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Provisional Peer-Reviewed Toxicity Values for

4-Chloro-3-Methylphenol (*p*-Chloro-*m*-Cresol)
(CASRN 59-50-7)

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Commonly Used Abbreviations

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 4-CHLORO-3-METHYLPHENOL (CASRN 59-50-7)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths

and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may 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), or OSRTI.

INTRODUCTION

p-Chloro-*m*-cresol is a substituted phenol bactericidal preservative used in several consumer products, such as sunscreens, topical drugs, and other applications. Allergic contact dermatitis is a commonly reported health effect, and there is evidence that the chemical may produce malignant hyperthermia in genetically predisposed individuals (see below). Table 1 includes the available reference values from the literature. No RfD, RfC, or carcinogenicity assessment for *p*-chloro-*m*-cresol is available on IRIS (U.S. EPA, 2008). The Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997a) lists a subchronic RfD of 2 mg/kg-day, originally derived in a Health and Environmental Effects Document (HEED) for *p*-chloro-*m*-cresol (U.S. EPA, 1988), based on a NOAEL of 200 mg/kg-day for decreased body-weight gain in rats treated by gavage for 28-days (Madsen et al., 1986). A chronic RfD is not derived in the HEED due to the short duration of the key study available at that time (U.S. EPA, 1988). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994) includes no relevant documents other than the HEED (U.S. EPA, 1988). The Drinking Water Standards and Health Advisories list (U.S. EPA, 2006) does not include *p*-chloro-*m*-cresol. An OPP (EPA, Office of Pesticide Programs) Reregistration Eligibility Decision (RED) for *p*-chloro-*m*-cresol (U.S. EPA, 1997b) used a NOAEL of 30 mg/kg-day (based on maternal effects, i.e., clinical signs and decreased body-weight gain), in a rat developmental toxicity study by Miles Inc. (1992a). The RED used a margin of exposure (MOE) of 100 for subchronic exposure. The chronic value in the RED used a LOAEL of 28 mg/kg-day (based on decreased brain weight in females in a chronic rat feeding study by Bayer AG, 1992) with a MOE of 300 for chronic exposure.

The Agency for Toxic Substances and Disease Registry (ATSDR, 2008) has not produced a Toxicological Profile that includes *p*-chloro-*m*-cresol. No Environmental Health Criteria Document for *p*-chloro-*m*-cresol is available from the World Health Organization (WHO, 2008). *p*-Chloro-*m*-cresol has not been evaluated for carcinogenicity by the International Agency for Research on Cancer (IARC, 2008) or the National Toxicology Program (NTP, 2005, 2008). The Occupational Safety and Health Administration (OSHA, 2008), the National Institute for Occupational Safety and Health (NIOSH, 2008), and American Conference for Governmental Industrial Hygienists (ACGIH, 2007) have not derived occupational exposure

lists for *p*-chloro-*m*-cresol. The California Environmental Protection Agency (CalEPA, 2002, 2005a,b) has not derived a recommended exposure limit (REL) or cancer potency factor for *p*-chloro-*m*-cresol.

Table 1. Reference Values in Current Literature

Agency	NOAEL	Reference Value	Source
EPA-HEAST	200 mg/kg-day	2 mg/kg-day	Madsen et al., 1986
OPP-RED	30 mg/kg-day	0.3 mg/kg-day	Miles Inc., 1992a
OPP-RED	28 mg/kg-day	0.1 mg/kg-day	Bayer AG, 1992

Literature searches were conducted in December 2007, using the following databases: MEDLINE, TOXLINE, BIOSIS (August 2000−December 2007), TSCATS1/2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents (prior 6 months). The MEDLINE search was updated in July 2009. Except where noted, the literature searches were not limited by date. Reviews produced by the Cosmetic Ingredient Review Expert Panel (Anderson, 1997, 2006) were also examined for relevant studies.

REVIEW OF PERTINENT DATA

Human Studies

Oral Exposure

There are no relevant studies involving oral exposure of humans to *p*-chloro-*m*-cresol, and oral exposure are likely rare because the uses are predominantly topical.

Inhalation Exposure

Dossing et al. (1986), a case report, indicates that *p*-chloro-*m*-cresol (chlorocresol) may be toxic to humans by the inhalation route of exposure. A woman who was occupationally exposed to chlorocresol vapors in the sterilizing department of a large pharmacy at various unknown concentrations experienced left-sided facial palsies. A provocation test elicited facial palsy after 3 minutes of exposure (a few drops of 0.1% in a sink full of water) to airborne chlorocresol. The study authors indicated that the facial palsies were probably the result of hyperreactivity to chlorocresol since no symptoms were seen in any other workers in contact with chlorocresol. No other information was located concerning noncancer health effects in humans following inhalation exposure to *p*-chloro-*m*-cresol.

Other Routes

p-Chloro-*m*-cresol is used as preservative in skin care products (not common) and in pharmaceuticals including anesthetics, electrode creams, muscle relaxants, heparin, and insulin preparations (Anderson, 1997). The FDA does not report tolerances for *p*-chloro-*m*-cresol in cosmetic preparations, but the European Union authorizes its members to use *p*-chloro-*m*-cresol as a preservative in cosmetics to a maximum concentration of 0.2%. Noncosmetic preparations, such as pharmaceuticals, contain *p*-chloro-*m*-cresol at concentrations ranging from 0.05 to 0.5% (Anderson, 1997). The FDA reports a maximum allowable tolerance of 0.75% for *p*-chloro-*m*-cresol in topical emulsion/creams approved for pharmaceutical use in the United

States (FDA, 2008). As *p*-chloro-*m*-cresol is considered to be an excipient[1], other uses of *p*-chloro-*m*-cresol in pharmaceuticals (such as insulin, heparin, anesthetics, etc.) are evaluated by the FDA on a case-by-case basis as part of the drug approval process for the individual pharmaceutical products (FDA, 2005).

Clinical studies indicate that 2% *p*-chloro-*m*-cresol causes skin irritation in humans. Predictive patch tests with 5% *p*-chloro-*m*-cresol were negative, but provocative patch tests conducted on patients with allergic contact dermatitis or eczema produced positive results in a few individuals (Anderson, 1997).

As discussed below in the "Mechanistic/Sensitive Sub-populations" section, *p*-chloro-*m*-cresol in pharmaceutical preparations may trigger muscular calcium imbalance and a syndrome known as Malignant Hyperthermia (MH) in genetically predisposed sensitive individuals.

