NTP REPORT ON THE

TOXICITY STUDIES OF

CRESOLS

(CAS NOS. 95-48-7, 108-39-4, 106-44-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

National Toxicology Program
P.O. Box 12233
Research Triangle Park, NC 27709

February 1992

NTP TOX 9

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

These studies were supported in part by funds from the Comprehensive Environmental Response, Compensation, and Liability Act trust fund by an interagency agreement with the Agency for Toxic Substances and Disease Registry, U.S. Public Health Service.

FOREWARD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this toxicity study report were performed under the direction of the NIEHS and were conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals.

These studies are designed and conducted to characterize and evaluate the toxicologic potential of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's toxic or carcinogenic potential.

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National Toxicology Program
P.O. Box 12233
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February 1992
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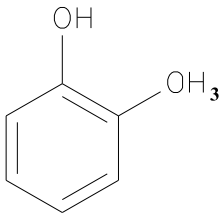
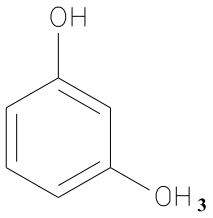
ABSTRACT



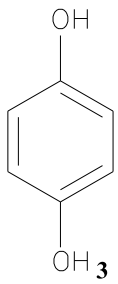
***o*-cresol**

CAS No. 95-48-7



***m*-cresol**

CAS No. 108-39-4



***p*-cresol**

CAS No. 106-44-5

C_7H_8O Molecular Weight: 108.13

***o*-cresol synonyms:** phenol, 2-methyl- (9CI); 2-cresol; *o*-cresylic acid; 1-hydroxy-2-methylbenzene; 2-hydroxytoluene; *o*-hydroxytoluene; 2-methylphenol; *o*-methylphenol; *o*-methylphenylol; *o*-oxytoluene; RCRA Waste Number U052; *o*-toluol; UN 2076
***m*-cresol synonyms:** phenol, 3-methyl- (9CI); 3-cresol; *m*-cresole; *m*-cresylic acid; 1-hydroxy-3-methylbenzene; 3-hydroxytoluene; *m*-hydroxytoluene; *m*-kresol; 3-methylphenol; *m*-methylphenol; *m*-oxytoluene; RCRA Waste Number U052; *m*-toluol; UN 2076
***p*-cresol synonyms:** phenol, 4-methyl- (9CI); 4-cresol; *p*-cresylic acid; 1-hydroxy-4-methylbenzene; 4-hydroxytoluene; *p*-hydroxytoluene; *p*-kresol; 1-methyl-4-hydroxybenzene; *p*-methylhydroxybenzene; 4-methylphenol; *p*-methylphenol; *p*-oxytoluene; RCRA Waste Number U052; *p*-toluol; *p*-tolyl alcohol; UN 2076

Cresols are monomethyl derivatives of phenol, and are found as constituents of coal tar, in various industrial solvents and resins, and in some essential oils. In 28-day toxicity studies, F344/N rats and B6C3F$_1$ mice of both sexes were given *o*-cresol, *m*-cresol, *p*-cresol, or *m*/*p*-cresol (60:40) at concentrations from 300 ppm to 30,000 ppm in the diet. In 90-day studies, *o*-cresol or *m*/*p*-cresol (60:40) were added to the diet in concentrations as high as 30,000 ppm to F344/N rats and 20,000 ppm (*o*-cresol) or 10,000 ppm (*m*/*p*-cresol) to B6C3F$_1$ mice.

In the 28-day studies, all rats survived (5 per sex per dose), but some mice given *o*-cresol at 30,000 ppm, or *m*-cresol or *p*-cresol at 10,000 ppm or 30,000 ppm died before the end of the studies. Feed consumption was depressed during the first study week in all high-dose groups of animals and weight gains were generally less than controls in groups given 10,000 or 30,000 ppm in the four 28-day studies. Increased relative liver weights and kidney weights were noted in both rats and mice given concentrations of cresols as low as 3,000 ppm. However, there were no consistant microscopic changes associated with these weight increases. Bone marrow hypoplasia and uterus, ovary and occasional mammary gland atrophy were seen primarily at the highest dietary concentration, but also at 10,000 ppm with certain cresols. An effect specific to the *p*-cresol and *m*/*p*-cresol studies was atrophy and regenerative changes in the nasal epithelia and forestomach,

presumably a direct result of the irritant effects of the chemical or its vapors.

In the 13-week studies, no deaths of rats (20 per sex per dose) or mice (10 per sex and dose) could clearly be related to administration of either *o*-cresol or *m*/*p*-cresol. Hematology, clinical chemistry, and urinalysis results were generally unremarkable in all studies, although an accumulation of bile acids in high-dose rats was considered evidence of a deficit in hepatocellular function resulting from ingestion of the chemical. Results of microscopic analyses were consistent with findings in the 28-day studies, and revealed evidence of mild bone marrow hypocellularity in rats and forestomach hyperplasia in mice given diets containing the higher concentrations of *o*-cresol. Evidence of nasal irritation was present in rats and mice receiving feed containing *m*/*p*-cresol. Additional lesions in rats receiving *m*/*p*-cresol included bone marrow hypocellularity and uterine atrophy. Results of reproductive tissue evaluations and estrus cycle characterizations with *o*-cresol and *m*/*p*-cresol in the 13-week studies gave no indication of adverse effects to the male reproductive system, but the estrus cycle was lengthened in rats and mice receiving the higher concentrations of *o*-cresol and rats receiving *m*/*p*-cresol. When compared to the results of the 28-day studies, there was little evidence of a significant increase in toxic effects with lengthened administration of *o*-cresol or *m/p-cresol* in the 13-week studies.

The cresol isomers exhibited a generally similar pattern of toxicities in rats and mice. Dietary concentrations of 3,000 ppm appeared to be minimal effect levels for increases in liver and kidney weights and deficits in liver function. Histopathologic changes, including bone marrow hypocellularity, irritation to the gastrointestinal tract and nasal epithelia, and atrophy of female reproductive organs, occasionally occurred at 10,000 ppm, but were more common at the high-dose of 30,000 ppm.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft report on the toxicity studies on cresols on November 19-20, 1990 are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members act to determine if the design and conditions of the NTP studies were appropriate and to ensure that the toxicity study report presents the experimental results and conclusions fully and clearly.

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SUMMARY OF PEER REVIEW COMMENTS

On November 20, 1990, the draft NTP report on the toxicity studies of cresols received public review by the National Toxicology Program Board of Scientific Counselor's Technical Report Review Subcommittee and associated panel of experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. Dennis Dietz began the discussion by reviewing the results of the study.

Dr. Carlson, a principal reviewer suggested a number of editorial changes and questioned whether the NTP had considered a dermal route of exposure as a more appropriate route than via diet Dr. Dietz responded that since these studies were part of the "superfund" initiative concerned with identifying hazards associated with ground water contamination, an oral route of exposure was selected.

Dr. Garman, the second principal reviewer was satisfied with the report as written.

Seeing no objections, Dr. Scala accepted the report with the suggested editorial changes on behalf of the panel.

INTRODUCTION

PHYSICAL PROPERTIES, OCCURRENCE, PRODUCTION, USE, AND EXPOSURE

Cresols are monomethyl derivatives of phenol and display chemical and biological properties similar to those of phenol (NIOSH, 1978; Deichmann and Keplinger, 1981; Sax and Lewis, 1989). They are obtained by chemical synthesis or by distillation from petroleum or coal tar. The *meta* and *para* isomers have similar boiling points and are often used as a mixture (Windholz *et al.*, 1983; IARC, 1985). Physical properties of the cresol isomers are detailed in Table 1.

Cresol mixtures are natural constituents of coal, petroleum, and wood (Hawley, 1981; Windholz *et al.*, 1983; Verschueren, 1983; Sax and Lewis, 1989). Coal tar containing cresols exhibits antipruritic and keratolytic properties and is used to treat psoriasis and eczematous dermatoses (Bowman and Rand, 1980; IARC, 1985). Coal tar products containing cresol are also used as pharmaceutical vehicles such as creams, ointments, pastes, lotions, bath and body oils, shampoos, soaps, and gels (IARC, 1985). Industrial and agricultural uses of cresols include the production of wire enamel solvents, automotive cleaners, phenolic resins, tricresyl phosphate, and cresyl diphenyl phosphate (NIOSH, 1978; EPA, 1986). Several essential oils used as flavoring agents and fragrances contain *p*-cresol (Furia, 1968; Bedoukian, 1967; Opdyke, 1974; Sax and Lewis, 1989). *Para*-cresol is the only cresol isomer detectable in human biological samples (urine), and the FDA has established allowable levels of *p*-cresol in food products (Furia and Bellanca, 1975).

Total U.S. production of all cresols in 1984 was approximately 117.5 million pounds (EPA, 1986). An estimated 148,000 to 300,000 people are exposed to cresols in the workplace and over 45 million pounds of cresols are released into the environment (EPA, 1983; EPA, 1986). Nonoccupational or environmental exposures to cresols occur from a variety of sources including contact with creosote as a wood preservative (Heikkila *et al.*, 1987), automobile exhaust (Roumeliotis *et al.*, 1981; Verschueren, 1983), cigarette smoke (Williams *et al.*, 1986), air pollution emissions from coal (Bezacinsky *et al.*, 1984) or wood (Hawthorne *et al.*, 1989) combustion, the degradation of atmospheric toluene (Dumdei and O'Brien, 1984), and thermal degradation products of styrene-containing thermoplastics (Hoff *et al.*, 1982). A nonoccupational cresol exposure of concern is groundwater contamination by industrial effluents (Ellis *et al.*, 1982; Demirgian, 1984) and landfill leachates (Reinhard and Goodman, 1984).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Exogenous cresols are absorbed from the gastrointestinal tract and are subsequently conjugated with glucuronide or sulfate (Bray *et al.*, 1950; Mandel, 1971; DeBruin, 1976a; DeBruin, 1976b). At physiological pH, the conjugated metabolites are more completely ionized than the parent cresol which reduces renal reabsorption and therefore aids in excretion by the kidney (Mandel, 1971). In addition to urinary excretion, cresols undergo enterohepatic circulation (Deichmann and Keplinger, 1981). The maintenance of this cycle is dependent upon conjugate hydrolysis via bacterial enzymes in the gut (Scheline, 1973).

There are known species, sex, and age differences in the specific conjugation reactions of cresol isomers (Mandel, 1971; Scheline, 1973). Rabbits exposed orally to cresols excreted 60% to 72% of all three isomers as glucuronides and 10% to 15% of the isomers as sulfates in the urine (Bray *et al.*, 1950; DeBruin, 1976b). Other significant metabolic pathways following oral administration of cresols to rabbits were found: (1) selective hydroxylation of *o*-cresol and *m*-cresol (3% of the dose) to 2,5-dihydroxytoluene and *p*-cresol (<1% of the dose) to 3,4-dihydroxytoluene and (2) side chain oxidation of *p*-cresol (10% of dose) to *p*-hydroxybenzoic acid (Bray *et al.*, 1950; El-Masry *et al.*, 1956; Hook and Smith, 1967; Kaubisch *et al.*, 1972; Goldstein *et al.*, 1974; DeBruin, 1976b).

TABLE 1
Physical Properties of Cresols[a]

	o-Cresol	*m*-Cresol	*p*-Cresol
Physical state	solid	liquid	solid
Appearance	colorless to yellow crystals	colorless to yellow liquid	colorless to white crystals
Odor	phenolic	phenolic	phenolic
Boiling point	190.95° C	203° C	201.9° C
Flammable limits in air (% by volume)	Lower: 1.35% at 300° F Upper: no data available	Lower: 1.1% at 302° F Upper: 1.35%	Lower: 1.1% at 302° F Upper: no data available
Melting point	30.94° C	10° C - 12° C	35.26° C
Flash point	81° C	86° C closed cup	86° C closed cup
Autoignition temperature	598° C	558° C	558° C
Specific gravity (water = 1)	1.047 (20° C/4° C)	1.034 (20° C/4° C)	1.0341 (20° C/4° C)
Vapor pressure	5 mm Hg at 64° C 1 mm Hg at 38.2° C 0.2453 mm Hg at 25° C	5 mm Hg at 76° C 1 mm Hg at 52° C 0.1528 mm Hg at 25° C 0.04 mm Hg at 20° C	1 mm Hg at 53° C 0.1080 mm Hg at 25° C 0.04 mm Hg at 20° C
Vapor density (air = 1)	3.72	3.72	3.72
Solubility			
Miscible	Alcohol, chloroform, and ether	Alcohol, chloroform, and ether	
Soluble	Acetone, benzene, carbon tetrachloride, fixed alkali hydroxides, hot water, ordinary organic solvents, and vegtable oil (30° C)	Acetone, benzene, carbon tetrachloride, fixed alkali hydroxides, and ordinary organic solvents	Acetone, alcohol, benzene, carbon tetrachloride, ether, and hot water
Slightly soluble	Water	Water	Water

[a] Furia and Bellanca, 1975; Mackison *et al.*, 1978; Clayton and Clayton, 1981; Hawley, 1981; ITII, 1981; Verschueren, 1983; Windholz *et al.*, 1983; USCG, 1985; Radian, 1986; TDB, 1986

Para-cresol is a normal constituent of human urine with levels of excretion ranging from 16 to 74 mg/24 hours (Bone *et al.*, 1976; Deichmann and Keplinger, 1981; Schaltenbrand and Coburn, 1985). The anaerobic microflora of the ileum reportedly produce this isomer from the amino acid tyrosine (Bone *et al.*, 1976).

BIOCHEMICAL EFFECTS

At levels ranging from 25 to 125 μg/mL, the cresols are *in vitro* inhibitors of red blood cell, platelet, and brain ATPase (Wardle, 1979) leading to inhibition of a variety of membrane-associated transport systems (Phillips and Hayes, 1989). Cresols have been shown to antagonize the neuromuscular blocking action of curare (Mogey and Young, 1949; Otsuka and Nonamura, 1963). It is suggested that the antagonistic action results from increased acetylcholine release from motor nerve endings or from an increased sensitivity of motor endplates to the neurotransmitter. These actions are consistent with the findings of Bunna and Jabbur (1970) showing that other phenolic chemicals are capable of facilitating spinal synaptic transmission. Several other phenolic chemicals inhibit the activity of catechol-*o*-methyltransferase (COMT), the enzyme responsible for the catabolism of catecholamines at sympathetic nerve endings (Crout *et al.*, 1961; Ross and Haljasmaa, 1964; Angel and Rogers, 1968).

Cresol exposures have been associated with hemolysis, methemoglobinemia, and acute Heinz-body anemia (Larcan *et al.*, 1974; Cote *et al.*, 1984). A mechanism for these hematological effects has not been described, but reactions between various phenols and oxyhemoglobin yield phenoxyradicals, methemoglobin, and hydrogen peroxide (Wallace and Caughey, 1975; Sawahata *et al.*, 1985). This result is compatible with the ability of the phenols to act as electron donors (Irons and Sawahata, 1985) and accounts for the antioxidant properties of the cresols shown by their ability to depress lipid peroxide formation in liver microsomes (Wills, 1969; Lindgren *et al.*, 1977).

TOXICITY

Acute Toxicity

Information regarding acute cresol toxicity has been obtained from suicide case studies involving Lysol®. In the United States, the manufactured product no longer contains cresols, while in the United Kingdom, the product still contains cresols.

Symptoms of acute toxicity in humans following the ingestion of cresols (1 to 60 mL) correspond to the signs of acute toxicity in rodents. These include involuntary muscle movements followed by paresis; gastrointestinal disturbances; renal toxicity; an initial central nervous system stimulation followed by depression; brief tachycardia, peripheral vasoconstriction, and increased blood pressure followed by circulatory collapse; dyspnea progressing to possible respiratory arrest; acute pancreatitis; and hematological changes (Chan *et al.*, 1971; NIOSH, 1978; Harvey, 1980; Deichmann and Keplinger, 1981; Craft, 1983; Cote *et al.*, 1984; Gosselin *et al.*, 1984; Arena and Drew, 1986; Plunkett, 1987). Target sites following repeated and/or prolonged cresol exposures are the same as those following acute exposures with the addition of liver injury. Gross and microscopic changes observed with cresol toxicity include a generalized hemorrhagic response; liver congestion and fatty degeneration; parenchymatous and hemorrhagic nephritis; myocardial degeneration; nerve demyelination; and pancreatitis. Effects of local exposure can include severe skin and eye irritation, severe idiosyncratic reactions in hypersensitive subjects, corrosive effects upon the skin and mucous membranes, and skin depigmentation (NIOSH, 1978; Deichmann and Keplinger, 1981; Sax and Lewis, 1989). Cresols can be absorbed through the skin in fatal amounts, the LD_{50} values for dermal exposures of cresols in rats being in the range of 620 to 1,100 mg/kg (Sweet, 1987).

Although similar toxic effects occur by all routes of exposure, including the percutaneous route (NIOSH, 1978; Deichmann and Keplinger, 1981), acute inhalation exposure to cresols under normal circumstances is generally not considered hazardous due to the low vapor pressure of the cresols and a distinct odor recognizable at <1.0 ppm (Verchueren, 1983; Ruth, 1986). Industrial hazards are primarily related to dermal exposures. The EPA has used toxicity data from oral studies to estimate risk from cresol exposure in the workplace (EPA, 1986).

