*-test.

At the highest gavage dose of 600 mg/kg-day, 19 females and 9 males died during the 13-week treatment period (Dietz and Mulligan, 1988). An average of 1−2 male rats died weekly such that by Week 7, 8 rats had died and only 9/10 males in the 600-mg/kg-day dose group were available for interim sacrifice. An average of 2−3 female rats died weekly such that by Week 7, 17 females had died, and only 7/10 rats in the 600-mg/kg-day dose group were available for interim sacrifice. Postdosing observations revealed signs of central nervous system (CNS) depression including lethargy, tremors, and coma at the 600-mg/kg-day dose in both males and females (data for other doses not presented in original study report) (see Table B-1). All animals at the high dose became lethargic and experienced tremors within 15−30 minutes of dosing. In more severe cases, tremors were followed by a state of coma and convulsions. Dyspnea was also observed occasionally at 600 mg/kg-day. However, approximately 1 hour after dosing, some surviving rats "recovered" and appeared normal. Signs of CNS depression occurred most frequently during the first 4−5 weeks of the study and again at Weeks 9−11. At 600 mg/kg-day, the animals became increasingly more difficult to dose and would contort their bodies to resist the gavaging procedure. At 175 mg/kg-day, one female experienced tremors and became comatose on Day 23, while another exhibited lethargy and tremors on Day 27. No other clinical signs were observed in this dose group or in the low-dose group at any other time.

At 600 mg/kg-day, decreases in food intake were observed in males during the first half of the study and to a lesser extent in females (Dietz and Mulligan, 1988). Statistically significantly decreased food consumption was observed during Weeks 1−6 and 9 in males and

during Week 1 in females at 600 mg/kg-day. There were statistically significant reductions in male mean body weights at 600 mg/kg-day during Weeks 2−10, but not at study termination. Reduction in weight gain in males at 600 mg/kg-day was observed during Weeks 1−9, and, by the end of the study, the study authors reported weight gain to be reduced by slightly greater than 10% of controls. In males at the 175-mg/kg-day dose, there was a statistically significant reduction in mean body weight at Week 2 and increases in body weight gain at Weeks 10−11, but this effect was not observed at study termination. Body weights of females at the low dose of 50 mg/kg-day during Weeks 6 and 8−14 were statistically significantly increased compared to controls, and changes in body-weight gain were statistically significantly greater at Weeks 5 and 7−13. However, this was not considered biologically significant by the study authors.

Clinical chemistry, hematology, and urinalysis parameters showed sporadic increases and decreases that were not considered to be biologically significant by the study authors (Dietz and Mulligan, 1988). No ophthalmic lesions were observed. Relative left and right kidney weights of male rats were elevated in the 600 mg/kg-day group compared to controls, but this difference was not statistically significant. The study authors attributed the kidney weight differences to lower terminal body weights of the high-dose animals. No effects on testicular or ovarian weight were observed at any dose. There were a few other sporadic increases and decreases in organ weights that were not considered to be biologically significant by the study authors.

Necropsy and histopathology revealed no treatment-related lesions (Dietz and Mulligan, 1988). The cause of death in the animals at 600 mg/kg-day could not be ascertained from pathological examinations, but the study authors hypothesized that it was due to the CNS depression observed clinically. In many animals at 600 mg/kg day, lung lesions including congestion and edema were found, but were not considered a direct effect of treatment. Oil droplets were found in the lungs of the rats and were thought by the study authors to have been aspirated during convulsions or seizures. None of the surviving rats at 600 mg/kg-day demonstrated histopathological changes in the lungs.

Dietz and Mulligan (1988) noted that the biological effects of 2-methylphenol were generally restricted to the high-dose level (a frank effect level [FEL] of 600 mg/kg-day). They stated that 175 mg/kg-day appeared to be the dose at or below which no significant toxicological effects—other than transient decreases in weight and weight gain in males, and infrequent clinical signs of tremors and coma—were observed. However, the LOAEL in this study is identified as 175 mg/kg-day for CNS depression in two female rats (i.e., tremors, coma, lethargy) and the NOAEL is 50 mg/kg-day.

NTP (1992)

NTP (1992) carried out 13-week feeding studies in rats and mice. Groups of 20 F344/N rats per sex were fed diets containing 0-, 1,880-, 3,750-, 7,500-, 15,000-, or 30,000-ppm 2-methylphenol (>99% purity) ad libitum for 13 weeks. These concentrations were converted by EPA to adjusted daily doses[3] of 0, 126, 247, 510, 1,017, and 2,028 mg/kg-day in males and 0, 129, 256, 513, 1,021, and 2,004 mg/kg-day in females. The study was performed in accordance with GLP. A complete histopathological examination was conducted on all control animals and all animals in higher dose groups, including those dying early. The study authors did not specify

[3]Adjusted dose = dose in ppm × (daily food consumption ÷ body weight), where food consumption and rat body weights were obtained from NTP (1992).

the dose groups on which histopathological examinations were conducted. Ten rats from each group were analyzed for clinical chemistry, urine, and hematological parameters. The remaining rats were used for reproductive toxicity analysis (i.e., sperm morphology and vaginal cytology), gross pathology, target organ weights (i.e., brain, liver, right kidney, thymus, heart, lungs), clinical pathology, and histopathological analysis.

No early mortality was observed in the rats (NTP, 1992). Mean terminal body weights and mean body-weight gains for males at 30,000-ppm and females at 15,000- and 30,000-ppm were statistically significantly decreased (>10%) compared with those of controls using nonparametric multiple comparison tests. Feed consumption was statistically significantly decreased during the first week of the study in males and females dosed at 30,000-ppm. No clinical signs of toxicity were observed.

Relative kidney weights were statistically significantly increased (>10%) for males and females dosed at 30,000-ppm (see Tables B-2A and B-2B). Relative liver weights were statistically significantly increased (>10%) for males and females in the 7,500-, 15,000-, and 30,000-ppm groups while absolute liver weights were statistically significantly increased (>10%) at 15,000-ppm in males (see Tables B-2A and B-2B). Additionally, absolute lung and heart weights in males and females were statistically significantly decreased (>10%) in the 30,000-ppm group, and relative brain weights were statistically significantly elevated (>10%) in the 30,000-ppm groups. Relative right testis weight was statistically significantly increased (14%) for 30,000-ppm males, and absolute thymus weights were statistically significantly decreased (15%) for females at 30,000-ppm.

Hematology findings were generally unremarkable (NTP, 1992). Some transient changes occurred such as evidence of hemoconcentration in dosed animals early in the study. In addition, concentrations of serum total bile acids increased early on and in the middle of the study at 15,000 and 30,000 ppm in both sexes, which the study authors suggested could indicate the liver's impaired ability to take up bile acids from the blood stream. There was no evidence of hepatocellular necrosis (i.e., no change in alanine aminotransferase levels) or overt cholestasis (i.e., no change in 5'-nucleotidase or alkaline phosphatase). Results of urinalyses gave no indications of renal damage.

Histopathologic examination revealed increased incidence of bone marrow hypocellularity in males at 30,000-ppm and in females at 15,000- and 30,000-ppm (NTP, 1992). However, the study authors stated that these changes were minimal to mild in severity and were considered likely to be a secondary effect from insufficient weight gain, as indicated by decreased body weight and body-weight gains observed early in the study, rather than due to direct chemical toxicity. This conclusion was further supported by the early period of maximum feed rejection by animals at 30,000-ppm and the substantial reduction of reticulocyte counts in blood samples from males (and to a lesser extent females) at 30,000-ppm, on the fifth day of the study.

Based on the results of this subchronic-duration study in rats (NTP, 1992), the LOAEL is identified at 510 mg/kg-day for statistically significant (>10%) increased relative liver weights in males. The corresponding NOAEL is 247 mg/kg-day.

In a companion 13-week subchronic-duration study by NTP (1992), groups of 10 $B6C3F_1$ mice per sex per dose were fed diets containing 0-, 1,250-, 2,500-, 5,000-, 10,000-, or 20,000-ppm 2-methylphenol (greater than 99% purity). These dietary concentrations were calculated by EPA to be equivalent to adjusted daily doses[4] of 0, 199, 400, 794, 1,460, and 2,723 mg/kg-day in males, and 0, 237, 469, 935, 1,663, and 3,205 mg/kg-day in females. The study was performed in accordance with GLP. At study termination, organ weights were obtained and a complete histopathological examination was conducted in mice similarly as indicated above for rats. All mice survived the duration of the study. Mean terminal body weights for males and females at 20,000 ppm were statistically significantly (>10%) decreased compared to controls (see Table B-3A and B-3B). Feed consumption was depressed in the highest dose group (20,000-ppm) during the first week of the study. Females in the 10,000- or 20,000-ppm groups and all male dose groups except the 2,500-ppm group gained less weight than controls by the end of the study. Clinically, males at 20,000-ppm were observed to have hunched posture and rough hair coat. Hunched posture was also noted for one male at 10,000-ppm.

Males in the 2,500-, 10,000-, and 20,000-ppm groups dose groups, and females in the 10,000-, and 20,000-ppm groups had statistically significantly increased (>10%) relative liver weights (see Table B-3A and B-3B) (NTP, 1992). Absolute liver weights were statistically significantly increased (>10%) at 2,500-, 10,000-, and 20,000-ppm in males only. Females at 20,000-ppm had statistically significantly increased relative kidney weights, but this change did not reach 10%. Males at 20,000-ppm had statistically significantly increased relative right testis (17%) and relative thymus weights (31%) (see Table B-3A and B-3B). Increases in the relative thymus weight for females at 20,000-ppm were also statistically significant (32%). Relative brain weights at the highest dose were statistically significantly elevated in both males (16%) and females (19%). The absolute weights of the heart and lung were statistically significantly decreased (19% and 14%, respectively) at 20,000-ppm in females only (data not shown in this PPRTV assessment).

There were no significant changes in hematology, clinical chemistry, and urinalysis parameters examined (NTP, 1992). A moderate increase in serum alanine aminotransferase and 5'-nucleotidase were noted in high-dose females; however, there was no evidence of liver damage or cholestasis upon microscopic examination. Total bile acids were not elevated in dosed animals. Histopathological examination revealed minimal forestomach epithelial hyperplasia in 4/10 males and 3/10 females at 20,000-ppm; this lesion occurred sporadically in lower dose groups as well. The study authors commented that the effect may have been due to the result of direct chemical irritation or may have been secondary to decreased feed consumption; however, the effect was not accompanied by inflammation, erosion, or other forestomach lesions.

Based on statistically significantly increased relative liver weights in male mice, a LOAEL of 400 mg/kg-day is identified. The lowest dose of 199 mg/kg-day is identified as the NOAEL.

[4]Adjusted dose = dose in ppm × (daily food consumption ÷ body weight), where food consumption and mouse body weights were obtained from NTP (1992).

TRL (1986)

In an oral neurotoxicity study, groups of 10 Sprague-Dawley rats per sex were gavaged daily with 2-methylphenol (purity unknown) for 13 weeks at doses of 0, 50, 175, 450, or 600 mg/kg-day. This study was identified as U.S. EPA (1987) and was a co-principal study in the IRIS summary for the development of the RfD for 2-methylphenol. This study is described as unpublished data submitted by Toxicity Research Laboratories (TRL) to U.S. EPA (as cited in ATSDR, 2008, Toxicological Profile).

Mortality occurred in the two highest dose groups: 1/10 males and 1/10 females at 450 mg/kg-day and 4/10 males and 7/10 females at 600 mg/kg-day. Clinical signs and neurological toxicity were observed. Neurotoxicity was evidenced by hypoactivity, rapid labored respiration, excessive salivation, and tremors at 50 mg/kg or greater. Additionally, decreased body weights were observed in the 50-mg/kg-day dose group (TRL, 1986). Decreased growth was implied to be associated with decreased food consumption. Neurobehavioral tests designed to assess demeanor and motor and reflex activity were performed six times throughout the 13 weeks and showed only sporadic differences from controls, indicating that behavioral alterations were not dose related. No brain-weight changes or histopathological lesions in the brain or other nervous tissues were found. More serious neurological effects, such as convulsions, were observed at 450 and 600 mg/kg/day which are identified as FELs for increased mortality. The LOAEL is identified at 50 mg/kg-day (the lowest dose tested) for neurological effects and decreased body weight in rats. No NOAEL can be identified.