Animal Studies

Oral Exposure

Subchronic Studies—There are two subchronic studies in the literature. In the first, Madsen et al. (1986) administered *p*-chloro-*m*-cresol in soybean oil to groups of 10 male and 10 female rats (strain not reported) by gavage at doses of 0, 50, 200, or 400 mg/kg-day for 28 days. Blood samples were taken from eight males and eight females in each group after 21 days of dosing. Hematological analysis included hemoglobin, packed cell volume, total erythrocyte count, and glucose in whole blood. Plasma concentrations of creatinine and urea and activity of aspartate aminotransferase and alkaline phosphatase were determined. Upon necropsy, the kidneys, spleen, brain, adrenals, liver, and testes were weighed and examined microscopically along with tissue samples from the stomach, small intestine, pancreas, lung, aorta, heart, thymus, thyroid, and parathyroid. These tissues were fixed in 10% formalin and prepared for light microscopy by staining with hematoxin-eosin (all organs), PAS (liver), and Pearl (liver and spleen). Frozen sections of the liver and heart were stained with Oil red O. There were no clinical signs of toxicity in any of the treated groups. A significant decrease in body-weight gain was noted in high-dose males (32% lower: 14.1 ± 5.7 g versus 20.7 ± 5.0 g in controls) and females (41% lower: 5.5 ± 2.9 g versus 9.3 ± 3.0 g in controls), compared to controls. Absolute body weights were not reported in the study. Hematological and clinical chemistry variables were examined and found to be within the normal range in all experimental animals. There were no significant treatment-related effects on relative organ weights and no pathological indications of treatment-related effects (data not shown). The authors considered the growth retardation in high-dose males and females to be toxicologically significant. The NOAEL for this study is 200 mg/kg-day. The LOAEL is 400 mg/kg-day based on decreases in body-weight gain in *p*-chloro-*m*-cresol-exposed rats.

In the second study, Bayer AG (1992, unpublished) briefly mentions a subchronic range-finding study in which groups of male and female Wistar rats (20/sex/group) were fed diets containing 0, 150, 500, or 1500 ppm of *p*-chloro-*m*-cresol (0, 12, 41, or 120 mg/kg-day for males and 0, 17, 54, or 167 mg/kg-day for females) for 13 weeks. The study protocol is not described further by the study authors, but they reported the following result: slightly decreased

[1]Nonactive ingredients such as fillers, diluents, extending agents, preservatives, solvents, emulsifiers, coloring agents, etc. that are added intentionally to therapeutic or diagnostic products (FDA, 2005).

body-weight gain (5−6%) in comparison with controls was observed in males at 500 and 1500 ppm. No treatment-related effects were observed for clinical signs, food consumption, clinical biochemistry, urinalysis, organ weights, or gross or microscopic pathology. The highest dose tested, 167 mg/kg-day, is the NOAEL for this study because the toxicological significance of a 5−6% decrease in body-weight gain in adult rats is unknown and the study protocol was not described.

Chronic Studies—There is one chronic study in the literature. Groups of 60 male and 60 female Wistar rats (5−6 weeks of age) were fed Preventol CMK (*p*-chloro-*m*-cresol, ≥99.9% pure) in the diet at concentrations of 0, 400, 2000, or 10,000 ppm (Bayer AG, 1993, unpublished). Interim sacrifices were made for 10 rats/sex/group after 12 months of treatment. The remaining 50 rats/sex/group were treated for a total of 24 months. Average doses of *p*-chloro-*m*-cresol over the 24-month period of exposure were 0, 21, 103.1, and 558.9 mg/kg-day for males and 0, 27.7, 134.3, and 743.5 mg/kg-day for females. Animals were observed daily for clinical signs. Food and water intake were monitored and body weights were recorded weekly. There were 20 animals from each study group that were randomly selected for ophthalmologic examination prior to initiation of exposure. Additional ophthalmologic examinations were performed on 20 randomly-selected animals from each of the control and high-dose groups following 52 and 104 weeks of treatment. Clinical chemistry and hematological examinations were performed on blood samples taken from 10 rats per group following 27, 53, 79, and 104 weeks of exposure. Hematological variables included hemoglobin, hematocrit, mean corpuscular volume, prothrombin time, and erythrocyte morphology, as well as erythrocyte, leukocyte, thrombocyte, and reticulocyte counts. Clinical chemistry variables included alkaline phosphatase, aspartate and alanine aminotransferases, gamma-glutamyltransferase, glutamate-dehydrogenase, plasma and erythrocyte cholinesterase, albumin, bilirubin, cholesterol, creatinine, creatine kinase, glucose, calcium, chloride, iron, and inorganic phosphate. Urinalysis was performed during Weeks 26/27, 51/52, 78/79, and 103/104. Gross pathological examinations of all major tissues and organs were performed on all rats found dead or moribund prior to study termination, as well as those scheduled for interim or terminal sacrifice. The brain, heart, liver, kidneys, spleen, and testes/ovaries were weighed in animals killed at scheduled sacrifices. Samples of all major organs and tissues, as well as all suspected tumors, were prepared for detailed histological examination after fixation with 10% formalin.

There were no treatment-related effects on survival and other than nonspecific poor general condition in high-dose females, and there were no treatment-related clinical signs of toxicity in any group (Bayer AG, 1993). Body weight was significantly lower ($p < 0.01$) than controls for high-dose males (up to 8%) throughout the study. Body weight for all treated females was significantly lower ($p < 0.01$) than controls throughout the study. Body weights in the *p*-chloro-*m*-cresol groups were up to a maximum of 10%, 11%, and 20% lower than control body weights for females in the 400-, 2000-, and 10,000-ppm groups, respectively. However, the average body-weight decreases relative to controls were 8.9%, 8.7%, and 18.7% for the low-, mid-, and high-dose females throughout the period of active growth and maturity with the largest deviation between controls and *p*-chloro-*m*-cresol-exposed groups (Week 12 through Week 104). As a 10% decrease in body weight is considered toxicologically relevant, the observed reductions in body weight are considered to be adverse only in high-dose females. Thus, the 10,000-ppm dose is considered the LOAEL and the 2000-ppm dose is considered a NOAEL. Mean food and water intakes per kg-body weight were comparable among control, 400-, and

2000-ppm males, but the intakes were increased[2] among 10,000-ppm males (6% for food, 9% for water) relative to controls. A similar pattern was observed for females, with food and water intakes per kg-body weight increased by 10% and 16%, respectively, in comparison with controls.