Subchronic Toxicity

Uzhdavini *et al.* (1972) conducted numerous inhalation studies of *o*-cresol using various species of animals. Mice exposed to concentrations ranging from 26 to 76 mg/m³ (mean concentration, 50 mg/m³) for one month showed irritation of the respiratory mucosa. Microscopic changes occurred in the central nervous system (nerve and glial cell

degeneration), respiratory tract (petechial hemorrhage, inflammation, and proliferation of cellular elements), and heart (degenerative changes). In addition, the administration of *o*-cresol was associated with degeneration in kidney and liver cells. Rats and guinea pigs exposed to *o*-cresol (mean concentration, 9 mg/m^3) for 4 months showed signs of behavioral depression (conditioned defensive reflex in rats), an elevated leukocyte count in male rats, depressed erythroid bone marrow elements in rats, increased hexobarbital narcosis time in rats, a decreased R wave component in the electrocardiograms of guinea pigs, and unspecified changes in the hemoglobin concentration of guinea pigs.

Savolainen (1979) gave male rats *o*-cresol in drinking water (0.3 g/L) and killed groups after 5, 10, 15, and 20 weeks of compound administration. The *in vivo* results from the study showed no significant treatment-related effects, but homogenates of the cerebrum had increased RNA content, decreased glutathione, and lower azoreductase activity in treated rats compared to controls.

Dietz *et al.* (1987) and Henck *et al.* (1987) conducted 13-week subchronic cresol toxicity studies using Sprague-Dawley rats treated by gavage, with *o*-cresol at dose levels of 0 to 600 mg/kg per day, *m*-cresol at dose levels of 0 to 450 mg/kg per day, or *p*-cresol at dose levels of 0 to 600 mg/kg per day. Preliminary reports from these 13-week subchronic studies showed treatment-related mortality primarily restricted to 600 mg/kg *o*-cresol and *p*-cresol groups and depressed body weight gain in males receiving doses of 450 mg/kg *m*-cresol and 600 mg/kg *p*-cresol. Transient clinical signs occurred in the higher dose groups during the first few weeks of the study including lethargy, dyspnea, tremor, salivation, convulsions, and coma.

Reproductive and Developmental Toxicity

Women exposed in the workplace to varnishes containing tricresol (a mixture of *o*-cresol, *m*-cresol, and *p*-cresol), used in the manufacture of enamel-insulated wire, have reported increased gynecological problems (Syrovadko and Malysheva, 1977). These reproductive disorders include menstrual disturbances, hormonal disturbances, increased frequency of perinatal mortality, and increased abnormal development of newborns.

Chronic inhalation exposure to tricresol (0.6 to 4.0 mg/m^3) by female rats caused a decreased number of primary follicles in the ovaries and enhanced the process of atresia (Pashkova *et al.*, 1973). In addition, tricresol (1.0 mg/m^3) prolonged the estrual period and shortened the diestrus period. [Currently, the NTP is conducting reproduction/fertility studies in Swiss (CD-1) mice with *o*-cresol and the *m/p*-cresol mixture using dosed feed.]

Genetic Toxicity

Dean (1985) presented a summary of the genotoxicity data on the cresol isomers. The available data indicate that the cresol isomers are not mutagenic in bacteria. However, possible weak genotoxicity in higher organisms is suggested based upon results from onion root tip mitotic studies and sister chromatid exchange (SCE) tests in mammalian cells. Mixed isomers were tested for mutagenicity in *Salmonella typhimurium* strains TA100, TA1535, TA97, and TA98 with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 with no increase in revertant colonies seen in any of the strains (Appendix E). *Meta*-cresol, *o*-cresol, and *p*-cresol were also negative for induction of gene mutations in *Salmonella typhimurium* (Haworth *et al.*, 1983). Sharma and Ghosh (1965) reported that individual cresol isomers (0.025% solutions) induced anaphase aberrations and mitotic spindle abnormalities in *Allium cepa* root tips. The individual isomers were tested at concentrations up to 8 mM (864 μg/mL) for *in vitro* induction of SCE in human fibroblasts. Only *o*-cresol produced a significant increase in SCE; the response was weak even at the highest nontoxic concentration tested, 8 mM (Cheng and Kligerman, 1984). None of the isomers increased SCE in mouse bone marrow, lung, or liver cells in *in vivo* studies (Cheng and Kligerman, 1984). Peripheral blood analysis of the NTP 13-week study animal groups (this study) showed no increase in percent micronucleated polychromatic or normochromatic erythrocytes at any dose (Appendix E).

Study Rationale

Annually, over 45 million pounds of cresols are estimated to be released into the environment (EPA, 1983). Among organic chemicals, the cresols rank 36th among those occurring in chemical waste sites (Mitre Corporation, 1983). Due to its moder-

ate water solubility, cresols can be carried into ground and surface waters. Chemical analyses of leachate samples from landfills have shown groundwater contamination by cresols (Reinhard and Goodman, 1984).

The primary rationale for conducting the cresol studies detailed in this report was to provide additional information regarding the potential toxic effects of cresols in drinking water. Although ingestion via contaminated groundwater would be mimicked more closely by a drinking water study, the dosed feed route was chosen due to the limited solubility of cresols in water. Solubility limits are 2.3% to 3.0% cresol at elevated temperatures and/or alkaline pH (Windholz *et al.*, 1983). Also potential palatability problems are associated with the odor (1.4 mg/L) and taste thresholds (0.003 mg/L) of cresols in water (Verschueren, 1983). Other investigators have studied the effects of continuous exposures to cresols via the drinking water but at much lower levels of exposure (0.03%) (Savolainen, 1979). The highest dose of cresols selected for the studies reported here was 30,000 ppm (3% by weight) in feed. Four separate 28-day studies of *o*-cresol, *m*-cresol, *p*-cresol, and a *m/p*-cresol mixture (60%/40%) were performed to allow comparison of their toxicity. Based upon these four studies, doses for 13-week prechronic studies of *o*-cresol and the *m/p*-cresol mixture (60%/40%) were then selected. *Ortho*-cresol was selected for the 13-week studies because it is the most widely produced pure isomer (EPA, 1983; EPA, 1986), and the 60%/40% *m/p*-cresol mixture was selected because it is the approximate composition of "cresols" prepared from coal tar (Deichmann and Keplinger, 1981; Sax and Lewis, 1989).

In addition to describing the comparative toxicity of isomeric cresols, data from these studies may be used to design 2-year carcinogenicity studies. The carcinogenic potential of cresols has not been rigorously evaluated, though various reports raise some concern about this issue. The tumor-promoting activity for mouse skin tumorigenesis of cresols has been demonstrated (Boutwell and Bosch, 1959; Wynder and Hoffman, 1968). Other investigators have suggested that naturally occurring phenolics produced from tyrosine by the gut microflora may be causative agents in the development of hepatic and large bowel cancers, because animal studies show a correlation between the incidence of these cancers and dietary protein. Also, decreased incidences have been shown in germ free animals (Bone *et al.*, 1976). Finally, phenolic chemicals are not known to induce experimental brain tumors, but several occupational cohorts exposed to these chemicals show an elevated brain tumor risk (Thomas and Waxweiler, 1986).

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CRESOLS

All cresols were obtained through Midwest Research Institute (MRI, Kansas City, MO) from the following sources: *o*-cresol was manufactured by Koppers Company, Inc. (Pittsburgh, PA), *m*-cresol by Merichem Company (Houston, TX), and *p*-cresol by PMC Specialties Group, Inc. (Chicago, IL). MRI prepared the *m/p*-cresol mixture from chemicals received from the suppliers. One lot of each cresol was used throughout the studies (*o*-cresol, F860326; *p*-cresol, M050786; *p*-cresol, 1156; *m/p*-cresol, M083086). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory at MRI and confirmed by the study laboratory.

Ortho-cresol is a colorless to yellow crystalline material; *m*-cresol is a colorless to yellow liquid; and p-cresol is a colorless to white crystalline material. All three compounds emit a phenolic odor. *Ortho*-cresol, *m*-cresol, and *p*-cresol were identified by elemental analysis, thin-layer and gas chromatography, and infrared, ultraviolet/visible, and nuclear magnetic resonance spectrometry. Purities were found to be greater than 99%, 98%, and 98% for the *ortho-*, *meta-*, and *para-* isomers by Karl Fischer water analysis and phenol titration. *Meta/para*-cresol used during the studies was identified as 58.5% *m*-cresol and 40.9% *p*-cresol by gas chromatography and infrared spectrometry. MRI found all three pure isomers to be stable as bulk chemicals when stored protected from light and in a nitrogen atmosphere for 2 weeks at temperatures up to 60° C. As recommended by MRI, the bulk chemicals were stored during the studies at room temperature (approximately 25° C) and protected from light in containers with a nitrogen headspace sealed with Teflon-lined lids.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Formulated diets were prepared by adding a dry premix to the appropriate amount of feed. Results from studies at MRI suggested that feed dosed with *o*-cresol may be stored in sealed glass containers at 5° C for 3 weeks in the dark and dosed feed containing *m*-cresol, *p*-cresol, or *m/p*-cresol may be stored in sealed glass containers at -20° C for 3 weeks in the dark without significant loss of the cresol. During the studies, feed dosed with *o*-cresol was stored at 4° C and used within 3 weeks. Feed dosed with the other isomers or the mixture was stored at -20° C and used within 3 weeks. The homogeneity of diet mixtures formulated at the analytical chemistry and study laboratories was evaluated by extracting feed samples (taken from three locations in the blender) with acetonitrile:water (*o*-cresol — 80:20, v/v; *m*-cresol, *p*-cresol, and *m/p*-cresol — 2700:300 v/v). The samples were combined with an internal standard solution, *p*-ethyl phenol, and analyzed by gas chromatography using a flame ionization detector. The dose formulations used in the 28-day studies were tested prior to study initiation. The dose formulations used in the 13-week studies were analyzed prior to study initiation, at the study midpoint, and at study termination. All formulations analyzed at the analytical chemistry and study laboratories were within ± 10% of the target concentration. Preliminary studies to assess the stability of the various cresol isomer-feed mixtures demonstrated losses from 10% to 12% after storage for 7 days under simulated cage conditions. Fresh chemical-diet mixtures were, therefore, supplied twice weekly during the studies.

28-DAY STUDIES

Four- to five-week old F344/N rats and 4-week old B6C3F$_1$ mice of each sex were obtained from Simonsen Labs (Gilroy, CA). Before being placed on study, the rats were observed for 13 to 14 days and the mice were observed for 13 to 15 days.

Groups of five animals of each species and sex were fed diets containing 0, 300, 1,000, 3,000, 10,000, or 30,000 ppm *o*-cresol, *m*-cresol, *p*-cresol or *m/p*-cresol. The appropriate feed was supplied twice weekly and available *ad libitum* for 28 days. Water was also available *ad libitum*. Rats were housed five per cage; mice were caged individually. Feed consumption was recorded twice weekly. Water consumption was not recorded. The animals were

observed twice daily for signs of toxicity; they were weighed at study initiation, weekly, and at study termination. Details of experimental design and animal maintenance are summarized in Table 2.

A necropsy was performed on all animals. Organ weights were recorded for brain, heart, right kidney, liver, lungs, and thymus for all animals, and the right testis of all males. Tissues were preserved in 10% neutral buffered formalin. Tissues collected for histopathology were trimmed, embedded, sectioned, and stained with hematoxylin and eosin. A complete histopathologic examination was conducted on all control animals, all animals in the highest dose group with at least 60% survivors at study termination, and all animals in higher dose groups inclusive of early deaths. Target organs and gross lesions were examined at lower doses until a no-observed chemical effect was determined. Table 2 lists those tissues and organs that were examined microscopically.

13-Week Studies

Study Design

Groups of 20 rats of each sex were fed diets containing 0, 1,880, 3,750, 7,500, 15,000, or 30,000 ppm *o*-cresol for 13 weeks. Groups of 10 mice of each sex were fed diets containing 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm *o*-cresol for 13 weeks.

Groups of 20 rats each sex were fed diets containing 0, 1,880, 3,750, 7,500, 15,000, or 30,000 ppm *m/p*-cresol for 13 weeks. Groups of 10 mice of each sex were fed diets containing 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm *m/p*-cresol for 13 weeks.

In each 13-week study, samples obtained from 10 male and 10 female rats were used for the clinical chemistry, hematology, and urinalysis studies. The remaining 10 male and 10 female rats were used in reproductive toxicity, gross pathology, organ weight, clinical pathology, and histopathology studies.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY) for the *o*-cresol studies and from the Frederick Cancer Research Facility (Frederick, MD) for the *m/p*-cresol studies. After a quarantine period (12 days for rats; 13 or 19 days for mice), five animals of each species and sex were randomly selected and killed for parasite evaluation and gross observation of disease. The animals' health throughout the studies was assessed by serologic analyses performed at study termination according to the protocols of the NTP Sentinel Animal Program. Animals were placed in the study when rats were 6 to 7 weeks old and mice were 5 to 6 weeks old.

Animal Maintenance

Rats were housed five to a cage and mice were housed individually. Feed and water were available *ad libitum*. Feed consumption was recorded twice weekly. Water consumption was not recorded. Further details of animal maintenance are given in Table 2.

Clinical Examinations and Pathology

All animals were observed twice daily for signs of toxicity. Body weights were recorded for all animals at study initiation, weekly, and at study termination.

Clinical pathology analyses were performed on blood obtained from the retroorbital sinus of rats or the supraorbital sinus of mice. Hematologic analyses included leukocyte, lymphocyte, segmented neutrophil, monocyte, eosinophil, erythrocyte, hematocrit, reticulocyte, and platelet counts; hemoglobin concentration; mean cell hemoglobin; mean cell hemoglobin concentration; and mean cell volume. Hematology parameters were measured using Baker 9000 Hematology Analyzer methodologies. Serum chemistry analyses included alanine aminotransferase, alkaline phosphatase, bile acids, urea nitrogen, sorbitol dehydrogenase, 5'-nucleotidase, and creatinine. All analyses were performed using a Baker Centrifichem 400 analyzer. Analyses of total serum bile acid concentrations and activities of sorbitol dehydrogenase were performed using kits obtained from Sigma Chemical Company (St. Louis, MO). All other assays were performed using methods supplied by the manufacturer. Urinalysis determinations included volume, appearance, specific gravity, and activities of aspartate aminotransferase and N-acetyl-B-glucose aminidase. Reproductive toxicity analyses included sperm motility, sperm density, and vaginal cytology. The methods for the reproductive studies are presented in Appendix A.

During necropsy, all organs and tissues were examined for grossly visible lesions. Organ weights were recorded for brain, heart, right kidney, liver, lungs, and thymus for all animals, and the right testis of all males. Tissues were fixed in 10% neutral buf-

fered formalin and processed for microscopic examination (trimmed, embedded, sectioned, and stained with hematoxylin and eosin). A complete histopathologic examination was conducted on all control animals, all animals in the highest dose group with at least 60% survivors at study termination, and all animals in higher dose groups inclusive of early deaths. Target organs and gross lesions were examined at lower doses until a no-observed chemical effect was determined. Target organs were examined to a no-effect level. Table 2 lists those tissues and organs that were examined microscopically.

Pathology evaluations were completed by the study laboratory pathologist and the pathology data was entered into a computerized data management system. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. A quality assessment pathologist reviewed selected tissues for accuracy and consistency of lesion diagnosis.

The quality assessment report and slides were submitted to the Pathology Working Group (PWG) chairperson, who reviewed tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of potential chemical-related lesions and examples of disagreements in diagnosis between the laboratory and quality assessment pathologists were selected by the PWG chairperson for review by the PWG. The PWG included the quality assessment pathologist as well as other pathologists experienced in rodent toxicologic pathology, who examined these tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the final diagnosis was changed to reflect the opinion of the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985).

Statistical Methods

Analysis of Continuous Variables

For all end points, dosed groups were compared with the control group using the nonparametric multiple comparison test of Dunn (1964) or Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose response trends and to determine whether Dunn's or Shirley's test was more appropriate for pairwise comparisons.

Analysis of Vaginal Cytology Data

An arcsine transformation was used to bring estrus stage data into closer conformance with normality assumptions. Treatment effects upon the stages of estrus were then investigated by multivariate analysis of variance (Morrison, 1976).

Quality Assurance Methods

The prechronic studies were conducted in compliance with Good Laboratory Practice Regulations (21 CFR Part 58). The Quality Assurance Unit of Microbiological Associates performed audits and inspections of protocols, procedures, data, and reports throughout the studies. The operations of the Quality Assurance Unit were monitored by the NTP, including a site visit during the period of study performance.