Savolainen (1979)

In a peer-reviewed study, Savolainen (1979) examined toxicity to the nervous system and glial cells in the brain after exposing rats to 2-methylphenol via drinking water. Forty male Wistar rats (10/group) were given drinking water containing 300 mg/L 2-methylphenol (purity unknown) for 5, 10, 15, or 20 weeks. This dose was calculated by the study authors to be equivalent to approximately 30 mg/kg-day. An additional 40 rats served as controls and were sacrificed at the same time. Water intake and weight gain were measured weekly. GLP status was not discussed in this study, and analyses of organ weight, gross necropsy, and microscopic histopathology were also not discussed. Glial cells were isolated from five treated rats for evaluation of 2',3'-cyclic nucleotide 3'-phosphohydrolase activity, while the five other rats had cerebral samples analyzed for RNA content, glutathione levels, acid proteinase activity, NADPH-diaphorase, superoxide dismutase activity, and azoreductase activity.

Water intake was significantly increased in rats in the 4-week group[5] and significantly decreased in the 20-week group compared to control rats (Savolainen, 1979). Dosed rats had slower body-weight gain; however, this was not statistically significant at any point during the experiment. The study author stated qualitatively that the intestines appeared similar to controls on inspection, which may justify the assumption that the acute effects of the treatment were small.

Changes in the cerebral homogenate were noted by the study author as inconspicuous (Savolainen, 1979). Total RNA (expressed as µg/mg protein) was slightly elevated at 4 weeks while at 10 weeks, superoxide dismutase activity was elevated in the dosed groups. No changes in any endpoint were observed at 15 weeks; however, at 20 weeks, exposed groups had

[5]The author originally stated that rats were dosed for 5 weeks but only reported results at 4 weeks.

statistically significantly decreased glutathione levels and azoreductase activity compared to controls. NADPH-diaphorase activity was not statistically significantly different from controls, but displayed a trend of increasing activity.

Glial cells showed significant increases in acid proteinase activity at 20 weeks, and increased 2',3'-cyclic nucleotide 3'-phosphohydrolase activity after 10 and 20 weeks of 2-methylphenol exposure (Savolainen, 1979). According to the study author, the increased 2',3'-cyclic nucleotide 3'-phosphohydrolase activity could reflect biochemical changes in the myelin-forming glia, while decreased azoreductase activity in the brain could indicate the beginning of impairment of electron transfer because glutathione had also diminished. Other effects, such as increasing NADPH-diaphorase or superoxide dismutase, could indicate that the significance of oxidation reactions in methylphenol metabolism is small at this dose level.

The LOAEL is 300 mg/L (equivalent to approximately 30 mg/kg-day) for elevated superoxide dismutase in the brain and elevated 2',3'-cyclic nucleotide 3'-phosphohydrolase activity in glial cells of male rats at 10 weeks (Savolainen, 1979). No NOAEL is identified since only one dose was tested.

Chronic-Duration Studies

No chronic studies by the oral route of exposure were identified for 2-methylphenol in animals.

Developmental Studies

Tyl (1988b)

In a non-peer-reviewed developmental toxicity study, 25 pregnant Sprague-Dawley rats per group were exposed to 2-methylphenol (99.7% pure) by gavage at doses of 0, 30, 175, or 450 mg/kg-day using corn oil as a vehicle on Gestational Days (GDs) 6–15 (Tyl, 1988b). A concurrent control group of 50 animals administered only corn oil was used. This study was performed in compliance with GLP. Clinical observations were taken twice daily during dosing and once daily thereafter. Food consumption was measured daily throughout gestation from GDs 0−21, and maternal body weights were obtained on GDs 0, 6, 11, 15, and 21. Dams were observed twice daily for morbidity and mortality. On GD 21, gross necropsy was performed on the ovaries, cervix, vagina, and abdominal and thoracic organs and cavities. Body weights, liver, and gravid uterine weights were determined. Number of ovarian corpora lutea and number and status of implantation sites (i.e., resorption, dead fetuses, and live fetuses) was obtained. All live fetuses were dissected, counted, weighed, sexed, and examined for external malformations (including cleft palate) and variations. In addition, half of the live fetuses in each litter were examined for visceral malformations and variations, and for soft tissue craniofacial malformations. All intact fetuses of each litter were examined for skeletal malformations and variations. Results were analyzed using Levene's test, ANOVA, and Bonferroni *t*-tests for pairwise comparisons; pooled *t*-tests, Kruskal-Wallis tests, and Mann-Whitney U tests for nonparametric data; and Fisher's Exact test for incidence data.

Four dams (16%) died at the highest dose of 450 mg/kg-day (Tyl, 1988b). In addition, clinical toxicity in the form of hypoactivity, ataxia, tremors, twitches, prone positioning, audible respiration, and perioral wetness were observed at 450 mg/kg-day (see Table B-4). One dam experienced hypoactivity and three dams experienced perioral wetness at 175 mg/kg-day. Food

consumption was reduced at 450 mg/kg-day during the dosing period (see Table B-4). There was a statistically significant reduction in maternal body weight and weight gain at 450 mg/kg-day during the dosing period (GDs 0−15) (see Table B-4). Gestational weight gain, as well as relative gestational weight gain corrected for gravid uterus weight, was also significantly reduced at 450 mg/kg-day during GDs 0−21. The pregnancy rate was reduced (not statistically significant) for all 2-methylphenol groups. No dams aborted or delivered early.

No differences in absolute or relative liver weight were observed for 2-methylphenol treated animals (Tyl, 1988b). No treatment-related lesions were observed in dams at necropsy. There was no evidence of embryotoxicity or teratogenicity. Gestational parameters unaffected by treatment included: number of ovarian corpora lutea, number of total (nonlive or live) implants, and sex ratio per litter. There were no treatment-related effects on fetal body weights.

In the offspring, three skeletal variations were found to have statistically significantly reduced incidences compared to controls: "parietal skull bone poorly ossified" at 175 mg/kg-day, "sternebra #4 poorly ossified" at 30 mg/kg-day, and "some proximal phalanges of the hindlimb poorly ossified" at 450 mg/kg-day. Two skeletal variations were statistically significantly increased: "majority of the proximal phalanges of the hindlimb poorly ossified" at 175 mg/kg-day, and "some metatarsals of the hindlimb poorly ossified" at 30 mg/kg-day. However, the study authors stated that these skeletal variations did not exhibit a dose-response. The visceral variation ("dilated lateral ventricles of the brain with no tissue compression") was significantly increased at 450 mg/kg-day, and was thought by the study authors to be indicative of slight fetotoxicity. The study authors stated that there were no statistically significant changes in the incidence of pooled visceral or skeletal variations, total variations, or malformations.

The study authors stated that the no-observed-effect-level (NOEL) for maternal toxicity (reduction of maternal body weight and gestational weight gain) following 2-methylphenol exposure was 175 mg/kg-day, and the NOEL for developmental toxicity was 175 mg/kg-day (Tyl, 1988b). However, for this PPRTV assessment, the NOAEL for maternal toxicity is identified at 175 mg/kg-day based on death and neurotoxicity (i.e., hypoactivity, twitching, and ataxia) reported at the 450 mg/kg-day dose. Identification of a LOAEL for maternal toxicity is precluded because 450 mg/kg-day is an FEL. Based on the visceral variations observed at this dose, the NOAEL for developmental toxicity is identified at 175 mg/kg-day, and the LOAEL at 450 mg/kg-day.

Tyl (1988a)

In a developmental toxicity study by (Tyl, 1988a), 14 New Zealand white rabbits were exposed to 2-methylphenol (99.7% pure) by gavage at doses of 0, 5, 50, or 100 mg/kg-day using corn oil as a vehicle on GDs 6–18. A concurrent control group of 28 animals administered only corn oil was used. This study was not peer reviewed but it was performed in compliance with GLP. Clinical observations were taken twice daily during dosing and once daily thereafter. Food consumption was measured daily throughout gestation from GDs 0−29, and maternal body weights were obtained on GDs 0, 6, 12, 18, 24, and 29. Animals were observed twice daily for morbidity and mortality. On GD 29, gross necropsy was performed on the ovaries, cervix, vagina, and abdominal and thoracic organs and cavities. Body weights, liver weights, and gravid uterine weights were determined. The number of ovarian corpora lutea and number and status of implantation sites (i.e., resorption, dead fetuses, and live fetuses) was recorded. All live fetuses were dissected, counted, weighed, sexed, and examined for external malformations and

variations, including cleft palate. In addition, half of the live fetuses in each litter were examined for visceral malformations and variations, and for soft tissue craniofacial malformations. Intact fetuses of each litter were examined for skeletal malformations and variations. Results were analyzed using Levene's test, ANOVA, and Bonferroni *t*-tests for pairwise comparisons; pooled *t*-tests, Kruskal-Wallis tests, and Mann-Whitney U tests for nonparametric data; and Fisher's Exact test for incidence data.

There was no mortality, and none of the does aborted or delivered early (Tyl, 1988a). Clinical signs of toxicity, such as hypoactivity, audible respiration, and ocular discharge, were observed at 50 and 100 mg/kg-day but these were not statistically significant (see Table B-5). Food consumption was comparable to that of controls except for intermittent increases during the dosing and postdosing period. No statistically significant changes in maternal body weight or weight gain were observed except for increased weight gain in the 50-mg/kg-day dose group compared to controls. No treatment-related lesions in the does or changes in maternal organ weights were observed. There was no evidence of embryotoxicity or teratogenicity. Results for all gestational parameters were normal, including the number of ovarian corpora lutea; the number of implantation sites including total nonviable (i.e., early or late resorptions or dead fetuses) and viable percent live fetuses per litter; sex ratio; and fetal body weights per litter.

No statistically significant differences in the incidence of malformations were reported (Tyl, 1988a). One external variation, "ecchymosis (subepidermal hematoma) on the head," and one skeletal variation, "poorly ossified sternebra number six," were observed to be statistically significantly increased at the 100 mg/kg-day dose (see Table B-5). The study authors thought this could be indicative of slight fetotoxicity to the offspring. Two other skeletal variations had reduced incidences relative to controls but the biological significance of these findings is unclear.

The study authors identified a NOEL for maternal toxicity of 5 mg/kg-day and a NOEL for developmental toxicity of 50 mg/kg-day based on external and skeletal variations (Tyl, 1988a). However, maternal clinical findings are not statistically significant even at the high dose (100 mg/kg-day). Hence, for the purpose of this PPRTV assessment, a NOAEL of 100 mg/kg-day (highest dose tested) is selected for maternal effects and a NOAEL of 50 mg/kg-day is selected for developmental effects. Identification of a LOAEL for maternal effects is precluded, but a LOAEL of 100 mg/kg-day is identified for developmental effects based on external and skeletal variations.

Reproductive Studies

Gulati et al. (1988)

Reproductive effects of 2-methylphenol were assessed in a non-peer-reviewed dietary study in rats (Gulati et al., 1988). F344 rats (number unknown) of both sexes were administered concentrations of 0, 0.188%, 0.75%, or 3.0% 2-methylphenol (purity unknown) in the diet for 90 days (calculated by EPA to be equivalent to adjusted daily doses[6] of 0, 188, 750, and 3,000 mg/kg-day for males and 0, 212, 847, and 3,387 mg/kg-day for females). Terminal body

[6]Adjusted dose = dose in ppm × (daily food consumption ÷ body weight). For F3444 rats, the default subchronic body weight values (0.180 kg for males, 0.124 kg for females) were used with default subchronic daily food intakes (0.018 kg for males, 0.014 kg for females) from U.S. EPA (1988). For B6C3F1 mice, the default subchronic body weight values (0.0316 kg for males, 0.0246 for females) were used with default subchronic daily food intakes (0.0057 kg for males, 0.0048 kg for females) from U.S. EPA (1988).

weights were decreased by approximately 16 and 15% in male and female rats, respectively, at the dose level of 3.0% in the diet. The study authors observed no effect on sperm motility, sperm count, or testicular weight per gram of caudal tissue in males, and no effect on the estrous cycle in female rats at any dose level administered. It is unknown whether the study was conducted according to GLP. No additional details were obtained because the original study was not available for review at the time this PPRTV assessment was developed. Although food consumption data were not available in this study, a LOAEL of 3,000 mg/kg-day is identified for decreased terminal body weight (>10%) in males, with a corresponding NOAEL of 750 mg/kg-day.

