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Provisional Peer-Reviewed Toxicity Values for

4-Methylphenol (*p*-Cresol)
(CASRN 106-44-5)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
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 reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
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
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 4-METHYLPHENOL (P-CRESOL) (CASRN 106-44-5)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency'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) EPA's Integrated Risk Information System (IRIS)
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in 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 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 EPA IRIS Program. All provisional toxicity values receive internal review by a panel of six 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 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

An RfD for 4-methylphenol (*p*-cresol) is not available on IRIS (U.S. EPA, 2008) or the Drinking Water and Health Advisories list (U.S. EPA, 2006). The Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997) lists a chronic RfD of 0.005 mg/kg-day for *p*-cresol that was originally derived in a 1991 Health and Environmental Effects Document (HEED) for 4-methylphenol (U.S. EPA, 1991a). The critical effects were symptoms of overt maternal toxicity (respiratory distress, cyanosis, ocular discharge, hypoactivity, and death) at 50 mg/kg-day or higher in a gavage developmental toxicity study in rabbits (BRRC, 1988a). The RfD was derived by applying a UF of 1000 (10 for extrapolation to chronic exposure, 10 for extrapolation from animals to humans, and 10 for human variability) to the NOAEL of 5 mg/kg-day for maternal effects. Confidence in the RfD was considered medium. In the HEAST (U.S. EPA, 1997), the chronic RfD was also adopted as the subchronic RfD. In addition to the previously mentioned HEED, the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991b, 1994) references a Health Effects Assessment (HEA) (U.S. EPA, 1984) and a Health and Environmental Effects Profile (HEEP) for Cresols (U.S. EPA, 1985). However, at the time those documents were produced, the oral data were not adequate for use in deriving toxicity values.

The Agency for Toxic Substances and Disease Registry (ATSDR, 2006) recently released a public comment draft update toxicological profile for cresols in which an intermediate-duration oral MRL of 0.1 mg/kg-day was derived for *m*/*p*-cresol from a $BMDL_{10}$ of 13.94 mg/kg-day for nasal lesions in a 13-week dietary study of an *m*/*p*-cresol (60:40) mixture in rats. ATSDR (2006) concluded that the MRL for *m*/*p*-cresol should also be protective for exposures to the individual isomers (i.e., can be adopted for *o*-, *m*-, and *p*-cresol). ATSDR (2006) considered only dietary studies in deriving this MRL based on the conclusion that gavage studies showed markedly different effects than dietary studies and the premise that dietary exposure is more relevant than gavage with regard to human exposure. Due to a lack in chronic oral data, a chronic oral MRL was not derived. As presented in an Environmental Health Criteria document for cresols (WHO, 1995), the World Health Organization derived an acceptable daily intake (ADI) of

0.17 mg/kg-day for all three cresol isomers (*o*-, *m*-, and *p*-cresol) based on a NOAEL of 50 mg/kg-day in (unspecified) subchronic studies. The California Environmental Protection Agency (CalEPA, 2005a) has not derived a chronic oral REL for 4-methylphenol.

No RfC values for 4-methylphenol are reported in IRIS (U.S. EPA, 2008) or the HEAST (U.S. EPA, 1997). ATSDR declined to derive inhalation MRLs due to limitations in the available inhalation data (ATSDR, 2006). CalEPA (2005a, 2005b) derived a chronic inhalation REL of 600 μg/m^3 (100 ppb) for cresol mixtures. The REL is based on oral subchronic toxicity data and was adopted for *p*-cresol (4-methylphenol) and the other cresol isomers.

Based on the limited data that were available, the National Institute for Occupational Safety and Health (NIOSH) established a recommended exposure limit-time weighted average (REL-TWA) of 2.3 ppm (10 mg/m^3) (NIOSH, 1978, 2005). The American Conference of Governmental Industrial Hygienists (ACGIH) took a different approach and recommended a threshold limit value-time weighted average (TLV-TWA) of 5 ppm (22 mg/m^3) with a skin notation, based on analogy to phenol (ACGIH, 2001, 2007). The Occupational Safety and Health Administration permissible exposure limit-time weighted average (OSHA PEL-TWA) is 5 ppm (22 mg/m^3) with a skin notation (OSHA, 2008).

A carcinogenicity assessment for 4-methylphenol is available on IRIS (U.S. EPA, 2008). This assessment is derived from the 1985 HEEP for Cresols (U.S. EPA, 1985). 4-Methylphenol was assigned to cancer weight-of-evidence Group C, *possible human carcinogen* based on an increased incidence of skin papillomas in mice in a dermal initiation-promotion study (Boutwell and Bosch, 1959). Supporting data from genotoxicity tests include positive results from an unpublished study of induction of unscheduled DNA synthesis in human lung fibroblasts (with metabolic activation) treated with 4-methylphenol and positive results in a number of other genotoxicity tests using a mixture of 2-, 3-, and 4-methylphenol isomers. Limited anecdotal data from occupationally exposed individuals were considered to be inadequate. The HEAST (U.S. EPA, 1997) reports the availability of the weight-of-evidence assessment on IRIS but contains no additional information. The International Agency for Research on Cancer (IARC) has not evaluated 4-methylphenol for carcinogenicity (IARC, 2007). The National Toxicology Program (NTP, 2006) has not tested the chronic toxicity/carcinogenicity of 4-methylphenol (*p*-cresol), but a 2-year study of mixed *m*/*p*-cresol (60:40) isomers in rats and mice was recently completed and the results are available in a preliminary report. NTP (2005) did not include 4-methylphenol in the 11th Report on Carcinogens. CalEPA (2002) has not derived a cancer potency factor for 4-methylphenol.

Literature searches were conducted from 1960s through January 2010 for studies relevant to the derivation of provisional toxicity values for 4-methylphenol. The following databases were searched: MEDLINE, TOXLINE (Special), BIOSIS, TSCATS 1/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents.

REVIEW OF PERTINENT DATA

Human Studies

An English abstract of a study published in Japanese reported the presence of fecal 4-methylphenol in 8/8 colonic carcinoma patients and 28/30 rectal carcinoma patients (Kubo, 1990). The authors stated these findings in cancer patients differed significantly ($p < 0.01$) from healthy controls, suggesting a possible association between increased excretion of 4-methylphenol and cancer. The source of the 4-methylphenol[1], and whether or not 4-methylphenol is a causal agent or a by-product of a carcinogenic process, was not determined.

Renwick et al. (1988) found high variability in the excretion of 4-methylphenol and phenol in 32 patients with histologically confirmed carcinoma of the urinary bladder and in a group of sex- and age-matched controls. Their findings suggest that endogenously produced phenols—including 4-methylphenol—do not contribute significantly to the development of bladder cancer in humans. However, a more recent study by Schepers et al. (2007) discussed briefly in the "Mechanistic" section, indicates that a metabolite of 4-methylphenol, rather than the parent compound, could be responsible for increasing pro-inflammatory vascular damage that subsequently leads to development of urinary system pathology.

Oral Exposure

No information was located concerning health effects in humans following oral exposure to 4-methylphenol (*p*-cresol) alone. Case studies of individuals who drank cresol-containing disinfectants report irritation of mouth and throat, abdominal pain, and vomiting (summarized by ATSDR, 2006; WHO, 1995). Primary targets of ingested cresols appear to be the central nervous system (reduced consciousness, coma), blood (methemoglobinemia, hemoglobinemia, hemoglobinuria, reduced erythrocyte glutathione levels), and kidneys (irritation, tubular degeneration). There is also some indication of toxicity in lungs, heart, and liver.

Inhalation Exposure

No studies regarding the effects of inhalation exposure to 4-methylphenol in humans were identified. Due to its low vapor pressure, exposure to methylphenols is not likely to occur except under conditions where aerosols are formed or at high temperatures. A few studies that discuss effects associated with exposure to other methylphenol isomers and mixtures are summarized briefly.

Uzhdavini et al. (1972) reported that 8/10 volunteers exposed to 6 mg/m^3 of a vapor/aerosol mixture of 2-methylphenol complained of throat irritation and nasal constriction and dryness. The duration of exposure is not reported, but 6 mg/m^3 appears to be the threshold concentration for mucosal irritation. Molodkina et al. (1985) observed circulatory disturbances and minor hematological changes (decreased RBC, WBC, and platelets; decreased glucose-6-phosphatase dehydrogenase activity and sulfhydryl group concentrations within erythrocytes; and reduced life span of erythrocytes) in female workers exposed to tricresol (a mixture of 2-, 3-, and 4-methylphenol) while producing enameled wire. Mean exposure concentrations of 1.4 mg/m^3 and maximum concentrations of 3.6−5.0 mg/m^3 were recorded. Of the 96 women included in the study, 70% were exposed for 10 years or more. In another study,

[1] 4-methylphenol is an endogenous byproduct of metabolism as well as an environmental contaminant.

reproductive disorders (hormonal shifts, menstrual problems, high perinatal mortality, and abnormal development of children) were reported among female workers exposed to tricresol during the production of enameled wire (Syrovadko and Malysheva, 1977). Pashkova (1973) also reported an increased incidence of menstrual disturbances in women workers exposed to tricresol (along with phosphoryl chloride and tricresylphosphate). These incidences were related to increased estrogen and decreased progesterone activity resulting from ovarian dysfunction. It is uncertain whether the workers in these studies were exposed to other chemicals and whether dermal exposure was an important factor.