TABLE 2
Materials and Methods in the Dosed Feed Studies of Cresols

28-Day Studies	13-Week Studies
Strain and Species F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source Simonsen Labs (Gilroy, CA)	*o*-cresol: Taconic Farms (Germantown, NY) *m*/*p*-cresol: Frederick Cancer Research Facility (Frederick, MD)
Size of Study Groups 5 males and 5 females of each species	Rats: 20 male and 20 female rats (10 of each group designated for clinical pathology studies) Mice: 10 male and 10 female mice
Time Held Before Study 13-15 days	*o*-cresol: 12-19 days *m*/*p*-cresol: 12-13 days
Method of Animal Distribution Randomized for each sex on the basis of body weight into groups per sex.	Same as 28-day studies
Diet NIH-07 Rat and Mouse Ration (Ziegler Brothers, Inc., Gardners, PA) available *ad libitum*	Same as 28-day studies
Animal Room Environment Temperature: 72° ± 3° F Humidity: 50% ± 15% Fluorescent light: 12 hours/day Room air changes: 10-12 changes/hour	Same as 28-day studies
Isomers Studied *o*-cresol, *m*-cresol, *p*-cresol, and *m*/*p*-cresol (60%/40%)	*o*-cresol and *m*/*p*-cresol (60%/40%)
Doses 0, 300, 1,000, 3,000, 10,000, or 30,000 ppm	*o*-cresol: rats - 0, 1,880, 3,750, 7,500, 15,000, or 30,000 ppm mice - 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm *m*/*p*-cresol: rats - 0, 1,880, 3,750, 7,500, 15,000, or 30,000 ppm mice - 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm
Type and Frequency of Observation Observed twice daily; body weights taken initially, weekly, and at termination; feed consumption by cage recorded twice weekly.	Same as 28-day studies

TABLE 2
Materials and Methods in the Dosed Feed Studies of Cresols (continued)

28-Day Studies	13-Week Studies
Necropsy and Histologic Examinations Necropsy and tissue collection performed for all animals.A complete histopathologic examination was conducted on all control animals, all animals in the highest dose group with at least 60% survivors at study termination, and all animals in higher dose groups inclusive of early deaths. The following organs and/or tissues were included in complete histopathological examinations, as well as any tissue masses, gross lesions, and associated regional lymph nodes: adrenals, aorta, bone (sternebrae, femur, or vertebrae, including marrow), brain, bronchi, clitoral gland, epididymis, esophagus, gallbladder (mice only), heart, kidneys, large intestines (cecum, colon, rectum), liver, lungs, lymph nodes (mesenteric), mammary glands, nasal cavity and turbinates, oral cavity, ovaries, pancreas, parathyroids, pharynx, pituitary, preputial gland, prostate, salivary glands, scrotal sac, seminal vesicles, skin, small intestines (duodenum, ileum, jejunum), spleen, stomach, testes, thymus, thyroid, tongue, trachea, tunica vaginalis, urinary bladder, uterus, and Zymbal's glands. Target organs and gross lesions were examined at lower doses until a no-observed chemical effect was determined. Target organs included the following: for *o*-crcsol, uterus and ovaries (female mice); for *m*-cresol, uterus (female rats and mice), ovaries and mammary gland (female mice); for *p*-cresol, nasal epithelium and bone marrow (rats and mice, both sexes), uterus (female rats), liver, kidney, and lymphoid organs (male and female mice); for *m/p*-cresol, nasal epithelium, bone marrow, forestomach, and esophagus (rats and mice, both sexes), thyroid (male and female rats), lung (male and female mice), uterus and ovaries (female mice). Organ weights recorded for the brain, liver, right kidney, thymus, heart, and lungs of all animals, and the right testis of all males.	Necropsy performed on all animals. A complete histopathologic examination was conducted on all control animals, all animals in the highest dose group with at least 60% survivors at study termination, and all animals in higher dose groups inclusive of early deaths. The following organs and/or tissues were included in complete histopathological examinations, as well as any tissue masses, gross lesions, and associated regional lymph nodes: adrenals, aorta, bone (sternebrae, femur, or vertebrae, including marrow), brain, bronchi, clitoral gland, epididymis, esophagus, gallbladder (mice only), heart, kidneys, large intestines (cecum, colon, rectum), liver, lungs, lymph nodes (mesenteric), mammary glands, nasal cavity and turbinates, oral cavity, ovaries, pancreas, parathyroids, pharynx, pituitary, preputial gland, prostate, salivary glands, scrotal sac, seminal vesicles, skin, small intestines (duodenum, ileum, jejunum), spleen, stomach, testes, thymus, thyroid, tongue, trachea, tunica vaginalis, urinary bladder, uterus, and Zymbal's glands. For lower level dose groups in the *o*-cresol studies, all gross lesions and the following target organs were examined histologically: bone marrow (15,000 ppm female rats) and forestomach (5,000 ppm and higher male mice). For lower level dose groups in the *m*/*p*-cresol studies, all gross lesions and the following target organs were examined histologically: bone marrow (15,000 ppm male rats), nasal mucosa (1,880 ppm male and female rats; 5,000 ppm male mice), thyroid gland (15,000 ppm male rats and 7,500 ppm and higher female rats), and uterus (15,000 ppm female rats). Organ weights recorded for the brain, liver, right kidney, thymus, heart, and lungs of all animals, and the right testis of all males. Hematologic, clinical chemistry, and urinalysis determinations performed at necropsy. Sperm morphology and vaginal cytology examinations were performed.

RESULTS

28-DAY STUDIES

Rats

Comparative mean compound consumption data for rats in the 28-day studies of cresols are presented in Table 10. The minimum effective doses for rats in the 28-day studies of cresols are given in Table 11.

o-Cresol: All rats lived to the end of the study (Table 3). Mean final body weight for females receiving 30,000 ppm was significantly lower than that of the controls. Mean body weight gains of males and females receiving 30,000 ppm were significantly lower than those of controls. Feed consumption was depressed by as much as 58% and 53% in males and females receiving the high dose during the first week of the study. Feed consumption of dosed groups was comparable to that of controls after the first week. No clinical signs of toxicity were observed in rats receiving *o*-cresol.

At study termination, liver weights were significantly increased for males and females in the two highest dose groups (10,000 and 30,000 ppm); relative liver weights were significantly increased for males in the three highest dose groups and females in the two highest dose groups (Appendix C, Table C1). Kidney weights were significantly increased for males in the two highest dose groups; relative kidney weights were significantly increased for males in the three highest dose groups. Relative brain weight was slightly increased for females receiving the high dose, but this was probably a result of the reduced body weight gain in this group.

No gross lesions were observed at necropsy. No treatment-related lesions were noted in the microscopic evaluation of tissues from the control and high-dose animals.

m-Cresol: All rats lived to the end of the study (Table 4). Decreases in mean final body weights and mean body weight gains for males and females receiving 30,000 ppm were statistically significant compared to the controls. Feed consumption was depressed in males and females receiving the high dose by as much as 47% and 38% during the first week of the study. No clinical signs of toxicity were observed in rats receiving *m*-cresol.

At study termination, relative liver weights for males and females in the two highest dose groups (10,000 and 30,000 ppm) were significantly increased compared to controls (Appendix C, Table C2). Males receiving 10,000 ppm showed a significant increase in liver weight compared to controls. Relative brain weight and relative kidney weight for the high-dose animals of both sexes were marginally increased compared to controls.

No gross lesions were noted at necropsy. Histopathologic evaluation revealed minimal to mild uterine atrophy in 4 of the 5 high-dose females (Table 5). Uterine changes were characterized by reduced cross-sectional diameter of the uterine horns and by decreased sizes of stromal and smooth muscle cells.

p-Cresol: All rats lived to the end of the study (Table 6). Decreases in mean final body weights and mean body weight gains for males and females receiving 30,000 ppm were statistically significant compared to the controls. Feed consumption was depressed by as much as 75% and 79% in males and females receiving the high dose during the first week of the study. Clinical signs of toxicity observed in all high-dose animals during the first week included hunched posture, rough hair coat, and thin appearance.

At study termination, relative liver weights for males receiving 10,000 or 30,000 ppm and females receiving 3,000, 10,000 or 30,000 ppm were significantly increased compared to controls (Appendix C, Table C3). Significant increases in relative kidney weights for males in the two highest dose groups and females in the high-dose group were also

TABLE 3
Survival and Mean Body Weights of Rats in the 28-Day Feed Studies of *o*-Cresol

Concentration (ppm) (%)	Survival[a]	Mean Body Weights (g)			Relative to Controls
		Initial[b]	Final	Change[c]	
Male					
0	5/5	109 ± 3	247 ± 5	138 ± 4	
300	5/5	119 ± 3	263 ± 9	144 ± 7	106
1,000	5/5	115 ± 5	254 ± 12	139 ± 6	103
3,000	5/5	110 ± 5	244 ± 6	133 ± 3	99
10,000	5/5	116 ± 5	252 ± 5	135 ± 1	98
30,000	5/5	114 ± 3	223 ± 8	109 ± 6*	90
Female					
0	5/5	91 ± 4	161 ± 2	70 ± 3	
300	5/5	94 ± 5	164 ± 4	70 ± 2	102
1,000	5/5	94 ± 3	157 ± 2	63 ± 5	97
3,000	5/5	95 ± 3	166 ± 6	70 ± 6	103
10,000	5/5	89 ± 5	155 ± 5	66 ± 3	96
30,000	5/5	89 ± 4	142 ± 4**	53 ± 1**	88

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Number of animals surviving at 28 days/number initially in group
[b] Initial group mean body weight ± standard error of the mean
[c] Mean body weight change ± standard error of the mean

TABLE 4
Survival and Mean Body Weights of Rats in the 28-Day Feed Studies of *m*-Cresol

Concentration (ppm) (%)	Survival[a]	Mean Body Weights (g)			Relative to Controls
		Initial[b]	Final	Change[c]	
Male					
0	5/5	117 ± 6	258 ± 7	141 ± 2	
300	5/5	125 ± 7	262 ± 5	137 ± 2	101
1,000	5/5	122 ± 5	256 ± 6	135 ± 3	99
3,000	5/5	122 ± 7	264 ± 6	142 ± 3	102
10,000	5/5	121 ± 5	257 ± 5	136 ± 2	99
30,000	5/5	125 ± 9	222 ± 12*	97 ± 3**	86
Female					
0	5/5	106 ± 2	174 ± 3	68 ± 3	
300	5/5	103 ± 5	160 ± 6	58 ± 4	92
1,000	5/5	101 ± 4	167 ± 2	65 ± 4	96
3,000	5/5	104 ± 5	166 ± 4	62 ± 2	96
10,000	5/5	103 ± 2	165 ± 3	62 ± 3	95
30,000	5/5	101 ± 3	146 ± 2**	45 ± 3**	84

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Number of animals surviving at 28 days/number initially in group
[b] Initial group mean body weight ± standard error of the mean
[c] Mean body weight change ± standard error of the mean

TABLE 5
Selected Histopathology Data for Rats in the 28-Day Feed Studies of *m*-Cresol

Organ and Diagnosis	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Female						
Uterus						
atrophy	0/5	–[a]	–	–	0/5	4/5 (1.5)[b]

[a] Histologic evaluation not performed
[b] Average severity based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

TABLE 6
Survival and Mean Body Weights of Rats in the 28-Day Feed Studies of *p*-Cresol

Concentration (ppm) (%)	Survival[a]	Mean Body Weights (g)			Relative to Controls
		Initial[b]	Final	Change[c]	
Male					
0	5/5	120 ± 5	255 ± 8	135 ± 3	
300	5/5	122 ± 2	260 ± 4	138 ± 2	102
1,000	5/5	122 ± 3	260 ± 9	138 ± 6	102
3,000	5/5	119 ± 6	247 ± 11	128 ± 6	97
10,000	5/5	126 ± 2	245 ± 6	119 ± 5	96
30,000	5/5	124 ± 4	180 ± 8**	56 ± 5**	70
Female					
0	5/5	105 ± 3	161 ± 6	57 ± 3	
300	5/5	109 ± 4	171 ± 6	62 ± 3	106
1,000	5/5	107 ± 4	173 ± 6	65 ± 3	107
3,000	5/5	110 ± 3	173 ± 2	63 ± 2	107
10,000	5/5	102 ± 2	154 ± 5	52 ± 4	95
30,000	5/5	104 ± 2	135 ± 2*	31 ± 2*	84

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Number of animals surviving at 28 days/number initially in group
[b] Initial group mean body weight ± standard error of the mean
[c] Mean body weight change ± standard error of the mean

recorded. Animals of both sexes receiving the high dose showed significant increases in relative brain weights compared to controls. The high-dose males also had a significantly increased relative testis weight. The changes in relative brain and testis weights were considered a result of the reduction in body weight gain of these groups.

No gross lesions were noted at necropsy. For femoral bone marrow, minimal to mild bone marrow depletion was evidenced by decreased numbers of hematopoietic cells. Bone marrow hypocellularity was noted in males in the three highest dose groups and females in the two highest dose groups (Table 7). Relative increases in the number of adipocytes corresponded to decreases in the number of hematopoietic cells in histologic sections of the bone marrow. Nasal cavity lesions demonstrated respiratory epithelial hyperplasia and squamous metaplasia, and olfactory epithelial atrophy. Hyperplasia of the respiratory epithelium was characterized by increased thickness of the epithelial layer due to stratification of cells with occasional mucosal folding. Squamous metaplasia was mild and incipient in nature, evidenced by altered polarity of superficial cells towards a horizontal orientation with respect to basal lamina. Olfactory epithelial atrophy consisted of decreased thickness with loss and disorientation of nuclei. Mild to moderate uterine atrophy was noted in 3 of the 5 females in the high-dose group. Uterine changes were characterized by reduced cross-sectional diameter of the uterine horns and decreased sizes of stromal and smooth muscle cells.

m/p-Cresol: All rats lived to the end of the study (Table 8). Mean final body weight for males receiving 30,000 ppm was significantly lower than that of controls. Mean body weight gains of male and females receiving 30,000 ppm were significantly lower than that of the controls. Feed consumption was depressed in males and females receiving the high dose by as much as 76% and 73% during the first week of the study. All rats receiving the high dose had a thin appearance by day 6 but not beyond day 7.

At study termination, relative kidney weights for the two highest male and female dose groups were significantly higher than those of controls (Appendix C, Table C4). Relative liver weights were increased for the three highest male dose groups and the four highest female dose groups. Males receiving the high dose also had a significantly increased relative brain weight and relative testis weight, reflecting the reduced body weight gain in this group.

No gross lesions were noted at necropsy. Respiratory epithelial hyperplasia of the nasal cavity was observed microscopically, and this lesion was characterized by increased numbers of goblet cells. The infolding of these hyperplastic cells resulted in pseudogland formation. These changes were primarily seen in the tissue sections of the anterior nasal cavity (Table 9). Hyperplastic areas were associated with single cell necrosis. There was increased colloid within thyroid follicles as shown by increased follicle diameter and flattening of epithelial cells. In femoral bone marrow, minimal to mild bone marrow hypocellularity was evidenced by decreased numbers of hematopoietic cells and corresponding relative increases in adipocytes. Minimal to mild epithelial hyperplasia and hyperkeratosis of the esophagus and forestomach were noted among males and females at the three highest doses.

TABLE 7
Selected Histopathology Data for Rats in the 28-Day Feed Studies of *p*-Cresol

Organ and Diagnosis	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Male						
Bone marrow						
Hypocellularity	0/5	–[a]	0/5	1/5 (2.0)[b]	1/5 (2.0)	5/5 (3.0)
Nasal						
Olfactory epithelium						
Atrophy	0/5	–	0/5	0/5	0/5	5/5 (2.0)
Respiratory epithelium						
Hyperplasia	0/5	–	0/5	1/5 (1.0)	4/5 (2.7)	5/5 (2.8)
Squamous metaplasia	0/5	–	0/5	0/5	0/5	2/5 (2.0)
Female						
Bone marrow						
Hypocellularity	0/5	–	–	0/5	1/5 (2.0)	3/5 (2.7)
Nasal						
Olfactory epithelium						
Atrophy	0/5	–	0/5	1/5 (1.0)	0/5	4/5 (1.7)
Respiratory epithelium						
Hyperplasia	0/5	–	0/5	1/5 (1.0)	3/5 (3.0)	3/5 (2.3)
Squamous metaplasia	0/5	–	0/5	0/5	1/5 (2.0)	0/5
Uterus						
Endometrium						
Atrophy	0/5	0/1	0/1	0/1	0/5	3/5 (2.7)

[a] Histologic evaluation not performed
[b] Average severity score based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

TABLE 8
Survival and Mean Body Weights of Rats in the 28-Day Feed Studies of *m/p*-Cresol

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Relative to Controls (%)
		Initial[b]	Final	Change[c]	
Male					
0	5/5	122 ± 6	265 ± 5	143 ± 2	
300	5/5	123 ± 7	266 ± 10	143 ± 3	104
1,000	5/5	114 ± 5	256 ± 8	142 ± 4	97
3,000	5/5	114 ± 5	254 ± 9	140 ± 5	96
10,000	5/5	119 ± 4	256 ± 6	136 ± 3	96
30,000	5/5	120 ± 6	217 ± 8**	96 ± 3**	82
Female					
0	5/5	86 ± 5	155 ± 7	70 ± 2	
300	5/5	86 ± 5	158 ± 3	72 ± 3	102
1,000	5/5	86 ± 5	161 ± 4	74 ± 3	104
3,000	5/5	94 ± 4	159 ± 1	65 ± 4	102
10,000	5/5	93 ± 3	157 ± 3	64 ± 3	101
30,000	5/5	92 ± 4	146 ± 3	54 ± 3*	94

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Number of animals surviving at 28 days/number initially in group
[b] Initial group mean body weight ± standard error of the mean
[c] Mean body weight change ± standard error of the mean

TABLE 9
Selected Histopathology Data for Rats in the 28-Day Feed Studies of *m/p*-Cresol

Organ and Diagnosis	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Male						
Bone marrow						
HHypocellularity	0/5	–[a]	–	–	0/5	3/5 (1.0)[b]
Esophagus						
Epithelium						
Hyperkeratosis	0/5	–	0/5	3/5 (1.0)	4/5 (1.0)	5/5 (1.2)
Hyperplasia	0/5	–	0/5	3/5 (1.0)	4/5 (1.0)	5/5 (1.2)
Forestomach						
Epithelium						
Hyperplasia	0/5	–	–	0/5	2/5 (1.0)	5/5 (1.4)
Nasal						
Respiratory epithelium						
Hyperplasia	0/5	0/5	0/5	5/5 (2.0)	5/5 (2.4)	5/5 (3.2)
Thyroid gland						
Follicular cell						
Increased colloid	0/5	–	0/5	3/5 (1.0)	5/5 (1.0)	5/5 (1.8)
Female						
Bone marrow						
Hypocellularity	0/5	–	–	0/5	1/5 (1.0)	5/5 (1.2)
Esophagus						
Epithelium						
Hyperkeratosis	0/5	–	0/5	2/5 (1.0)	3/5 (1.0)	5/5 (1.2)
Hyperplasia	0/5	–	0/5	3/5 (1.0)	3/5 (1.0)	5/5 (1.0)
Forestomach						
Epithelium						
Hyperkeratosis	0/5	–	–	0/5	2/5 (1.0)	5/5 (1.2)
Hyperplasia	0/5	–	–	0/5	2/5 (1.0)	5/5 (1.0)
Nasal						
Respiratory epithelium						
Hyperplasia	0/5	0/5	3/4 (1.0)	5/5 (1.0)	5/5 (1.6)	5/5 (2.8)
Thyroid gland						
Follicular cell						
Increased colloid	1/5 (1.0)	–	0/5	4/5 (1.0)	5/5 (1.8)	4/5 (3.2)