Gulati et al. (1988) also assessed reproductive effects of 2-methylphenol in a dietary study in mice. $B6C3F_1$ mice (number unknown) of both sexes were administered concentrations of 0%, 0.125%, 0.5%, or 2.0% 2-methylphenol (purity unknown) in the diet for 90 days (calculated by EPA to be equivalent to adjusted daily doses[6] of 0, 226, 902, and 3,608 mg/kg-day for males and 0, 244, 976, and 3,902 mg/kg-day for females). Terminal body weights were decreased by approximately 15% in male and female mice at the 2.0% dose. In males, there was no effect on sperm motility, sperm count, or testicular weight per gram of caudal tissue. However, Andersen (2006) reported a dose-related trend of decreased caudal epididymal weights, "At 0.5%-*o*-cresol, right epididymal weights and caudal weights were significantly decreased at the 2.0%-dose level." Thus, the results of decreased caudal and epididymal weights is not clearly understood. Average estrous cycle length in female mice increased significantly from 4.2 days in control mice to 4.8 days at the 2.0%-dose level. It is unclear whether the Gulati et al. (1988) study was conducted according to GLP. No additional details were obtained because the original report by Gulati et al. (1988) was not available for review at the time this PPRTV assessment was developed. Although food consumption data were not available in this study, a LOAEL of 3,608 mg/kg-day is identified for decreased terminal body weight (>10%) in males, with a corresponding NOAEL of 902 mg/kg-day.

Tyl and Neeper-Bradley (1989)

In a two-generational reproductive study, 25 Sprague-Dawley weanling rats per sex per group were exposed to 2-methylphenol (purity 99.7%) by gavage at doses of 0, 30, 175, or 450 mg/kg-day using corn oil for 5 days per week for a total of 20 weeks (10 weeks pre-mating, 3 weeks during mating and 7 weeks during gestation/lactation). This study was not peer reviewed, but it was performed in accordance with GLP. Control animals (25 per sex) were gavaged with corn oil alone. Rats were examined twice daily for signs of toxicity as well as mortality and food consumption, and body weights were recorded weekly. Complete gross necropsy and histopathologic examination were performed for any parental animals found moribund during examination. Gross internal examination was performed on offspring appearing abnormal or nonviable during necropsy of dams.

Following the pre-mating dosing period, study animals (F0) were randomly paired within dose groups for a 3-week mating period (Tyl and Neeper-Bradley, 1989). Study females that did not successfully mate with males in the first week were remated with proven fertile males from the same dose group for the remainder of the mating period. Dosing of females was increased to 7 days per week throughout mating, gestation, and lactation. Dosing of F0 males was increased to 7 days per week throughout the mating period until sacrifice postmating. Doses delivered during gestation and lactation were based on body weights measured at GDs 0 and 7. Mated

females were weighed on GDs 0, 7, 13, and 20. Dams delivering litters were weighed on Postnatal Days (PNDs) 0, 4, 7, 14, and 21 and dams that did not deliver were weighed on GDs 0, 7, 13, 20, 28, 35, 42, 49, and 56. Reproductive indices included: percentage mating index in males and females, percentage fertility index in males and females, gestational index, live birth index, 4-day survival index, 7-day survival index, 14-day survival index, 21-day survival index, and lactation index. Statistical analyses were conducted using Levene's test for equal variances, ANOVA, Student's *t*-tests, Kruskal-Wallis tests, and Mann-Whitney U test for nonparametric data and pairwise comparisons, as well as Fisher's Exact test.

Pups (F1) were individually examined, counted, and sexed on the date of birth (PND 0) and individually weighed, sexed, and examined on PNDs 1, 4, 7, 14, and 21 (day of weaning) (Tyl and Neeper-Bradley, 1989). After weaning of F1 pups, F0 females were sacrificed. Tissues from F0 parental animals (pituitary, vagina, uterus, ovaries, testes, epididymis, seminal vesicles, prostate, and other tissues with gross lesions identified as being potentially treatment related) were examined for histologic lesions in the 450-mg/kg-day group and control groups only.

At weaning, 25 F1 weanlings/sex/group were randomly selected to mate (Tyl and Neeper-Bradley, 1989). The remaining F1 weanlings were examined externally and discarded. F1 males and females were dosed with the same doses as their parents 5 days per week for 11 weeks, then paired and mated in a manner identical to the F0 generation. Dosing of F1 females was increased to 7 days per week throughout mating, gestation, and lactation. Dosing of F1 males was increased to 7 days per week throughout the mating period until sacrifice postmating. Pups from the F2 generation were examined in the same manner as the F1 litters. All F2 pups were examined externally and sacrificed at weaning.

During the prebreeding dosing period, significant mortality was observed in both F0 males (12/25) and females (10/25) at the highest dose of 450 mg/kg-day (see Table B-6A). Transient clinical signs of toxicity in both sexes at this dose included hypoactivity, ataxia, twitches, tremors, prostration, gasping and rapid respiration, lacrimation, and perioral wetness. Persistent clinical signs included audible respiration and increased incidence of urine stains in both sexes at 450 mg/kg-day (see Table B-6A). Food consumption was reduced at 450 mg/kg-day for F0 males in the first and third weeks of dosing and in F0 females during the first week of dosing. However, food consumption was increased in females at the 30- and 175-mg/kg-day doses during the second week of dosing. During this prebreeding dosing period, F0 males demonstrated reduced body weights and reduced weight gain at 450 mg/kg-day in the first week of dosing. F0 females demonstrated reduced body weight for the first week of dosing and reduced weight gain during the second week of treatment at 450 mg/kg-day. However, F0 females at the 30 mg/kg-day dose demonstrated increased body weights for Weeks 3, 4, and 6 of the dosing period and increased weight gain during the first week of dosing.

During the mating and gestational periods, two additional deaths in F0 dams occurred at 450 mg/kg-day (Tyl and Neeper-Bradley, 1989). Body weights of F0 males were significantly reduced (by 10%) at 450 mg/kg-day during the last week of F0 mating. Body-weight gain in males was reduced at 175 and 450 mg/kg-day for the first week of mating and at all doses for the second week of mating. Except for increased lactational weight gain in dams at 450 mg/kg-day during Lactational Days (LDs) 14−21, there were no additional gestational or lactational weight gains in treated F0 dams. There were no gross or treatment-related histological lesions in organs

from high-dose and control group parental F0 adults. The study authors noted that F0 lactating dams were erroneously dosed with volumes calculated based on their gestational rather than lactational weights. However, they noted that volumes were never more than 18.2% (0.128 μL) of the correct volume.

There were no treatment-related changes in F1 litter size, sex ratio, pup body weight and pup weight gain, litter viability, or pup survival indices (Tyl and Neeper-Bradley, 1989). No gross lesions were observed in F1 pups during lactation. Similar to what was observed in the F0 generation, 8/25 F1 males and 14/25 F1 females in the 450-mg/kg-day group died during the 11-week prebreeding dosing period (see Table B-6B). Clinical signs observed in both sexes at this highest dose included hypoactivity; ataxia; twitches; tremors; prostration; and labored, audible, rapid, and slow respiration. Labored respiration, increased incidence of urine stains, and urogenital area wetness were observed in F1 females at 450 mg/kg-day. F1 females at 175 mg/kg-day showed statistically significantly increased incidence of hypoactivity, ataxia, and perioral wetness (see Table B-6B). Perioral wetness was also observed in F1 males at 175 and 450 mg/kg-day but the biological relevance of these findings is not known (see Table B-6B).

Food consumption in F1 males at the 450 mg/kg-day dose was reduced in the first week of the 11-week prebreeding dosing period, but was transiently increased at the 30-mg/kg-day dose (Weeks 2−3, 4−9) and at the 175-mg/kg-day dose (Weeks 4−5, 7−9) (Tyl and Neeper-Bradley, 1989). Food consumption was increased in F1 females at varying weeks for all three treatment groups during the dosing period. F1 males at the 450 mg/kg-day dose had reduced mean body weight (14%) at the start of the dosing period and continued to show reduced body weights for 8 of the 11 weeks. Weight gain in F1 males was reduced initially during the first two treatment weeks. F1 males at 30 and 175 mg/kg-day had increased body weights, observed at Weeks 5−11 (30 mg/kg-day) and Weeks 9−10 (175 mg/kg-day). Increased weight gains were observed in males at 30 mg/kg-day for Weeks 1−6 and 8−9. Body-weight gain in females was comparable to controls; however, weight gain was increased in all treatment groups during the third week of treatment.

Two males died during the F1 mating period, one belonging to the 30-mg/kg-day group and the other to the 450-mg/kg-day group (Tyl and Neeper-Bradley, 1989). Reproductive parameters including gestational length were unaffected by treatment. At the 450-mg/kg-day dose, one nonpregnant F1 female died, and three pregnant F1 females died during gestation. Upon microscopic examination, two of the three pregnant females that died at 450 mg/kg-day were found to have uteri containing one or more masses of necrotic mineralized material, which may have either been macerated fetuses or retained placentas. At sacrifice, one female at 30 mg/kg-day was also found to have an autolyzed fetus.

F1 male body weights were increased at 30 and 175 mg/kg-day during the 3 weeks of breeding (Tyl and Neeper-Bradley, 1989). Maternal F1 gestational body weights were comparable to controls, but gestational body-weight gains were reduced in F1 females at 450 mg/kg-day for GDs 0−7 and 0−20. During lactation, two F1 females at the highest dose died. Lactational body weight was increased on Day 0 at 30 mg/kg-day, but lactational body-weight gains were reduced at 450 mg/kg-day for Days 0−4 and at 30 mg/kg-day for Days 0−21. The study authors stated that mean litter size, sex ratio, F2 pup body weights, and weight gains per litter were unaffected by treatment. Increased pup deaths at 450 mg/kg-day

occurred on LDs 14 and 21 due to euthanization of two litters following deaths of their dams, and therefore, the F2 pup lactational index was decreased at 450 mg/kg-day. There were no treatment-related gross lesions in F2 pups that died during lactation and no treatment-related lesions during histopathological examination of organs of F1 adults in the control and high-dose groups.

In summary, 2-methylphenol was observed to produce severe systemic toxicity and mortality at doses of 450 mg/kg-day (Tyl and Neeper-Bradley, 1989). According to the pathologist's report, 2-methylphenol "may have been responsible for pregnancy abnormalities (fetal death and/or retained placenta) in a small number of female rats, particularly in the high dose group. It produced minimal gross and no significant microscopic lesions in the tissues examined other than the uterus in rats which survived to sacrifice at any dosage level" (Tyl and Neeper-Bradley, 1989). It must be noted that only the control and 450-mg/kg-day groups, as well as any parental animals dying during the study, were examined microscopically for histological lesions.

The study authors stated that no reproductive effects were observed in either of the two generations. The parental NOAEL is 30 mg/kg-day and the LOAEL is 175 mg/kg-day based on observed neurotoxicity in adult F1 female rats. The developmental NOAEL is 175 mg/kg-day and the LOAEL is 450 mg/kg-day based on reduced body weight in male offspring (F1 pups) at the beginning of the dosing period.

George et al. (1992) and Heindel et al. (1997)

Reproductive toxicity was assessed in Swiss CD-1 mice using the risk assessment by continuous breeding (RACB) protocol (Heindel et al., 1997; George et al., 1992). Following a preliminary dose range-finding study (Task 1), a reproduction and fertility study (Task 2) was undertaken. Concentrations in feed were administered at 0, 0.05%, 0.2%, or 0.5% 2-methylphenol (>99% purity) to 20 mice per sex per dose for 1 week premating, and then for 14 weeks during cohabitation. Dose equivalents were reported by the study authors to vary widely (week by week) throughout the study because of differences in food consumption among animals but mean doses were reported to be equivalent to 0, 60, 220, and 660 mg/kg-day for the F0 generation. Forty males and 40 females served as controls. Males were sacrificed 10 days after separation of the breeding pairs (end of Week 15) and randomly selected animals (20 controls, 10 at the 0.5% high dose) were necropsied for collection of data on body weight, testes weight, liver weight, paired kidney weight, and testicular histology. Females were sacrificed after weaning of their last litter on PND 21, and data on body weight, liver weight, and paired kidney weight from 20 controls and 10 high-dose (0.5%) females were obtained. Histopathology was not performed on any tissues from females. In addition, fertility and reproductive competence were assessed, including: number producing a litter/number of breeding pairs, live litters per pair, live pups per litter, proportion of pups born alive, sex ratio of live pups, and pup body weights. Statistical analyses were performed using nonparametric multiple comparison tests (Dunn's, Shirley's, Jonckheere's), Cochran-Armitage tests for proportions, and χ^2 for pairwise comparisons as well as parametric analysis of covariance.

In Task 2 (reproduction and fertility study), there were no mortalities or clinical signs of toxicity in F0 mice, except for alopecia, which the study authors stated as not treatment related. Food and water consumption and body weight of F0 mice (including body weight at delivery or during lactation in dams) were not significantly different than controls at any dose. There were no alterations to kidney and liver weights in mice (measured only at the highest dose), except for a statistically significant decrease in absolute (12%), but not relative, kidney weights in high-dose females. In males, absolute right testis weight was normal. Spermatid concentration was statistically significantly decreased (19%) in the 0.2%-dose group compared to controls, but was statistically significantly increased (21%) in the 0.5%-dose group compared to controls. This effect was noted by the study authors not to be dose dependent. In females, estrous cycle length was normal. Cumulative days to deliver the last litter were 2−3 days longer for dosed dams versus controls; however, the study authors noted that no dose-response relationship was apparent, and no "worsening" of the effect occurred over time; therefore, the biological relevance of this effect is unclear. None of the fertility indices were affected by exposure to 2-methylphenol. No microscopic lesions in the testicles were observed.