Animal Studies

Oral Exposure

Subchronic Studies—Sprague-Dawley rats (30/sex/group) were given 4-methylphenol (99.9% pure) in corn oil by gavage at doses of 0, 50, 175, or 600 mg/kg-day, once daily, for 13 weeks (MBA, 1988). Clinical signs were observed twice daily. Body weights were recorded on the first day of dosing and weekly thereafter, and weekly food consumption was noted. Rats were subjected to weekly physical examinations. Ophthalmologic examinations were performed prior to treatment initiation and during treatment Week 13. Subgroups (10/sex/dose) were sacrificed during Week 7 for interim evaluation of hematology and urinalysis. Hematology and urinalysis were evaluated again just prior to study termination. Complete gross necropsy was conducted on all rats in the study. All major tissues and organs from all control and high-dose animals sacrificed at study termination as well as those that died during the study were examined microscopically. Individual organ weights (heart, spleen, brain, kidneys, gonads, adrenals, and thyroid/parathyroid) were recorded from animals surviving until terminal sacrifice.

The authors noted death in 3/30 high-dose female rats within the first 3 days of dosing (MBA, 1988). Two of the females that died had tremors or convulsions, and both were comatose prior to death. The third female died without manifesting clinical signs. Of the surviving rats, clinical signs were observed throughout the 13 weeks of the study only in high-dose rats. The most common clinical signs were excessive salivation and lethargy, with occasional tremors; these signs disappeared within 1 hour postdosing. The authors reported no deaths or clinical signs of toxicity in mid- or low-dose groups. Significantly ($p < 0.05$) reduced food consumption was apparent in the high-dose males and females and in the mid-dose males during early weeks of dosing. The high-dose male and female rats had significantly ($p < 0.05$) lower final mean body weights (15 and 8%, respectively) and reduced mean body-weight gains (21 and 13%, respectively), relative to controls. Effects on body weight in mid- and low-dose rats were seen during the first few weeks of dosing, but were no longer apparent by study termination. At study termination, dose-related reductions in red blood cell count, hemoglobin concentration, and hematocrit were seen in mid- and high-dose female (but not male) rats. Table 1 summarizes the data.

Table 1. Significant Results for Rats at Study Termination Following Gavage Administration of 4-Methylphenol (*p*-Cresol) for 13 Weeks[a]

Variable	0 mg/kg-day	50 mg/kg-day	175 mg/kg-day	600 mg/kg-day
Females (n = 10 unless noted otherwise)				
RBC (× 10^6 mm^3)	8.83 ± 0.48	8.44 ± 0.44	8.18 ± 0.50[b]	8.09 ± 0.54[b]
Hgb (g/dL)	16.3 ± 0.7	15.9 ± 0.7	15.3 ± 0.8[b]	15.1 ± 0.7[b]
HCT (%)	46.4 ± 2.3	44.4 ± 2.0	42.9 ± 2.1[b]	42.1 ± 1.8[b]
ALT (iu/L)	32 ± 17	38 ± 29	39 ± 12	158 ± 195[b]
AST(iu/L)	79 ± 15	90 ± 35	79 ± 17	189 ± 64[b]
Cholesterol (mg/dL)	96.1 ± 14.0	95.2 ± 14.3	109.5 ± 22.4	139.0 ± 43.4[b]
Males (n = 10 unless noted otherwise)				
Phosphate (mg/dL)	10.0 ± 2.0	8.9 ± 0.9	9.9 ± 1.3 (9)	8.4 ± 1.0[b]
Total Protein (g/dL)	6.8 ± 0.30	7.0 ± 0.30	7.3 ± 0.4[b]	7.6 ± 0.6[b]

[a]MBA, 1988; values are mean ± SD.
[b]Statistically significant from controls, $p \leq 0.05$, Analysis of Variance, Dunnett's test.

Mean serum ALT was significantly elevated in high-dose females at the interim evaluation (MBA, 1988). Both ALT and AST were significantly elevated in high-dose females (but not males) at the end of the study. The elevated ALT and AST values can be attributed to unusually high values in 4/10 females, two of which also had chronic hepatic inflammation. Other changes in clinical chemistry variables were noted at study termination and included increased serum cholesterol in high-dose females, decreased total phosphate in high-dose males, and increased total protein (mostly globulins) in mid- and high-dose males. Table 1 summarizes these clinical chemistry values. The increases in ALT, AST, and cholesterol can be attributed to treatment-related effects on the liver. The increase in serum protein could be due to nutritional status and/or metabolic derangement; liver and kidney pathology is usually accompanied by decreases, rather than increases, in serum proteins. The decrease in phosphate at the high dose lacks biological relevance and appears to be an artifact of statistical testing.

Significant changes in organ weights that were considered to be treatment-related included elevated relative kidney weights (increased by approximately 17 and 10% in high- and mid-dose males, respectively and 11% in high-dose females) and elevated relative (6% higher) but decreased absolute (10% lower) liver weight in high-dose males only (MBA, 1988). Other typically slight, but significant ($p < 0.05$) changes in organ weights were noted for the heart and testes of high-dose males, brain of high-dose males and females, ovaries of high-dose females, and spleen of low-dose females. In the high-dose groups, at least some of these changes in relative organ weights were attributed to depressed body-weight gain. In male rats, a slight—but statistically significant ($p < 0.05$)—increase in the incidence of minimal-to-mild nephropathy was noted in low-dose (11/20) and high-dose (12/20) male rats compared with 4/20 in controls; at mid-dose, the incidence (7/20) did not reach statistical significance. Incidences of nephropathy in the control groups of male rats used in *o*-cresol and *m*-cresol studies conducted

concurrently by the same laboratory were 10/20 and 7/20, respectively. Due to the variable incidence of this lesion (even among controls), the absence of a dose-related increased incidence or severity and the absence of nephropathy in female rats, the observed nephropathy in male rats is considered to be an equivocal treatment-related effect. Trachea-epithelial metaplasia was noted in 10/20 high-dose males and 9/20 high-dose females versus none in sex-matched controls. The NOAEL for the study is 50 mg/kg-day. The LOAEL for the study is 175 mg/kg-day, based on anemia (reduced RBC count, hemoglobin, and hematocrit) in female rats.

In a subchronic neurotoxicity study, CD rats (10/sex/group) were exposed to 4-methylphenol in corn oil by gavage once daily at doses of 50, 175, or 600 mg/kg-day for 13 weeks (TRL, 1986). Groups of 20 male and 20 female rats served as vehicle controls. Body weights and food consumption were recorded weekly. Clinical observations were made at least twice daily throughout the study. Observations for signs of neurotoxicity were made once during the pretreatment period, 1- and 6-hours postdosing on Day 1 and prior to dosing on Days 2, 7, 14, 30, 60, and 90. Each animal was observed for respiration, salivation, urination, tremors, piloerection, diarrhea, pupil size, pupil response, lacrimation, hypothermia, vocalization, exophthalmos, palpebral closure, and convulsions, followed by tests for positional passivity, wire maneuverability, forelimb grip strength, positive geotropism, extensor thrust, limb rotation, tail pinch, toe pinch, and hind-limb splay. Randomly selected animals from each test group received neuropathological examinations as follows. The brain and spinal cord of 10 controls per sex and 5 per sex of each treatment group were grossly examined for signs of treatment-related toxicity. Microscopic exams of forebrain, center of cerebrum, midbrain, cerebellum, pons, medulla oblongata, cervical and lumbar portions of the spinal cord, dorsal root ganglia, ventral root fibers, Gasserian ganglia, proximal sciatic nerve, sural nerve, tibial nerve, and eye and optic nerve were conducted for an additional 10 male and 10 female controls and for 5 rats per sex of each treatment group. Gross pathological examinations were performed on the contents of cranial, thoracic, and peritoneal cavities of animals found dead during the course of the study. Esophagus, stomach, lungs with trachea, and some gross lesions taken from animals succumbing early were prepared for microscopic evaluation.

Mortality was noted in 4/10 high-dose rats of each sex (TRL, 1986). Of these eight deaths, seven were considered to be directly compound-related (five were associated with respiratory distress). There were no deaths in any of the other study groups. Compound-related mortality was greatest during the first few treatment weeks. Treatment-related effects on body weight or food consumption were confined to the high-dose groups and consisted of significant ($p < 0.05$) lower mean body weight in males during the first week of the study only and reduced mean food consumption in males and females during the initial portion of the study. Clinical signs were dose-related in incidence and include salivation, myotonus, tremors, urine wet abdomen, hypoactivity, rapid respiration, myoclonus, low body posture, and labored respiration. Convulsions were also reported to occur in a few high-dose animals. Incidences of salivation, myotonus, tremors, and urine-wet abdomen increased or remained the same throughout the study. The tables that summarize the detailed incidence data for the clinical signs reported in the study narrative are not in the report (TRL, 1986), and, therefore, are not presented here. However, available clinical symptoms discussed in this report are clear indications of neurotoxicity endpoint and considered relevant for development of toxicity values. Myotonus was observed only among high-dose animals. The incidences of hypoactivity and rapid respiration appeared to increase during the first few weeks of treatment and all dose groups were affected in a dose-related manner. Dose-related incidences of myoclonus, low body posture, and

labored respiration (mid- and high-dose groups only), noted only in a few rats, were greatest during the first week of treatment and sporadic thereafter. The study authors indicated that the 50 mg/kg-day dose level appeared to be an "adverse effect level" for clinical signs related to neurotoxicity, although diminished response with repeated dosing indicated that there might have been some degree of adaptation to exposure to 4-methylphenol. The results of neurobehavioral tests and neuropathological examinations were negative. The NOAEL for this study is 50 mg/kg-day. The LOAEL is 175 mg/kg-day, and it is based on clinical signs of neurotoxicity.