[a] Histologic evaluation not performed
[b] Average severity score based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

TABLE 10
Comparative Mean Compound Consumption by Rats in the 28-Day Feed Studies of Cresol[a]

Dose	*o*-Cresol		*m*-Cresol		*p*-Cresol		*m/p*-Cresol[b]	
	M	F	M	F	M	F	M	F
0 ppm	0	0	0	0	0	0	0	0
300 ppm	27	27	25	25	25	25	26	27
1,000 ppm	87	89	85	82	87	83	90	95
3,000 ppm	266	271	252	252	256	242	261	268
10,000 ppm	861	881	870	862	835	770	877	886
30,000 ppm	2,610	2,510	2,470	2,310	2,180	2,060	2,600	2570

[a] Compound consumption in mg per kg body weight per day
[b] 60% *m*-cresol/40% *p*-cresol

TABLE 11
Minimum Effective Doses in Rats in the 28-Day Feed Studies of Cresol

o-Cresol	*m*-Cresol	*p*-Cresol	*m*/*p*-Cresol
Mortality			
None	None	None	None
Body Weight Gain (–)			
♂ and ♀ : 30,000 ppm	♂ and ♀ : 30,000 ppm	♂ and ♀ : 30,000 ppm	♂ and ♀ : 30,000 ppm
Feed Consumption (–)			
♂ and ♀ : 30,000 ppm (week 1)	♂ and ♀ : 30,000 ppm (week 1)	♂ and ♀ : 30,000 ppm (week 1)	♂ and ♀ : 30,000 ppm (week 1)
Clinical Observations			
None	None	30,000 ppm ♂ and ♀ : Hunched posture, rough hair coat, and thin appearance	30,000 ppm ♂ and ♀ : Thin appearance
Increased Relative Organ Weights			
Brain 30,000 ppm ♀ Kidney 3,000 ppm ♂ Liver 3,000 ppm ♂ 10,000 ppm ♀	Brain 30,000 ppm ♂ and ♀ Kidney 30,000 ppm ♂ and ♀ Liver 10,000 ppm ♂ and ♀	Brain 30,000 ppm ♂ and ♀ Kidney 10,000 ppm ♂ 30,000 ppm ♀ Liver 10,000 ppm ♂ 3,000 ppm ♀ Testis 30,000 ppm ♂	Brain 30,000 ppm ♂ Kidney 10,000 ppm ♂ and ♀ Liver 3,000 ppm ♂ 1,000 ppm ♀ Testis 30,000 ppm ♂
Histopathology			
None	Uterus 30,000 ppm ♀	Bone marrow 3,000 ppm ♂ 10,000 ppm ♀ Nasal epithelium 3,000 ppm ♂ and ♀ Uterus 30,000 ppm ♀	Bone marrow 30,000 ppm ♂ 10,000 ppm ♀ Esophagus 3,000 ppm ♂ and ♀ Forestomach 10,000 ppm ♂ and ♀ Nasal epithelium 3,000 ppm ♂ 1,000 ppm ♀ Thyroid 3,000 ppm ♂ and ♀

Mice

Comparative mean compound consumption data for mice in the 28-day studies of cresols are presented in Table 20. The minimum effective doses for mice in the 28-day studies of cresols are given in Table 21.

o-Cresol: Two male mice and one female mouse receiving 30,000 ppm died or were sacrificed moribund between days 5 and 9 of the study (Table 12). The surviving mice in the high-dose groups lost weight, and the mean final body weights for the male and female high-dose groups were significantly lower than that of the controls. Mean body weight gains of males and females receiving the two highest doses were also significantly lower than that of the controls. Feed consumption was depressed in males and females receiving the high dose during the first week of the study. A reduction in feed consumption was also noted for males receiving 3,000 and 10,000 ppm for the first 3 days of the study. Clinical signs of toxicity observed in all high-dose animals included hunched posture, lethargy, rough hair coat, and thin appearance. Hypothermia, rapid breathing, and tremors were also noted in high-dose males.

At study termination, relative liver weights for males and females in the three highest dose groups were significantly increased compared to those of controls (Appendix C, Table C5). Relative kidney weights were increased for 10,000 ppm males and females and 30,000 ppm females. A significantly increased relative brain weight was noted in high-dose females.

No gross lesions were noted at necropsy. Histopathologic evaluation revealed ovarian atrophy at the highest dose and uterine atrophy at the two highest doses (Table 13). Mice that died early did not show notable histopathologic changes.

m-Cresol: Two males and two females receiving 30,000 ppm, one female receiving 10,000 ppm, and one control male were found dead or sacrificed moribund during the study (Table 14). Surviving mice in the high-dose groups lost weight during the studies. Mean final body weights for the high-dose males and females were significantly decreased compared to controls. Mean body weight gain of high-dose males was significantly lower than controls. High-dose males had depressed feed consumption during the first week of the study; high-dose females had depressed feed consumption during the first and third weeks of the study. Clinical signs of toxicity observed in all high-dose animals included hunched posture, rough hair coat, and thin appearance. High-dose males and females exhibited lethargy and tremors. Hypothermia was also noted in high-dose females. Hunched posture and rough hair coat were recorded for males and females receiving 10,000 ppm. Females receiving this dose also showed labored respiration, lethargy, and sunken eyes.

At study termination, relative liver weights for males in the three highest dose groups and all female dose groups were significantly increased compared to controls (Appendix C, Table C6). Males receiving 3,000 ppm and females receiving the high dose had significantly increased relative kidney weights compared to control values. High-dose males had significantly increased relative brain weight.

No gross lesions were noted at necropsy. Histopathologic evaluation showed mammary gland, ovarian, and uterine atrophy in the three females receiving the highest dose that survived to study termination (Table 15). Histopathologic changes in early death animals were not remarkable.

p-Cresol: All high-dose males and females and one male receiving 10,000 ppm died or were sacrificed moribund by study termination (Table 16). Mean final body weight and mean body weight gain for surviving male mice receiving 10,000 ppm were decreased significantly compared to controls. Feed consumption was depressed for females receiving 10,000 ppm throughout the first 2 weeks of the study. Males receiving 10,000 ppm consumed less feed than the control animals during the first 5 days of the study and at the beginning of week 2. High-dose animals that died or were sacrificed moribund during week 1 showed one or more of the following clinical signs of toxicity: hunched posture, lethargy, rough hair coat, hypothermia, and thin appearance. Labored respiration was also noted in a high-dose male surviving beyond week 1. Males receiving 10,000 ppm displayed hunched posture, hypothermia, labored respiration, lethargy, paleness, rough hair coat, and thin appearance.

TABLE 12
Survival and Mean Body Weights of Mice in the 28-Day Feed Studies of *o*-Cresol

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Relative to Controls (%)
		Initial[b]	Final	Change[c]	
Male					
0	5/5	20.4 ± 0.5	24.1 ± 0.5	3.7 ± 0.3	
300	5/5	19.6 ± 0.8	24.1 ± 0.5	4.5 ± 1.0	100
1,000	5/5	19.5 ± 1.4	24.9 ± 0.4	5.3 ± 1.6	103
3,000	5/5	21.3 ± 0.6	25.2 ± 0.5	3.9 ± 0.3	105
10,000	5/5	20.2 ± 0.6	22.9 ± 0.6	2.6 ± 0.2*	95
30,000	3/5[d]	20.9 ± 0.8	17.3 ± 0.6*	−3.6 ± 0.5*	72
Female					
0	5/5	17.2 ± 1.3	22.3 ± 0.6	5.1 ± 0.8	
300	5/5	16.7 ± 0.6	21.2 ± 0.4	4.5 ± 0.8	95
1,000	5/5	16.4 ± 0.9	21.4 ± 1.0	5.1 ± 1.1	96
3,000	5/5	16.8 ± 0.6	21.1 ± 0.7	4.3 ± 0.3	95
10,000	5/5	18.2 ± 0.8	21.4 ± 0.7	3.2 ± 0.4*	96
30,000	4/5[e]	17.5 ± 0.4	15.2 ± 0.3**	−2.3 ± 0.7**	68

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Number of animals surviving at 28 days/number initially in group
[b] Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
[c] Mean body weight change of the survivors ± standard error of the mean
[d] Day of death: 5,9
[e] Day of death: 7

TABLE 13
Selected Histopathology Data for Mice in the 28-Day Feed Studies of *o*-Cresol

Organ and Diagnosis	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Female						
Ovary						
atrophy	0/5	–[a]	–	–	0/5	3/5 (2.0)[b]
Uterus						
atrophy	0/5	–	–	0/5	5/5 (1.8)	4/5 (3.0)

[a] Histologic evaluation not performed
[b] Average severity score based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

TABLE 14
Survival and Mean Body Weights of Mice in the 28-Day Feed Studies of *m*-Cresol

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Relative to Controls (%)
		Initial[b]	Final	Change[c]	
Male					
0	4/5[d]	22.4 ± 0.9	25.4 ± 0.7	3.8 ± 0.4	
300	5/5	21.8 ± 0.7	25.5 ± 0.8	3.8 ± 0.4	100
1,000	5/5	22.4 ± 0.4	25.0 ± 0.4	2.6 ± 0.5	98
3,000	5/5	22.0 ± 0.4	25.7 ± 0.2	3.6 ± 0.3	101
10,000	5/5	20.6 ± 0.5	23.5 ± 0.7	2.9 ± 0.7	93
30,000	3/5[e]	22.2 ± 0.8	20.4 ± 1.3**	−2.8 ± 0.6**	80
Female					
0	5/5	18.7 ± 1.1	22.6 ± 1.1	3.9 ± 0.2	
300	5/5	18.5 ± 0.9	22.9 ± 0.9	4.4 ± 0.4	101
1,000	5/5	19.0 ± 0.5	23.9 ± 0.6	4.9 ± 0.5	106
3,000	5/5	18.7 ± 0.7	23.0 ± 0.7	4.3 ± 0.4	102
10,000	4/5[f]	18.5 ± 0.4	21.9 ± 0.8	3.2 ± 0.4	97
30,000	3/5[g]	18.8 ± 0.4	17.6 ± 1.2*	−1.2 ± 0.9	78

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Number of animals surviving at 28 days/number initially in group
[b] Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
[c] Mean body weight change of the survivors ± standard error of the mean
[d] Day of death: 8
[e] Day of death: 5,5
[f] Day of death: 6
[g] Day of death: 4,5

TABLE 15
Selected Histopathology Data for Mice in the 28-Day Feed Studies of *m*-Cresol

Organ and Diagnosis	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Female						
Mammary gland						
atrophy	0/5	–[a]	–	–	0/4	3/5 (2.7)[b]
Ovary						
atrophy	0/5	–	–	–	0/5	3/5 (2.0)
Uterus						
atrophy	0/5	–	–	–	0/5	3/5 (3.0)

[a] Histologic evaluation not performed
[b] Average severity score based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

TABLE 16
Survival and Mean Body Weights of Mice in the 28-Day Feed Studies of *p*-Cresol

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Relative to Controls (%)
		Initial[b]	Final	Change[c]	
Male					
0	5/5	22.7 ± 0.7	26.3 ± 0.7	3.6 ± 0.2	
300	5/5	22.6 ± 0.3	26.2 ± 0.6	3.6 ± 0.3	99
1,000	5/5	23.3 ± 0.8	26.8 ± 0.7	3.5 ± 0.3	102
3,000	5/5	22.9 ± 0.7	26.4 ± 0.3	3.5 ± 0.7	100
10,000	4/5[d]	21.3 ± 0.5	21.8 ± 0.9*	0.3 ± 0.4**	83
30,000	0/5[e]	23.2 ± 0.7	–	–	–
Female					
0	5/5	18.4 ± 0.4	21.9 ± 0.4	3.5 ± 0.2	
300	5/5	18.3 ± 0.4	22.7 ± 0.5	4.4 ± 0.3	104
1,000	5/5	17.3 ± 0.3	21.6 ± 0.3	4.3 ± 0.2	99
3,000	5/5	18.3 ± 0.5	21.4 ± 0.8	3.0 ± 0.3	98
10,000	5/5	18.8 ± 0.8	21.1 ± 0.3	2.3 ± 0.6	96
30,000	0/5[f]	18.4 ± 0.7	–	–	–

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Number of animals surviving at 28 days/number initially in group
[b] Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
[c] Mean body weight change of the survivors ± standard error of the mean
[d] Day of death: 24
[e] Day of death: 4,5,5,5,26; no data reported due to 100% mortality in this dose group
[f] Day of death: 4,4,4,5,5; no data reported due to 100% mortality in this dose group

At study termination, relative liver weights for males receiving 10,000 ppm and females receiving 3,000 and 10,000 ppm were increased significantly compared to controls (Appendix C, Table C7). Males receiving 10,000 ppm had a significantly increased relative heart weight. This group as well as males receiving 3,000 ppm showed significantly increased relative kidney weight.

No gross lesions were noted at necropsy. Histopathologic evaluation of the 10,000 ppm dose group revealed the nose to be a target organ in both males and females. Minimal to mild hyperplasia of the nasal respiratory epithelium was present in all animals receiving this dose (Table 17). The no-observed effect level for this lesion in males was 300 ppm, while the no-observed effect level was not achieved for females. Early, mild squamous metaplasia of the respiratory epithelium, consisting of flattening of superficial cells in hyperplastic areas, was an additional nasal lesion noted in 2 of 5 males receiving 10,000 ppm. Olfactory epithelial atrophy and squamous metaplasia were nasal lesions less frequently observed in animals receiving doses of 10,000 ppm or lower.

The high-dose animals, which all died early, had several lesions in addition to the aforementioned nasal lesions; these lesions did not occur in the lower dose groups. Most of these lesions (*e.g.* lymphoid necrosis and depletion in various lymphoid tissues including the spleen) were considered secondary to moribund condition or stress. Lesions of renal and hepatic necrosis and bone marrow hypocellularity were possibly the direct result of cresol toxicity (Table 17).

m/p-Cresol: All mice lived to the end of the study (Table 18). High-dose males and females lost weight. Mean final body weights and mean body weight gains for high-dose animals were significantly decreased from those of the controls. Decreases in mean body weight gain in the 10,000 and 300 ppm male groups were also statistically significant. Feed consumption was depressed in males and females receiving the high dose during the first week of the study. High-dose females also had decreased feed consumption during the third week of the study. Clinical signs of toxicity observed in high-dose animals of both sexes included alopecia, dehydration, hunched posture, hypothermia, lethargy, rough hair coat, and thin appearance.

At study termination, relative liver weights for males receiving 1,000 ppm and higher and for females receiving 3,000 ppm and higher were significantly increased (Appendix C, Table C8). Males in the high-dose group also had a significantly increased relative brain weight and relative testis weight. Females in the high-dose group had increased relative brain weight and relative kidney weight. Females in the high-dose group had decreased brain weight.

No gross lesions were noted at necropsy. On microscopic examination, respiratory epithelial hyperplasia was observed, typically involving the dorsal meatus of anterior nasal sections and was characterized by increased number and stratification of cells. Frequent epithelial infoldings imparted a glandular appearance to the severely affected tissue areas. Olfactory epithelial lesions were seen in mice receiving the highest dose. These lesions consisted of atrophy and respiratory metaplasia. Atrophy was characterized by decreased thickness, loss and disorientation of nuclei, and single cell necrosis. Respiratory metaplasia of olfactory epithelium was characterized by the presence of well differentiated ciliated epithelial cells in middle nasal sections of the olfactory mucosa. Minimal to mild bronchiolar epithelial hyperplasia occurred in all study animals at the highest dose (Table 19). Lesions were particularly evident in the terminal bronchioles and exhibited epithelial thickening, loss of nuclear polarity, and increased cytoplasmic basophilia. Bone marrow hypocellularity occurred in 2 of the 5 males and 1 of the 5 females at the highest dose. Minimal esophageal squamous epithelial hyperplasia and minimal forestomach epithelial hyperplasia were noted in one male each at the high dose. Uterine and ovarian atrophy were observed in one female receiving the highest dose.