Because no reproductive effects were detected by the study authors in Task 2, no determination of the affected sex test (Task 3) was deemed necessary (Heindel et al., 1997; George et al., 1992). In Task 4 (offspring assessment), control and high-dose F1 mice were weaned at 21 days of age and then administered doses of 0 or 0.5%—reported by the study authors to be equivalent to a mean of 773 and 1,128 mg/kg-day in F1 males and females, respectively—until sexual maturity at Day 74. Breeding pairs were then cohabited for 7 days or until a vaginal copulatory plug was found. Data collected for F1 adults included body weight and selected organ weights for both sexes; epididymal and testicular weights, prostate weight, seminal vesicle weight, and spermatozoa evaluations in males; and vaginal cytology in females. For F2 pups, only pup weight and the proportion of pups born alive were reported.

In Task 4 (offspring assessment), and similar to results in Task 2, no mortality or treatment-related clinical signs were noted in F1 rats (Heindel et al., 1997; George et al., 1992). However, in the high-dose F1 group, there was a statistically significant decrease in male pup body weight at PND 74 and in female pup body weight at PNDs 21, 74, and at necropsy. The reduction in adjusted pup body weight (type of adjustment performed not specified by the study authors) was approximately 4%; all other fertility indices and reproductive competence were unchanged. Necropsies performed on F1 mice demonstrated no changes in male body weights or weights of liver, epididymis, kidney, prostate, seminal vesicle, or testis, or in sperm parameters (i.e., sperm concentration, motility, percent abnormal sperm, or testicular spermatid concentration). Organ histopathology revealed increased incidence and severity of renal hydronephrosis in males in the 0.5%-dose group (see Table B-7); however, these kidney effects were considered by the study authors to be equivocal treatment-related lesions. Female mice consuming 0.5% 2-methylphenol weighed 5% less than controls, but absolute liver and kidney weights were unchanged (see Table B-7), as were ovarian histopathology, vaginal cytology, and length of estrous cycle. No microscopic lesions were associated with exposure to 2-methylphenol.

Overall, the study authors noted that the compound did not appear to be a reproductive toxicant in either the F0 or F1 generations (Heindel et al., 1997; George et al., 1992). The study authors stated: "The NOAEL for the parent generation of Swiss mice in the present study was

0.2% (2-methylphenol) in feed. The LOAEL based on body weight for F1 females was 0.5% (2-methylphenol) in feed." However, body weight changes in F1 females did not reach 10%. Therefore, for this PPRTV assessment, the parental NOAEL is identified at 0.5% (660 mg/kg-day for the F0 generation, 773 mg/kg-day for F1 males, and 1,128 mg/kg-day for F1 females) based on lack of reproductive effects. Identification of a LOAEL is precluded.

Hornshaw et al. (1986)

A peer-reviewed reproductive toxicity test was conducted in standard dark minks (Hornshaw et al., 1986). Sixteen animals (4 males, 12 females) were exposed for approximately 2 months to 0-, 100-, 400-, or 1,600-ppm 2-methylphenol in the diet. The dose conversion is not known because the study authors did not provide complete feed consumption data. It was not reported whether this study was conducted in accordance with GLP. Minks were mated after 2 months and exposed continuously throughout weaning of the kits at 6 weeks postpartum. Body weights were measured only during the prebreeding period to minimize adverse effects from handling during pregnancy, while feed consumption was measured during Weeks 5 through 8 of the prebreeding period.

Minks were mated within their dietary dose groups. Mated females were checked during the whelping period for kits, which were then counted and weighed on the day of birth and at 3and 6 weeks of age. Four males and four randomly chosen females were weighed and sampled for hematologic parameters (red blood cells, hemoglobin, and hematocrit) at termination of the study. Necropsies were performed and organ weights were obtained similar to that done for the subchronic-duration study. Reproductive parameters (i.e., number of females bred out of total, females whelped out of those bred, gestation length, kits alive at birth out of females whelped, total kits out of females whelped, mean kit body weight, mean litter weight, and percent kit survival) were analyzed by single-factor ANOVA and Dunnett's method. Data pertaining to kit survival were analyzed by contingency table, and significant differences were tested by Bonferroni's χ^2 test.

No overt signs of toxicity were observed (Hornshaw et al., 1986). One female at the highest dose died from enteritis, which the study authors presumed was not related to chemical exposure. No effect on feed consumption was observed, although males at 1,600-ppm gained significantly less weight ($p < 0.01$) than controls. Mean birth weight of kits from mothers in the lowest exposed group of 100-ppm was statistically significantly higher than controls ($p \leq 0.05$). No obvious birth defects were noted, and no gross lesions were observed in adults at necropsy. Hematologic parameters revealed a significant increase in red blood cell count in the 1,600-ppm adults (not differentiated by sex). Relative liver-to-body weights were stated to be statistically significantly increased compared to controls. However, the quantitative data were not provided by the study authors and the study authors did not clarify whether weight changes differed by sex or were dose-response related.

No birth defects were noted and no reproductive parameters differed from controls (Hornshaw et al., 1986). Therefore, no LOAEL is identified for reproductive effects and the NOAEL is identified at 1,600-ppm (dose conversion not known), the highest dose tested in the study.

Other Studies

In a short-term-duration immunotoxicity study, female B6C3F$_1$ mice (number unknown) were exposed to 2-methylphenol in the drinking water at doses of 0, 6.5, 32.5, 65, or 130 mg/kg-day for 14 days (CIIT, 1983). Immunotoxicity was measured as changes in hematological values, lymphoid organ weights, altered lymphoid cell morphology, and cell or humoral-mediated immune function. Host resistance to tumor cell and *Listeria monocytogenes* challenges were performed. No changes in immune functions were observed at any dose, and exposed mice had the same mortality following the challenge as did the control animals (CIIT, 1983). No additional details, including peer-review and GLP status, were obtained because the original source was not available at the time this PPRTV assessment was prepared. The NOAEL for this study is 130 mg/kg-day for the absence of immunotoxicity at the highest dose in mice. No LOAEL is identified

Inhalation Exposures

The effects of inhalation exposure of animals to 2-methylphenol have been evaluated in two short-term-duration studies (ATSDR, 1992; Uzhdavini et al., 1972), five subchronic-duration studies (Pereyma, 1977; Kurlyandskiy et al., 1975; Uzhdavini et al., 1972), and one reproductive study (WHO, 1995; Pashkova, 1973, 1972). No chronic-duration, carcinogenic, or developmental studies of inhalation exposure of 2-methylphenol have been identified.

Short-Term-Duration Studies (Inhalation)

Uzhdavini et al. (1972)

In a month-long inhalation study, Uzhdavini et al. (1972) exposed, mice (sex, number, and strain unknown) to 2-methylphenol vapor and aerosol (purity unknown) for 2 hours/day, 6 days/week at concentrations of 0 and 26−76 mg/m^3 (average = 50 mg/m^3). The human equivalent concentration (HEC) is estimated to be 50 mg/m^3. Clinical signs of respiratory irritation were observed at the start of the exposure followed by hypoactivity lasting until the end of the exposure. After 18−20 days, the tails of some animals mummified and fell off. No mortality was recorded. Body-weight gains were reduced compared to controls (no data or information regarding statistical significance of this change was provided). Microscopic examination showed signs of irritation in the respiratory tract that included edema, cellular proliferation, and small hemorrhages in the lungs. There was also degeneration of the heart muscle, liver, kidney, and nerve cells and glial elements of the CNS. No additional details were available from the original study, including peer-review or GLP status. Effects appear to have been seen at the range of exposures tested (~50 mg/m^3), therefore this average is considered the LOAEL$_{HEC}$. A NOAEL cannot be established.

ATSDR (1992)

In this inhalation study, cats (sex, number, and strain unknown) were exposed to 2-methylphenol vapor (purity unknown) for 2−6 hours/day at nominal concentrations of 9−50 mg/m^3 for a month or longer (exact duration not provided) (ATSDR, 1992). Effects were reported to include inflammation and irritation of the upper respiratory tract, pulmonary edema, and hemorrhage and perivascular sclerosis in the lungs. No additional details were available from the original study, including whether a control group was included and the peer-review or GLP status. The LOAEL is identified at 9−50 mg/m^3 and a NOAEL cannot be identified.

Subchronic-Duration Studies

Uzhdavini et al. (1972)

In a subchronic-duration study, rats (sex, number, and strain unknown) were exposed to 2-methylphenol vapor (purity unknown) for 4 months (4 hours/day, 5 days/week for 2 months followed by 6 hours/day, 5 days/week for another 2 months) at concentrations of 0 or 9 mg/m^3. The HEC is estimated to be 3.2 mg/m^3. The study authors provided no details on the parameters (e.g., body weight, hematology, etc.) that were measured. The study reported that "weight coefficients" of organs did not differ between control and experimental animals, and that morphological studies showed no significant variations in the microstructure of the organs examined. Changes in the rats were observed that included accelerated loss of elementary conditioned defensive reflex. Statistically significant differences were also observed in the amount of time animals spent in specific parts of the exposure chamber. In the respiratory system, irritation and inflammation in the upper respiratory tract were observed along with local edema and perivascular sclerosis in the lungs. Other internal organs showed signs of parenchymal dystrophy, swelling of vesicular endothelium, and plethora.

No differences occurred in the serum protein content in exposed rats (Uzhdavini et al., 1972). Increases were observed in the number of blood leukocytes in male rats by the second and fourth month of dosing, although after dosing this blood parameter become normal. Changes in hematopoietic tissue was observed, namely in the red portion of the bone marrow where there was a decreased leukocytes:erythrocytes ratio. In the white portion of the bone marrow, an increase was observed in the number of eosinophils. The "duration of hexanol narcosis" (indicating possibly impaired liver function) was increased. Slightly decreased reactivity of the pituitary-adrenal system was observed.

This study was conducted prior to the establishment of GLP guidelines and no additional details were available regarding its peer-review status (Uzhdavini et al., 1972). This study was noted to contain flaws, including the use of endpoints not commonly used in toxicology as well as unusual results reported (e.g., elevation of white blood cells in male but not female rats) (Cal/EPA, 2000). The $LOAEL_{HEC}$ for this study is 3.2 mg/m^3 based on hematopoietic, neurobehavioral changes, and presumed respiratory effects in rats. A NOAEL cannot be established because effects were seen at the single dose tested.

In the same study by Uzhdavini et al. (1972), guinea pigs (sex, number, and strain unknown) were exposed to 2-methylphenol vapor (purity unknown) for 4 months (4 hours/day, 5 days/week for 2 months and 6 hours/day, 5 days/week for 2 months) at concentrations of 0 or 9 mg/m^3. The HEC is estimated to be 0.68 mg/m^3. It was stated that "weight coefficients" of organs did not differ between control and experimental animals, and that morphological studies showed no significant variations in the microstructure of the organs. Changes were observed in the quantity of hemoglobin in guinea pigs; however the direction of the changes was not described. No changes were observed in the red portion of the bone marrow in guinea pigs, although there was an increase in the number of eosinophils in the white portion. Electrocardiograms (EKGs) revealed a slight reduction in the voltage of the R wave. The excretion of phenol in urine of guinea pigs did not change after 2 months, but after 4 months urinary excretion of phenol was significantly increased compared to controls.

The $LOAEL_{HEC}$ for this study is 0.68 mg/m^3 based on hematopoietic/blood changes, heart activity changes, and presumed respiratory effects in guinea pigs. A NOAEL cannot be identified because the effects were seen at the single dose.

Kurlyandskiy et al. (1975)

In another subchronic-duration inhalation study, 6 rats (sex and strain unknown) per group were exposed to mixed methylphenols at concentrations of to 0, 0.0052, or 0.05 mg/m^3 for 3 months. Frequency of inhalation exposure was not stated. HECs could not be calculated due to the unknown composition of the methylphenol mixture used in this study. Parameters measured included: body weight, CNS effects, oxygen and carbon dioxide metabolism, total protein content in blood, tertiary structure of an unspecified protein molecule in the lung, cardiovascular effects, and activity of an unnamed liver transaminase.

Rats exposed at the highest concentration showed decreased weight gain, increased CNS "excitability", higher oxygen consumption and carbon dioxide excretion, and decreased concentration of blood gamma globulins. The tertiary structure of globular and aglobular portions of lung protein molecules were altered (denatured). However, observed changes were reversible after the exposure ended.