Hirose et al. (1986) fed groups of 15 male Syrian golden hamsters 0 or 1.5% 4-methylphenol (25% of the LD_{50}) of >98% purity in the diet for 20 weeks (equivalent to 1500 mg/kg-day). Three animals of each group were dosed intraperitoneally with radiolabeled thymidine before sacrifice and evaluated for increased thymidine uptake in the epithelium of the glandular stomach and bladder. Increased thymidine uptake is indicative of an increase in mitosis that could be a precursor to proliferative changes such as cancer. The liver, kidneys, lungs, cheek pouch, esophagus, stomach, pancreas, and urinary bladder were removed from all animals. Livers and kidneys were weighed and fixed in formalin. Sections of the forestomach, glandular stomach, and urinary bladder were evaluated histologically. Data for body weight, liver weight, forestomach histopathology, and thymidine uptake in the forestomach, pyloric region, and urinary bladder are shown in the report.

4-Methylphenol induced small and nonsignificant increases of mean thymidine uptake in the forestomach and pyloric region (1.5 times that of controls), and a large—but nonsignificant (3.5 times)—increase in the urinary bladder (Hirose et al., 1986). The lack of statistical significance in the latter effect is likely due to the large standard deviation in the treatment group (0.28 ± 0.39 versus 0.08 ± 0.14 in controls). Statistically significant ($p < 0.05$) mild (15/15 treated versus 7/15 controls) to moderate hyperplasia (10/15 treated versus 1/15 controls) was observed without papillomatous lesions in the forestomach of treated hamsters. Exposure was not continued long enough to determine whether the forestomach lesions would progress to neoplasia or whether the increased mitosis in the bladder could have been a precursor to tumor formation. The LOAEL for this study is 1500 mg/kg-day (only dose tested).

Forestomach hyperplasia was not observed in male and female Wistar rats following dietary exposure to 4-methylphenol at a concentration of 2% (2000 mg/kg-day, assuming a food factor of 0.1 for subchronic or shorter duration in rats) for an unspecified period of time (Altmann et al., 1986). The purpose of this investigation was to compare the effects of 3-tert-butyl-hydorxyanisole (BHA) on the forestomach with a variety of structurally similar compounds. No further details were provided with regard to 4-methylphenol.

NTP (1992a) fed groups of F344/N rats and $B6C3F_1$ mice (5/sex/species) diets containing 0, 300, 1000, 3000, 10,000, or 30,000 ppm of 4-methylphenol (>98% pure) for 28 days. Based on data presented by the authors, mean doses of 4-methylphenol were 0, 25, 87, 256, 835, and 2180 mg/kg-day in male rats; 0, 25, 83, 242, 770, and 2060 mg/kg-day in female rats; 0, 50, 163, 469, and 1410 mg/kg-day in male mice; and 0, 60, 207, 564, and 1590 mg/kg-day in female mice. Doses at the high concentration in mice were not calculated due to 100% early mortality. Food consumption was recorded twice weekly. Animals were observed twice daily for clinical signs of toxicity. Body weights were recorded weekly. Necropsy was performed on all animals. Organ weights were recorded for brain, heart, right kidney, liver, lungs, thymus, and right testis. Complete histopathologic examinations were performed on all control animals, all rats in the

highest-dose group and all mice in the two highest-dose groups (inclusive of early deaths). Target organs and tissues (nasal epithelium and bone marrow of male and female rats and mice; uterus of female rats; liver, kidney, and lymphoid organs of male and female mice) and gross lesions were examined in lower-dose groups to establish a no-effect level.

Survival was 100% in rats (NTP, 1992a). Relative to controls, higher-dose male and female rats had significant decreases ($p < 0.05$) in mean final body weight (29 and 16% lower in males and females, respectively) and mean body-weight gains (58 and 46% lower in males and females, respectively). The authors stated that food consumption was depressed by as much as 75% and 79% in high-dose males and females, respectively, during the first week of the study, but they did not show food consumption data. Clinical signs of toxicity observed in all high-dose rats during the first week included hunched posture, rough hair coat and thin appearance. Significant treatment-related organ-weight changes (data not shown) included increased relative liver weights (≥835 mg/kg-day in males and ≥242 mg/kg-day in females) and kidney weights (≥835 mg/kg-day in males and at 2060 mg/kg-day in females). Other organ (brain and testes) weight changes were considered by the investigators to be the result of reduced body-weight gain. No gross lesions were seen at necropsy. Table 2 summarizes the author's observations of histopathologic lesions in bone marrow, nasal epithelium, and the uterus. The small numbers of animals in each dose group preclude meaningful statistical analysis. The nasal lesions may be due to inhalation exposure via 4-methylphenol vapors released from the food and/or to direct nasal contact with 4-methylphenol during feeding. The NOAEL for rats in this study is 87 mg/kg-day. The LOAEL for rats is 242 mg/kg-day on the basis of nasal respiratory epithelial hyperplasia.

Table 2. Incidence (Mean Severity) of Relevant Histopathological Findings for Rats Fed 4-Methylphenol (*p*-Cresol) for 28 Days[a]

Male Rats						
	Dose for (mg/kg-day)					
Organ/Effect	**0**	**25**	**87**	**256**	**835**	**2180**
Bone marrow hypocellularity	0/5	NE	0/5	1/5 (2.0)	1/5 (2.0)	5/5 (3.0)
Nasal						
Olfactory epithelium atrophy	0/5	NE	0/5	0/5	0/5	5/5 (2.0)
Respiratory epithelium						
Hyperplasia	0/5	NE	0/5	1/5 (2.0)	4/5 (2.7)	5/5 (2.8)
Squamous metaplasia	0/5	NE	0/5	0/5	0/5	2/5 (2.0)
Female Rats						
	Dose for (mg/kg-day)					
Organ/Effect	**0**	**25**	**83**	**242**	**769**	**2060**
Bone marrow hypocellularity	0/5	NE	0/5	0/5	1/5 (2.0)	3/5 (2.7)
Nasal						
Olfactory epithelium atrophy	0/5	NE	0/5	1/5 (1.0)	0/5	4/5 (1.7)
Respiratory epithelium						
Hyperplasia	0/5	NE	0/5	1/5 (1.0)	3/5 (3.0)	3/5 (2.3)
Squamous metaplasia	0/5	NE	0/5	0/5	1/5 (2.0)	0/5
Uterus: Endothelium, atrophy	0/5	0/1	0/1	0/1	0/5	3/5

[a]NTP, 1992a: severity ratings, given in parentheses, are on a scale of 1−4 where 1 = minimal, 2 = mild, 3 = moderate and 4 = marked.

NE = Not examined.

All mice exposed to the highest concentration (30,000 ppm), one male at the next highest concentration (10,000 ppm), and one control male died or were sacrificed in moribund condition (NTP, 1992a). Compared to controls, mean final body weight and mean body-weight gain were significantly ($p < 0.05$) lower (17 and 83%, respectively) in 1410 mg/kg-day (10,000 ppm) males; food consumption was depressed for 1410 mg/kg-day males and 1590 mg/kg-day (10,000 ppm) females throughout most of the first 2 treatment-weeks. Clinical signs (hunched posture, labored breathing, lethargy, rough hair coat, hypothermia, and/or thin appearance) were observed in 469- and 1410-mg/kg-day males and 1590-mg/kg-day females. Significant treatment-related organ weight changes (data not shown) included increased relative liver weight (1410 mg/kg-day males and ≥564 mg/kg-day females), kidney weight (≥469 mg/kg-day males), and heart weight (1410 mg/kg-day males). No gross lesions were noted at necropsy. Table 3 summarizes the incidences of relevant histopathological lesions. The small numbers of animals in each dose group preclude meaningful statistical analysis.

Table 3. Incidence (Mean Severity) of Relevant Histopathological Findings for Mice Fed 4-Methylphenol (*p*-Cresol) for 28 Days[a]

Male Mice						
	Dose for (mg/kg-day)					
Organ/Effect	**0**	**50**	**163**	**469**	**1410**	**Nd[b]**
Bone marrow hypocellularity	0/5	NE	NE	NE	0/5	2/5 (1.5)
Kidney: Renal tubule necrosis	0/5	NE	NE	NE	0/5	4/5 (1.7)
Liver						
Centrolobular atrophy	0/5	NE	NE	NE	0/5	1/5 (3.0)
Centrolobular necrosis	0/5	NE	NE	NE	0/5	1/5 (2.0)
Necrosis	0/5	NE	NE	NE	0/5	2/5 (3.0)
Nasal						
Respiratory epithelium						
Atrophy	0/5	0/5	0/5	0/5	0/5	1/5 (2.0)
Hyperplasia	0/5	0/5	3/5 (1.0)	5/5 (1.8)	5/5 (2.0)	1/5 (2.0)
Olfactory epithelium						
Atrophy	0/5	0/5	0/5	0/5	0/5	1/5 (2.0)
Necrosis	0/5	0/5	0/5	0/5	0/5	2/5 (2.5)
Squamous metaplasia	0/5	0/5	0/5	0/5	1/5 (2.0)	1/5 (3.0)
Female Mice						
	Dose for (mg/kg-day)					
	0	**60**	**207**	**564**	**1590**	**Nd[c]**
Bone marrow hypocellularity	0/5	NE	NE	NE	0/5	3/5 (2.0)
Kidney: Renal tubule necrosis	0/5	NE	NE	NE	0/5	3/5 (1.7)
Liver						
Centrolobular necrosis	0/5	NE	NE	NE	0/5	1/5 (2.0)
Nasal						
Olfactory epithelium						
Atrophy	0/5	0/5	0/5	1/5 (1.0)	0/5	0/5
Necrosis	0/5	0/5	0/5	0/5	0/5	3/5 (2.0)
Respiratory epithelium						
Hyperplasia	0/5	1/5 (1.0)	2/5 (1.0)	4/5 (1.7)	5/5 (1.6)	1/5 (1.0)

[a]NTP, 1992a: severity ratings are on a scale of 1−4 where 1 = minimal, 2 = mild, 3 = moderate and 4 = marked.
[b]Not determined due to 100% mortality at the highest dietary concentration (30,000 ppm).