TABLE 17
Selected Histopathology Data for Mice in the 28-Day Feed Studies of *p*-Cresol

Organ and Diagnosis	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Male						
Bone marrow						
Hypocellularity	0/5	–[a]	–	–	0/5	5/5 (2.0)[b]
Kidney						
Renal tubule necrosis	0/5	–	–	–	0/5	4/5 (1.7)
Liver						
Centrilobular atrophy	0/5	–	–	–	0/5	1/5 (3.0)
Centrilobular necrosis	0/5	–	–	–	0/5	1/5 (2.0)
Necrosis	0/5	–	–	–	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)
Squamous metaplasia	0/5	0/5	0/5	0/5	2/5 (2.0)	0/5
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						
Bone marrow						
Hypocellularity	0/5	–	–	–	0/5	3/5 (2.0)
Kidney						
Renal tubule necrosis	0/5	–	–	–	0/5	3/5 (1.7)
Liver						
Centrilobular necrosis	0/5	–	–	–	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] Histologic evaluation not performed
[b] Average severity score based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

TABLE 18
Survival and Mean Body Weights of Mice in the 28-Day Feed Studies of *m/p*-Cresol

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Relative to Controls (%)
		Initial[b]	Final	Change[c]	
Male					
0	5/5	22.5 ± 0.7	27.2 ± 0.6	4.7 ± 0.5	
300	5/5	22.4 ± 0.7	25.7 ± 1.0	3.3 ± 0.3*	95
1,000	5/5	21.8 ± 0.5	26.1 ± 0.6	4.3 ± 0.4	96
3,000	5/5	21.9 ± 0.8	25.5 ± 0.7	3.7 ± 0.4	94
10,000	5/5	22.5 ± 1.1	24.7 ± 1.4	2.2 ± 0.5**	91
30,000	5/5	22.2 ± 0.8	19.7 ± 0.7**	−2.4 ± 0.5**	73
Female					
0	5/5	17.8 ± 0.8	21.7 ± 0.7	3.9 ± 0.1	
300	5/5	17.0 ± 0.3	21.0 ± 0.5	4.0 ± 0.4	97
1,000	5/5	18.4 ± 0.5	22.3 ± 0.5	3.9 ± 0.4	103
3,000	5/5	17.9 ± 0.6	21.9 ± 0.7	4.1 ± 0.1	101
10,000	5/5	17.9 ± 0.3	21.6 ± 0.3	3.7 ± 0.3	100
30,000	5/5	17.4 ± 0.2	17.0 ± 0.6*	−0.5 ± 0.6*	78

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Number of animals surviving at 28 days/number initially in group
[b] Initial group mean body weight ± standard error of the mean
[c] Mean body weight change ± standard error of the mean

TABLE 19
Selected Histopathology Data for Mice in the 28-Day Feed Studies of *m*/*p*-Cresol

Organ and Diagnosis	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Male						
Bone marrow						
Hypocellularity	0/5	–[a]	–	–	0/5	2/5 (1.5)[b]
Esophagus						
Epithelium						
Hyperplasia	0/4	–	–	–	0/4	1/5 (1.0)
Hyperkeratosis	0/4	–	–	–	0/4	1/5 (1.0)
Forestomach						
Squamous epithelium						
Hyperplasia	0/5	–	–	–	0/5	1/5 (1.0)
Lung						
Bronchiolar hyperplasia	0/5	–	–	–	0/5	5/5 (1.2)
Nasal						
Respiratory epithelium						
Hyperplasia	0/5	–	–	0/5	1/5 (1.0)	5/5 (1.6)
Olfactory epithelium						
Atrophy	0/5	–	–	0/5	0/5	2/5 (1.0)
Respiratory metaplasia	0/5	–	–	0/5	0/5	3/5 (1.3)
Female						
Bone marrow						
Hypocellularity	0/5	–	–	–	0/5	1/5 (1.0)
Lung						
Bronchiolar hyperplasia	0/5	–	–	–	0/5	5/5 (1.2)
Nasal						
Respiratory epithelium						
Hyperplasia	2/5 (1.5)	–	0/5	3/5 (1.0)	3/5 (1.7)	4/5 (1.5)
Olfactory epithelium						
Respiratory metaplasia	0/5	–	0/5	0/5	0/5	2/5 (1.0)
Ovary						
Atrophy	0/5	–	–	–	0/5	1/5 (2.0)
Uterus						
Atrophy	0/5	–	–	–	0/5	1/5 (3.0)

[a] Histologic evaluation not performed
[b] Average severity score based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

TABLE 20
Comparative Mean Compound Consumption by Mice in the 28-Day Feed Studies of Cresol[a]

Dose	*o*-Cresol		*m*-Cresol		*p*-Cresol		*m/p*-Cresol[b]	
	M	F	M	F	M	F	M	F
0 ppm	0	0	0	0	0	0	0	0
300 ppm	66	82	53	66	50	60	50	65
1,000 ppm	193	280	193	210	163	207	161	200
3,000 ppm	558	763	521	651	469	564	471	604
10,000 ppm	1,650	1,670	1,730	2,080	1,410	1,590	1,490	1,880
30,000 ppm	4,480	5000	4,710	4,940	–[c]	–	4,530	4,730

[a] Compound consumption in mg per kg body weight per day
[b] 60% *m*-cresol/40% *p*-cresol
[c] No data calculated due to 100% mortality

TABLE 21
Minimum Effective Doses in Mice in the 28-Day Feed Studies of Cresol

o-Cresol	*m*-Cresol	*p*-Cresol	*m*/*p*-Cresol
Mortality			
♂ and ♀ : 30,000 ppm	♂ : 30,000 ppm ♀ : 10,000 ppm	♂ : 10,000 ppm ♀ : 30,000 ppm	None
Body Weight Gain (–)			
♂ and ♀ : 10,000 ppm	♂ : 30,000 ppm	♀ : 10,000 ppm	♂ : 10,000 ppm ♀ : 30,000 ppm
Feed Consumption (–)			
♂ : 3,000 ppm (week 1) ♀ : 30,000 ppm (week 1)	♂ : 30,000 ppm (week 1) ♀ : 30,000 ppm (weeks 1 and 3)	♂ and ♀ : 10,000 ppm (weeks 1 and 2)	♂ : 30,000 ppm (week 1) ♀ : 30,000 ppm (weeks 1 and 3)
Clinical Observations			
30,000 ppm ♂ and ♀ : Hunched posture, lethargy, rough hair coat, and thin appearance ♂ 30,000 ppm: Hypothermia, rapid breathing, and tremors	30,000 ppm ♂ : Lethargy, thin appearance, and tremors 30,000 ppm ♀ : Hypothermia and tremors 10,000 ppm ♂ and ♀ : Hunched posture and rough hair coat 10,000 ppm ♀ : Labored breathing, lethargy, and sunken eyes 300 ppm ♀ : Thin appearance	30,000 ppm ♀ : Hunched posture, hypothermia, lethargy, rough hair coat, and thin appearance 10,000 ♂ : Hunched posture, hypothermia, labored respiration, lethargy, paleness, rough hair coat, and thin appearance	30,000 ppm ♂ and ♀: Alopecia, dehydration, hunched posture, hypothermia, lethargy, rough hair coat, and thin appearance
Increased Relative Organ Weights			
Brain 30,000 ppm ♀ Kidney 10,000 ppm ♂ and ♀ Liver 3,000 ppm ♂ and ♀	Brain 30,000 ppm ♂ Kidney 3,000 ppm ♂ 30,000 ppm ♀ Liver 3,000 ppm ♂ 300 ppm ♀	Heart 10,000 ppm ♂ Kidney 3,000 ppm ♂ Liver 10,000 ppm ♂ 3,000 ppm ♀	Brain 30,000 ppm ♂ and ♀ Kidney 30,000 ppm ♀ Liver 1,000 ppm ♂ 3,000 ppm ♀ Testis 30,000 ppm ♂

TABLE 21
Minimum Effective Doses in Mice in the 28-Day Feed Studies of Cresol (continued)

o-Cresol	*m*-Cresol	*p*-Cresol	*m*/*p*-Cresol
Histopathology			
Ovaries 30,000 ppm ♀ Uterus 10,000 ppm ♀	Mammary glands 30,000 ppm ♀ Ovaries 30,000 ppm ♀ Uterus 30,000 ppm ♀	Bone marrow 30,000 ppm ♂ and ♀ Kidney 30,000 ppm ♂ and ♀ Liver 30,000 ppm ♂ and ♀ Lymphoid organs 30,000 ppm ♂ and ♀ Nasal epithelium 1,000 ppm ♂ 300 ppm ♀ Spleen 30,000 ppm ♂ and ♀ Thymus 30,000 ppm ♂ and ♀	Bone marrow 30,000 ppm ♂ and ♀ Esophagus 30,000 ppm ♂ Forestomach 30,000 ppm ♂ Lung 30,000 ppm ♂ and ♀ Nasal epithelium 10,000 ppm ♂ 3,000 ppm ♀ Ovary 30,000 ppm ♀ Uterus 30,000 ppm ♀

13-WEEK STUDIES

Rats

o-Cresol: All rats lived to the end of the study except a female receiving 30,000 ppm that was discovered missing on day 8 (Table 22). Mean final body weight and mean body weight gain for males at the highest dose and females at the two highest doses were significantly less than those of the controls (Figure 1). Feed consumption was decreased for high-dose animals during the first week of the study (Appendix B, Tables B1 and B2). No clinical signs of toxicity were observed in rats receiving *o*-cresol.

Relative kidney weights were significantly increased for males and females receiving the two highest doses (Table 23). Relative liver weights were significantly increased for males and females at the three highest doses. Relative testis weight was significantly increased for high-dose males and relative thymus weights were significantly increased for males in the two highest dose groups. Other statistically significant absolute and relative organ weights are presented in Appendix C, Table C9.

Summarized results of hematology and clinical chemistry studies are shown in Tables 24 and 25 and Appendix D, Table D1. Hematology findings were generally unremarkable. There was some evidence of hemoconcentration in dosed animals early in the study. Increased concentrations of total bile acids in serum occurred at early and middle time points in males and females given 15,000 and 30,000 ppm. There was no evidence of hepatocellular necrosis (no change in alanine aminotransferase) or overt cholestasis (no change in 5′-nucleotidase or alkaline phosphatase). Results of urinalyses gave no indications of renal damage in animals given diets containing *o*-cresol.

Histopathologic examination revealed increased incidence of bone marrow hypocellularity among males receiving the highest dose and females receiving the two highest doses (Table 26). These changes were minimal to mild in severity and were considered likely secondary to the decreased weight gains and not indicative of direct chemical toxicity.

Evaluation of several reproductive tissue endpoints (Appendix A) revealed no changes in dosed males, but a lengthening of the estrus cycle was observed for dosed females. There were no histopathologic changes in the ovary or uterus.

m/p-Cresol: All rats lived to the end of the study (Table 27). Mean final body weights of males and females receiving the two highest doses were significantly decreased compared to controls. Males at the highest dose and females at the two highest doses had significant decreases in mean body weight gain compared to controls (Figure 2). Feed consumption was depressed for high-dose animals during the first week of the study (Appendix B, Tables B3 and B4). Clinical signs of toxicity for high-dose animals included rough hair coat for all high-dose animals and thin appearance for all high-dose females. Urine-stained fur was noted among the high-dose males and all females except those receiving the lowest dose.

Males at the three highest doses and females at the high dose had significantly increased relative kidney weights (Table 28). Animals of both sexes at the three highest doses had significant increases in relative liver weights. Relative testis weights were significantly increased for males at the two highest doses. Other statistically significant absolute and relative organ weights are presented in Appendix C, Table C10.

The results of hematology, clinical chemistry, and urinalysis studies are shown in Tables 29 and 30 and Appendix D, Table D2. The results of hematologic analyses were largely negative, with some evidence of hemoconcentration seen early in the study among high-dose animals. Increased serum alanine aminotransferase and sorbitol dehydrogenase (males) in high-dose animals sampled at day 5 are indicative of hepatocellular injury. This injury appeared to resolve, and increased serum enzyme levels were not seen later in the studies. As with *o*-cresol, total bile acids were substantially elevated in both males and females and these elevations extended into the lower dose levels. This is indicative of decreased hepatocellular function. There were also consistent decreases in the serum levels of 5′-nucleotidase. This may also be a consequence of the decreased flux or uptake of bile acids from the serum noted above.

TABLE 22
Survival, Mean Body Weights, and Compound Consumption of Rats in the 13-Week Feed Studies of *o*-Cresol

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)	Mean Feed and Compound Consumption	
		Initial[b]	Final	Change[c]		Feed[d]	Dose/Day[e]
Male							
0	20/20	138 ± 4	384 ± 7	246 ± 7		18.5	0
1,880	20/20	133 ± 5	377 ± 7	244 ± 7	98	18.1	126
3,750	20/20	143 ± 4	394 ± 4	251 ± 4	103	18.4	247
7,500	20/20	136 ± 3	379 ± 6	243 ± 6	99	18.2	510
15,000	20/20	139 ± 4	369 ± 5	230 ± 4	96	17.9	1,017
30,000	20/20	139 ± 2	327 ± 6**	188 ± 7**	85	16.6	2,028
Female							
0	20/20	117 ± 3	204 ± 3	88 ± 4		12.4	0
1,880	20/20	115 ± 2	203 ± 4	88 ± 3	99	11.8	129
3,750	20/20	115 ± 3	205 ± 3	91 ± 3	99	11.9	256
7,500	20/20	110 ± 3	200 ± 4	89 ± 5	98	11.6	513
15,000	20/20	115 ± 3	190 ± 3**	76 ± 3**	93	11.3	1,021
30,000	19/20[f]	113 ± 4	174 ± 3**	61 ± 3**	85	10.3	2,024

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Number of animals surviving at 13 weeks/number initially in the study
[b] Initial group mean body weight ± standard error of the mean for 10 animals selected prior to study initiation. Subsequent calculations are based on the number of these animals present at the end of the study.
[c] Mean body weight change ± standard error of the mean
[d] Feed given in grams of feed consumed per animal per day
[e] Doses given in mg compound per kg body weight per day
[f] Animal discovered missing on day 8

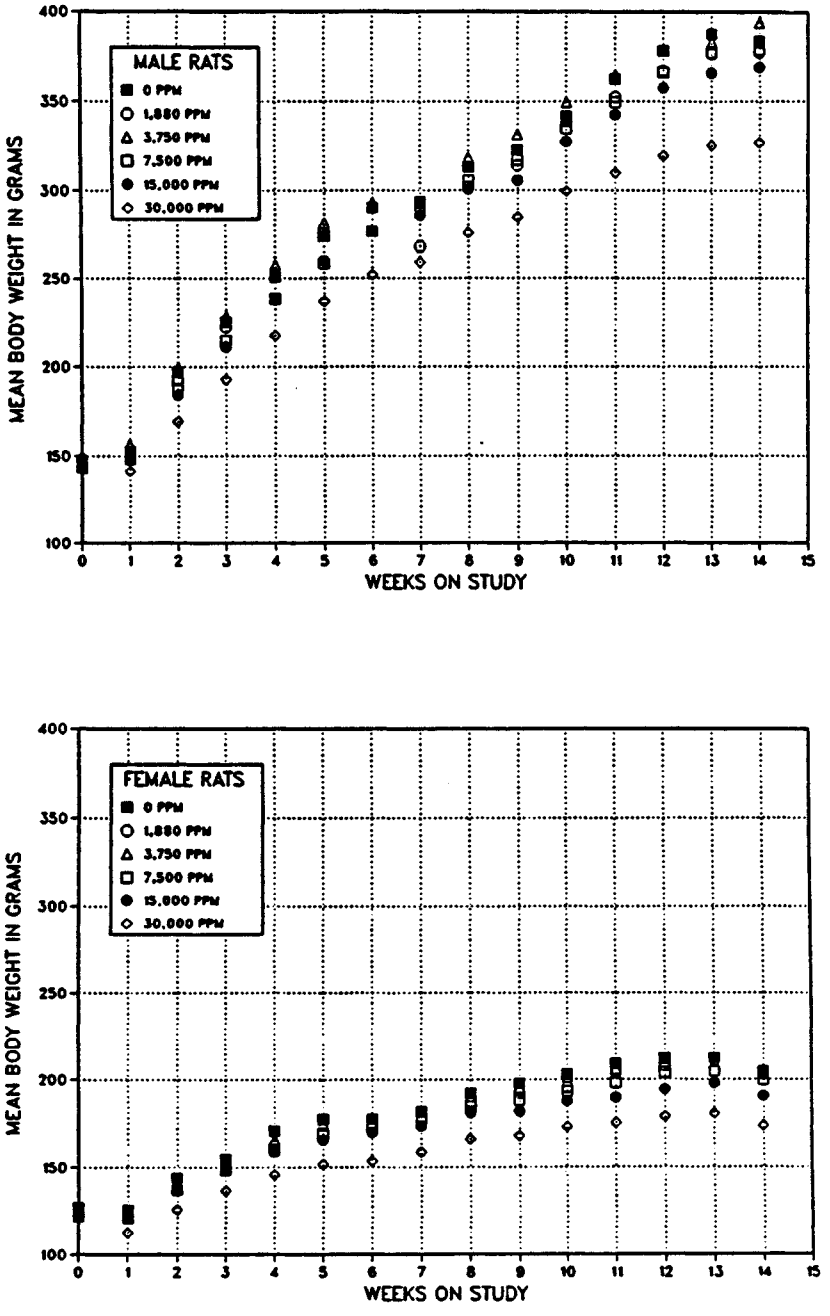

Figure 1
Growth Curves for Rats Fed Diets Containing *o*-Cresol for 13 Weeks

TABLE 23
Selected Organ Weight and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Studies of *o*-Cresol[a]

Organ	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male						
Necropsy body wt	392 ± 7	382 ± 7	396 ± 4	383 ± 6	369 ± 5*	328 ± 6**
R. Kidney						
Absolute	1.42 ± 0.03	1.34 ± 0.02	1.46 ± 0.03	1.44 ± 0.03	1.44 ± 0.03	1.39 ±0.04
Relative	3.6 ± 0.0	3.5 ± 0.1	3.7 ± 0.1	3.8 ± 0.1	3.9 ± 0.1**	4.2 ± 0.1**
Liver						
Absolute	14.18 ± 0.26	14.10 ± 0.35	14.85 ± 0.27	15.49 ± 0.30**	15.58 ± 0.28**	14.25 ± 0.43
Relative	36.2 ± 0.6	36.9 ± 0.5	37.5 ± 0.5	40.4 ± 0.7**	42.2 ± 0.7**	43.4 ± 0.7**
R. Testis						
Absolute	1.55 ± 0.03	1.53 ± 0.05	1.60 ± 0.037	1.55 ± 0.021	1.51 ± 0.02	1.49 ± 0.03
Relative	4.0 ± 0.1	4.0 ± 0.1	4.0 ± 0.1	4.1 ± 0.1	4.1 ± 0.1	4.5 ± 0.1**
Thymus[b]						
Absolute	324.1 ± 13.12	306.30 ± 10.76	372.50 ± 18.87	320.20 ± 11.40	349.60 ± 15.59	303.00 ± 10.37
Relative	0.83 ± 0.04	0.80 ± 0.03	0.94 ± 0.05	0.84 ± 0.03	0.95 ± 0.04*	0.92 ± 0.03*
Female						
Necropsy body wt	211 ± 4	208 ± 4	212 ± 3	206 ± 4	197 ± 3*	179 ± 3**
R. Kidney						
Absolute	0.79 ± 0.02	0.81 ± 0.02	0.81 ± 0.017	0.76 ± 0.011	0.78 ± 0.010	0.75 ± 0.03
Relative	3.8 ± 0.1	3.9 ± 0.1	3.8 ± 0.1	3.7 ± 0.1	4.0 ± 0.1*	4.2 ± 0.1**
Liver						
Absolute	6.46 ± 0.14	6.37 ± 0.16	6.78 ± 0.11	6.94 ± 0.14**	6.93 ± 0.27*	6.69 ± 0.18
Relative	30.6 ± 0.0	30.7 ± 0.1	32.0 ± 0.0	33.7 ± 0.1**	35.1 ± 0.1**	37.3 ± 0.1**
Thymus[b]						
Absolute	271.20 ± 10.43	255.10 ± 10.90	269.20 ± 11.56	271.10 ± 9.70	254.60 ± 8.94	230.20 ± 9.59**
Relative	1.29 ± 0.05	1.23 ± 0.06	1.27 ± 0.06	1.32 ± 0.04	1.29 ± 0.05	1.28 ± 0.04

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test..
** $P \leq 0.01$
[a] Weights are given in grams except where noted; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). n=10 for all groups
[b] Thymus weights are given in milligrams.