No alterations were seen in rats exposed to methylphenols at the lower concentration of 0.0052 mg/m^3 compared to controls, and the study authors recommended this value as the "mean daily maximum permissible concentration" Kurlyandskiy et al. (1975). This study was conducted prior to the establishment of GLP guidelines. No additional details were available, including peer-review status, as the original source could not be obtained at the time this PPRTV assessment was prepared. The difficulty of assessing data from this limited study was noted by NIOSH (1978) and Cal/EPA (2000). The NOAEL from this study is identified at 0.0052 mg/m^3 and the LOAEL at 0.05 mg/m^3 for the methylphenol mixture.

Pereyma (1977)

In this study, rats (sex, number, and strain unknown) were exposed to 0 or 0.01 mg/L 2-methylphenol (purity unknown) for 40 days, (frequency not reported), with a 20 day observation period following exposure. The specific exposure protocol was not described, and an HEC could not be calculated due to the uncertainty of the reported concentration units. A summarized translation of the study was available from the ECB (2000). Until Day 39 of the experiment, increasing amounts of 2-methylphenol (16.4 mg/g tissue) were observed in lung homogenates, although concentrations decreased during the recovery period (1.1 mg/g tissue by Day 12). Discovery of aminophenols was noted in the lung at Day 16. This study was conducted prior to the establishment of GLP guidelines. No additional details were available, including peer-review status, because the original source could not be obtained at the time this PPRTV assessment was prepared. The LOAEL from this study is identified at 0.01 mg/L with no NOAEL identified.

In a second study discussed by Pereyma (1977), rats (sex, number, and strain unknown) were exposed to 0 or 0.01 mg/L 2-methylphenol (purity unknown) for 16 weeks, (frequency not reported) with an 8-week observation period following exposure. The specific exposure protocol was not described, and an HEC could not be calculated due to the uncertainty of the reported concentration units. A summarized translation of the study was available from the ECB (2000). The only result discussed was the initial increase of dehydrogenase activity in the lung, followed

by a decrease. Due to lack of details in the reporting of the exposure protocol, concentration units, and experimental data, neither a NOAEL nor a LOAEL were identified.

Chronic-Duration Studies

No chronic-duration inhalation studies were identified for 2-methylphenol in animals.

Developmental Studies

No developmental toxicity inhalation studies were identified for 2-methylphenol in animals.

Reproductive Studies for Mixed Methylphenols

Pashkova (1973, 1972)

The reproductive effects of inhaled mixed methylphenols in white rats (sex, number, and strain unknown) were studied by Pashkova (1973, 1972). Rats were administered concentrations of 0, 0.6, or 4.0 mg/m^3 in air for 4 months but the frequency of exposure was not specified. This study was conducted prior to the establishment of GLP guidelines. The highest concentration of 4.0 mg/m^3 had a detrimental effect on the function and structure of the ovaries. Morphological analysis revealed a decrease in the number of primary follicles in the ovaries which enhanced the process of follicular atresia (i.e., degeneration and resorption of follicles before maturity). Similar, but less pronounced morphological changes were observed at 0.6 mg/m^3. Based on the limited details available in this study, the LOAEL is identified at 0.6 mg/m^3 (the lowest concentration tested) for morphological changes observed in the ovaries, with no NOAEL.

OTHER DATA

Other studies that utilized 2-methylphenol are described below. These studies are not adequate for the determination of provisional reference dose (p-RfD), provisional reference concentration (p-RfC), provisional oral slope factor (p-OSF), or provisional inhalation unit risk (p-IUR) values but provide supportive data supplementing a weight-of-evidence approach. Table 4A provides an overview of genotoxicity/mutagenicity studies while Table 4B provides an overview of other supporting studies on 2-methylphenol, including mechanistic/toxicokinetic studies and studies using exposure routes other than oral and inhalation.

Table 4A. Summary of Studies Evaluating Genotoxicity and Mutagenicity of 2-Methylphenol

Endpoint	Test System	Dose/ Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537	0–100 µg/plate	(–)	(–)	None	Douglas et al. (1980); Florin et al. (1980); Litton Bionetics (1981c); Pool and Lin (1982); Haworth et al. (1983); Claxton (1985); Massey et al. (1994)
Genotoxicity studies in nonmammalian eukaryotic organisms						
No data						
Genotoxicity studies in mammalian cells—in vitro						
Chromosome aberration test	Chinese hamster V79 cells	15–601 µg/mL	(+)	(+)	Positive increases in chromosomally aberant cells were observed in the nonactivation assay at all doses (15−301 µg/mL). Increases in chromosomally aberant cells observed with metabolic activation at 301 and 601 µg/mL.	Murli (1988)
Chromosome aberration test	Mouse lymphoma L5178Y cells	NR	(–)	NA	None	Hazleton Laboratories (1988)
Sister chromatid exchange test	Chinese hamster V79 cells	50−700 nL/mL	(+)	(+)	Positive increases in sister chromatid exchanges were observed both without S9 activation (>50 nL/mL), and to a lesser extent with S9 activation (500−700 nL/mL).	Litton Bionetics (1981b)
Sister chromatid exchange test	Cultured human lung fibroblasts	0–30 mM	(±)	(±)	Results are equivocal. Positive results were observed at 8 mM while negative results were observed at 30 mM.	Cheng and Kligerman (1984)

Table 4A. Summary of Studies Evaluating Genotoxicity and Mutagenicity of 2-Methylphenol

Endpoint	Test System	Dose/ Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Sister chromatid exchange test	Human lymphocytes	0–0.5 mM	(–)	(–)	None	Jansson et al. (1986)
Unscheduled DNA synthesis	Primary rat hepatocytes	NR	(–)	(–)	None	MRI (1980)
Cell transformation assay	Mouse BALB/c-3T3 cells	NR	(–)	NA	None	LBI (1981); Hazleton Laboratories (1988)
Forward mutation assay	Mouse lymphoma L5178Y cells	NR	(–)	NA	None	Litton Bionetics (1981a)
DNA damage	Human peripheral lymphocytes	NR	(+)	NA	No details reported	Li et al. (2005)
MN induction	ND					
DNA adducts	ND					
Genotoxicity studies—in vivo						
Mutagenicity (eye *w*/*w*+ assay)	ND					
Mutagenicity (Wing spot test)	ND					
Micronucleus test	B6C3F1 mouse peripheral blood erythrocytes	2% in feed	(–)	NA	Negative in males and females	Witt et al. (2000)
Micronucleus test	Mouse bone marrow	NR	(+)	NA	None	Li et al. (2005)
Sister chromatid exchange test	DBA/2 mouse liver cells, alveolar macrophages, and bone marrow	200 mg/kg	(–)	NA	Males only, single i.p. injection	Cheng and Kligerman (1984)
Chromosome aberration test	ICR mouse bone marrow	NR	(–)	NA	None	Hazleton Laboratories (1989a)
DNA damage	ND					
DNA adducts	ND					

Table 4A. Summary of Studies Evaluating Genotoxicity and Mutagenicity of 2-Methylphenol

Endpoint	Test System	Dose/ Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Mouse biochemical or visible specific locus test	ND					
Sex-linked recessive lethal assay	*Drosophila melanogaster*	NR	(–)	NA	None	Hazleton Laboratories (1989b)
Genotoxicity studies in subcellular systems						
DNA binding	ND					

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive, – = negative, +/– = equivocal, NA = not applicable, ND = no data, NR = not reported.

Table 4B. Mechanistic and Other Studies Examining 2-Methylphenol Toxicity				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Human studies				
No studies were located regarding the toxicity or carcinogenicity of 2-methylphenol in humans using alternative routes of exposure.				
Animal toxicity studies				
Dermal cancer promotion study: Sutter mice	Female Sutter mice were applied a single dose of the initiator 9,10-dimethyl-1,2-benzanthracene (DMBA, in 0.3% acetone) to shaved skin. This was followed 1 week later by applications (25 µL) of 2-methylphenol (20% in benzene) twice-weekly for 12 weeks.	Positive	Average number of skin papillomas per mouse and percentage of exposed mice with at least one papilloma were increased in treated mice.	Boutwell and Bosch (1959)
Intravenous neuroexcitation study: F344 rats	Six male F344 rats were administered 1.0 or 1.5% 2-methylphenol ("purified grade") intravenously in buffered saline at 0.6 mg/min (total number of minutes not provided).	Positive	Exposure to 2-methylphenol induced somatosensory-evoked potential excitation, involuntary muscle movements and tremors, and electrophysiological changes.	Mattsson et al. (1989)
Immunotoxicity	ND			
Neurotoxicity	ND			
Studies of absorption, distribution, metabolism, or elimination (ADME)				
ADME	ND			
Studies of mode of action/mechanism/therapeutic action				
Mode of action/mechanistic	ND			

ND = no data.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present a summary of noncancer reference values and cancer values, respectively.

Table 5. Summary of Noncancer Reference Values for 2-Methylphenol (CASRN 95-48-7)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UFc	Principal Study
Subchronic p-RfD (mg/kg-day)	Rat/Female	Hypoactivity	2×10^{-1}	$BMDL_{10HED}$	6.9	30	Tyl and Neeper-Bradley (1989)
Chronic RfD (mg/kg-day) IRIS	Rat/Male and Female	Decreased body weights and neurotoxicity	5×10^{-2}	NOAEL	50	1,000	U.S. EPA (1987, 1986B) (also known as Dietz and Mulligan, 1988 and; TRL, 1986)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

NDr = not determined

Table 6. Summary of Cancer Values for 2-Methylphenol (CASRN 95-48-7)

Toxicity Value	Reference Value	Tumor Type or Precursor Effect	Species/Sex	Principal Study
p-OSF	NDr			
p-IUR	NDr			

NDr = not determined

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic p-RfD

There are no human studies examining the health effects from subchronic-duration oral exposure to 2-methylphenol. However, a variety of repeated-dose toxicity animal studies were located and are considered for derivation of a subchronic p-RfD. In several rodent short-term and subchronic-duration studies, increases in absolute and/or relative liver weight were observed (NTP, 1992; Hornshaw et al., 1986). Another short-term study described increased adrenal weight gain in rats (BioFax, 1969); however, the lack of details regarding experimental design and study results precludes further analysis of this study. Neurotoxicity was observed in two subchronic-duration studies (Dietz and Mulligan,(1988)[also identified as U.S. EPA,(1986b)];

TRL,(1986)[also identified as U.S. EPA,(1987)]). A subchronic-duration study in rats by Savolainen (1979) observed increased 2', 3'-cyclic nucleotide 3'-phosphohydrolase, a marker of demyelination. Similarly, neurotoxicity was observed in adult rats in one developmental and one reproductive toxicity study (Tyl and Neeper-Bradley, 1989; Tyl, 1988b). Two developmental toxicity studies reported increases in visceral and skeletal variations in rats and rabbits, respectively (Tyl, 1988a, b). One reproductive toxicity study reported effects on the estrous cycle length of female mice (Gulati et al., 1988), while three others in rats, mice, and minks reported no significant reproductive effects (George et al., 1992; Gulati et al., 1988; Hornshaw et al., 1986).

Among all available studies, the short-term rat study by BioFax (1969) provided the lowest LOAEL of 22.6 mg/kg-day based on significantly increased adrenal weight gain. However, because no detailed information is available regarding experimental design or study results and no other studies reported adrenal effects following oral 2-methylphenol exposure, this study is not appropriate for the derivation of a subchronic p-RfD. Two other studies provide effect levels for consideration: a short-term study in minks identified a LOAEL of 66 mg/kg-day, and a corresponding NOAEL of 33 mg/kg-day, based on increased relative liver weight in males (Hornshaw et al., 1986); and a reproductive toxicity study by Tyl and Neeper-Bradley (1989) identified a LOAEL of 175 mg/kg-day, and a corresponding NOAEL of 30 mg/kg-day, based on neurotoxicity in adult F1-generation female S-D rats. The subchronic-duration toxicity study (Dietz and Mulligan, 1988) selected by IRIS as the principal study in the assessment of 2-methylphenol identified a NOAEL of 50 mg/kg-day based on neurotoxicity in females S-D rats observed at the 175 mg/kg-day dose.