There were no treatment-related adverse effects on eyes or hematological variables (Bayer AG, 1993). Reduced cholesterol and triglycerides were observed in high-dose male and female rats throughout the study (statistically significant some of the time) and significantly lower phosphate concentrations were observed in high-dose male rats at all examination time points (Treatment Weeks 26, 51, 78, and 103). However, the study authors reported that these values fell within their respective historical control ranges and, as such, were not considered to be of toxicological relevance. No consistent treatment-related effects were observed for other clinical chemistry variables. With regard to urinalysis, high-dose males had slightly lower mean urine density (1013−1031 g/L versus 1032−1043 for controls) accompanied by slightly increased urine volume (7−15 ml versus 5−7 mL for controls) at all examination time points (statistically significant at most time points). Significantly lower mean protein excretion was observed in high-dose female rats at the 51-, 78-, and 103- (but not 26) week examination points (1.0−5.0 mg versus 2.5−9.5 for controls), in low-dose females at 51 and 78 (but not 26 or 103) weeks (0.9−2.3 mg versus 2.5−6.2 mg for controls) and in mid-dose females at 51 (but not 26, 78, or 103) weeks (1.3 mg versus 2.5 mg for controls). There were no other potentially relevant significant changes in other urinalysis variables. These observations together suggest a consistent adverse effect on the urinary system of the male rat, with a NOAEL of 103.1 and a LOAEL of 558.9 mg/kg-day.

At interim and terminal sacrifices, there were small, statistically significant (variable *p*-values) changes in occasional absolute and/or relative organ weights (primarily in females) (Bayer AG, 1993). These changes appeared to reflect the general decrease in body weight relative to controls (i.e., decreased absolute weights and/or increased relative weights), rather than specific target-organ effects. The organ weight changes were not considered to be toxicologically relevant by the researchers.

No treatment-related gross or microscopic findings were revealed at interim pathology examinations (Bayer AG, 1993). At terminal necropsy (Week 104), the only gross treatment-related finding was the observation of kidney histopathology in 6/44 high-dose male rats. Incidences of histopathological lesions of interest at study termination, limited to lesions in the kidneys and testes in males, are shown in Table 2.

A statistically significant ($p < 0.01$) increase in the incidence of unilateral and combined unilateral and bilateral degeneration of seminiferous tubules in comparison with controls was observed in mid- and high-dose males (Bayer AG, 1993). A statistically significant ($p < 0.05$) decrease in unilateral and combined unilateral and bilateral spermatozoa in the epididymides was also observed in these dose groups. Significantly ($p < 0.05$) increased incidences of renal papillary necrosis and cortical fibrosis were observed only in high-dose males. The occurrence of kidney lesions only in male rats is suggestive of male rat specific alpha-2u-accumulation leading to nephropathy; however, no further evaluations were conducted to determine whether

[2]The seemingly anomalous increase in food and water consumption reported in parallel with decreased body weight was attributed to "delayed body weight development" by the study authors.

the renal lesions observed in this study were associated with alpha-2u-globulin. Given that the nephritic endpoint was not the most sensitive endpoint, it was not further considered. No treatment-related statistically significant nonneoplastic histopathological changes were observed in females.

Table 2. Incidence of Histopathological Findings of Interest in Male Rats[a]

Target/Lesion	Mean Dose (mg/kg-day)			
	0	**21**	**103.1**	**558.9**
Kidney (number examined)	50	49	50	50
Renal papillary necrosis				
- unilateral	2[b]	0	0	8
- bilateral	0	0	0	1
- truncated papilla	0[b]	0	0	6[c]
Renal cortical fibrosis	0[b]	0	0	7[c]
Testes/Epididymides—number examined	50	49	49	50
Reduced spermatozoa				
- unilateral	1[b]	2	8[c]	7
- bilateral	2	1	1	4
- combined	3[d]	3	9	11[c]
Degeneration of seminiferous tubules				
- unilateral	0	3	7[c]	4
- bilateral	2	1	0	5
- combined	2[d]	4	7	9

[a]Bayer AG, 1993
[b]Significant trend $p < 0.05$, as determined by the researchers
[c]Significantly different from controls $p < 0.05$, as determined by the researchers
[d]Significant trend $p < 0.05$ in Cochran-Armitage test performed for this review, although not labeled as a significant trend by the researchers

There were no statistically significant treatment-related effects on the incidence of neoplastic changes (Bayer AG, 1993). Female rats in the mid-, but not high-, dose group had a statistically significant increase in the incidence of pituitary adenomas (18/50, 20/49, 28/50, 25/49 for control, 400, 2000, and 10,000-ppm groups, respectively). These data failed to provide a statistically significant dose-related trend. Pituitary carcinoma was identified in only one low-dose female. A statistically significant ($p < 0.05$) increase in the incidence of pituitary adenomas was also observed in low-dose males (13/50) but not in mid- (9/50) or high-dose (4/50) males (compared with 5/50 controls). In males, there was a statistically significant ($p < 0.05$) decreasing trend for these tumors, although the incidence was within the historical control range. There were no treatment-related effects on other tissues or organs.

The NOAEL for this study (Bayer AG, 1993) is 400 ppm (21 mg/kg-day). The LOAEL is 2000 ppm (103.1 mg/kg-day) based on combined incidence of unilateral and bilateral degeneration of seminiferous tubules and combined unilateral and bilateral incidence of reduced epididymal spermatozoa in males.

Reproductive/Developmental Studies—In a developmental toxicity study (Miles Inc., 1992a, unpublished), groups of 25 pregnant Wistar rats were given 0, 30, 100, or 300 mg/kg of Preventol CMK (*p*-chloro-*m*-cresol) by gavage in 0.5% aqueous methyl cellulose, once per day on Days 6−15 of gestation. Clinical examinations were performed daily, food and water intake were noted and body weights were recorded on gestation days (GD) 0, 6−15, and 20. Gross pathological examinations were performed on GD 20, at which time uteri were removed and examined for numbers of corpora lutea, implantations, live fetuses, and live fetuses per sex. Uterine and fetal weights were recorded and fetuses were examined for signs of external malformations. Half of the fetuses were examined for gross and skeletal malformations; the other half were prepared for visceral examination.