NE = Not examined.

NTP (1992a) concluded that the renal tubule and hepatic necrosis and minimal-to-mild bone marrow hypocellularity, all limited to the high-dose group with 100% mortality (30,000 ppm), were possibly the direct result of 4-methylphenol toxicity. The nasal lesions may be indicative of inhalation exposure via 4-methylphenol vapors released from the food and/or direct nasal contact with 4-methylphenol during feeding. Other lesions not shown in Table 3 but seen in high-dose mice (lymphoid necrosis and depletion in various lymphoid tissues including the spleen) were considered secondary to mortality. The NOAEL for the study with mice is not established. Nasal epithelial hyperplasia observed in females in all groups may possibly be unrelated to systemic effects via oral exposure.

NTP (1992a) conducted similar 28-day dietary studies with 2-methylphenol (*o*-cresol), 3-methylphenol (*m*-cresol) and *m*/*p*-cresol and 13-week studies with *o*- and *m*/*p*-cresol and concluded that the toxicity of the individual isomers was generally equivalent in both qualitative and quantitative terms. In general, the toxicity observed following 28-day administration of *m*/*p*-cresol could be accounted for by results observed following administration of either *m*- or *p*-isomers alone. For example, in rats, the increased relative organ weights (brain, liver, kidney, testes), bone marrow histopathology, and nasal epithelial changes were observed at identical doses following either *p*-cresol or *m*/*p*-cresol exposure. Changes observed in rats following exposure to *m*/*p*-cresol that were not observed following exposure to *p*-cresol alone were increased colloid in thyroid follicular cells (≥3000 ppm) and an increased incidence of forestomach hyperplasia (≥10,000 ppm). In mice, there were several findings observed following administration of *m*/*p*-cresol that were not observed following administration of the individual isomers. Increased incidences of bronchiolar hyperplasia (both sexes) and hyperplasia of the forestomach and esophagus (males only) were observed at the highest dietary concentration (30,000 ppm). Critical dose-response data for the studies with isomers other than *p*-cresol are summarized in Table 4, along with results for *p*-cresol, and are considered further in the dose-response assessment.

Table 4. Summary of Oral Noncancer Dose-Response Information

Species/ isomer	Sex	Dose (mg/kg-day)	Exposure Duration	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Subchronic Dietary Exposure								
Hamster *p*-cresol	M	0 or 1.5% in diet (approx. 1500 mg/kg-day)	20 weeks	none	1500	Moderate hyperplasia of the forestomach (10/15 treated vs. 1/15 controls)		Hirose et al., 1986
Rat *p*-cresol	M	0, 25/25, 87/83, 256/242, 835/769, or 2180/2060 mg/kg-day (male/female)	28 days	87	242	Nasal respiratory epithelial hyperplasia	No forestomach hyperplasia	NTP, 1992a
Rat *m*/*p*-cresol	M/F	0, 26/27, 90/95, 261/268, 877/886, or 2600/2570 mg/kg-day (male/female)	28 days	27	95	Nasal respiratory epithelial hyperplasia	Thyroid follicular cell colloid in males/females at ≥261/268 mg/kg-day, epithelial hyperplasia and hyperkeratosis of esophagus and/or forestomach in males/females at ≥261/268 mg/kg-day	NTP, 1992a
Rat *m*/*p*-cresol	M/F	0, 123/131, 241/254, 486/509, 991/1024, or 2014/2050 mg/kg-day (male/female)	13 weeks	none (M)	123 (M)	Nasal respiratory epithelial hyperplasia	Thyroid follicular cell colloid in females/males at ≥509/991 mg/kg-day	NTP, 1992a
Mouse *p*-cresol	F	0, 50/60, 163/207, 469/564, or 1410/1590 mg/kg-day (male/female)	28 days	none	60	Nasal respiratory epithelial hyperplasia	The NOAEL/LOAEL for this effect in males is 50/163 mg/kg-day	NTP, 1992a

Table 4. Summary of Oral Noncancer Dose-Response Information

Species/ isomer	Sex	Dose (mg/kg-day)	Exposure Duration	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Mouse *m*/*p*-cresol	M/F	0, 50/65, 161/200, 471/604, 1490/1880, or 4530/4730 mg/kg-day (male/female)	28 days	200 (F)	604 (F)	Nasal respiratory epithelial hyperplasia		NTP, 1992a
Mouse *m*/*p*-cresol	M/F	0, 96/116, 194/239, 402/472, 776/923, or 1513/1693 mg/kg-day (male/female)	13 weeks	none (M)	96 (M)	Nasal respiratory epithelial hyperplasia		NTP, 1992a
Subchronic Gavage Exposure								
Rat *p*-cresol	F	0, 50, 175, or 600	13 weeks	50	175	Reductions in red blood cell count, hemoglobin concentration and hematocrit	Tremors, convulsions, mortality, and tracheal-epithelial metaplasia were observed in both sexes at 600 mg/kg-day	MBA, 1988
Rat *p*-cresol	M	0, 50, 175, or 600	13 weeks	50	175	Clinical signs of neurotoxicity but no effects on neurobehavioral performance or neurohistopathology	Neurotoxicity study; mortality at high dose	TRL, 1986

Table 4. Summary of Oral Noncancer Dose-Response Information

Species/ isomer	Sex	Dose (mg/kg-day)	Exposure Duration	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Chronic Dietary Exposure (no chronic gavage studies were identified)								
Rat *m*/*p*-cresol (60:40)	M	0, 70, 230, or 720	105 weeks	none	70	Nasal respiratory epithelial and goblet cell hyperplasia	≥230: Respiratory epithelial squamous metaplasia 720: Reduced body weight, increased renal pelvis epithelial hyperplasia, marginally increased renal tubule; respiratory epithelial inflammation	NTP, 2007
Mouse *m*/*p*-cresol (60:40)	F	0, 100, 300, or 1040	106−107 weeks	none	100	Lung: bronchiolar hyperplasia; Thyroid: follicular degeneration	≥300: Reduced body weight, nasal respiratory epithelial hyperplasia 1040: Increased forestomach squamous cell papilloma	NTP, 2007
Reproductive/Developmental Toxicity (all are gavage studies except mouse reproduction study by NTP)								
Rat reproductive *p*-cresol	M,F	0, 30, 175, or 450 to both sexes	Two generations	30 (parental toxicity) 450 (reproductive toxicity)	175 (parental toxicity) none (reproductive toxicity)	Clinical signs of toxicity immediately following dosing	Reduced body weight gain at 450 mg/kg-day in F0 and F1 males and F1 females; perinatal body-weight gain reduced in F2 pups at 450 mg/kg-day. No reproductive toxicity	BRRC, 1989
Rat, developmental *p*-cresol	F	0, 30, 175, or 450	GDs 6−15	175 (maternal) 175 (fetal)	450 (maternal) 450 (fetal)	Maternal toxicity: clinical signs of neurotoxicity and mortality. Developmental toxicity: skeletal variations and decreased fetal body weight		BRRC, 1988b
Rat developmental *p*-cresol	F	0, 100, 333, 667, or 1000	GD 11	1000	none		No maternal or fetal toxicity was observed	Kavlock, 1990

Table 4. Summary of Oral Noncancer Dose-Response Information

Species/ isomer	Sex	Dose (mg/kg-day)	Exposure Duration	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Rabbit developmental (range-finding study) *p*-cresol	F	0, 50, 150, 300, 500	GDs 6−11	none (maternal) 150 (fetal)	50 (maternal) 300 (fetal)	Respiratory distress (maternal) Forelimb and pelvic girdle variations were seen in 300 mg/kg-day fetuses but not in other groups		BRRC, 1987
Rabbit developmental *p*-cresol	F	0, 5, 50, or 100	GDs 6−18	5 (maternal) 100 (fetal)	50 (maternal) none (fetal)	Mortality and clinical signs: hypoactivity, respiratory distress, ocular irritation	No developmental toxicity was observed at any dose	BRRC, 1988a.
Mouse dietary reproductive *m*/*p*-cresol (60:40)	M, F	0, 362, 1390, or 1682 (average of mean M and F doses)	Two generations	1390	1682	Increased cumulative day to fifth litter and decreased number of live pups/litter in F1 generation	Continuous breeding protocol	NTP, 1992b

Chronic Studies—No chronic oral studies conducted with 4-methylphenol alone have been identified. NTP (2007) reports preliminary findings from chronic dietary studies conducted with mixed *m*/*p*-cresols (60/40) in rats and mice. As of May 2008, the report has not been finalized, but the draft abstract, pathology data, and survival and growth data are available on the NTP Web site. The only details currently available for this study are presented below.

F344/N rats (50 males/dose) were fed mixed *m*/*p*-cresol isomers (60/40) in the diet at concentrations of 0, 1500, 5000, or 15,000 ppm (equivalent to 0, 70, 230, or 720 mg/kg-day) for 105 weeks (NTP, 2007). There were no treatment-related effects on survival, and body weights were comparable between controls and all but high-dose rats throughout the study. Body weight was significantly reduced in the high-dose rats throughout the study. At study termination, body weight of the high dose male group was 85% of the control weight. Significant nonneoplastic lesions were observed in the highest dose groups in the kidney (increased incidence and severity of hyperplasia of the transitional epithelium of the renal pelvis [0/50, 0/50, 2/50, and 8/50] and liver [eosinophilic focus: 14/50, 14/50, 13/50, and 23/50]). Increased incidences of nasal lesions were observed at all doses. Goblet cell hyperplasia was observed at incidences of 23/50, 40/50, 42/50, and 47/50 for 0, 70, 230, and 720 mg/kg-day, respectively. Respiratory epithelium hyperplasia was observed at incidences of 3/50, 17/50, 31/50, and 47/50 for 0, 70, 230, and 720 mg/kg-day, respectively. Significantly ($p < 0.05$) increased incidences of metaplasia of the respiratory epithelium were observed in the mid-and high-dose groups, and the incidence of inflammation was significantly ($p < 0.05$) increased in the high-dose group. There were no statistically significant treatment-related neoplastic changes. However, there was an increased incidence of renal tubule adenomas in high-dose males (3/50 regular tissue slices; 4/50 when regular and extended examinations are combined) in comparison with controls (0/50), low (0/50), and mid-dose (0/50) groups. The incidence of renal tubule adenomas in high-dose males was outside the historical control range and was considered to provide equivocal evidence of carcinogenicity in male rats. As reported for mice (NTP, 1992a), the nasal effects in rats may possibly be unrelated to systemic effects via oral exposure. No NOAEL was established.