Benchmark dose (BMD) analyses were conducted using the U.S. EPA's Benchmark Dose Software (BMDS, version 2.4). Data from the short-term study by Hornshaw et al. (1986) could not be modeled because the mean and standard deviation were not provided for each data point. Also, data from the subchronic-duration study by Dietz and Mulligan (1988) could not be modeled because neurotoxicity data was only presented for the highest dose. Because the ataxia and hypoactivity data from the Tyl and Neeper-Bradley (1989) study are in adult F1-generation female S-D rats, BMD modeling was performed utilizing a BMR of 10% and the results are summarized in Appendix C. Following BMD modeling, the most sensitive effect was hypoactivity in adult F1-generation female rats, with a BMD_{10} of 51.4 mg/kg-day and a $BMDL_{10}$ of 28.8 mg/kg-day. Although the study by Tyl and Neeper-Bradley (1989) was not peer-reviewed, it was performed in accordance with GLP guidelines. Furthermore, the studies utilized by IRIS (Dietz and Mulligan, 1988; TRL, 1986) as well as the Tyl and Neeper-Bradley (1989) study, point to the CNS as a major target of 2-methylphenol. Therefore, Tyl and Neeper-Bradley (1989) is selected as the principal study, with the $BMDL_{10}$ of 28.8 mg/kg-day based on hypoactivity in adult F1-generation females as the point of departure (POD) for derivation of the subchronic p-RfD.

The U.S. EPA 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. Another approach may include using chemical-specific information, including what is known about the toxicokinetics and toxicodynamics of the chemical, to derive chemical-specific adjustments. In lieu of chemical-specific information to derive human equivalent oral exposures, U.S. 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. Following EPA guidance, the $BMDL_{10}$ obtained from modeling the hypoactivity data from F1-generation adult female rats (Tyl and Neeper-Bradley, 1989) is converted to an HED through an 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 BW_a of 0.25 kg for rats and a standard BW_h of 70 kg for humans the resulting DAF is 0.24. Applying this DAF to the $BMDL_{10}$ obtained from modeling the hypoactivity data from F1-generation adult female rats (Tyl and Neeper-Bradley, 1989) yields a $BMDL_{10HED}$ as follows:

$$\begin{aligned} BMDL_{10HED} &= BMDL_{10} \times DAF \\ &= 28.8 \text{ mg/kg-day} \times 0.24 \\ &= 6.9 \text{ mg/kg-day} \end{aligned}$$

The subchronic p-RfD for 2-methylphenol, based on the $BMDL_{10HED}$ of 6.9 mg/kg-day for hypoactivity in F1-generation adult female rats, is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= BMDL_{10HED} \div UF_C \\ &= 6.9 \text{ mg/kg-day} \div 30 \\ &= \mathbf{2 \times 10^{-1} \text{ mg/kg-day}} \end{aligned}$$

Table 7 summarizes the uncertainty factors for the subchronic p-RfD for 2-methylphenol.

Table 7. Uncertainty Factors for the Subchronic p-RfD for 2-Methylphenol

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) has been applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following oral 2-methylphenol exposure. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent dose (HED) through application of a dosimetric adjustment factor (DAF) as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* .
UF_D	1	A UF_D of 1 is applied because the database includes three acceptable subchronic-duration studies in mice and rats (NTP, 1992; Dietz and Mulligan, 1988; TRL, 1986), two acceptable two-generation reproductive toxicity studies in rats and mice (George et al., 1992; Tyl and Neeper-Bradley, 1989), and two acceptable developmental toxicity studies in rats and rabbits (Tyl, 1988a, b).
UF_H	10	A UF_H of 10 has been applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 2-methylphenol in humans.
UF_L	1	A UF_L of 1 has been applied because the POD was developed using a BMDL.
UF_S	1	A UF_S of 1 has been applied because a reproductive toxicity study which encompasses subchronic-duration exposure was selected as the principal study.
UF_C	30	Composite Uncertainty Factor ($UF_A \times UF_D \times UF_H \times UF_L \times UF_S$)

The confidence in the subchronic p-RfD for 2-methylphenol is medium as explained in Table 8 below.

Table 8. Confidence Descriptors for the Subchronic p-RfD for 2-Methylphenol

Confidence Categories	Designation[a]	Discussion
Confidence in study	M	Confidence in the principal study is medium. The Tyl and Neeper-Bradley (1989) study has a sound experimental design for a reproductive toxicity study in rats. Although this study is not peer reviewed, experiments were performed according to GLP guidelines. Also, the reported neurotoxicity effects are supported by two subchronic-duration rat studies previously evaluated by IRIS (Dietz and Mulligan, 1988; TRL, 1986).
Confidence in database	M	The database includes three acceptable subchronic-duration studies in mice and rats (NTP, 1992; Dietz and Mulligan, 1988; TRL, 1986 [a neurotoxicity study]) [a neurotoxicity study]) and two acceptable two-generation reproductive toxicity studies in rats and mice (George et al., 1992; Tyl and Neeper-Bradley, 1989). There are also two acceptable developmental toxicity studies in rats and rabbits (Tyl, 1988a, b). However, several of these studies were not peer-reviewed or did not present details regarding methods used.
Confidence in subchronic p-RfD[b]	M	The overall confidence in the subchronic p-RfD is medium.

[a]L = Low, M = Medium, H = High.
[b]The overall confidence cannot be greater than lowest entry in table.

Derivation of Chronic p-RfD

There are no studies in humans or animals examining the health effects from chronic oral exposure to 2-methylphenol. IRIS (U.S. EPA, 1990) has established a chronic RfD based on two principal and supporting subchronic-duration rat studies (U.S. EPA, 1987, 1986b). Based on the results of these two studies, a LOAEL of 150 mg/kg-day and a NOAEL of 50 mg/kg-day were identified for decreased body weights and neurotoxicity. Following the application of a composite uncertainty factor of 1,000, the chronic oral RfD was established by IRIS as 5×10^{-2} mg/kg-day (U.S. EPA, 1990).

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

There is one case study in humans examining the health effects from inhalation exposure to 2-methylphenol (Uzhdavini et al., 1972). The effects of inhalation exposure to animals have been evaluated in a number of short-term-duration, subchronic-duration, or reproductive studies. Unfortunately, all of these studies lack critical study details and have inadequate reporting of results, bringing into question the validity of the studies. For example, purity of the chemical, frequency of inhalation exposure, exact concentrations (rather than ranges), and the number, strain, sex, or even species of animals are often not described. Furthermore, these studies are often described in secondary sources that were translated from non-English languages (ATSDR, 1992; Pereyma, 1977; Pashkova, 1973, 1972; Uzhdavini et al., 1972). In addition, GLP and peer-review status are not discussed, and, some of the studies examined uncommon toxicity

endpoints and/or did not provide data on prototypical toxicity endpoints such as organ weight, gross necropsy, or histopathology. As a result, no reliable studies are available for the derivation of a provisional reference concentration (p-RfC).

Derivation of Subchronic p-RfC

No subchronic p-RfC can be derived due to insufficient data.

Derivation of Chronic p-RfC

No chronic p-RfC can be derived due to insufficient data.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

No human or animal data are available on the carcinogenicity of 2-methylphenol via the oral or inhalation route. 2-Methylphenol has been designated as a Group C carcinogen ("Possible Human Carcinogen") by IRIS based on U.S. EPA's 1986 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a) This classification, last updated in 1991, was based on the WOE from limited human and animal carcinogenicity data. Specifically, the classification was: "…based on an increased incidence of skin papillomas in mice in an initiation-promotion study. The three cresol isomers produced positive results in genetic toxicity studies both alone and in combination." (U.S. EPA, 1990). However, no quantitative estimate of carcinogenic risk was listed in IRIS.

Although positive results have been found for genotoxicity assays conducted for methylphenol mixtures (Litton Bionetics, 1980a, b, c), genotoxicity studies of 2-methylphenol tested alone primarily demonstrate negative results (see Table 4A). No oral or inhalation carcinogenicity studies could be located to evaluate the carcinogenic potential of 2-methylphenol. Therefore, based on U.S. EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) the WOE suggests that there is "*Inadequate Information to Assess Carcinogenic Potential*" (see Table 9).

Table 9. Cancer WOE Descriptor for 2-Methylphenol

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	N/A	N/A	
"Likely to Be Carcinogenic to Humans"	N/A	N/A	
"Suggestive Evidence of Carcinogenic Potential"	N/A	N/A	
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No human or animal cancer studies are available for 2-methylphenol via the oral or inhalation routes. Genotoxicity studies are generally negative.**
"Not Likely to Be Carcinogenic to Humans"	N/A	N/A	

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of adequate data on the carcinogenicity of 2-methylphenol precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

APPENDIX A. PROVISIONAL SCREENING VALUES

No provisional screening values were derived for this assessment.

APPENDIX B. DATA TABLES

Table B-1. Incidences of CNS findings from Male and Female Sprague-Dawley Rats Exposed to 2-Methlyphenol via Gavage for 13 Weeks[a]

CNS signs for rats at 600 mg/kg-day (high dose)[c]						
	Lethargy[b]		Tremors[b]		Coma[b]	
Weeks	Male	Female	Male	Female	Male	Female
1	13/30	30/30	9/30	17/30	6/30	6/30
3	10/26	16/24	4/26	7/24	2/26	3/24
5	12/24	14/18	6/24	13/18	–	–
9	11/13	3/6	6/13	3/6	2/13	4/6
11	8/12	5/6	3/12	1/6	2/12	1/6

[a]Dietz and Mulligan (1988).
[b]Number of animals affected/number of animals alive at beginning of indicated week.
[c]Incidences in controls or lower doses not presented by study authors.

Table B-2A. Thirteen Week Feeding Study in F344/N Rats (Males)[a]

Parameter	Control	126 mg/kg-day (1,880 ppm)	247 mg/kg-day (3,750 ppm)	510 mg/kg-day (7,500 ppm)	1,017 mg/kg-day (15,000 ppm)	2,028 mg/kg-day (30,000 ppm)
Number animals	20	20	20	20	20	20
Terminal body weight	384 ± 7	377 ± 7	394 ± 4	379 ± 6	369 ± 5	327 ± 6[b]
Organ weights						
Right Kidney (g)						
Absolute	1.42 ± 0.03	1.34 ± 0.03	1.46 ± 0.03	1.44 ± 0.03	1.44 ± 0.03	1.39 ± 0.04
Relative	3.6 ± 0	3.5 ± 0.1	3.7 ± 0.1	3.8 ± 0.1	3.9 ± 0.1[b] (↑8%)	4.2 ± 0.1[b] (↑36%)
Liver (g)						
Absolute	14.18 ± 0.26	14.10 ± 0.35	14.85 ± 0.27	15.49 ± 0.30[b] (↑9%)	15.58 ± 0.28[b] (↑10%)	14.25 ± 0.43
Relative	36.2 ± 0.6	36.9 ± 0.5	37.5 ± 0.5	40.4 ± 0.7[b] (↑11.6%)	42.2 ± 0.7[b] (↑17%)	43.4 ± 0.7[b] (↑20%)
Right testes						
Absolute	1.55 ± 0.3	1.53 ± 0.05	1.6 ± 0.037	1.55 ± 0.021	1.51 ± 0.02	1.49 ± 0.03
Relative	4.0 ± 0.1	4.0 ± 0.1	4.0 ± 0.1	4.1 ± 0.1	4.1 ± 0.1	4.5 ± 0.1[b] (↑13%)
Thymus (mg)						
Absolute	324.1 ± 13.12	306.3 ± 10.76	372.5 ± 18.87	320.2 ± 11.4	349.6 ± 15.59	303.00 ± 10.37
Relative	0.83 ± 0.04	0.80 ± 0.03	0.94 ± 0.05	0.84 ± 0.03	0.95 ± 0.04[b] (↑14%)	0.92 ± 0.03[b] (↑11%)
Nonneoplastic lesions						
Bone marrow hypocellularity	0/10	0/10	0/10	0/10	0/10	2/10 [C = 1][b]

[a]NTP (1992). Values for weight changes are expressed as the mean ± SD (% of control); % of control calculated by U.S. EPA.
[b]Statistically significant $p < 0.05$.

[C] Severity score, average (1 = minimal, 2 = mild, 3 = moderate, and 4 = marked).