Clinical signs of toxicity, including prostration and convulsions, were observed in high-dose dams on Day 6 of gestation (Miles Inc., 1992a). From GD 8 onward, clinical signs of toxicity became increasingly apparent and included labored breathing and bloody nasal exudate. Between GD 12 and 18, five of the high-dose dams died and another was sacrificed after being found in a moribund state. Preliminary pathological findings in these dams included gas-filled intestines and vaginal bleeding in 3/6. Food intake in the high-dose dams was significantly lower ($p < 0.05$) than that of controls throughout the treatment period (GD 6−15) and until terminal sacrifice on GD 20. Decreased water intake was also noted in high-dose dams, but actual data were not presented. Mean maternal body-weight gain in high-dose dams was decreased by 96%, relative to controls. Labored breathing was observed in some mid-dose dams following treatment. Lower food intake and significantly decreased body weight (25%) were observed in mid-dose dams in comparison with controls during the treatment period. There were no clinical or pathological signs of maternal toxicity within the low-dose group and no pathological treatment-related changes in any treated rats that survived to study termination relative to controls. No significant treatment-related effects were found for number of corpora lutea, implantations, live fetuses, and live fetuses per sex in any of the dose groups. Signs of fetotoxicity were observed only in the high-dose group and included significantly increased early resorptions (a mean of 1.8/dam in the high-dose group compared with 0.6/dam in controls) and significantly decreased mean fetal weight (approximately 8% lower than controls). There was a significant ($p < 0.05$) skewing of the normal sex ratio from 55.6% males to 45.6% males at the mid-dose. There were no treatment-related fetal malformations at any dose level. The maternal NOAEL and LOAEL (labored breathing and decreased body weight) for the study are 30 and 100 mg/kg-day, respectively. The developmental NOAEL and LOAEL (changes in sex ratio) for the study are 30 and 100 mg/kg-day, respectively. This may be indicative of an estrogenic/anti-androgenic property of the chemical as also indicated by male reproductive endpoints identified in Bayer AG (1993) above, as well as the in vitro endocrine disruption section below.

Miles Inc. (1992a) reported the existence of a precipitate in the solution used to expose the 300 mg/kg animals. This finding is consistent with the chemical properties of *p*-chloro-*m*-cresol. At 10 mL/kg dose volume, the solution for the high-dose animals would have contained 30 mg/mL *p*-chloro-*m*-cresol. According to the Merck Index (Budavari et al., 1989),

the solubility of *p*-chloro-*m*-cresol in water is 3.8 mg/mL, while it is freely soluble in oil or alcohol. The addition of 0.5% methylcellulose to the aqueous solution does not appear to have been adequate to dissolve the required amount of *p*-chloro-*m*-cresol in this study. However, the identity of the precipitate was not determined by the investigators, so the potential effect of precipitation on the concentration of the high-dose stock solution or whether it may have influenced the study in some other fashion, cannot be determined. The high-dose data were not used to reflect this uncertainty.

Inhalation Exposure

No subchronic, chronic, reproductive, or developmental toxicity studies conducted by the inhalation route of exposure were located for *p*-chloro-*m*-cresol.

Other Studies

Toxicokinetics

There is little relevant information on the toxicokinetics of *p*-chloro-*m*-cresol. A review by Paulus and Genth (1983) reported that a single oral dose of *p*-chloro-*m*-cresol was rapidly cleared through the kidneys (Schmidt, 1980). The same review cites a publication by Schmidt and Bomhard (1981) that reports no accumulation of *p*-chloro-*m*-cresol in the liver or fat of rats exposed to *p*-chloro-*m*-cresol in the diet for 13 weeks. Anderson (1997) report estimated dermal permeability coefficients for *p*-chloro-*m*-cresol of 302×10^{-3} and 235×10^{-3} cm/hr for viable tissue and stratum corneum, respectively, on the basis of tests conducted with abdominal skin from mice.

Acute/Short-term Toxicity

Miles Inc. (1992b) reported clinical signs of toxicity such as tremors, convulsions, immobilization, bloody urine, salivation, and lacrimation in groups of Sprague-Dawley rats administered *p*-chloro-*m*-cresol in single gavage doses of 2000−7683 mg/kg (males) or 1500−5762 mg/kg (females). Clinical signs occurred within 0.5 hours of dosing and persisted for 5 or 6 days following dosing for the majority of treatment groups. All of the observed deaths occurred within the same time frame. The acute oral LD_{50} values were 5129 and 3636 mg/kg for male and female rats, respectively. A review by Anderson (1997) reported an oral LD_{50} value of 1830 mg/kg for male Wistar II rats administered *p*-chloro-*m*-cresol by gavage (unpublished data from Bayer AG). Robenek et al. (1980) reported morphological evidence of cellular changes (increased mitochondria, cytoplasmic vacuolation, dilation of sinusoids, activation of Kupffer cells) in the livers of Wistar rats given a single 400 mg/kg oral dose of *p*-chloro-*m*-cresol in peanut oil and sacrificed 60 hours later.

The 4-hour inhalation LC_{50} for *p*-chloro-*m*-cresol is greater than 583 mg/m^3 in rats (Paulus and Genth, 1983 as cited by Anderson, 1997).

Mechanistic Studies/Sensitive Sub-population Studies

p-Chloro-*m*-cresol is a potent ryanodine receptor agonist, known to affect RyR1 and RyR2 isoforms present in skeletal muscle, cardiac muscle, nerve tissue and B-lymphocytes (Anderson et al., 2008; Jacobson et al., 2006; Fessenden et al., 2006; Klegris et al., 2007; Herrmann-Frank et al., 1996; Bina et al., 2006; Yang et al., 2003; Wehner et al., 2003;

McKinney et al., 2006; Suzuki et al., 2007)[3]. This has significance for certain sensitive individuals in the human population who have mutations in the ryanodine receptor (mainly the RyR1 isoform) that are associated with an autosomal dominant condition known as malignant hyperthermia (MH). MH is a pharmacogenetic disorder characterized by hypermetabolism, hypercapnia, tachycardia, hyperthermia, hypoxemia, muscle rigidity, and metabolic acidoses. It is triggered by an uncontrolled release of calcium through RyR1 in the sarcoplasmic reticulum following exposure to a number of pharmaceutical agents, including inhalational anesthetics and depolarizing muscle relaxants. It is one of the main causes of anesthesia-related death (Zucchi and Ronca-Testoni, 1997) with an estimated incidence ranging from 1 in 2000 to 1 in 8500 individuals (Anderson et al., 2008; Wehner et al., 2003).

Succinyl choline is a muscle relaxant commonly used during anesthesia and cases of MH have been associated with use of this drug (Anderson et al., 2008). Tegazzin et al. (1996) demonstrated in vitro that a *p*-chloro-*m*-cresol-containing commercial preparation of succinylcholine (Midarine®, Welcome, Pomezia, Italy), but not preservative-free succinylycholine, caused enhancement of ryanodine receptor mediated release of calcium in muscle samples from MH-sensitive individuals. This observation fosters concern that *p*-chloro-*m*-cresol could be responsible for some anesthesia-related cases of MH onset (Zucchi and Ronca-Testoni, 1997). There is one case study involving *p*-chloro-*m*-cresol that demonstrates the onset and development of MH in correlation with time from the start of an insulin drip in a young man hospitalized with new-onset diabetes mellitus (Baluch and Oommen, 2007). The young male presented with the symptoms of MH following institution of the insulin drip, and subsequently died. Six other cases where newly emerging diabetic adolescents developed MH-like symptoms following treatment with insulin for the first time (Hollander et al., 2003 as cited by Baluch and Oommen, 2007). However, in these cases, the potential doses of *p*-chloro-*m*-cresol are unknown. Muscle biopsies (to confirm the MH diagnosis) were not done.