B6C3F1 mice (50 females/dose) were fed mixed *m*/*p* cresol isomers (60/40) in the diet at concentrations of 0, 1000, 3000, or 10,000 ppm (0, 100, 300, or 1040 mg/kg-bw/day) for 106−107 weeks (NTP, 2007). Survival was comparable among treatment groups. Body weight was significantly lower than controls in mid- and high-dose mice, but food consumption was reduced only in the high-dose group. Significantly increased incidences of nonneoplastic lesions were observed in the thyroid (follicular degeneration at all doses), lung (bronchiolar hyperplasia at all doses), nose (epithelial hyperplasia at the mid-and high-doses), and liver (eosinophilic focus at the high-dose). The LOAEL for nonneoplastic effects in the mouse study is 100 mg/kg-day (lowest dose tested) for follicular degeneration of thyroid and bronchiolar hyperplasia. No NOAEL was established. The incidence of squamous cell papilloma of the forestomach was significantly increased in high-dose mice with respect to controls (0/50, 1/50, 1/49, 10/50 at 0, 100, 300, 1040 mg/kg-day, respectively). NTP (2007) considered the latter observation to provide some evidence of potential carcinogenicity to humans.

Reproductive/Developmental Studies—In a reproductive toxicity study (BRRC, 1989), Sprague-Dawley rats (25/sex/group) were administered 4-methylphenol (98.93% pure) in corn oil by gavage at doses of 0 (vehicle only), 30, 175, or 450 mg/kg-day, 5 days/week for 10−11 weeks premating. Males and females were dosed daily through mating, and females were also dosed daily during gestation and lactation. Groups of F1 rats were treated in the same

manner as the parental generation to produce the F2 generation. Clinical signs, body weight, and food consumption were monitored. All animals were subjected to gross pathological examination. All control and high-dose animals received histopathological examination of the pituitary, vagina, uterus, ovaries, testes, epididymides, seminal vesicles, prostate, and other tissues with gross lesions identified as being potentially treatment related. Additionally, any of the above tissues or organs in other dose groups that showed gross alterations were evaluated microscopically. Gross and histopathological examinations were conducted for any parental animals that died during the study. Gross pathological examinations were also performed on F1 or F2 pups that appeared abnormal or died during the study. Reproductive variables (mating success, fertility, number of females with live litters, number of live pups at birth, lactation index 4-, 7-, 14-, and 21-day survival indices) were assessed in F0 and F1 rats.

Significant ($p < 0.05$) mortality was observed in high-dose adult F0 and F1 male (28−36%) and female (32−40%) rats (BRRC, 1989). Treatment-related decreases in body weight and body-weight gains were observed primarily in high-dose F0 and F1 males and F1 females during prebreeding treatment. For example, F0 males in the high-dose group weighed approximately 13% less than their control counterparts on Week 13 of the study and gained only 9.5 ± 6.02 grams ($n = 25$) in comparison with controls who gained 17.6 ± 5.43 grams ($n = 25$) from the 12th to 13th week of exposure. The decreases in body weight (8% less than controls at greatest point of deviation) and body weight gain were less in F1 females than in males, and were significant only during the first 4 weeks of treatment. Decreased food consumption was also noted in high-dose male and female rats and was more pronounced early in the treatment period. Clinical signs of toxicity were observed in high-dose males and females during exposure and/or within 15 minutes following exposure and included hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration, and perioral wetness. Perinasal encrustation and urogenital wetness were also seen in F0 females. Increased incidences of perioral wetness (salivation/drooling) were observed in F0 and F1 males and females of the 175 mg/kg-day dose group. There were no clear signs of treatment-related perinatal toxicity in F1 pups. No treatment-related gross or histologic lesions were observed in rats that survived to sacrifice. Gross and histologic findings in rats that died prior to scheduled sacrifice mainly involved color changes in lungs, crusted or stained skin, and lung congestion. There were no treatment-related adverse reproductive effects. Based on clinical signs of toxicity observed in mid- and high-dose parental rats (175 and 450 mg/kg-day dose groups, respectively), the NOAEL for parental toxicity in this study is 30 mg/kg-day. The LOAEL for parental toxicity is 175 mg/kg-day for clinical signs of toxicity following dosing. The NOAEL for reproductive toxicity is 450 mg/kg-day (highest dose tested).

In a developmental toxicity study (BRRC, 1988b), groups of 25 mated Sprague-Dawley rats were treated with 4-methyphenol (99.7% pure) in corn oil by gavage at doses of 30, 175, or 450 mg/kg-day on Gestation Days (GD) 6−15. A group of 50 mated dams served as vehicle controls. Clinical observations were made twice daily during treatment and once per day otherwise. Food consumption was measured throughout gestation. Maternal body weights were recorded on GDs 0, 6, 11, and 15 and at terminal sacrifice on GD 21, at which time dams were also evaluated for liver and gravid uterine weights, number of *corpora lutea*, resorptions, and dead and live fetuses. All live fetuses were weighed and examined for external malformations and variations. Approximately one-half of the live fetuses from each litter were examined for visceral and craniofacial malformations; the other half was examined for skeletal abnormalities.

Maternal and fetal effects were limited to the 450-mg/kg-day dose group (BRRC, 1988b). Death was noted in three high-dose dams and two others were removed from the study, due to dosing error. Significantly increased incidences of clinical signs of treatment-related toxicity included hypoactivity, ataxia, tremors, twitches, prone positioning, urogenital area wetness, labored and audible respiration, gasping, perinasal encrustation, perioral wetness and encrustation, and red fluid expelled from the mouth. Food consumption during treatment was approximately 24% lower than controls. Mean body weight on GD 15 and body-weight gain during the treatment period were significantly lower than controls (reduced approximately 7 and 40%, respectively). There were no treatment-related effects on gestational parameters or on the incidence of external, soft tissue, or skeletal malformations. The incidences of bi-lobed cervical centrum #6, reduced number of ossified caudal segments, and unossified sternebrae #5 were significantly increased in fetuses of the 450-mg/kg-day dose group, relative to controls. There were no other significant dose-related adverse skeletal effects. Fetal body weight per litter was significantly lower (approximately 6%) in the high-dose fetuses in comparison with controls. The NOAEL for maternal toxicity in this study is 175 mg/kg-day. Mortality and clinical signs of toxicity (hypoactivity, respiratory distress, signs of central nervous system toxicity) were observed at 450 mg/kg-day. The NOAEL for fetal effects in this study is 175 mg/kg-day. The LOAEL for fetal effects (skeletal variations, depressed fetal body weight) is 450 mg/kg-day.

Groups of 14 mated New Zealand white rabbits were exposed to 4-methylphenol (99.7% pure) in corn oil by gavage at doses of 5, 50, or 100 mg/kg-day on GDs 6−18 (BRRC, 1988a). A group of 28 mated females served as vehicle controls. Clinical observations were made twice daily during treatment and once per day otherwise. Food consumption was measured throughout gestation. Maternal body weights were recorded on GD 0, then every 6 days until terminal sacrifice on GD 29, at which time does were also evaluated for liver and gravid uterine weights, number of *corpora lutea*, resorptions, and dead and live fetuses. All live fetuses were weighed and examined for external malformations and variations and then prepared for visceral examination. The sex ratios were noted for each litter, and approximately one-half of the live fetuses in each litter were examined for soft tissue craniofacial malformations. All fetuses were examined for skeletal abnormalities.

One dose each from the mid- and high-dose groups was removed from the study due to dosing error (BRRC, 1988a). Death prior to scheduled necropsy was noted in 5/14 high-dose and 2/13 mid-dose does and was considered to be due to 4-methylphenol toxicity. Clinical signs of treatment-related maternal toxicity in the mid- and high-dose groups included hypoactivity, respiratory distress (gasping, cyanosis, labored and audible rapid breathing), and ocular discharge. No clinical signs of toxicity were noted in the low-dose group. Food consumption was not significantly affected by 4-methylphenol treatment. There were no significant dose-related adverse effects on maternal body weight, gravid uterine weight, or liver weight. There were no signs of treatment-related gross maternal lesions at necropsy. No significant treatment-related effects were observed with respect to numbers of *corpora lutea*, implantation sites, live and dead fetuses, sex ratio, or fetal malformations. The NOAEL for maternal toxicity is 5 mg/kg-day. Mortality and clinical signs of toxicity (hypoactivity, respiratory distress, and ocular irritation) were observed at 50 mg/kg-day, making 50 mg/kg-day the LOAEL for maternal toxicity. The NOAEL for fetal effects is 100 mg/kg-day (highest dose tested).