Table B-2B. Thirteen Week Feeding Study in F344 in Rats (Females)[a]

Parameter	Control	129 mg/kg-day (1,880 ppm)	256 mg/kg-day (3,750 ppm)	513 mg/kg-day (7,500 ppm)	1,021 mg/kg-day (15,000 ppm)	2,024 mg/kg-day (30,000 ppm)
Number animals	20	20	20	20	20	20
Terminal body weight	204 ± 3	203 ± 4	205 ± 3	200 ± 4	190 ± 3[b] (↓7%)	174 ± 3[b] (↓15%)
Organ weights						
Right kidney (g)						
Absolute	0.79 ± 0.02	0.81 ± 0.02	0.81 ± 0.017	0.76 ± 0.011	0.78 ± 0.010	0.75 ± 0.03
Relative	3.8 ± 0.1	3.9 ± 0.1	3.8 ± 0.1	3.7 ± 0.1	4.0 ± 0.1[b] (5%)	4.2 ± 0.2[b] (↑11%)
Liver (g)						
Absolute	6.46 ± 0.14	6.37 ± 0.16	6.78 ± 0.11	6.94 ± 0.14[b] (↑7%)	6.93 ± 0.27[b] (↑7%)	6.69 ± 0.18
Relative	30.6 ± 0	30.7 ± 0.1	32.0 ± 0	33.7 ± 0.1[b] (↑10.1 %)	35.1 ± 0.2[b] (↑15%)	37.3 ± 0.1[b] (↑22%)
Thymus (mg)						
Absolute	271.20 ± 10.43	255.1 ± 10.90	269.2 ± 11.56	271.10 ± 9.70	254.6 ± 8.94	230.2 ± 9.59[b] (↓15%)
Relative	1.29 ± 0.05	1.23 ± 0.06	1.27 ± 0.06	1.32 ± 0.04	1.29 ± 0.05	1.28 ± 0.04
Nonneoplastic lesions						
Bone marrow hypocellularity	0/10	1/10 [C = 1]	0/10	1/10 [C = 1]	3/10 [C = 1.3]	8/10[b] [C = 1.2]
Reproductive effects						
Estrous cycle length (days)	4.9 (0.2)	4.7 (0.2)	NA	5.1 (0.2)	NA	5.3 (0.2)

[a]NTP (1992). Values for weight changes are expressed as the mean ± SD (% of control); % of control calculated by U.S. EPA.
[b]Statistically significant $p < 0.05$.

[C] Severity score, average (1 = minimal, 2 = mild, 3 = moderate, and 4 = marked).

Table B-3A. Thirteen Week Feeding Study in B6C3F$_1$ Mice (Males)[a]

Parameter	Control	199 mg/kg-day (1,200 ppm)	400 mg/kg-day (2,500 ppm)	794 mg/kg-day (5,000ppm)	1,460 mg/kg-day (10,000 ppm)	2,723 mg/kg-day (20,000 ppm)
Number animals examined	10	10	10	10	10	10
Terminal body weight	31.6 ± 0.8	30.9 ± 0.8	30.8 ± 1.1	29.7 ± 0.7	30.8 ± 0.9	26.7 ± 1[b] (↓16%)
Clinical chemistry						
ALT (IU/L)[c]	153 ± 18	143 ± 28	136 ± 29	162 ± 15	124 ± 19	146 ± 21
5'-Nucleotidase (IU/L)	16.7 ± 0.8	16.0 ± 1.0	18.4 ± 0.8	19.9 ± 1.5	19.4 ± 0.8	18.4 ± 0.9[b]
Organ weights						
Liver (g)						
Absolute	1.390 ± 0.031	1.471 ± 0.052	1.570 ± 0.060[b] (↑13%)	1.459 ± 0.061	1.623 ± 0.030[b] (↑17%)	1.474 ± 0.060[b] (↑6%)
Relative	42.9 ± 0.71	46.0 ± 0.77[b] (↑7%)	48.5 ± 0.98[b] (↑13%)	46.8 ± 1.64[b] (↑9%)	51.2 ± 1.58[b] (↑19%)	53.2 ± 1.80[b] (↑24%)
Right testis(g)						
Absolute	0.117 ± 0.002	0.120 ± 0.004	0.122 ± 0.003	0.116 ± 0.002	0.121 ± 0.004	0.115 ± 0.003
Relative	3.6 ± 0.10	3.8 ± 0.09	3.8 ± 0.07	3.7 ± 0.07	3.8 ± 0.09	4.2 ± 0.11[b] (↑17%)
Thymus (mg)						
Absolute	43.40 ± 4.16	42.70 ± 3.41	44.30 ± 1.26	47.80 ± 2.44	44.6 ± 2.80	47.5 ± 3.58
Relative	1.3 ± 0.13	1.3 ± 0.10	1.4 ± 0.06	1.5 ± 0.09	1.4 ± 0.09	1.7 ± 0.15[b] (↑31%)

[a]NTP (1992). Values are expressed as the mean ± SD (% of control); % of control calculated by U.S. EPA.
[b]Statistically significant $p < 0.05$.
[c]Alanine aminotransferase.

Table B-3B. Thirteen Week Feeding Study in B6C3F$_1$ Mice (Females)[a]

Parameter	Control	237 mg/kg-day (1,200 ppm)	469 mg/kg-day (2,500 ppm)	935 mg/kg-day (5,000 ppm)	1,663 mg/kg-day (10,000 ppm)	3,205 mg/kg-day (20,000 ppm)
Number animals examined	10	10	10	10	10	10
Terminal body weight	27.4 ± 0.4	26.3 ± 0.08	26.8 ± 0.5	25.8 ± 1.0	24.8 ± 0.7[b] (↓9%)	21.7 ± 0.5[b] (↓21%)
Clinical chemistry						
ALT (IU/L)[c]	78 ± 8	116 ± 9	93 ± 8	108 ± 20	80 ± 11	176 ± 33[b]
5'-Nucleotidase (IU/L)	39.6 ± 2.4	37.3 ± 2.2	39.2 ± 1.4	39.8 ± 3.5	47.6 ± 1.9[b]	61.3 ± 1.9[b]
Organ weights						
Liver (g)						
Absolute	1.290 ± 0.028	1.289 ± 0.040	1.336 ± 0.038	1.354 ± 0.045	1.362 ± 0.040	1.171 ± 0.017
Relative	47.9 ± 0.75	48.6 ± 0.41	48.9 ± 1.11	52.0 ± 1.10[b] (↑9%)	53.8 ± 1.11[b] (↑12%)	53.6 ± 0.99[b] (↑32%)
Right kidney (g)						
Absolute	0.196 ± 0.004	0.193 ± 0.007	0.210 ± 0.006	0.198 ± 0.007	193 ± 0.007	0.170 ± 0.004[b] (↓13%)
Relative	7.3 ± 0.13	7.3 ± 0.11	7.7 ± 0.18	7.6 ± 0.10	7.6 ± 0.11	7.8 ± 0.14[b] (↑7%)
Thymus (mg)						
Absolute	52.20 ± 4.44	53.8 ± 2.06	59.6 ± 2.86	58.1 ± 3.22)	58.4 ± 2.59	54.8 ± 2.24
Relative	1.9 ± 0.17	2.0 ± 0.08	2.2 ± 0.10	2.2 ± 0.11	2.3 ± 0.09	2.5 ± 0.11[b] (↑32%)
Reproductive effects						
Estrous cycle length (days)	4.2 ± 0.2	4.2 ± 0.1	Not measured	4.1 ± 0.1	Not measured	4.8 ± 0.2[b]

[a]NTP (1992). Values are expressed as the mean ± SD (% of control); % of control calculated by U.S. EPA.
[b]Statistically Significant $p < 0.05$.
[c]Alanine aminotransferase.

Table B-4. Selected Changes in Sprague-Dawley Rats Treated with 2-Methylphenol via Gavage on GDs 6−15[a]

Parameter	0 mg/kg-day	30 mg/kg-day	175 mg/kg-day	450 mg/kg-day
Maternal effects				
Mortality[c]	0/50	0/25	0/25	4/25 (16%)[b]
Labored respiration[c]	0/46	0/22	0/21	4/21 (19%)[b]
Audible respiration[c]	0/46	0/22	0/21	4/21 (19%)[b]
Prone positioning[c]	0/46	0/22	1/21 (5%)	7/21 (33%)[b]
Hypoactivity[c]	0/46	0/22	1/21	8/21 (38%)[b]
Twitch[c]	0/46	0/22	0/21	11/21 (52%)[b]
Ataxia[c]	0/46	0/22	0/21	14/21 (67%) [b]
Tremors[c]	0/46	0/22	0/21	16/21 (76%) [b]
Perioral wetness[c]	0/46	0/22	3/21 (14%)	19/21 (90%)[b]
Material body Weight on GD 15 (g)[d]	300.69 ± 16.193	295.88 ± 15.716	297.43 ± 17.700	282.17 ± 22.13[b] (↓6.6%)
Maternal body weight on GD 21 (g)[d]	391.17 ± 28.157	385.43 ± 24.153	383.87 ± 32.891	371.24 ± 34.381
Maternal body weight gain GDs 0−21 (g)[d]	163.09 ± 20.695	157.08 ± 20.554	153.98 ± 25.726	140.48 ± 28.776[b] (↓16.1%)
Maternal weight gain during GDs 6−15 (treatment-g)[d]	41.42 ± 8.307	39.85 ± 10.606	36.38 ± 6.718	21.71 ± 14.840[b]
Maternal weight gain during GDs 15−21 (post treatment g)[d]	90.49 ± 16.026	89.56 ± 12.068	86.55 ± 18.965	86.19 ± 23.021
Maternal food consumption GDs 6−15 (g/d)[d]	22.44 ± 2.705	21.08 ± 2.143	21.49 ± 2.104	19.15 ± 2.516[b] (↓17.2%)
Maternal food consumption on GDs 15−21(g/d)[d]	26.57 ± 2.418	25.24 ± 2.70	26.17 ± 2.638	25.22 ± 3.202
Number of pregnant females[c]	46/50 (92%)	22/25 (88%)	21/25 (84%)	21/25 (84%)
Fetal effects				
Number of fetuses(litters) with dilation of lateral brain ventricle[c]	32/332 (20/46)	18/161 (10/22)	23/144 (12/21)	21/119 (13/17)[b]

Table B-4. Selected Changes in Sprague-Dawley Rats Treated with 2-Methylphenol via Gavage on GDs 6−15[a]

Parameter	0 mg/kg-day	30 mg/kg-day	175 mg/kg-day	450 mg/kg-day
% of fetuses (litters) with dilation of the lateral brain ventricle (%)[c]	9.6 (43.5)	11.2 (45.5)	16.9 (57.1)	17.6 (76.5)

[a]Tyl (1988b).
[b]Statistically Significant $p < 0.05$.
[c]Number affected/number examined.
[d]Values are expressed as the mean ± SD (% of control); % of control calculated by U.S. EPA.

Table B-5. Clinical Parameters in Adult and Fetal New Zealand White Rabbits Following Maternal Exposure to 2-Methylphenol via Gavage from GDs 6–18[a]

Category	Gestation Days	0.0 mg/kg-day	5.0 mg/kg-day	50.0 mg/kg-day	100.0 mg/kg-day
Pregnant Rabbits Exposed	NA	28	14	14	14
Maternal effects					
Hypoactive	6−18	0	0	0	1
Audible Respiration	6−18	0	0	0	2
Ocular Discharge, Red (eye-right)	6−18	0	0	1	0
Ocular Discharge, Other (Eye-both, eye right)	6−18	0	0	1	1
Developmental effects					
Number fetuses (litters) with ecchymosis [subepidermal hematoma][c]	N/A	0/212 (0/23)	1/115 (1/13)	0/107 (0/13)	4/129 (4/14)[b]
Number of fetuses (litters) with poorly ossified sternebra number 6 [c]	N/A	62/212 (16/23)	41/115 (9/13)	39/107 (9/13)	52/129 (14/14)[b]

[a]Tyl (1988a).
[b]Statistically Significant $p < 0.05$.
[c]Number affected/number examined.

Table B-6A. Selected Changes in Parental (F0) Sprague-Dawley Rats Exposed to 2-Methylphenol by Gavage in a Two-Generation Reproductive Toxicity Study[a]

	Control	30 mg/kg-day	175 mg/kg-day	450 mg/kg-day
F0 Males				
Mortality	0/25	0/25	0/25	12/25[b] (48%)
Clinical Signs[c]				
Gasping	0/25	0/25	0/25	8/25[b] (32%)
Labored respiration	0/25	0/25	0/25	21/25[b] (84%)
Rapid Respiration	0/25	0/25	0/25	23/25[b] (92%)
Audible respiration	0/25	1/25 (4%)	1/25 (4%)	22/25[b] (88%)
Urine stains	0/25	1/25 (4%)	1/25 (4%)	8/25[b] (32%)
Prostration	0/25	0/25	0/25	17/25[b] (68%)
Tremor	0/25	0/25	0/25	13/25[b] (52%)
Twitch	0/25	0/25	0/25	19/25[b] (76%)
Lacrimation	0/25	0/25	0/25	21/25[b] (84%)
Ataxia	0/25	0/25	0/25	7/25[b] (28%)
Hypoactive	0/25	0/25	0/25	24/25[b] (96%)
Perioral wetness	1/25 (4%)	1/25 (4%)	3/25 (12%)	25/25[b] (100%)
F0 Females				
Mortality	0/25	0/25	0/25	10/25[b] (40%)
Clinical Signs[c]				
Gasping	0/25	0/25	2/25 (8%)	10/25[b] (40%)
Labored respiration	0/25	0/25	3/25 (12%)	16/25[b] (64%)
Rapid respiration	0/25	1/25 (4%)	0/25	23/25[b] (92%)
Audible respiration	0/25	0/25	0/25	22/25[b] (88%)
Urine stains	0/25	0/25	0/25	9/25[b] (36%)
Prostration	0/25	0/25	0/25	16/25[b] (64%)
Tremor	0/25	0/25	0/25	17/25[b] (68%)
Twitch	0/25	0/25	1/25 (4%)	20/25[b] (80%)
Lacrimation	1/25 (4%)	2/25 (8%)	0/25	10/25[b] (40%)
Delayed of loss of righting reflex	0/25	0/25	0/25	6/25[c] (24%)
Ataxia	0/25	0/25	0/25	17/25[b] (68%)
Hypoactive	1/25 (4%)	0/25	0/25	21/25[b] (84%)
Perioral wetness	1/25 (4%)	1/25 (4%)	4/25 (16%)	24/25[b] (96%)

[a]Tyl and Neeper-Bradley (1989).
[b]Statistically Significant $p < 0.05$.
[c]Number affected/number examined.