TABLE 24
Selected Hematology Summary for Rats in the 13-Week Feed Studies of *o*-Cresol[a]

Analysis	Day 5	Day 21	Day 43	Day 90
Male				
Hematocrit	+ (30,000 ppm)	NS	NS	NS
Hemoglobin	+ (30,000 ppm)	+ (30,000 ppm)	+ (30,000 ppm)	NS
Red blood cell	+ (≥ 15,000 ppm)	NS	NS	NS
Mean cell volume	NS	+ (≥ 7,500 ppm)	+ (≥ 15,000 ppm)	+ (3,750 ppm and ≥ 15,000 ppm)
Mean cell hemoglobin	NS	NS	+ (30,000 ppm)	+ (1,880 and 30,000 ppm)
Mean cell hemoglobin concentration	NS	NS	NS	NS
Platelets	NS	+ (30,000 ppm)	NS	NS
Reticulocytes	– (≥ 15,000 ppm)	NS	NS	NS
White blood cell	+ (30,000 ppm)	NS	NS	NS
Segmented neutrophils	NS	NS	– (30,000 ppm)	NS
Lymphocytes	+ (30,000 ppm)	NS	NS	NS
Female				
Hematocrit	NS	NS	NS	NS
Hemoglobin	+ (30,000 ppm)	NS	NS	NS
Red blood cell	NS	NS	NS	NS
Mean cell volume	NS	– (30,000 ppm)	NS	NS
Mean cell hemoglobin	NS	NS	NS	+ (30,000 ppm)
Mean cell hemoglobin concentration	+ (30,000 ppm)	NS	+ (30,000 ppm)	NS

TABLE 24
Selected Hematology Summary for Rats in the 13-Week Feed Studies of *o*-Cresol (continued)

Analysis	Day 5	Day 21	Day 43	Day 90
Females (continued)				
Platelets	+ (30,000 ppm)	+ (30,000 ppm)	NS	NS
Reticulocytes	NS	NS	NS	NS
White blood cell	+ (30,000 ppm)	NS	+ (30,000 ppm)	NS
Segmented neutrophils	NS	NS	NS	NS
Lymphocytes	+ (30,000 ppm)	NS	NS	NS

[a] Statistically significant ($P \leq 0.01$) groups given after each significant increase (+) and decrease (–). NS = not significant. Dose groups significant at the $P<0.05$ level as indicated in Appendix D.

TABLE 25
Selected Clinical Chemistry Summary for Rats in the 13-Week Feed Studies of *o*-Cresol[a]

Analysis	Day 5	Day 21	Day 43	Day 90
Male				
Urea nitrogen	– (30,000 ppm)	NS	– (30,000 ppm)	NS
Creatinine	NS	NS	NS	NS
Alkaline phosphatase	NS	NS	NS	NS
Alanine aminotransferase	+ (≥ 15,000 ppm)	NS	NS	– (15,000 ppm)
5'-Nucleotidase	– (30,000 ppm)	NS	NS	NS
Bile acids	+ (30,000 ppm)	+ (30,000 ppm)	+ (30,000 ppm)	NS
Female				
Urea nitrogen	NS	NS	NS	NS
Creatinine	– (1,880 ppm)	NS	NS	NS
Alkaline phosphatase	NS	NS	NS	NS
Alanine aminotransferase	NS	NS	NS	NS
5'-Nucleotidase	– (≥ 7,500 ppm)	– (30,000 ppm)	– (3,750 and 30,000 ppm)	NS
Bile acids	+ (≥ 15,000 ppm)	NS	+ (≥ 15,000 ppm)	NS

[a] Statistically significant ($P \leq 0.01$) groups given after each significant increase (+) and decrease (–). NS = not significant. Dose groups significant at the $P<0.05$ level as indicated in Appendix D.

TABLE 26
Selected Histopathology Data for Rats in the 13-Week Feed Studies of *o*-Cresol

Organ and Diagnosis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male						
Bone marrow						
hypocellularity	0/10	0/10	0/10	0/10	0/10	2/10 (1.0)[a]
Female						
Bone marrow						
hypocellularity	0/10	1/10 (1.0)	0/10	1/10 (1.0)	3/10 (1.3)	8/10 (1.2)

[a] Average severity score based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

TABLE 27
Survival, Mean Body Weights, and Compound Consumption of Rats in the 13-Week Feed Studies of *m/p*-Cresol

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)	Mean Feed and Compound Consumption	
		Initial[b]	Final	Change[c]		Feed[d]	Dose/Day[e]
Male							
0	20/20	141 ± 4	371 ± 7	230 ± 8		17.5	0
1,880	20/20	139 ± 4	357 ± 7	218 ± 6	96	17.2	123
3,750	20/20	139 ± 3	375 ± 5	236 ± 5	101	17.4	241
7,500	20/20	141 ± 4	364 ± 6	223 ± 5	98	17.2	486
15,000	20/20	139 ± 3	346 ± 6*	206 ± 7	93	16.8	991
30,000	20/20	139 ± 4	308 ± 6**	169 ± 4**	83	15.7	2,014
Female							
0	20/20	106 ± 3	202 ± 3	96 ± 3		11.3	0
1,880	20/20	105 ± 3	199 ± 3	94 ± 3	99	11.4	131
3,750	20/20	106 ± 2	203 ± 3	97 ± 2	100	11.1	254
7,500	20/20	107 ± 3	197 ± 2	90 ± 3	97	11.0	509
15,000	20/20	106 ± 3	191 ± 2**	85 ± 2*	95	10.8	1,024
30,000	20/20	105 ± 2	177 ± 3**	72 ± 4**	88	10.2	2,050

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Number of animals surviving at 13 weeks/number initially in the study
[b] Initial group mean body weight ± standard error of the mean for 10 animals selected prior to study initiation
[c] Mean body weight change ± standard error of the mean
[d] Feed given in grams of feed consumed per animal per day
[e] Doses given in mg compound (60% *m*-cresol/40% *p*-cresol) per kg body weight per day

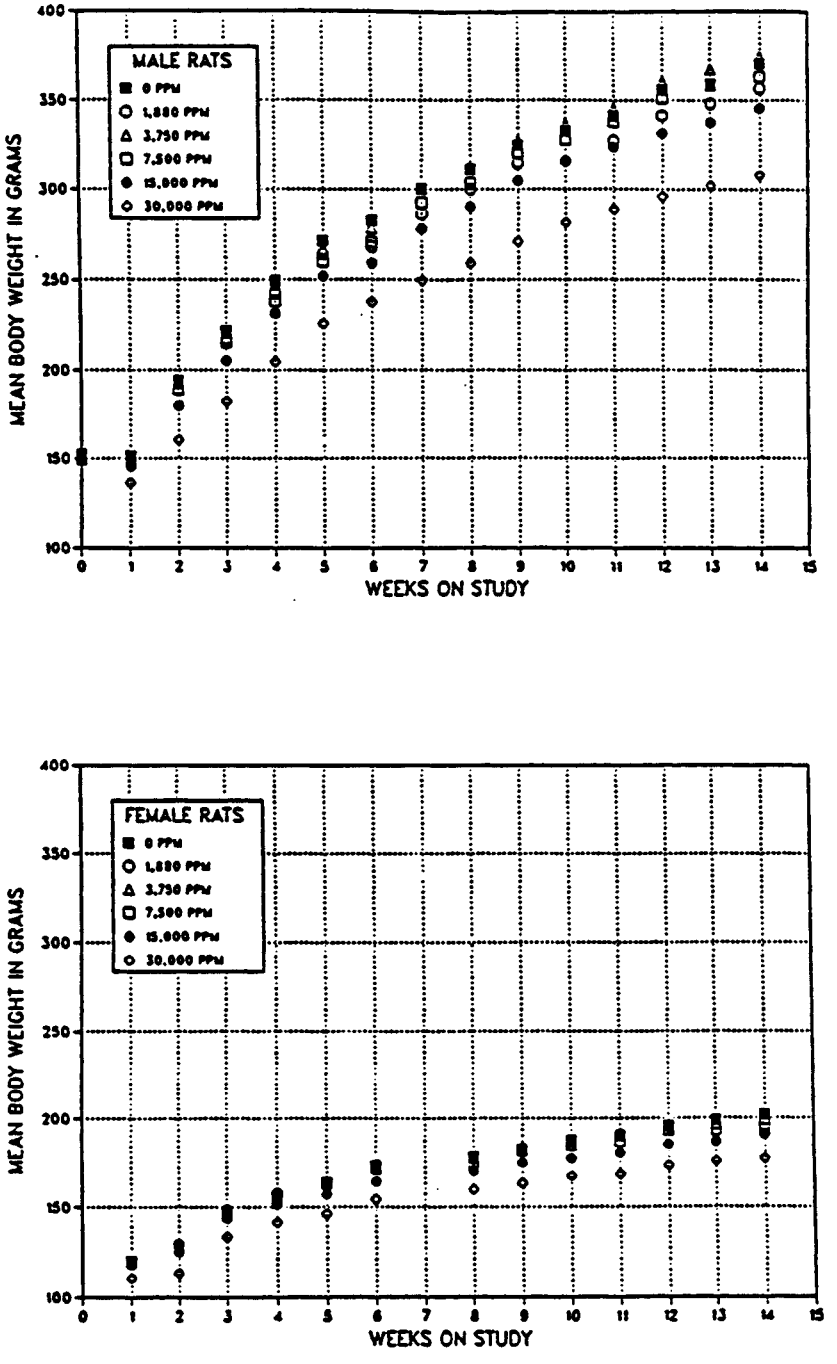

Figure 2
Growth Curves for Rats Fed Diets Containing *m/p*-Cresol for 13 Weeks

TABLE 28
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Studies of *m/p*-Cresol[a]

Organ	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male						
Necropsy body wt	368 ± 7	355 ± 6	376 ± 4	366 ± 6	348 ± 6	310 ± 6**
R. Kidney						
Absolute	1.25 ± 0.03	1.25 ± 0.02	1.33 ± 0.02*	1.32 ± 0.03	1.38 ± 0.03**	1.31 ± 0.03*
Relative	3.38 ± 0.07	3.52 ± 0.04	3.55 ± 0.06	3.60 ± 0.05*	3.98 ± 0.08**	4.24 ± 0.07**
Liver						
Absolute	13.11 ± 0.39	12.83 ± 0.22	13.91 ± 0.20*	14.51 ± 0.51*	15.57 ± 0.29**	14.92 ± 0.29**
Relative	35.5 ± 0.5	36.2 ± 0.4	37.0 ± 0.6	39.6 ± 0.9**	44.7 ± 0.5**	48.2 ± 0.8**
R. Testis						
Absolute	1.52 ± 0.01[b]	1.50 ± 0.03	1.56 ± 0.02	1.56 ± 0.03	1.56 ± 0.02	1.53 ± 0.02
Relative	4.16 ± 0.07[b]	4.23 ± 0.05	4.15 ± 0.07	4.3 ± 0.1	4.48 ± 0.08*	4.95 ± 0.08**
Female						
Necropsy body wt	201 ± 3	200 ± 3	203 ± 3	198 ± 2	192 ± 2*	175 ± 3**
R. Kidney						
Absolute	0.73 ± 0.02	0.73 ± 0.01	0.75 ± 0.02	0.73 ± 0.02	0.73 ± 0.01	0.73 ± 0.01
Relative	3.65 ± 0.05	3.63 ± 0.05	3.69 ± 0.08	3.70 ± 0.09	3.81 ± 0.05	4.18 ± 0.09**
Liver						
Absolute	6.121 ± 0.11	6.263 ± 0.10	6.231 ± 0.17	6.498 ± 0.09*	6.732 ± 0.010**	6.784 ± 0.08**
Relative	30.5 ± 0.4	31.4 ± 0.4	30.6 ± 0.7	32.8 ± 0.4**	35.0 ± 0.3**	38.7 ± 0.5**

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). n=10 for all groups except where noted
[b] n=9

TABLE 29
Selected Hematology Summary for Rats in the 13-Week Feed Studies of *m/p*-Cresol[a]

Analysis	Day 5	Day 21	Day 43	Day 90
Male				
Hematocrit	+ (30,000 ppm)	NS	NS	NS
Hemoglobin	+ (30,000 ppm)	NS	NS	NS
Red blood cell	+ (30,000 ppm)	NS	NS	NS
Mean cell hemoglobin	NS	NS	NS	NS
Platelets	NS	+ (30,000 ppm)	NS	NS
Reticulocytes	NS	NS	NS	NS
White blood cell	NS	+ (15,000 ppm)	NS	NS
Lymphocytes	NS	NS	NS	NS
Monocytes	+ (1,880, 3,750, and 30,000 ppm)	NS	NS	NS
Eosinophils	NS	NS	NS	NS
Female				
Hematocrit	NS	NS	NS	NS
Hemoglobin	+ (30,000 ppm)	NS	NS	NS
Red blood cell	+ (30,000 ppm)	+ (30,000 ppm)	NS	NS
Mean cell volume	– (30,000 ppm)	– (30,000 ppm)	– (≥ 15,000 ppm)	– (≥ 15,000 ppm)
Mean cell hemoglobin	NS	NS	NS	NS
Mean cell hemoglobin concentration	+ (30,000 ppm)	NS	+ (30,000 ppm)	NS
Platelets	NS	+ (15,000 ppm)	NS	NS
Reticulocytes	– (30,000 ppm)	NS	NS	NS

TABLE 29
Selected Hematology Summary for Rats in the 13-Week Feed Studies of *m/p*-Cresol (continued)

Analysis	Day 5	Day 21	Day 43	Day 90
Females (continued)				
White blood cell	NS	NS	NS	NS
Monocytes	NS	NS	NS	NS
Eosinophils	NS	NS	NS	NS

[a] Statistically significant ($P \leq 0.01$) groups given after each significant increase (+) and decrease (–). NS = not significant. Dose groups significant at the $P<0.05$ level as indicated in Appendix D.

TABLE 30
Selected Clinical Chemistry Summary for Rats in the 13-Week Feed Studies of *m/p*-Cresol[a]

Analysis	Day 5	Day 21	Day 43	Day 90
Male				
Urea nitrogen	+ (15,000 ppm)	NS	– (1,880 ppm and ≥ 7,500 ppm)	– (≥ 15,000 ppm)
Alkaline phosphatase	NS	– (30,000 ppm)	– (30,000 ppm)	NS
Alanine aminotransferase	+ (30,000 ppm)	NS	NS	NS
5'-Nucleotidase	NS	– (≥ 7,500 ppm)	– (≥ 15,000 ppm)	– (30,000 ppm)
Sorbitol dehydrogenase	+ (≥ 15,000 ppm)	NS	NS	NS
Bile acids	+ (≥ 15,000 ppm)	+ (30,000 ppm)	+ (30,000 ppm)	+ (3,750 ppm and ≥ 15,000 ppm)
Female				
Urea nitrogen	+ (≥ 15,000 ppm)	NS	– (3,750 and 7,500 ppm)	NS
Alanine aminotransferase	+ (30,000 ppm)	NS	NS	NS
Alkaline Phosphatase	NS	NS	NS	NS
5'-Nucleotidase	– (≥ 15,000 ppm)	– (≥ 7,500 ppm)	– (≥ 15,000 ppm)	– (≥ 3,750 ppm)
Sorbitol dehydrogenase	NS	NS	NS	NS
Bile acids	NS	+ (≥ 1,880 ppm)	+ (≥ 15,000 ppm)	+ (30,000 ppm)

[a] Statistically significant ($P \leq 0.01$) groups given after each significant increase (+) and decrease (–). NS = not significant. Dose groups significant at the $P<0.05$ level as indicated in Appendix D.