Based on in vitro studies, *p*-chloro-*m*-cresol has been found to induce muscle contracture in tissue from MH-susceptible individuals at concentrations of 25−75 micromolar (Tegazzin et al., 1996; Baur et al., 2000). Based on standard in vitro contracture tests on muscle specimens from 202 patients from six European MH centers, 75 micromolar *p*-chloro-*m*-cresol appears to be the optimum concentration for distinguishing between MH-susceptible and MH-nonsusceptible individuals (Baur et al., 2000).

In summary, the existing studies demonstrate that *p*-chloro-*m*-cresol has a potent effect on calcium fluxes in vitro on tissues from individuals genetically predisposed to MH and is implicated in the sequalae of negative health outcomes following the use of pharmaceuticals that contained *p*-chloro-*m*-cresol. However, no studies were located that quantify exposure to *p*-chloro-*m*-cresol in vivo along with toxicologically significant effects that could be due to imbalances in calcium fluxes modulated by the ryanodine receptor (i.e., no human studies or acute, subchronic or chronic animal studies that demonstrate a quantifiable dose-response with

[3]Ryanodine receptors, named for their ability to bind the plant alkaloid, ryanodine, are calcium-release channels expressed as three isoforms (RyR1, RyR2, and RyR3) in mammalian tissues, including muscle, brain, and liver tissue (Zucchi and Ronca-Testoni, 1997). The flux of calcium necessary for muscle contraction is mediated by ryanodine receptors. The function of ryanodine receptors in other tissues is uncertain.

relevant measurable pathology, especially with regard to the heart, skeletal muscle, and possibly the nervous system).

Genotoxicity

Information on the genotoxicity of *p*-chloro-*m*-cresol is limited. *p*-Chloro-*m*-cresol was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98, either with or without metabolic activation (Madsen et al., 1986). *p*-Chloro-*m*-cresol induced SOS DNA repair in *Escherichia coli* (*E. coli*) strain PQ37 in the absence of metabolic activation (Malaveille et al., 1994). The chemical was negative in a rat hepatocyte UDS assay (U.S. EPA, 1997c).

In Vitro Neurotoxicity

Located in the auditory brainstem, the Calyx of Held is the largest presynaptic neuron in the mammalian brain. *p*-Chloro-*m*-cresol caused a dramatic increase in the amplitude of excitatory postsynaptic currents (EPSCs) and prolonged action potentials in the Calyx of Held isolated from the brain of rats (Suzuki et al., 2007). These changes occurred in parallel with *p*-chloro-*m*-cresol inhibition of voltage-gated potassium channels (-53% relative to control values), but *p*-chloro-*m*-cresol had no effect on voltage-gated calcium currents. Based on these results, the study authors concluded that *p*-chloro-*m*-cresol facilitates nerve-evoked transmitter release through inhibition of voltage-gated potassium channels.

In Vitro Endocrine Disruption

Regardless of the presence or absence of metabolic activation (rat S9 mix), *p*-chloro-*m*-cresol was positive in estrogen-receptor (ER) and yeast estrogen screen (YES) assays (Nakama et al., 2007). Positive results in these in vitro assays suggest that *p*-chloro-*m*-cresol should be tested further for endocrine-disrupting activity in vivo, particularly given the reproductive toxicity in male rats discussed previously.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR *p*-CHLORO-*m*-CRESOL

Subchronic p-RfD

Table 3 shows the available studies that can be used to address the oral subchronic and chronic toxicity of *p*-chloro-*m*-cresol. The subchronic range-finding study by Bayer AG (1992) is reported in limited detail and does not present a thorough evaluation of toxicity. The only finding reported was decrease in body weight gain (5−6% relative to controls) in a study with inadequate reporting protocols. The NOAEL for the study is 167 mg/kg-day (highest dose tested).

During the interim evaluations in the chronic rat study (Bayer AG, 1993), there were no statistically significant treatment-related findings other than reduced body weight (743.5 mg/kg-day in high-dose females) (the more sensitive reproductive endpoints appeared with longer durations of exposure).

Table 3. Summary of Oral Noncancer Dose-Response Information for *p*-Chloro-*m*-Cresol

Species	Sex	Dose (mg/kg-day)	Exposure Regimen (*route, frequency, duration)*	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Subchronic Exposure								
Rat, Wistar	M F	0, 12, 41, or 120 0, 17, 54, or 167	Diet, 13 weeks	167	None		Range-finding study; limited reporting	Bayer AG, 1992
Rat, Strain Not Reported	M, F	0, 50, 200, or 400	Gavage, 28 days	200	400	Significant decrease in body-weight gain in males (-32%) and females (-41%)	Short-term study	Madsen et al., 1986
Chronic Exposure								
Rat, Wistar	M F	0, 21, 103.1, or 558.9 0, 27.7, 134.3, or 743.5	Diet, 104 weeks	21	103.1	Seminiferous tubule degeneration and decreased epididymal spermatozoa	Reproductive effects were not observed at the 1-year interim sacrifice.	Bayer AG, 1993
Developmental/Reproductive Toxicity								
Rat, Wistar	F	0, 30, 100, or 300	Gavage, 6-15 gestation	Maternal: 30 Fetal: 30	100 100	Decreased body weight, labored breathing Skewed sex ratios	Unidentified precipitate in highest dose preparation; mortality inconsistent with acute studies and results from the 28-day study of Madsen et al., 1986	Miles Inc., 1992a

Madsen et al. (1986) performed a 28-day gavage study in male and female Wistar rats and identified a NOAEL of 200 mg/kg-day and a LOAEL of 400 mg/kg-day (the highest dose examined) for decreased body-weight gain in both male and female rats. No changes in clinical signs, serum chemistry, or histological endpoints were reported at any dose level.

Miles Inc. (1992a) exposed pregnant rats by gavage to up to 300 mg/kg-day of *p*-chloro-*m*-cresol in 0.5% aqueous methylcellulose from GD 6−15. At 300 mg/kg-day, 6/25 dams died prior to study termination and body-weight gain was decreased by 96% relative to controls. However, a precipitate identified in the high-dose stock solution makes analyses of this endpoint difficult. At 100 mg/kg-day, body-weight gain of the dams was decreased 25% and labored breathing was observed in some of the dams following treatment. Signs of fetotoxicity were observed only at the highest dose level and fetal malformations were not reported at any exposure level examined. A significant ($p < 0.05$) skew of the sex ratio from 55.6% males to 45.6% males was seen at the mid-dose, but was not significant at the low-dose. The change was from 54.4% males in the control, to 47.7% males at the low-dose, and 44.4% males at the mid-dose.