Table B-6B. Selected Changes in First-Generation (F1) Sprague-Dawley Rats Exposed to 2-Methylphenol by Gavage in a Two-Generation Reproductive Toxicity Study[a]

	Control	30 mg/kg-day	175 mg/kg-day	450 mg/kg-day
F1 Males				
Mortality	0/25	1/25 (4%)	0/25	8/25[b] (32%)
Clinical Signs[c]				
Slow respiration	0/25	0/25	0/25	7/25[b] (29%)
Rapid respiration	0/25	0/25	0/25	15/25[b] (60%)
Audible respiration	0/25	0/25	0/25	14/25[b] (56%)
Prostration	0/25	0/25	0/25	17/25[b] (68%)
Tremor	0/25	0/25	0/25	17/25[b] (68%)
Twitch	0/25	0/25	0/25	18/25[b] (72%)
Ataxia	0/25	2/25 (8%)	2/25 (8%)	22/25[b] (88%)
Hypoactive	0/25	2/25 (8%)	4/25 (16%)	20/25[b] (80%)
Perioral wetness	0/25	2/25 (8%)	10/25[b] (40%)	21/25[b] (84%)
F1 Females				
Mortality	0/25	0/25	0/25	14/25[b] (56%)
Clinical Signs				
Labored respiration	0/25	0/25	0/25	9/25[b] (36%)
Slow respiration	0/25	0/25	2/25 (8%)	12/25[b] (48%)
Rapid respiration	0/25	0/25	1/25 (4%)	22/25[b] (88%)
Audible respiration	1/25 (4%)	2/25 (8%)	2/25 (8%)	20/25[b] (80%)
Urogenital wetting	0/25	0/25	0/25	8/25b (32%)
Urine stains	0/25	0/25	0/25	12/25[b] (48%)
Prostration	0/25	0/25	1/25 (4%)	21/25[b] (84%)
Tremor	0/25	0/25	1/25 (4%)	23/25[b] (92%)
Twitching	0/25	0/25	3/25 (12%)	23/25b (92%)
Ataxia	0/25	0/25	7/25[b] (28%)	24/25[b] (96%)
Hypoactive	0/25	2/25 (8%)	8/25[b] (32%)	22/25[b] (88%)
Perioral wetness	0/25	3/25 (12%)	24/25[b] (96%)	23/25[b] (92%)
Body-weight gain				
GDs 0−7	26.90 ± 7.951	26.93 ± 8.544	24.09 ± 5.470	16.69 ± 8.202[b]
GDs0−20	126.69 ± 19.562	120.57 ± 17.496	120.74 ± 18.662	106.112 ± 22.24[b]
Days 0−4 of lactation	15.52 ± 12.263	7.75 ± 14.367	11.49 ± 10.151	2.62 ± 10.10[b]
Days 0−21 of lactation	25.29 ± 19.486	11.27 ± 16.545[c]	16.23 ± 13.344	21.44 ± 13.758

[a]Tyl and Neeper-Bradley (1989).
[b]Statistically Significant $p < 0.05$.
[c]Number affected/number examined (total number examined corresponds to 25 randomly selected pups per treatment group).
[d]Values are expressed as the mean ± SD (% of control); % of control calculated by U.S. EPA.

Table B-7. Selected Organ Weight and Histopathology Data on F1-Generation Swiss CD-1 Mice Exposed In Feed to 2-Methylphenol in a Two-Generation Reproductive Toxicity Study[a]

Parameter	Control	0.5%
Males		
Terminal body weight[c]	33.1 ± 0.5	32.9 ± 0.88
Liver Absolute weight (g)[c]	1.5 ± 0.06	1.6 ± 0.07
Kidneys/adrenals Absolute weight (mg)[c]	671.8 ± 25.6	692.0 ± 33.8
Kidney histopathology		
Nephropathy[d]	3/19	4/19
Hydronephrosis[d]	0/19	5/19
Cyst, cortex[d]	0/19	1/19
Females		
Terminal body weight	28.9 ± 0.42	27.4 ± 0.47[b] (↓5%)
Liver Absolute weight (g)	1.7 ± 0.05	1.6 ± 0.04
Kidneys/adrenals Absolute weight (mg)	474.3 ± 10.9	466.3 ± 13.3
Kidney histopathology		
Nephropathy[d]	6/20	2/19
Atrophy, cortex[d]	0/20	1/19
Cyst, cortex[d]	0/20	2/19

[a]George et al. (1992).
[b]Statistically Significant $p < 0.05$.
[c]Values are expressed as the mean ± SE (% of control).
[d]Number affected/number examined.

APPENDIX C. BMD OUTPUTS

MODEL-FITTING PROCEDURE FOR QUANTAL NONCANCER DATA

The model-fitting procedure for dichotomous noncancer data is as follows. All available dichotomous models in the EPA BMDS (version 3.3) are fit to the incidence data using the extra risk option. The multistage model is run for all polynomial degrees up to $n - 1$ (where n is the number of dose groups including control). Adequate model fit is judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all the models providing adequate fit to the data, the lowest BMDL is selected as the point of departure when the difference between the BMDLs estimated from these models is more three-fold (unless it is an outlier); otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) is chosen. In accordance with U.S. EPA (2012b) guidance, benchmark doses (BMDs) and lower bounds on the BMD (BMDLs) associated with a BMR of 10% extra risk are calculated for all models.

MODEL FITTING RESULTS FOR ATAXIA IN F1-GENERATION FEMALE RATS

Table C-1. Model Predictions for Increased Incidence of Ataxia in F1-Generation Female Sprague-Dawley Rats Treated with 2-Methylphenol

Model Name	χ^2	*p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)	Conclusions
Gamma	0.013	0.9971	42.06	123.6	80.81	
Logistic	0.606	0.45	44.36	127.5	94.18	
LogLogistic	0.006	0.9978	42.05	131.5	93.944	
LogProbit	0	1	42.04	131.9	93.50	
Multistage (2° polynomial)	-0.549	0.816	41.34	88.92	62.11	**Lowest AIC, best fitting model**
Multistage (3° polynomial)	0.136	0.9137	42.38	109.74	60.39	
Probit	0.633	0.5637	43.70	124.1	89.77	
Weibull	0.11	0.9441	42.26	112.5	72.35	
Quantal-Linear	-1.654	0.0171	54.51	30.43	22.35	

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.

χ^2 = scaled residual of interest; AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

MODEL FITTING RESULTS FOR HYPOACTIVITY IN F1-GENERATION FEMALE RATS

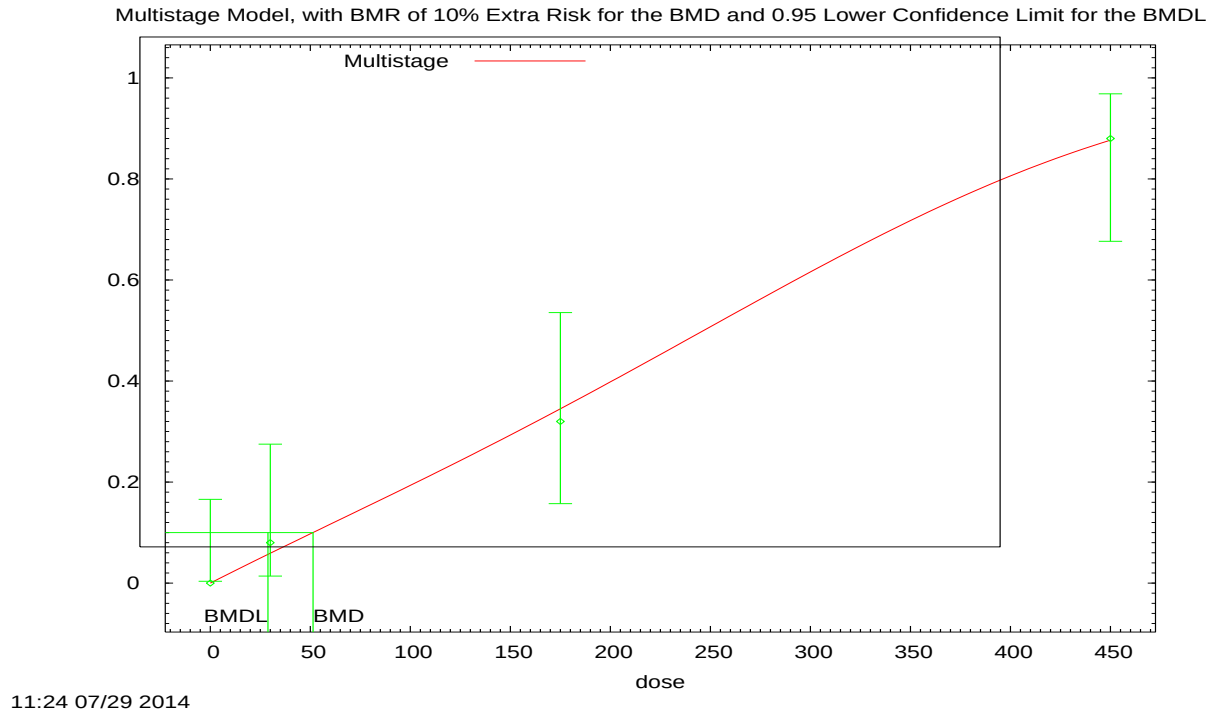
Table C-2. Model Predictions for Increased Incidence of Hypoactivity in F1-Generation Female Sprague-Dawley Rats Treated with 2-Methylphenol

Model Name	χ^2	*p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)	Conclusions
Gamma	0.767	0.3597	69.64	51.81	25.0	
Logistic	0.568	0.416	70.50	105.6	78.0	
LogLogistic	1.129	0.1501	71.29	55.533	25.93	
LogProbit	1.171	0.1048	72.12	53.87	39.49	
Multistage (2° polynomial)	0.645	0.6732	68.37	54.90	28.3	
Multistage (3° polynomial)	**0.445**	**0.8747**	**67.88**	**51.37**	**28.8**	**Lowest AIC, best fitting model**
Probit	0.459	0.4703	70.07	98.74	73.9	
Weibull	0.872	0.4392	69.16	55.43	26.1	
Quantal-Linear	-0.287	0.373	69.00	30.98	23.0	

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.

χ^2 = scaled residual of interest; AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

BMD OUTPUT FOR MULTISTAGE 2 MODEL FOR INCREASED INCIDENCE OF HYPOACTIVITY IN F1-GENERATION FEMALE RATS




```
BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


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


                  Default Initial Parameter Values
                     Background =    0.0143537
```

```
                        Beta(1) =   0.00168954
                        Beta(2) =            0
                        Beta(3) = 1.47633e-008


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(3)

   Beta(1)            1        -0.83

   Beta(3)        -0.83            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0           *               *                   *
        Beta(1)        0.0020167           *               *                   *
        Beta(2)                0           *               *                   *
        Beta(3)     1.29853e-008           *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -31.8141         4
   Fitted model          -31.939         2     0.249865      2          0.8826
  Reduced model         -62.6869         1      61.7457      3         <.0001

           AIC:          67.8781


                                Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          25        0.000
   30.0000     0.0590         1.476     2.000          25        0.445
  175.0000     0.3446         8.615     8.000          25       -0.259
  450.0000     0.8764        21.910    22.000          25        0.055

 Chi^2 = 0.27      d.f. = 2        P-value = 0.8747


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95
```

```
              BMD =        51.3712

             BMDL =        28.8176

             BMDU =        113.245

Taken together, (28.8176, 113.245) is a 90     % two-sided confidence
interval for the BMD
```

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