Normal circulating levels of 5′-nucleotidase depend to some extent on the solubilization of this enzyme from canalicular and plasma membranes of hepatocytes by bile acids. There was no clear evidence of renal injury in the urinalysis results. Increases in the specific activity of urine aspartate aminotransferase and N-acetyl B-glucose aminidase were generally associated with low urine volumes.

Dose-related hyperplasia of the nasal respiratory epithelium occurred at the most anterior portions of the nasal septum, dorsal arch, and medial aspect of the nasal turbinates in all dose groups for both sexes (Table 31). The occurrence of nasal lesions included minimal to marked respiratory epithelial glandular hyperplasia characterized by increased numbers of goblet cells and pseudogland formation due to the infolding of the hyperplastic cells. These changes were primarily present in anterior nasal sections and the hyperplastic areas were associated with single cell necrosis. Increased colloid within thyroid follicles was seen in males receiving the two highest doses and females receiving the four highest doses. Increased colloid was characterized by increased follicle diameter and flattening of the follicular epithelial cells. Minimal hypocellularity of bone marrow was noted among males in the two highest dose groups and females in the highest dose group. Minimal to mild uterine atrophy was noted among females in the two highest dose groups. Uterine changes were characterized by reduced cross-sectional diameter of the uterine horns and by decreased sizes of stromal and smooth muscle cells.

Evaluation of other reproductive endpoints revealed no biologically significant findings in dosed males, but a lengthened estrus cycle was observed in dosed females (Appendix A).

TABLE 31
Selected Histopathology Data for Rats in the 13-Week Feed Studies of *m/p*-Cresol

Organ and Diagnosis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male						
Bone marrow						
Hypocellularity	0/10	0/10	0/10	0/10	1/10 (1.0)[a]	8/10 (1.0)
Nasal						
Respiratory epithelium						
Glandular hyperplasia	0/10	3/10 (1.0)	8/10 (1.5)	10/10 (1.6)	9/10 (2.6)	9/10 (3.8)
Hyperplasia	0/10	3/10 (1.0)	8/10 (1.1)	10/10 (1.4)	8/10 (2.2)	10/10 (3.8)
Thyroid gland						
Follicle						
Iincreased colloid	0/10	0/10	0/10	0/10	7/10 (1.1)	9/10 (1.6)
Female						
Bone marrow						
Hypocellularity	0/10	0/10	0/10	0/10	0/10	6/10 (1.0)
Nasal						
Respiratory epithelium						
Glandular hyperplasia	0/10	2/10 (1.0)	6/10 (1.3)	10/10 (2.1)	8/10 (2.5)	6/10 (2.8)
Hyperplasia	3/10 (1.0)	1/10 (1.0)	5/10 (1.2)	9/10 (1.7)	8/10 (2.0)	10/10 (2.8)
Thyroid gland						
Follicle						
Increased colloid	0/10	0/10	1/10 (1.0)	6/10 (1.2)	7/10 (1.6)	8/10 (1.6)
Uterus						
Atrophy	0/10	0/10	0/10	0/10	3/10 (1.0)	7/10 (1.7)

[a] Average severity score based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

Mice

o-Cresol: All mice lived to the end of the study (Table 32). Mean final body weights for males at the highest dose and females at the three highest doses were significantly decreased compared to controls. Females at the three highest doses and all male dose groups except the group receiving 2,500 ppm gained less weight than the controls (Figure 3). Feed consumption was depressed for high-dose animals during the first week of the study (Appendix B, Tables B5 and B6). Hunched posture and rough hair coat were recorded for all high-dose males. Hunched posture was also noted for one male receiving 10,000 ppm.

High-dose females had a significantly increased relative kidney weight (Table 33). All male dose groups and females in the three highest dose groups had significantly increased relative liver weights. High-dose males had significantly increased relative testis and relative thymus weights. The relative thymus weight for high-dose females was also significantly increased. Other statistically significant absolute and relative organ weights are presented in Appendix C, Table C11.

The results of hematology, clinical chemistry, and urinalysis studies are shown in Appendix D, Table D3. There were no biologically significant changes in the data. A moderate increase in serum alanine aminotransferase and 5′-nucleotidase were noted at day 90 in high-dose females; however, there was no evidence of liver damage or cholestasis upon microscopic examination. Total bile acids were not elevated in dosed animals.

Histopathologic examination revealed minimal forestomach epithelial hyperplasia in 4 of 10 males and 3 of 10 females in the high-dose group; this lesion occurred sporadically in lower dose groups as well. This effect may have been the result of direct chemical irritation, or secondary to decreased feed consumption.

An evaluation of vaginal cytology revealed a lengthened estrus cycle in dosed mice; there was no change in male reproductive endpoints in dosed mice that was considered to be biologically significant (Appendix A).

m/p-Cresol: All mice lived to the end of the study (Table 34). Mean final body weights for high-dose animals were significantly decreased compared to controls. Mean body weight gain for high-dose males was decreased significantly compared to controls (Figure 4). Slightly decreased feed consumption was noted for high-dose animals of both sexes for the 13-week studies (Appendix B, Tables B7 and B8). Rough hair coat was noted for 3 of the 10 high-dose females. Relative liver weights were significantly increased for males at the two highest doses and females at the highest dose (Table 35).

The results of hematology, clinical chemistry, and urinalysis studies are shown in Appendix D, Table D4. Hematology and clinical chemistry analyses were largely unremarkable. Serum sorbitol dehydrogenase levels were marginally increased in high-dose males and 5′-nucleotidase levels were increased in high-dose females. There were no corresponding liver lesions evident microscopically.

Hyperplasia of the nasal respiratory epithelium occurred at the most anterior portions of the nasal septum, dorsal meatus, and medial aspect of the nasal turbinates in males at the two highest doses and females in the three highest doses (Table 36). The nasal lesions included minimal to mild respiratory epithelial glandular hyperplasia characterized by increased numbers of goblet cells and pseudogland formation due to the infolding of the hyperplastic cells. These changes were primarily present in anterior nasal sections. Hyperplastic areas were associated with single cell necrosis.

Evaluation of several reproductive system endpoints (Appendix A) revealed no biologically significant changes in males and females.

TABLE 32
Survival, Mean Body Weights, and Compound Consumption of Mice in the 13-Week Feed Studies of *o*-Cresol

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)	Mean Feed and Compound Consumption	
		Initial[b]	Final	Change[c]		Feed[d]	Dose/Day[e]
Male							
0	10/10	21.3 ± 0.5	31.6 ± 0.8	10.4 ± 0.4		4.3	0
1,250	10/10	22.3 ± 0.5	30.9 ± 0.8	8.6 ± 0.6*	98	4.3	199
2,500	10/10	21.2 ± 0.6	30.8 ± 1.1	9.6 ± 0.6	97	4.2	400
5,000	10/10	21.7 ± 0.6	29.7 ± 0.7	8.0 ± 0.4**	94	4.1	794
10,000	10/10	21.7 ± 0.5	30.8 ± 0.9	9.1 ± 0.5*	97	3.8	2,723
20,000	10/10	22.4 ± 0.8	26.7 ± 1.0**	4.3 ± 0.6**	85	3.3	2,723
Female							
0	10/10	17.1 ± 0.5	27.4 ± 0.4	10.3 ± 0.4		4.8	0
1,250	10/10	16.7 ± 0.5	26.3 ± 0.8	9.7 ± 0.7	96	4.2	237
2,500	10/10	17.3 ± 0.4	26.8 ± 0.5	9.5 ± 0.4	98	4.3	496
5,000	10/10	16.6 ± 0.4	25.8 ± 1.0*	9.2 ± 0.7	94	4.1	935
10,000	10/10	17.4 ± 0.6	24.8 ± 0.7**	7.5 ± 0.3**	93	3.6	1,663
20,000	10/10	16.8 ± 0.5	21.7 ± 0.5**	4.8 ± 0.4**	80	3.1	3,205

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Initial group mean body weight ± standard error of the mean
[c] Mean body weight change ± standard error of the mean
[d] Feed given in grams of feed consumed per animal per day
[e] Doses given in mg compound per kg body weight per day

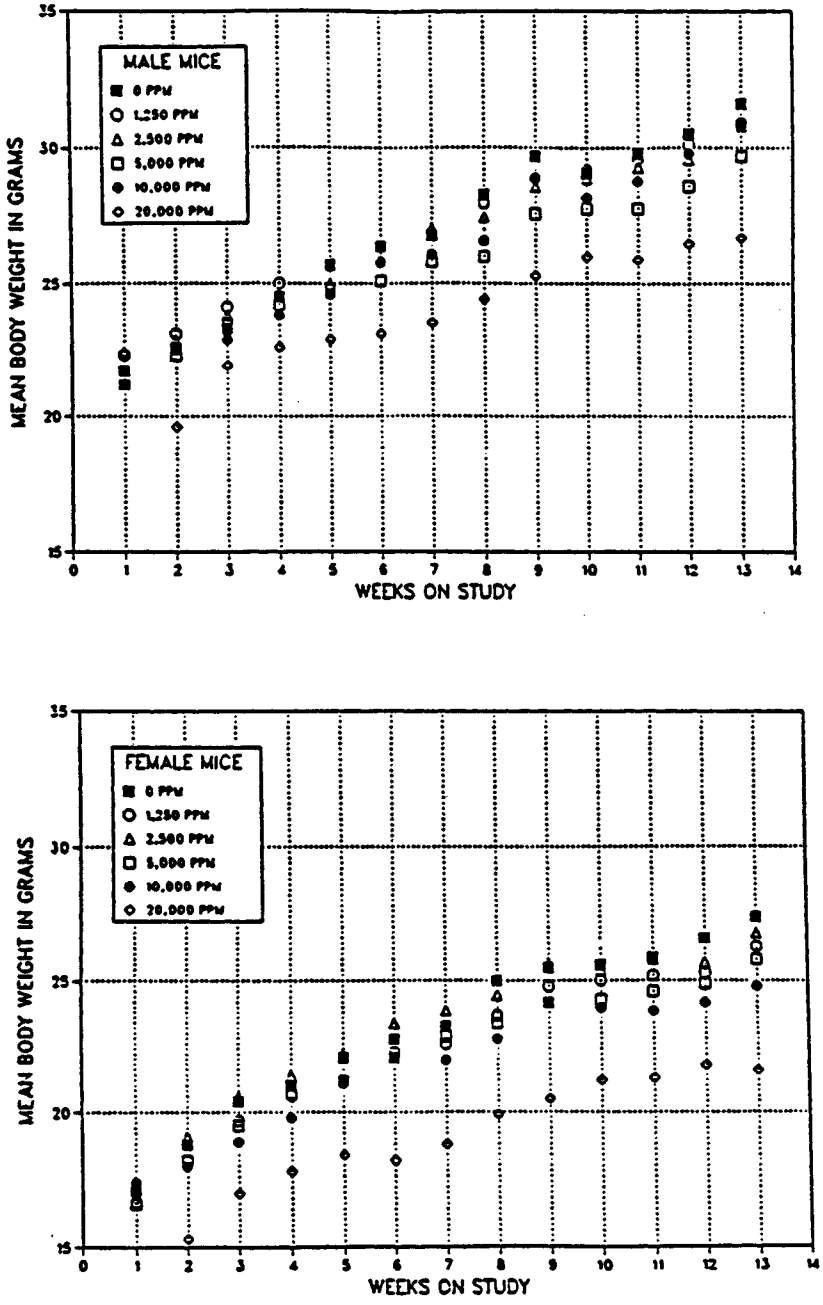

Figure 3
Growth Curves for Mice Fed Diets Containing *o*-Cresol for 13-Weeks

TABLE 33
Selected Organ Weight and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Studies of *o*-Cresol[a]

Organ	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Male						
Necropsy body wt	32.5 ± 0.8	31.9 ± 0.8	32.4 ± 1.2	31.1 ± 0.7	31.9 ± 0.9	27.7 ± 0.9**
R. Kidney						
Absolute	0.290 ± 0.006	0.303 ± 0.011	0.296 ± 0.007	0.296 ± 0.016	0.294 ± 0.007	0.264 ± 0.012
Relative	9.0 ± 0.29	9.5 ± 0.20	9.2 ± 0.17	9.5 ± 0.36	9.2 ± 0.27	9.6 ± 0.37
Liver						
Absolute	1.390 ± 0.031	1.471 ± 0.052	1.570 ± 0.060**	1.459 ± 0.061	1.623 ± 0.030**	1.474 ± 0.060*
Relative	42.9 ± 0.71	46.0 ± 0.77*	48.5 ± 0.98**	46.8 ± 1.64**	51.2 ± 1.58**	53.2 ± 1.80**
R. Testis						
Absolute	0.117 ± 0.002	0.120 ± 0.004	0.122 ± 0.003	0.116 ± 0.002	0.121 ± 0.004	0.115 ± 0.003
Relative	3.6 ± 0.10	3.8 ± 0.09	3.8 ± 0.07	3.7 ± 0.07	3.8 ± 0.09	4.2 ± 0.11**
Thymus[b]						
Absolute	43.40 ± 4.16	42.70 ± 3.41	44.30 ± 1.26	47.80 ± 2.44	44.60 ± 2.80	47.50 ± 3.58
Relative	1.3 ± 0.13	1.3 ± 0.10	1.4 ± 0.06	1.5 ± 0.09	1.4 ± 0.09	1.7 ± 0.15*
Female						
Necropsy body wt	26.9 ± 0.4	26.5 ± 0.7	27.3 ± 0.5	26.1 ± 1.0	25.3 ± 0.7	21.9 ± 0.3**
R. Kidney						
Absolute	0.196 ± 0.004	0.193 ± 0.007	0.210 ± 0.006	0.198 ± 0.007	0.193 ± 0.007	0.170 ± 0.004**
Relative	7.3 ± 0.13	7.3 ± 0.11	7.7 ± 0.18	7.6 ± 0.10	7.6 ± 0.11	7.8 ± 0.14*
Liver						
Absolute	1.290 ± 0.028	1.289 ± 0.040	1.336 ± 0.038	1.354 ± 0.045	1.362 ± 0.040	1.171 ± 0.017
Relative	47.9 ± 0.75	48.6 ± 0.41	48.9 ± 1.11	52.0 ± 1.10**	53.8 ± 1.11**	53.6 ± 0.99 **
Thymus[b]						
Absolute	52.20 ± 4.44	53.80 ± 2.06	59.60 ± 2.86	58.10 ± 3.22	58.40 ± 2.59	54.80 ± 2.24
Relative	1.9 ± 0.17	2.0 ± 0.08	2.2 ± 0.10	2.2 ± 0.11	2.3 ± 0.09	2.5 ± 0.11**

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Weights given in grams except where noted; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). n=10 for all groups
[b] Weights given in milligrams

TABLE 34
Survival, Mean Body Weights, and Compound Consumption of Mice in the 13-Week Feed Studies of *m/p*-Cresol

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)	Mean Feed and Compound Consumption	
		Initial[b]	Final	Change[c]		Feed[d]	Dose/Day[e]
Male							
0	10/10	21.6 ± 0.5	31.2 ± 0.8	9.6 ± 0.4		4.1	0
625	10/10	21.4 ± 0.4	30.8 ± 0.8	9.4 ± 0.6	99	4.1	96
1,250	10/10	21.3 ± 0.3	31.6 ± 0.5	10.3 ± 0.3	101	4.1	194
2,500	10/10	21.4 ± 0.6	31.1 ± 0.8	9.7 ± 0.4	100	4.2	402
5,000	10/10	21.5 ± 0.4	30.9 ± 0.8	9.4 ± 0.8	99	4.1	776
10,000	10/10	21.1 ± 0.6	28.4 ± 0.5**	7.3 ± 0.7*	91	3.8	1,513
Female							
0	10/10	17.8 ± 0.3	26.8 ± 0.6	9.0 ± 0.5		4.4	0
625	10/10	17.5 ± 0.2	26.0 ± 0.4	8.5 ± 0.4	97	4.2	116
1,250	10/10	17.5 ± 0.4	26.2 ± 0.8	8.7 ± 0.6	98	4.3	239
2,500	10/10	17.4 ± 0.3	25.4 ± 0.5	8.0 ± 0.3	95	4.2	472
5,000	10/10	17.7 ± 0.3	25.7 ± 0.5	8.0 ± 0.3	96	4.2	923
10,000	10/10	17.2 ± 0.3	25.0 ± 0.4*	7.8 ± 0.3	93	3.7	1,693

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Initial group mean body weight ± standard error of the mean
[c] Mean body weight change ± standard error of the mean
[d] Feed given in grams of feed consumed per animal per day
[e] Doses given in mg compound (60% *m*-cresol/40% *p*-cresol) per kg body weight per day