The weight of evidence shows the decrease in body-weight gain in rats as a consistent effect since it was seen in both studies by Madsen et al., 1986 and Bayer AG, 1993. The mortality reported in the study of Miles Inc. (1992a) is surprising based on the available acute toxicity and pharmacokinetic data. For example, the rat LD_{25} of *p*-chloro-*m*-cresol would be approximately 900 mg/kg (assuming a linear dose-response), based on an LD_{50} of 1830 mg/kg. Thus, a 24% mortality in rats exposed to 300 mg/kg-day for GD 6-15 (10 days in total) would suggest an accumulation of the compound. However, the review by Paulus and Genth (1983) reported a rapid elimination of *p*-chloro-*m*-cresol in the urine following a single oral dose, as well as little-to-no accumulation of *p*-chloro-*m*-cresol in the fat or liver of rats exposed for 13 weeks in the diet. Given that elimination of *p*-chloro-*m*-cresol is rapid and the available pharmacokinetic evidence does not suggest much bioaccumulation, the fact that Miles Inc. (1992a) reported 24% mortality in dams exposed to 300 mg/kg-day, over 5-fold lower than the lowest reported rat LD_{50} of 1830 mg/kg, on GD 6−15 is unexpected. The gavage rat study by Madsen et al. (1986) includes 28 days of exposure to doses as high as 400 mg/kg-day with no deaths or clinical signs. While pregnant animals could be more sensitive to exposure, the inconsistency with the rest of the available studies and presence of an unidentified precipitate in the high-dose solution raise doubts about the use of this study for quantitative risk assessment, particularly the high-dose.

The findings of the Madsen et al. (1986) and Bayer AG (1992, 1993) studies are consistent. Among these studies, the lowest LOAEL for less-than-chronic-duration exposure was 400 mg/kg-day for reduced body-weight gain in the Madsen et al. (1986) study, with a NOAEL of 200 mg/kg-day. Table 4 shows the body-weight gain data for this study. Dose-response modeling of these data was attempted, but the data were not amenable. The most sensitive endpoints are those from the Miles et al. (1992a) developmental study. Even neglecting the high-dose, there were significant maternal and fetal effects at the mid-dose that show a LOAEL of 100 mg/kg-day and a NOAEL of 30 mg/kg-day. Dose-response modeling of these data was attempted, but the data were not amenable. Due to the uncertainties associated with the unexpected early mortality and the lack of available details on the study methods, (in part because the study is unpublished, and in German) the Miles Inc. (1992a) report was not considered suitable for selection as principal study for derivation of the subchronic RfD.

U.S. EPA policy in the PPRTV program dictates that values derived from unpublished studies be termed "screening values" and be placed in an appendix (see Appendix A).

Table 4. Body Weight Gain (g) in Rats Exposed by Gavage to *p*-Chloro-*m*-cresol for 28 Days[a]

Dose (mg/kg-day)	0	50	200	400
Males (10/group)	20.7 ± 5.0	21.9 ± 7.5	21.1 ± 7.0	14.1 ± 5.7[b]
Females (10/group)	9.3 ± 3.0	11.9 ± 7.5	8.4 ± 3.9	5.5 ± 2.9[c]

[a]Madsen et al., 1986
[b]$p < 0.05$
[c]$p < 0.01$

Chronic p-RfD

There was only one chronic study available from which to derive a chronic RfD. The Bayer AG (1993) study is an unpublished study, therefore, a screening level value has been derived and is in Appendix B.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION p-RfC VALUES FOR *p*-CHLORO-*m*-CRESOL

Provisional RfC values for *p*-chloro-*m*-cresol cannot be derived due to the lack of suitable human and animal data.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR *p*-CHLORO-*m*-CRESOL

Weight-of-Evidence Descriptor

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "*Inadequate Information to Assess* [the] *Carcinogenic Potential*" of *p*-chloro-*m*-cresol. The existing evidence is summarized below.

The chronic toxicity and carcinogenicity study of rats exposed to *p*-chloro-*m*-cresol in the diet for 2 years did not identify statistically significant treatment-related neoplasms (Bayer AG, 1993). There was, however, a nonsignificant increase in interstitial cell tumors in the male rat, which may be interesting since the most sensitive effects are based on male reproductive endpoints (decreased spermatozoa and degeneration of seminiferous tubules), and the two observations may be linked because of an anti-androgenic mechanism resulting in lowered testosterone levels. The genotoxicity data for *p*-chloro-*m*-cresol are negative. No further studies relevant to the assessment of the carcinogenic potential of *p*-chloro-*m*-cresol to humans have been identified. Therefore, in accordance with current U.S. EPA cancer guidelines (U.S. EPA, 2005), the available data are too limited to support a quantitative assessment of human carcinogenic potential of *p*-chloro-*m*-cresol.

Quantitative Estimates of Carcinogenic Risk

Neither a provisional Oral Slope Factor (p-OSF) nor a provisional Inhalation Unit Risk (p-IUR) is derived because of the lack of supporting data.

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APPENDIX A. DERIVATION OF A SUBCHRONIC SCREENING VALUE FOR *p*-CHLORO-*m*-CRESOL

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for *p*-chloro-*m*-cresol because of the use of unpublished studies. However, information is available for this chemical, which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

Skewed sex ratios from the developmental study by Miles et al. (1992a) are the most sensitive endpoint, and it is deemed the critical effect. Given that both the developmental effect, and that the seminiferous tubule degeneration and decreased spermatozoa are critical effects following chronic exposure to *p*-chloro-*m*-cresol (Bayer AG, 1993), and given that *p*-chloro-*m*-cresol has yielded positive results in in vitro assays for estrogenic activity (Nakama et al., 2007), it is important in the future to determine whether additional negative reproductive effects would be observed following both male and female exposures, as these could be very sensitive endpoints. In addition, no in vivo subchronic studies that quantitatively address the toxicological implications of the known effects of *p*-chloro-*m*-cresol on ryanodine receptors (many studies cited above) or on nerve conduction (Suzuki et al., 2007) have been conducted. Such studies would ideally be designed to look for potential electrophysiological and pathological effects on the heart, skeletal muscle (in MH-susceptible and MH-nonsusceptible organisms), and nerve tissue (especially auditory brainstem).