In a range-finding developmental toxicity study (BRRC, 1987) to determine the doses to be used in the main study reported above (BRRC, 1988a), groups of eight mated New Zealand white rabbits were exposed to 4-methylphenol in corn oil by gavage during Days 6 through 18 of gestation. Vehicle controls consisted of 16 mated does. Mortality was noted in 0/8, 2/8, 4/8, and 7/8 rabbits in the 50-, 150-, 300-, and 500-mg/kg-day dose groups, respectively. Significantly reduced food consumption during GDs 6−11 was observed in does at ≥300 mg/kg-day. Significantly depressed mean body-weight gain was seen in the 150 mg/kg-day group during Days 6−12 of gestation and in the 300 mg/kg-day group throughout gestation. Clinical signs of central nervous system and cardiopulmonary toxicity were noted in does at ≥300 mg/kg-day. Respiratory distress was observed in a few of the does in the 50 mg/kg-day dose group. The only apparent treatment-related adverse fetal effects were forelimb and pectoral girdle variations in the 300 mg/kg-day dose group. No adverse fetal effects were observed in the 500 mg/kg-day dose group, but this observation is not reliable due to the small sample size of this dose group (only one dam at this dose group survived to produce a litter). The LOAEL for maternal toxicity is 50 mg/kg-day (lowest dose tested) on the basis of respiratory distress. The NOAEL for fetal toxicity is 150 mg/kg-day because the forelimb and pectoral girdle variations were seen at the next higher dose (LOAEL = 300 mg/kg-day).

Sprague-Dawley rats (13/group) were treated by gavage to a single dose of 4-methylphenol at 100, 333, 667, or 1000 mg/kg on Day 11 of gestation (Kavlock, 1990). A group of 17 pregnant dams served as vehicle controls. Rats were weighed on Days 10, 11, 12, 14, 17, and 21 of gestation. Rats were observed for clinical signs of toxicity for several hours postdosing and were allowed to deliver at term. Body weight and viability of the neonates was assessed on Postpartum Days 1, 3, and 6. Overt malformations were examined, perinatal loss was calculated, and litters were maintained until weaning, at which time they were examined for previously undetected external malformations. There were no treatment-related deaths. Mid- and high-dose dams lost body weight (-3 and -10 g, respectively; statistically significant only for the highest dose) during the first 24 hours of exposure, but they had weight gains that were not statistically different from controls by the 72-hour weigh-in. There were no significant differences between any treatment group and controls with regard to litter size, perinatal loss, mean pup weight, and litter biomass. No other adverse maternal or fetal effects were assessed or reported. The NOAEL for maternal and fetal toxicity is 1000 mg/kg-day (highest dose tested).

Reproductive effects following a continuous breeding protocol were examined in mice (8 per gender) exposed to a 60:40 mixture of *m*/*p*-cresol in the diet at concentrations of 0, 0.25, 1.0, and 1.5% (equivalent to doses of 0, 362, 1390, or 1682 mg/kg-day; page 50, Table 2-8, average of male and female values for Task 2) for two generations (NTP, 1992b). Endpoints examined in the study include clinical signs, body weight, food consumption, gross necropsy, reproductive performance, vaginal cytology, sperm variables, and testicular histopathology. The NOAEL for parental and reproductive toxicity in this study is equivalent to an average dose of 1390 mg/kg-day. Reduced body weight and food consumption and parallel changes in various organ weights were observed at the higher dose. An increased cumulative day to production of the fifth litter (difference of 3 days in comparison with controls) and decreased number of live pups/litter in the F1 generation (10.1 ± 0.6, n = 19 high-dose; versus 12.7 ± 0.4, n = 37 control) were also observed at the highest dose (1682 mg/kg-day). The LOAEL for parental and reproductive toxicity is, therefore, 1682 mg/kg-day.

Inhalation Exposure

The inhalation database is composed of translations of studies from the Russian literature that are lacking in details relevant to methods and results.

Subchronic Studies—Pereima (1975) exposed female rats (strain and numbers not reported) to 4-methylphenol aerosols at 10 mg/m^3 for 4 months followed by a 2-month observation period. Clinical signs of toxicity, including loss of appetite, emaciation, and reduced locomotor activity, were noted. Body-weight gain was reduced and remained depressed throughout the observation period. Dystrophic changes were observed in the lung and liver accompanied by a decrease in lung weight and an increase in liver weight. Hemorrhagic inflammation of the nasal mucosa and conjunctiva and inflammation of the skin and subcutaneous tissue were noted during the exposure period and remained evident throughout the recovery period. Exposed animals also developed oliguria that persisted through the recovery period. No further details are reported.

Cresol isomers other than 4-methylphenol have been tested in laboratory animals. Results for the relevant studies involving 2-methylphenol, 3-methylphenol, and cresol mixtures (dicresol and tricresol) are discussed below.

Mice were exposed to a combination of 2-methylphenol (*o*-cresol) aerosol and vapor at an average concentration of 50 mg/m^3, 3 hours/day, 6 days/week) for 1 month (Uzhdavini et al., 1972). No mortality was observed. Clinical signs of toxicity (respiratory irritation and hypoactivity), slightly reduced body-weight gain, respiratory tract lesions (edema, cellular proliferation, and small hemorrhages in the lung), and degenerative lesions in heart, liver, kidney, and CNS tissue were reported. No further details are reported.

Rats were exposed to an average concentration of 9 mg/m^3 of 2-methylphenol vapor 4−6 hr/day, 5 days/week for 4 months (Uzhdavini et al., 1972). Respiratory lesions (irritation and inflammation of the upper respiratory tract and edema and perivascular sclerosis in the lungs), hematological changes (increased leukocytes in blood, decreased erythropoietic elements in bone marrow), increased duration of hexanol narcosis (possibly indicating decreased liver function), and accelerated loss of a conditioned defense reflex were reported. Guinea pigs exposed under the same protocol had only minor hematological effects and a slight change in echocardiogram (Uzhdavini et al., 1972). No further details are reported.

Female rats were exposed to 10 mg/m^3 of 2-methylphenol aerosols for 4 months (Pereima, 1975). The effects observed in this study were almost identical to those reported above for 4-methylphenol. 3-Methylphenol (*m*-cresol) was also tested in this study, but the only effects observed are reduced body-weight gain, transient oliguria, and dystrophic changes in the lung and liver (Pereima, 1975). No further details are reported.

Rats exposed to 5 mg/m^3 of dicresol (a mixture of 3- and 4-methylphenol) for 4 months (4 hours/day, 5 days/week) had decreased growth, hematological changes (increased erythrocytes, decreased neutrophils), altered electrocardiogram, organ weight changes (increased kidney weight, decreased uterus weight), tissue lesions (fatty liver, dystrophic changes in the lungs, myocardium, kidney, and CNS), and altered adrenal cortical function. Only minor effects were reported for rats exposed similarly to 1.45 mg/m^3 (Uzhdavini et al., 1976). No further details are reported.

Rats exposed continuously to 0.05 mg/m^3 of tricresol (a mixture of 2-, 3-, and 4-methylphenol) vapor for 3 months had reduced growth, increased CNS excitability, structural changes in blood proteins, decreased gamma globulins in blood serum and microscopic lesions in the lung and liver, while rats exposed to 0.005 mg/m^3 did not show these effects (Kurlyandskiy et al., 1975; Uzhdavini and Gilev, 1976). No further details were reported.

Other Studies

Toxicokinetics—Methylphenols, including 4-methylphenol, are naturally occurring in humans due to amino acid metabolism by intestinal microflora. There is little toxicokinetic information regarding the absorption, distribution, and elimination of the methylphenols in animals or humans. Absorption is inferred from the observation of toxicity following oral, dermal, and inhalation administration (ATSDR, 2006). The following values were reported following intravenous administration of a 3 mg/kg dose of 4-methylphenol to rats: $t_{½}$ (blood) = 1.5 hours; total clearance from the blood = 23.2 mL/min/kg; and renal clearance = 4.8 mL/min/kg (Lesaffer et al., 2001). The authors suggested that processes such as exsorption (off-gassing from the blood), biotransformation, or biliary excretion may be responsible for the observed discrepancy between renal clearance and blood clearance.

Conjugation with glucuronic acid and inorganic sulfates is the primary metabolic pathway for all cresol isomers, and all isomers are eliminated primarily in the urine in conjugated form. All isomers undergo enterohepatic circulation (OECD-SIDS, 2003). *p*-Cresylsulfate is the primary metabolite of 4-methylphenol (Schepers et al., 2007). Oxidation to a reactive quinone methide intermediate has been proposed for 4-methylphenol based on in vitro studies with rat liver (Thompson et al., 1996). Another metabolic pathway involving aromatic oxidation of 4-methylphenol to 4-methyl-ortho-hydroquinone and the formation of 4-methyl-ortho-benzoquinone has recently been proposed following in vitro experiments with human liver microsomes (Yan et al., 2005).

The type of oral exposure may affect the types of toxic effects caused by 4-methylphenol and the doses at which they occur. Bray et al. (1950) observed greater toxicity in rabbits given *p*-cresol by gavage on an empty stomach than in rats given food 1−2 hours prior to dosing, suggesting that food might retard absorption of *p*-cresol. Further evidence for the idea that gavage exposure might result in a greater dose absorbed than dietary or drinking water exposure comes from examination of acute toxicity values. LD_{50} values for rats are 7−9 times lower following undiluted administration by gavage than those following administration of 4-methylphenol diluted in oil (Bray et al., 1950).

Morinaga et al. (2004) observed that a single gavage dose of *m*/*p*-cresol (to rats) in soap quickly disappeared from stomach contents, with 50% gone within 15 minutes and all gone within 8 hours. Conjugated derivatives were all gone from the blood within 4 hours. One interesting finding of these studies is that the liver and spleen had higher concentrations of unconjugated cresols than the blood over an 8-hour period. The authors suggested that these findings could be explained by the hypothesis that a gavage bolus could diffuse through the stomach and intestinal walls to nearby tissue. If true, this hypothesis could potentially explain some of the differences in toxicity observed in comparing the results of gavage versus dietary studies.