The skewed gender-ratios from Miles et al. (1992a) data proved unamenable to benchmark dose modeling so the NOAEL/LOAEL approach was used to derive a **screening subchronic p-RfD** from the developmental NOAEL as follows:

$$\begin{aligned} \textbf{Screening Subchronic p-RfD} &= \text{NOAEL} \div \text{UF} \\ &= 30 \text{ mg/kg-day} \div 300 \\ &= \textbf{0.1 or } \mathbf{1 \times 10^{-1}} \textbf{ mg/kg-day} \end{aligned}$$

The composite UF of 300 is composed of the following:

- An UF_A of 10 is applied for inter-species extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between rats and humans.
- An UF_H of 10 for intra-species differences is used to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- An UF_D of 3 is employed for database deficiencies. The toxicological database for subchronic oral exposure to *p*-chloro-*m*-cresol is composed of a subchronic

range-finding dietary study, the interim 1-year evaluation from a chronic dietary study, a short-term (28-day) gavage study, and a developmental toxicity study, all in rats. The database lacks a multigeneration reproduction study.

APPENDIX B. DERIVATION OF A CHRONIC SCREENING VALUE FOR *p*-CHLORO-*m*-CRESOL

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for *p*-chloro-*m*-cresol, primarily because of the use of unpublished key studies. However, information is available for this chemical, which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

The database for *p*-chloro-*m*-cresol contains one chronic study, the Bayer AG (1993) study in rats. The most sensitive endpoints in this study were degeneration of seminiferous tubules and reduced spermatozoa in mid- and high-dose males, with a LOAEL of 103.1 mg/kg-day and NOAEL of 21 mg/kg-day. Table B-1 shows the data for the BMD modeling that was conducted for both of these data sets.

Table B-1 BMD Data Sets for Male Rats[a]

Endpoint	Mean Dose (mg/kg-day)			
	0	21	103.1	558.9
# Examined	50	49	49	50
Reduced Spermatozoa (Combined Unilateral and Bilateral Incidences)	3	3	9	11
Degeneration of Seminiferous Tubules (Combined Unilateral and Bilateral Incidences)	2	4	7	9

[a]Bayer AG, 1993

Appendix C shows the modeling details for the data sets for both endpoints that are amenable to BMD modeling. The best-fitting model (log-logistic) for reduced spermatozoa yielded a $BMDL_{10}$ of 133 mg/kg-day. The best-fitting model for degeneration of seminiferous tubules (log-logistic) yielded a $BMDL_{10}$ of 174 mg/kg-day. The $BMDL_{10}$ of 133 mg/kg-day is significantly higher than the NOAEL used for the subchronic RfD, (30 mg/kg-day) which used a POD derived based upon altered sex-ratios in a developmental/reproductive study by Miles (1992a) or the NOAEL for the reduced spermatozoa from Bayer AG, 1993 (21 mg/kg-day). Skewed sex ratios from the developmental study by Miles et al. (1992a) are the most sensitive endpoint, and it is deemed the critical effect. Given that the reproductive effect (Miles, 1992a) was the most sensitive effect, irrespective of the duration of exposure, the NOAEL from Miles (1992a), is used as the POD for the derivation of a chronic p-RfD.

The **screening chronic RfD** for *p*-chloro-*m*-cresol is derived as follows:

Screening Chronic RfD = NOAEL ÷ UF
= 30 mg/kg-day ÷ 300
= **0.1 or 1×10^{-1} mg/kg-day**

The composite UF of 300 is composed of the following:

- An UF_A of 10 is applied for inter-species extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between rats and humans.
- A n UF_H of 10 for is applied for intra-species differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- An UF_S of 1 is applied, as the critical developmental effect occurs during a sensitive life-stage.
- An UF_D of 3 is applied due to uncertainties in the data literature. The toxicological database for chronic oral exposure to *p*-chloro-*m*-cresol is composed of a single chronic bioassay. There is a developmental toxicity study, also in rats. The database lacks a multigeneration reproduction study. The latter is critical because the male reproductive organs and male developmental effects were identified as the most sensitive target of *p*-chloro-*m*-cresol in the chronic, the subchronic and the developmental bioassays.

APPENDIX C. DETAILS OF BENCHMARK DOSE MODELING FOR A CHRONIC RfD

Description of Model Fitting Procedure for Dichotomous Data

The model fitting procedure for dichotomous data is as follows. All available dichotomous models in the EPA BMDS (version 1.4.1c) 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). Goodness-of-fit is assessed by the χ^2 test. When several models provide adequate fit to the data (χ^2 $p \geq 0.1$), models are compared using the Akaike Information Criterion (AIC). The model with the lowest AIC is considered to provide the best fit to the data. When several models have the same AIC, the model resulting in the lowest BMDL is selected. Benchmark doses (BMDs) and lower bounds on the BMD (BMDLs) associated with an extra risk of 10% are calculated for all models.

Results of Model Fitting for Datasets of Interest

There were two datasets that were modeled for oral exposure to p-chloro-m-cresol. Table C-1 presents the results of BMD modeling for reduced spermatozoa in male rats (Bayer AG, 1993). As shown in the table, all models except the log-probit provided adequate fit to the dataset. All models that fit yielded BMD/BMDL values within a factor of three, suggesting that the choice of model does not overly influence the outcome. Based on the lowest AIC value, the log-logistic model provides the best fit to the data. A graph of the log-logistic model for reduced spermatozoa in male rats is shown in Figure C-1.

Table C-1. Model Predictions for Combined Incidence of Unilateral and Bilateral Reduced Spermatozoa in Male Rats

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma (power≥ 1)	2	3.31	0.1909	151.717	294.697	158.59
Log-logistic (slope ≥ 1)	2	3.11	0.2110	151.539	269.043	133.333
Logistic	2	4.07	0.1306	152.471	401.434	273.584
Multistage (betas ≥ 0)[b]	2	3.31	0.1909	151.717	294.698	158.59
Log-probit (slope ≥ 1)	2	5.27	0.0717	153.58	NA	NA
Probit	2	3.99	0.1363	152.382	398.398	257.988
Weibull (power≥ 1)	2	3.31	0.1909	151.717	294.697	158.59

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]One degree polynomial shown. Higher degree polynomials default back to one degree.

NA = not applicable, model does not fit.

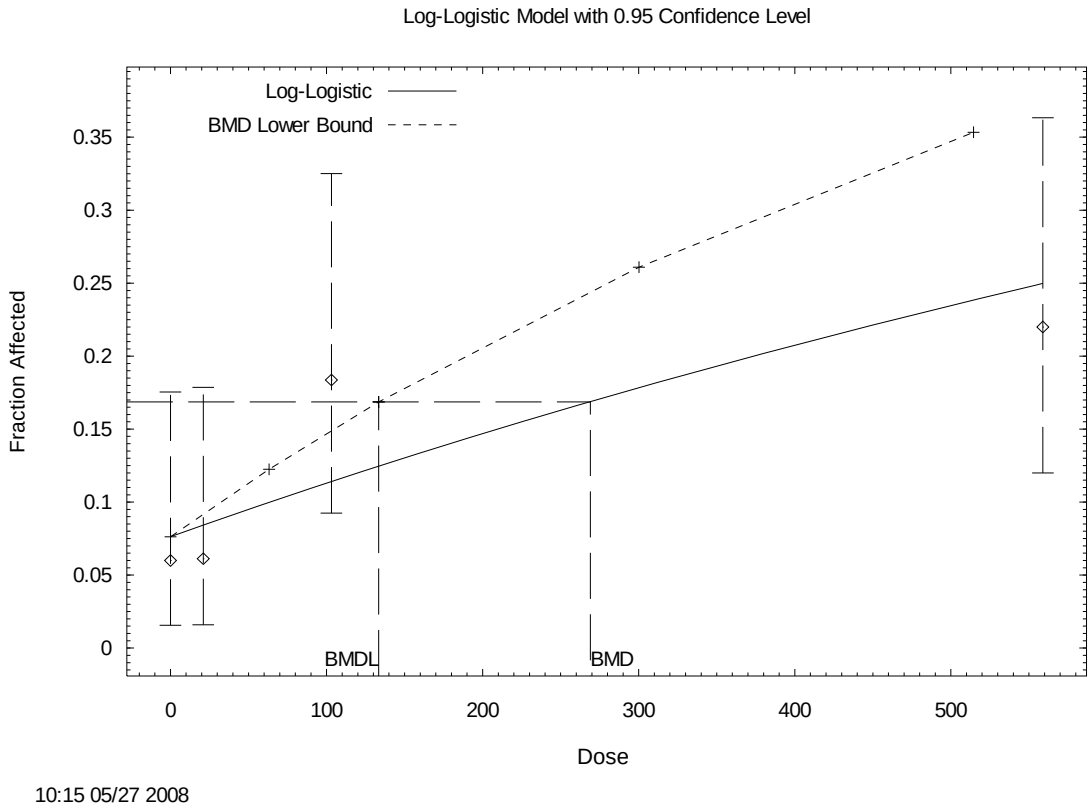

Figure C-1. Fit of Log-Logistic Model to Data on Reduced Spermatozoa in Male Rats

BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day.

Table C-2 presents the results of BMD modeling for degeneration of seminiferous tubules in male rats (Bayer AG, 1993). As shown in the table, all models provided adequate fit to the dataset. All models that fit yielded BMD/BMDL values within a factor of three, suggesting that the choice of model does not overly influence the outcome. Based on the lowest AIC value, the log-logistic model provides the best fit to the data. A graph of the log-logistic model for reduced degeneration of seminiferous tubules in male rats is shown in Figure C-2.

Table C-2. Model Predictions for Combined Incidence of Unilateral and Bilateral Degeneration of Seminiferous Tubules in Male Rats						
Model	**Degrees of Freedom**	**χ^2**	**χ^2 Goodness of Fit *p*-Value[a]**	**AIC**	**BMD_{10} (mg/kg-day)**	**$BMDL_{10}$ (mg/kg-day)**
Gamma (power≥ 1)	2	2.09	0.3525	137.916	404.195	197.405
Log-logistic (slope ≥ 1)	2	2.01	0.3667	137.834	384.557	174.022
Logistic	2	2.48	0.2898	138.351	491.706	314.629
Multistage (betas ≥ 0)[b]	2	2.09	0.3525	137.916	404.196	197.405
Log-probit (slope ≥ 1)	2	3.22	0.1998	139.105	542.152	330.425
Probit	2	2.43	0.2967	138.298	482.087	298.776
Weibull (power ≥ 1)	2	2.09	0.3525	137.916	404.2	197.405

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria
[b]One degree polynomial shown.

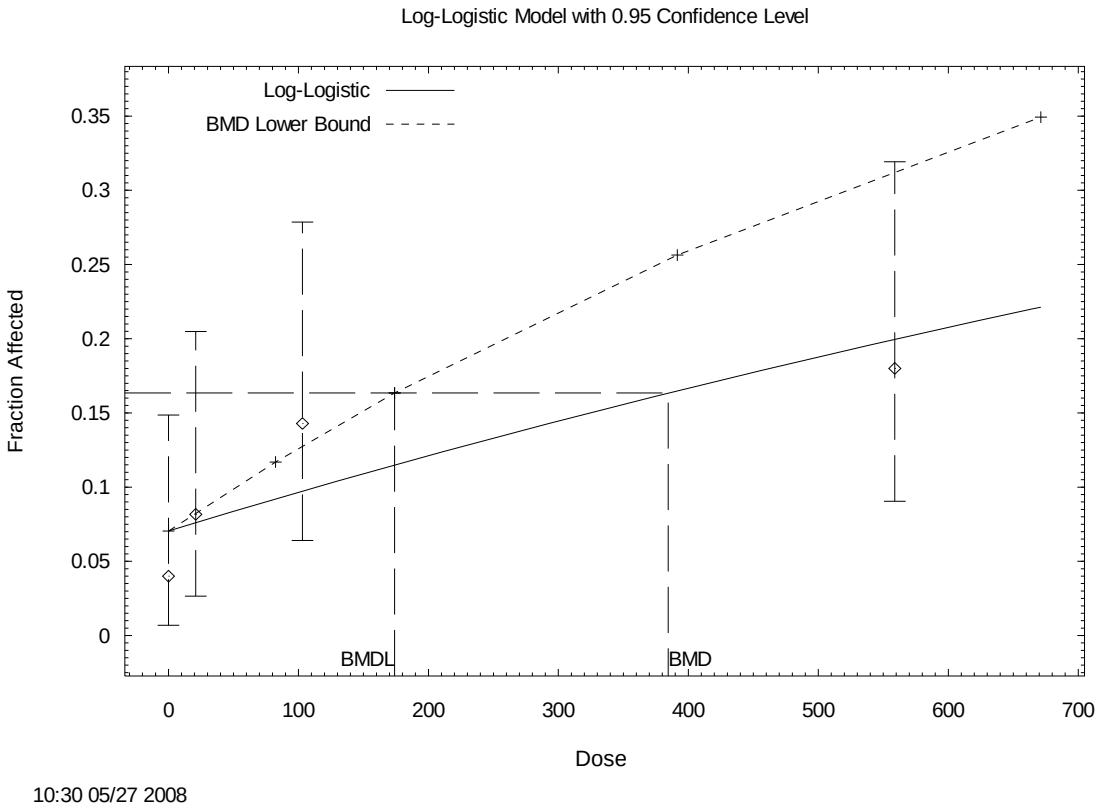

Figure C-2. Fit of Log-Logistic Model to Data on Degeneration of Seminiferous Tubules in Male Rats

BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day.