The toxicokinetic database for the methylphenol isomers does not include studies with dietary administration nor detailed information to make comparisons on the basis of total absorbed dose (e.g., area under the curve calculations) or peak blood concentrations.

Acute/Short-term Toxicity—WHO (1995) and OECD-SIDS (2003) summarize the available oral acute toxicity studies for *o*-, *m*-, and *p*-cresol. No studies are available for mixtures of the isomers. In general, *o*-cresol is the most toxic, followed by *p*-cresol and *m*-cresol. Administration of undiluted cresols resulted in lower LD_{50} values than when a vehicle was used. The LD_{50} values that are reported following undiluted administration of the test substance to rats are 121 mg/kg for *o*-cresol, 207 mg/kg for *p*-cresol, and 242 mg/kg for *m*-cresol. The LD_{50} values that are reported for rats following administration of the test substance in oil (10%) are 1350−1470 mg/kg for *o*-cresol, 1430−1800 mg/kg for *p*-cresol, and 2010−2020 for *m*-cresol. Mice are more sensitive than rats with LD_{50} values 3−4 times lower. The LD_{50} values for the test substance administered to mice in oil (10%) are 344 mg/kg for *o*-cresol, 344−440 mg/kg for *p*-cresol, and 600−828 for *m*-cresol. Following administration of undiluted isomers to rats, the clinical signs that preceded death (all three isomers except as noted) included hypoactivity, lethargy, excess salivation, dyspnea, hemorrhagic rhinitis (*p*-cresol only), lack of coordination, prostration, muscle twitches, tremors, convulsions, and coma. Gastrointestinal inflammation and hemorrhage and hyperemia of the lungs, liver, and kidney were noted upon necropsy of rats dying before study termination. Gastrointestinal inflammation was the only pathological finding in survivors and was limited to rats exposed to *p*-cresol. No gross pathological findings were noted in surviving rats treated with *o*- or *m*-cresol.

Pereima (1975) reported mean lethal concentrations of 29 mg/m^3 for both *o*- and *p*-cresols following acute inhalation exposures of rats. OECD-SIDS (2003) reports that no mortality, no clinical signs of toxicity, and no gross pathological changes were noted in 6 male rats exposed to *p*-cresol at a concentration of 710 mg/m^3 for 1 hour.

Other Routes—WHO (1995) reports dermal toxicity values as follows. Dermal LD_{50} values in rabbits are 890, 2830, 300, and 2000 mg/kg for *o*-, *m*-, *p*-, and mixed cresols, respectively. Dermal LD_{50} values in rats were 620, 1100, 750, and 825 mg/kg for *o*-cresol, *m*-cresol, *p*-cresol, and dicresol (a mixture of *m*- and *p*-cresols), respectively.

4-Methylphenol is corrosive to the skin and causes severe eye irritation and damage in animals (OECD-SIDS, 2003). 4-Methylphenol (4% in petrolatum) did not cause sensitization in 25 human volunteers who participated in a dermal maximization test (OECD-SIDS, 2003).

Boutwell and Bosch (1959) conducted initiation-promotion studies with a number of chemicals—including methylphenols. Female Sutter mice (27−29/group; 2−3 months of age) received a single dermal application of 25 µL of 0.3% dimethylbenzanthracene (DMBA) in acetone as the initiator, followed 1 week later by 25 µL of 20% by volume (v/v) *o*-, *m*-, or *p*-cresol in benzene twice weekly for 12 weeks. Skin papillomas were evaluated at 12 weeks. Many of the cresol-treated mice died—presumably of cresol toxicity. There was no mortality or evidence of skin papillomas in the benzene control group (benzene weekly after DMBA initiation). The numbers of surviving mice that developed skin papillomas at 12 weeks are as follows: 10/17, *o*-cresol; 7/14, *m*-cresol, and 7/20, *p*-cresol. None of the 12 mice in the benzene control group died or developed skin papillomas.

In another experiment, groups of 20 mice received a single dose (25 µL) of 0.3% DMBA in acetone, followed by twice-weekly applications of 5.7% *m*-cresol in benzene or 5.7% *p*-cresol in benzene for 20 weeks. No skin papillomas were observed in the 18 surviving benzene control mice; 4/17 *m*-cresol-, and 4/14 *p*-cresol-treated mice developed skin papillomas (Boutwell and Bosch, 1959).

These two experiments indicate that cresols can promote tumor formation by polycyclic aromatic hydrocarbons and are used to support a Group C, *possible human carcinogen*, weight-of-evidence finding for the carcinogenicity of 4-methylphenol verified on IRIS.

Neurotoxicity—As discussed in previous sections, clinical signs of toxicity including salivation, tremors, convulsions, and ataxia have been observed in the acute and subchronic oral studies conducted with 4-methylphenol. Despite the appearance of clinical signs, no adverse behavioral effects or neuropathology was observed in a subchronic gavage study specifically designed to investigate the neurotoxicity of 4-methylphenol (TRL, 1986). The study identifies a NOAEL of 50 mg/kg-day and a LOAEL of 175 mg/kg-day based on clinical signs (TRL, 1986).

Immunotoxicity—*Oxidative burst activity* is a marker for the inflammatory status of leukocytes. Baseline activation of leukocytes has been associated with vascular damage, which, in turn, has been associated with renal insufficiency in patients with kidney disease (Schepers et al., 2007). Schepers et al. (2007) demonstrated that *p*-cresylsulfate, a primary metabolite of 4-methylphenol, increased the oxidative burst activity of unstimulated leucocytes in whole blood drawn from healthy human volunteers.

Mechanistic—The metabolism of 4-methylphenol involves the formation of several intermediates that have been proposed as potential agents of toxicity. Schepers et al. (2007) demonstrated that *p*-cresylsulphate, a primary metabolite of 4-methylphenol, increased the pro-inflammatory activity of unstimulated leucocytes in blood drawn from healthy humans. This observation is congruent with the hypothesis that *p*-cresylsulfate causes vascular damage and subsequent renal insufficiency in humans with kidney disease. Thompson et al. (1996) demonstrated that substituted cresols—including 4-methylphenol—are toxic to rat liver slices (measured as loss of intracellular potassium as a proxy for cell viability) and are metabolized to quinone methide intermediates in rat liver slices and rat microsomes (measured as glutathione conjugate formation). Modifications to the parent compound (e.g., deuteration, ring-substitution) that affected the rate of metabolism and the stability of the quinone methide were correlated with observed toxicity (i.e., toxicity proportional to the presence of quinone methide), suggesting that the quinone methide is the reactive metabolite associated with liver toxicity.

Genotoxicity—U.S. EPA's weight-of-evidence classification for 4-methylphenol takes into account genotoxicity information for all of the individual cresol isomers as well as mixtures of isomers. Cresols (*o*-, *m*-, and *p*-) are not mutagenic in various strains of *Salmonella typhimurium* or *Escherichia coli* either in the presence or absence of mammalian liver homogenates (Crowley and Margard, 1978; Litton Bionetics, 1980a, 1981a; Florin et al., 1980; Douglas et al., 1980; Pool and Lin, 1982; Haworth et al., 1983; NTP, 2007).

A mixture of the three isomers was mutagenic in a mouse lymphoma forward mutation assay with mammalian liver homogenates, while *o*-cresol was not mutagenic with or without liver homogenates (Litton Bionetics, 1980b, 1981b). No isomer, when tested individually,

induced sister chromatid exchanges (SCEs) in vivo, but the mixture of the three isomers induced SCEs in Chinese hamster ovary (CHO) cells in vitro (Litton Bionetics, 1980c). Only *o*-cresol induced SCEs in human lung fibroblasts (Cheng and Kligerman, 1984) and CHO cells (Litton Bionetics, 1981c). In a screening test for putative carcinogens, infectious virus particles were produced from SV40-transformed weanling Syrian hamster kidney cells exposed to *m*-cresol (Moore and Coohill, 1983).

Studies on the induction of unscheduled DNA synthesis showed *p*-cresol to be positive in human lung fibroblast cells in the presence of hepatic homogenates (Crowley and Margard, 1978), the mixture of the three isomers to be weakly positive in primary rat hepatocytes, (Litton Bionetics, 1980d) and *o*-cresol to be negative in rat hepatocytes (Litton Bionetics, 1981e).

In cell-transformation assays using BALB/3T3 cells, a mixture of three cresol isomers was positive (Litton Bionetics, 1980e, 1981d) and *o*-cresol was negative. Positive mutagenic responses were found at noncytotoxic doses (Litton Bionetics, 1980e). In another cell transformation assay using *p*-cresol, negative results were obtained with the mouse fibroblast cell line C3H1OT1/2 (Crowley and Margard, 1978).

4-Methylphenol inhibited semiconservative DNA synthesis (25% inhibition compared with controls) and DNA repair (21% inhibition compared with controls) in human peripheral lymphocytes (Daugherty and Franks, 1986) and inhibited DNA synthesis (measured by radioactive thymidine incorporation) in V79 Chinese Hamster cells with a median inhibitory concentration (IC_{50}) of 0.15 mM (Richard et al., 1991). The latter result placed 4-methylphenol into a "moderate" category when compared with other phenolic compounds (e.g., *p*-nitrophenol considered inactive with an IC_{50} >3 mM; phenol considered low, with an IC_{50} of 2.4 mM; *p*-aminophenol considered high with an IC_{50} of 0.0018 mM).

4-Methylphenol gave a positive result in an in vitro carcinogenicity test using a bovine papillomavirus DNA-carrying mouse embryo fibroblast cell line (T1). The lowest effective concentration was 0.01 mg/mL (Kowalski et al., 2001).

4-Methylphenol did not increase the incidence of dominant lethal mutations in the germ cells of male mice given single oral doses of 4-methylphenol in corn oil at concentrations up to 550 mg/kg. Toxicity was noted at an initially tested high dose of 650 mg/kg (Hazleton Lab., 1989a). 4-Methylphenol was negative in a sex-linked recessive lethal test with *Drosophila melanogaster* SLRL following oral feeding of adult males with 0, 60, 300, or 600 µg/mL for 3 days (Hazleton Lab, 1989b).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 4-METHYLPHENOL

Subchronic and Chronic p-RFD

Table 4 summarizes the critical dose-response data for 4-methylphenol. In general, the observed toxicity following exposure to 4-methylphenol (*p*-cresol) is qualitatively and quantitatively similar to that of *m*/*p*-cresol (NTP, 1992a). The most sensitive endpoints following gavage exposure are clinical signs of neurotoxicity and mortality in pregnant rabbits

(BRRC, 1988a). While clinical signs of toxicity were observed, there were no treatment-related effects of cresol exposure on behavioral or neuropathological endpoints following subchronic gavage exposure (TRL, 1986). Clinical signs of neurotoxicity were not observed in any of the dietary studies. Nasal epithelial hyperplasia and other respiratory tract lesions are the most sensitive endpoints following dietary exposure. Nasal lesions were not observed in any of the gavage studies, suggesting the possibility that off-gassing from the food—either prior to ingestion or in the mouth during mastication—could be causing inhalation exposure and/or portal-of-entry irritation.

The critical study (i.e., BRRC, 1988a) identifies a NOAEL of 5 mg/kg-day and a FEL of 50 mg/kg-day, based on maternal toxicity (clinical signs of hypoactivity, respiratory distress, ocular irritation, and death) in New Zealand white rabbits exposed to 4-methylphenol by gavage during gestation. Support for choosing the NOAEL of 5 mg/kg-day as a possible point of departure (POD) for deriving a p-RfD comes from additional developmental toxicity studies in rabbits (i.e., BRRC, 1987) and rats (i.e., BRRC, 1988b), reproductive toxicity studies in rats (i.e., BRRC, 1989), a reproductive toxicity study with *m*/*p*-cresol in mice (i.e., NTP, 1992b), and subchronic toxicity studies in rats and mice (i.e., MBA, 1988; NTP, 1992a; TRL, 1986). Subchronic rodent studies reported clinical signs of neurotoxicity and hematopoietic effects at doses of 175 mg/kg-day and higher (TRL, 1986) and other toxic effects, such as reduced spleen weight and clinical symptoms of neurotoxicity in all exposed animals (50, 175, and 600 mg/kg-day, MBA, 1988). Furthermore, a rabbit dose-finding study (BRRC, 1987) to determine doses for the main developmental study (BRRC, 1988a) indicated both maternal and fetotoxicity at 50 mg/kg-day. Many of these studies reported similar effects as observed in the maternal rabbits, and all had higher effect levels. Preliminary results from chronic dietary exposure studies of male rats and female mice exposed to a 60/40 mixture of *m*/*p*-cresol (NTP, 2007) support previous findings from the existing subchronic and developmental toxicity studies conducted with 4-methylphenol alone and would not affect selection of the POD from which to derive an RfD for 4-methylphenol. NOAELs were not identified in the NTP (2007) chronic studies of *m*/*p*-cresol. A LOAEL of 70 mg/kg-day was identified for male rats on the basis of nasal lesions and a LOAEL of 100 mg/kg-day was identified for female mice on the basis of thyroid follicular degeneration and bronchiolar hyperplasia. Comparable effect-levels are derived from the 28-day studies with *p*-cresol (No NOAEL; LOAEL = 60 mg/kg-day for female mice based on nasal lesions). Effect levels in the NTP (1992a, 2007) studies exceed the NOAEL in the BRRC (1988a) study by more than an order of magnitude. BMD modeling of the sensitive endpoints from the NTP (2007) and NTP (1992a) studies is possible, but it does not yield BMDL values low enough to result in the derivation of a p-RfD lower than one derived on the basis of the NOAEL of 5 mg/kg-day.

ATSDR (2006) has raised the issue that dietary studies may be more appropriate than gavage studies as the basis for quantitative toxicity benchmarks for cresols and chose to eliminate gavage studies from consideration in the derivation of MRLs. The argument is based on the following observations: different toxic effects are observed following gavage versus dietary exposure; the doses at which toxic effects occur following gavage exposure are much lower than doses producing toxicity following dietary exposure; toxicity (measured as mortality) was less when gavage doses were administered to recently fed rabbits than to fasted rabbits (Bray et al., 1950); and dietary exposure is more relevant than gavage with respect to potential human exposure. A similar approach was taken by the U.S. EPA in the derivation of the RfD for phenol currently available on IRIS. However, the toxicokinetic database for phenol is more

complete than the database for cresols, including drinking water and gavage data. Furthermore, available data indicated that toxicity was correlated with peak blood concentrations rather than total dose. While the database for cresols suggests some similarities to phenol regarding the influence of gavage versus "natural" routes of oral exposure, the detailed comparative toxicokinetic data are lacking. As such, gavage studies were chosen for the derivation of provisional toxicity values. The rabbit maternal NOAEL of 5 mg/kg-day from the study by (BRRC, 1988a) was recommended as the POD for deriving subchronic p-RfD values.

The available data for the BRRC (1988a) study are not amenable to benchmark dose modeling as discussed in the study section. The subchronic p-RfD is derived by dividing the NOAEL of 5 mg/kg-day by an UF of 300 as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= 5 \text{ mg/kg-day} \div 300 \\ &= 0.0166 \\ &= \textbf{0.02 or } \mathbf{2 \times 10^{-2}} \textbf{ mg/kg-day} \end{aligned}$$

The subchronic p-RfD is based on maternal toxicity, and, although the effects were observed during the gestational period, the duration of exposure in the maternal animals is treated as subchronic. Furthermore, lack of chronic dose-response studies and uncertainties in the available subchronic studies precludes derivation of a chronic p-RfD.

The composite UF of 300 includes the following factors:

- A full UF of 10 is applied for interspecies extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between rats and humans.
- A full UF of 10 is applied for intraspecies differences in an effort to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A partial database uncertainty factor of 3 ($10^{0.5}$) is applied. The toxicological database includes developmental toxicity studies on two species and a two-generation reproduction study in rats. However, the database lacks a subchronic or chronic study for the sensitive species (rabbits) where effects were observed.

Confidence in the key study is medium. Although the critical study (BRRC, 1988a) was not of sufficient duration to be considered subchronic for maternal exposure, the NOAEL of 5 mg/kg-day is the highest NOAEL below all LOAELs. The NOAEL values identified in the rat subchronic studies (MBA, 1988; TRL, 1986) were equal to the LOAEL identified in the key study (BRRC, 1988a). The critical study identifies both a LOAEL and a NOAEL for maternal toxicity using an appropriate protocol. Confidence in the database is medium. Studies for subchronic toxicity, neurotoxicity, reproductive toxicity, and developmental toxicity have been conducted for 4-methylphenol. However, chronic studies for 4-methylphenol (alone) are not available and rabbits, which appear to be more sensitive than rodents on the basis of developmental toxicity studies, were not tested in subchronic studies. Therefore, confidence in the subchronic p-RfD is medium.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 4-METHYLPHENOL

None of the available studies regarding the inhalation toxicity of 4-methylphenol or the other methylphenol isomers or mixtures are reported with enough detail to be useful for quantitative toxicity assessment. Although limited, the available data suggest that 4-methylphenol and the other methylphenols are respiratory irritants and that portal-of-entry effects are likely to be important in determining quantitative toxicity values for these compounds. Therefore, extrapolation from the oral data is not recommended to derive inhalation toxicity values. The toxicity of methylphenol isomers following inhalation exposure is considered similar to that of phenol by ACGIH (2001). As such, ACGIH established a TLV for methylphenols based on the TLV for phenol. However, there currently is no verifiable RfC for phenol on IRIS that could serve as the basis for an RfC for 4-methylphenol. IRIS declined to derive an RfC for phenol due to the lack of appropriate data (U.S. EPA, 2008).

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 4-METHYLPHENOL

Weight-of-Evidence Descriptor

IRIS (U.S. EPA, 2008) lists a weight-of-evidence classification of Group C, *possible human carcinogen*, for 4-methylphenol on the basis of inadequate data in humans, limited data in animals (promotion of increased skin papillomas in mice; Boutwell and Bosch, 1959), and the supporting data from assays for mutagenicity conducted with individual cresols and mixtures of isomers. The data are not sufficient for quantitative toxicity assessment; therefore, no slope factor is derived. The study by Kubo (1990), in which 4-methylphenol was detected in the feces of colorectal cancer patients is suggestive of a possible relationship between 4-methylphenol excretion and cancer, but it is of no value in establishing that exposure to exogenous 4-methylphenol causes cancer. Forestomach hyperplasia and epithelial mitosis of the bladder were observed in hamsters exposed to one dose level of 4-methylphenol for 20 weeks (Hirose et al., 1986). However, due to the lack of higher exposure doses and the short duration of exposure, it is unknown whether these proliferative changes would progress to tumor formation. Preliminary results of the NTP (2007) chronic dietary study of *m*/*p*-cresols support the finding of possible carcinogenicity, providing equivocal evidence in rats and some evidence in mice as follows. An increased incidence of squamous cell papilloma in the forestomach was observed in female mice (0/50, 1/50, 1/49, and 10/50 at 0, 1000, 3000, and 10,000 ppm, respectively), and a nonsignificant increase in kidney renal tube adenoma was observed in male rats (0/50, 0/50, 0/50 and 4/50 at 0, 1500, 10,000, and 15,000 ppm, respectively).

Quantitative Estimates of Carcinogenic Risk

Limitations in the available data preclude derivation of quantitative estimates of cancer risk for 4-methylphenol.

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