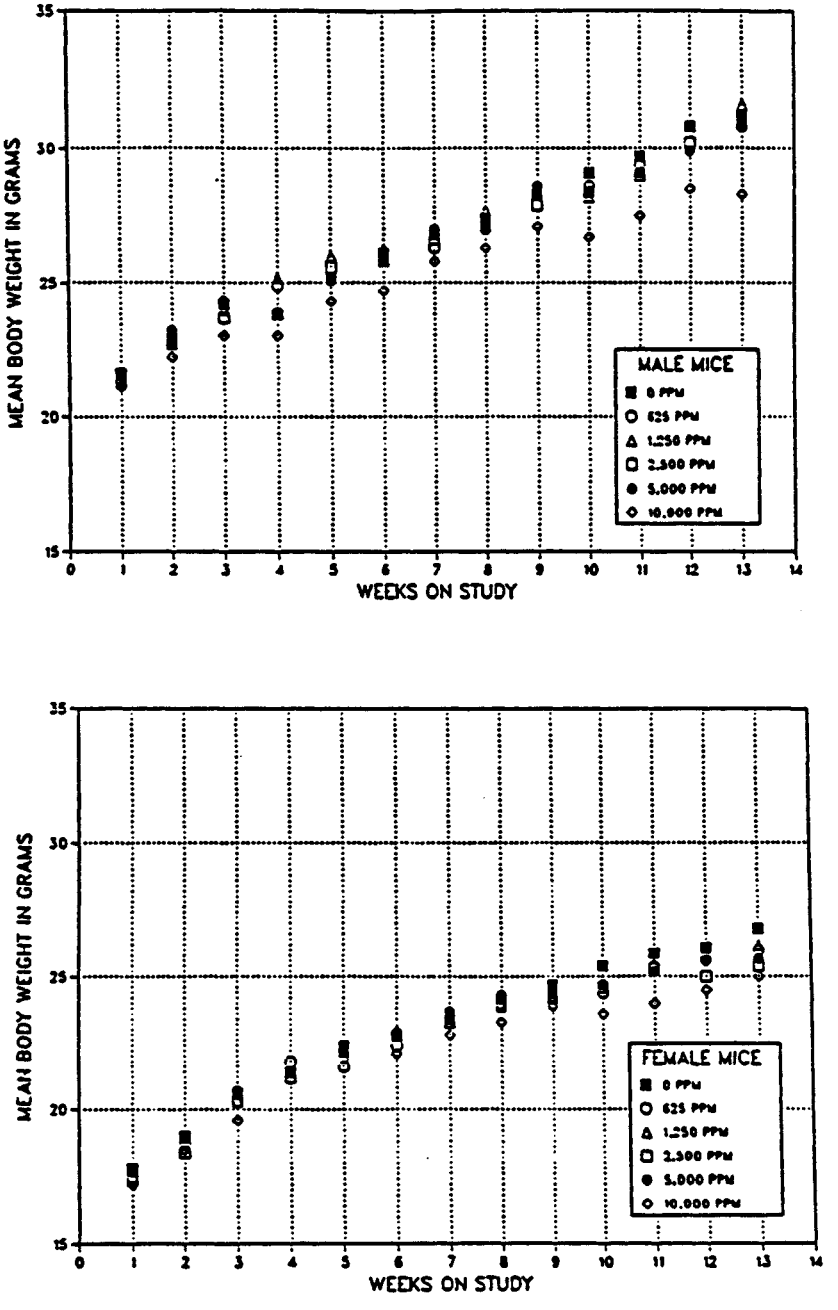

Figure 4
Growth Curves for Mice Fed Diets Containing *m/p*-Cresol for 13 Weeks

TABLE 35
Selected Organ Weight and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Studies of *m/p*-Cresol[a]

Organ	0 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male						
Necropsy body wt	31.4 ± 0.8	31.8 ± 0.7	32.1 ± 0.5	31.8 ± 0.9	31.5 ± 0.9	29.7 ± 0.4
Liver						
Absolute	1.295 ± 0.044	1.287 ± 0.036	1.375 ± 0.038	1.326 ± 0.028	1.458 ± 0.046*	1.505 ± 0.043**
Relative	41.2 ± 0.9	40.4 ± 0.7	42.8 ± 0.6	41.8 ± 0.6	46.3 ± 1.0**	50.6 ± 1.3**
Female						
Necropsy body weight	26.6 ± 0.6	26.2 ± 0.4	26.4 ± 0.7	25.9 ± 0.6	26.6 ± 0.7	25.0 ± 0.4*
Liver						
Absolute	1.277 ± 0.049	1.234 ± 0.028	1.313 ± 0.055[b]	1.232 ± 0.040	1.375 ± 0.041	1.393 ± 0.030
Relative	47.9 ± 1.0	47.2 ± 0.6	49.6 ± 1.6[b]	47.6 ± 0.9	51.9 ± 1.5	55.8 ± 0.7**

* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)
[a] Weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). n=10 for all groups except where noted
[b] n=9

TABLE 36
Selected Histopathology Data for Mice in the 13-Week Feed Studies of *m/p*-Cresol

Organ and Diagnosis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male						
Nasal						
Respiratory epithelium						
glandular hyperplasia	1/10 (1.0)	0/10	0/10	0/10	0/10	2/10 (1.0)
hyperplasia	1/10 (1.0)	0/10	0/10	0/10	4/10 (1.0)	8/10 (1.0)
Female						
Nasal						
Respiratory epithelium						
glandular hyperplasia	1/10 (1.0)	0/10	0/10	0/10	0/10	2/10 (1.5)
hyperplasia	2/10 (1.5)	0/10	0/10	3/10 (1.0)	2/10 (1.0)	5/10 (1.4)

[a] Average severity score based on a scale of 1 to 4; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

DISCUSSION AND CONCLUSIONS

The intent of these studies was to provide primary toxicity information and a comparison of the toxicities of the cresol isomers. *Ortho*-cresol, *m*-cresol, *p*-cresol, and a mixture of *m*/*p*-cresol (60:40) were evaluated in the 28-day feed studies and *o*-cresol and *m*/*p*-cresol in the 13-week studies. The concentrations used ranged as high as 3% in the diet for both the 28-day and 13-week studies. Due to the similarity in doses for the isomers between the studies, the results of the 28-day and 13-week studies will be considered concurrently in the discussion.

o-CRESOL

There were no deaths that could clearly be related to ingestion of diets containing as much as 30,000 ppm *o*-cresol for rats or 20,000 ppm for mice for 13 weeks. Several male and female mice given diets containing 30,000 ppm died in the 28-day studies. Body weight gains were generally reduced at the higher doses and feed consumption was lower relative to that of controls during the first week of the studies. This suggested poor palatability, a common finding with all the cresol isomers studied.

Kidney and liver weights were increased in a dose-related fashion in rats and mice of both sexes. There were no specific pathologic changes that were associated with these organ weight changes, nor were clearly chemically related changes seen in the tissues of mice that died early. Clinical chemistry studies suggested a deficit in liver function, as demonstrated by an impaired ability to take up bile acids from the blood stream. Bile acids are actively transported into hepatocytes from the sinusoidal blood coupled to Na^+ transport, a process driven by Na^+-K^+-ATPase activity (Scharschmidt, 1982). ATPase activity of the red blood cells, platelets, and brain has been shown to be sensitive to inhibition by cresols *in vitro* (Wardle, 1979).

There was a substantial reduction in the reticulocyte count in blood samples taken from high-dose male rats and a lesser reduction in female rats on the fifth day of the study. This coincided with the period of maximum feed rejection by the animals receiving the highest dose, suggesting that early poor nutrition may have contributed to bone marrow hypocellularity seen in rats at 13 weeks.

Reproductive effects seen in mice following *o*-cresol administration included histologic evidence of uterine and ovarian atrophy at 28 days and lengthening of the estrus cycle as determined by vaginal cytology in the 13-week studies. Uterine or ovarian atrophy may be seen in rodents which are debilitated or nutritionally deprived; food restriction in rats has been shown to result in selective reduction of uterine and ovarian relative organ weights and associated prolongation of estrus cycles (Nordio *et al.*, 1989). However, there is evidence that weight loss alone may not be sufficient for increased cycle lengths (Morrissey *et al.*, 1988a).

Hyperplasia of the forestomach was also seen in high-dose mice in the 13-week studies. Although this could represent a primary irritant effect, the change was minimal and not associated with inflammation, erosion, or other forestomach lesions.

m-CRESOL

No rats receiving *m*-cresol in the diet at concentrations as high as 30,000 ppm died during the 28-day studies. Several male and female mice receiving the high-dose and one female mouse receiving 10,000 ppm died during the first week of the study. Feed consumption of high-dose animals was reduced compared to controls early in the studies. Liver and kidney weights showed dose-related increases at the higher *m*-cresol concentrations, although no specific microscopic lesions were identified in these organs. Atrophy of the uterus was observed in high-dose rats and mice, and several affected mice also showed atrophic mammary glands and ovaries. A reproductive screen was not performed with *m*-cresol.

p-CRESOL

Generally, similar results were obtained with *p*-cresol in that no deaths of rats occurred in 28-day studies, but all male and female mice receiving the highest dose and one male mouse receiving 10,000 ppm died. Feed consumption was affected early in the studies and weight gains of rats in the higher dose

groups were less with *p*-cresol than with *o*-cresol or *m*-cresol. Liver and kidney weights were increased with no clear pathological account for these changes. Bone marrow hypocellularity in rats and mice was consistent with the findings with *o*-cresol in the rat, and uterine atrophy was again noted in high-dose rats. Mice that died early showed centrilobular atrophy and necrosis in the liver, renal tubular necrosis, and lymphoid depletion and necrosis in several organs. These changes are consistent with a moribund condition, or with agonal changes, but were more apparent in the mice that died early from ingestion of *p*-cresol, than in the early deaths in studies with the other isomers. Therefore, some of these changes may reflect direct chemical toxicity. In addition, a spectrum of atrophy, hyperplasia, and squamous metaplasia of the respiratory and olfactory epithelia of the nasal cavity occurred in dosed rats and to a lesser extent in dosed mice. These lesions were similar to those resulting from an inhaled irritant and were specific to *p*-cresol. All three isomers are considered both dermal and respiratory irritants, but it is clear that *p*-cresol produced vapors that were substantially more toxic to the nasal epithelia than *o*-cresol or *m*-cresol.

m/p-CRESOL

The approximately 60% *m*-cresol/40% *p*-cresol mixture resulted in toxicities which could be predicted based on the results from the individual isomers. Although there were no deaths among rats and mice in the 28-day studies, effects on food consumption, weight gain, and increases in liver and kidney weights were consistent findings. There were also signs of nasal epithelia irritation in rats and mice, and bronchiolar epithelial hyperplasia in high-dose mice. An additional finding in the 28-day rat studies was hyperplasia in stratified squamous epithelium of the esophagus and forestomach. These lesions were not seen at similar doses in the 13-week studies with rats nor was there any evidence of other inflammatory or degenerative changes. Estimates of the estrus cycle length showed a significant lengthening of the cycle in rats given the mixture in 13-week studies and this effect was associated with evidence of uterine atrophy in the animals sacrificed at 13 weeks.

Increased colloid within thyroid gland follicles was a treatment-related effect noted only in rats in both the 28-day and 13-week studies. The biological significance of this lesion is uncertain, as it was not noted with the individual isomers, nor was it associated with overt follicular cell hypertrophy and/or hyperplasia. Increased colloid may have been secondary to decreased food consumption and body weights; undernutrition in rats has been associated with increased thyroid gland weights, presumably due to physiologic disruption of the neuroendocrine axis (Nordio *et al.*, 1989). Alternatively, a direct effect by cresols on the thyroid gland is suggested by findings in which a number of phenolic compounds with diverse chemical structures have been shown to interfere with thyroid hormone metabolism (Chopra *et al.*, 1980; Goswami *et al.*, 1982; Haynes and Murad, 1985).

COMPARATIVE TOXICITY

Consistent with the fact that they ingested larger quantities of cresols per unit of body weight (Table 2), mice showed a greater toxic response to cresol exposures than rats, but the toxic effects did not appear to differ in character between the two species. In general, there were no significant indications of distinct toxicities between the three isomers. The combined study results indicate that *o*-cresol may be somewhat less toxic than *m*-cresol and *p*-cresol, and that *p*-cresol or *m/p*-cresol appears to be more irritating, resulting in proliferative lesions at contact areas, than *o*-cresol or *m*-cresol. Diets containing cresols have a very characteristic strong odor (odor threshold, 0.0012 mg/m^3; Ruth, 1986) suggesting nasal mucosa exposure during ingestion due to cresol volatilization from the feed. The results of these studies indicate, however, that *p*-cresol, with a lower relative vapor pressure (0.1080 mm Hg at 25 °C), is more potent relative to its ability to affect the respiratory mucosa than *o*-cresol or *m*-cresol, which have higher relative vapor pressures (0.2453 and 0.1528 mm Hg at 25 °C; Deichmann and Keplinger, 1981).

Proliferative responses to the cresols in the form of minimal hyperplasia were also observed in the gastrointestinal epithelium, the primary site of exposure for ingested cresols. Other reports describing cresol-mediated gastrointestinal toxicity in rodents were not found in the literature. Recently, however, Altmann *et al.* (1986) showed that the short-term oral administration (up to 4 weeks) of the phenolic antioxidant 3-tert-butyl-4-hydroxyanisole (BHA) induces mild hyperplasia and hyperkeratosis in the forestomach of rats and mice. They were unable to induce these changes using 2% dietary

p-cresol or phenol, however. Earlier studies by Ito *et al.* (1983) demonstrated that 2% dietary BHA is carcinogenic in the forestomach of F344/N rats.

Others have demonstrated that the cresols can promote proliferative reactions in the skin of mice following initiation with the carcinogen 9,10-dimethyl-1,2-benzanthracene (DMBA). Boutwell and Bosch (1959) showed that mice receiving a single application of 0.3% DMBA followed by twice weekly applications (25 µl/application) of 20% phenol or cresol (*o*-, *m*-, or *p*-) for 12 weeks developed papillomas while DMBA initiated (only) controls did not. The present studies indicate that non-initiated tissues may respond to cresol exposures by a proliferative response. It is interesting that proliferative responses (hyperplasia) in mice also occurred at a more distal site in the respiratory tract (bronchiolar epithelium) after exposures to 30,000 ppm m/*p*-cresol. Tye and Stemmer (1967) showed that aerosols containing phenolic and polycyclic aromatic hydrocarbon fractions derived from coal tars increased the incidence of intrabronchial adenoma and metaplasia in mice compared to those exposed to a control aerosol.

The cresols have been reported to be hepatic and renal toxins (Deichmann and Keplinger, 1981; Plunkett, 1987; Ellenhorn and Barceloux, 1988). Annotated reports have indicated that humans and laboratory animals that ingest toxic doses of cresols develop inflammatory reactions and fatty degeneration of the liver and parenchymatous and hemorrhagic nephritis (NIOSH, 1978; Deichmann and Keplinger, 1981). A condition known as pigment nephropathy characterized by renal failure and hemoglobinuria often occurs in humans during cresol poisoning (Porter and Bennett, 1981). There were few indications in the present studies of hepatic or renal effects from the cresols with the exception of a mild increase in organ weight and an increase in serum bile acids. The reasons for these different findings are not known.

Exposure to cresols has also been associated with hemolysis, methemoglobinemia, and acute Heinz body anemia (Larcan *et al.*, 1974; Cote *et al.*, 1984). Hematologic analyses performed during the 13-week studies with *o*-cresol and *m/p*-cresol gave little evidence of this, although methemoglobin levels were not specifically determined.

Although the cresols are not generally thought to affect reproductive tissues, chemical mixtures composed of cresols and chemicals containing the cresol moiety may be reproductive toxicants. Women exposed to tricresol (a mixture of *o*-cresol, *m*-cresol, and *p*-cresol) in industry have been reported to develop an increased incidence of gynecological problems (Syrovadko and Malysheva, 1977). In the present studies, the pattern of microscopic changes seen in the female reproductive organs coupled with the evidence for a lengthening of the estrual cycle agrees with the results of Pashkova *et al.* (1973) and suggests that the cresols may be female reproductive toxicants. For this reason, *o*-cresol and *m/p*-cresol are being evaluated in continuous breeding reproductive studies by the NTP.

In summary, the various cresol isomers exhibited a generally similar spectrum of toxicities in these studies, with a few exceptions as noted previously. There was little evidence to suggest a significant increase in toxicity with longer exposures in the 13-week studies when compared to the effects seen with similar doses in the 28-day studies. Dietary concentrations of 3,000 ppm appeared to be minimal effect levels for endpoints such as changes in organ weight (primarily liver and kidney weights) and concentrations of 15,000 ppm and higher gave evidence of deficits in liver function. Histopathologic changes involving bone marrow hypocellularity, irritation to the gastrointestinal tract and nasal cavity, and atrophic changes in female reproductive organs were occasionally seen with dietary levels of 10,000 ppm, but were more commonly observed with concentrations of 30,000 ppm.

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APPENDIX A
REPRODUCTIVE TISSUE EVALUATIONS AND ESTRUS CYCLE CHARACTERIZATION

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REPRODUCTIVE TISSUE EVALUATIONS AND ESTRUS CYCLE CHARACTERIZATION

Determinations of sperm motility and concentration were performed for male F344/N rats and B6C3F$_1$ mice in the 13-week studies of *o*-cresol and *m/p*-cresol. The length of the estrus cycle and relative frequency of the cycle stages were determined for female F344/N rats and B6C3F$_1$ mice.

METHODS

Sperm motility: The right epididymis was isolated, dissected free from the testicle, separated from the proximal ductus deferens, and immediately weighed. Following removal from the epididymal body (corpus epididymis), the tail of the epididymis (cauda epididymis) was also weighed. Isolation of the epididymal tail for weighing was accomplished by separation at the junction of the tail and distal epididymal body and at the point where the tail becomes continuous with the ductus deferens. Tyrodes buffer (mice-80 μL) or test yolk (rats-80 μL) was applied to two prewarmed slides, and a small incision was made at the distal border of the epididymal tail. The sperm effluxing from the incision were dispersed in the buffer on the slides; coverslips were applied and each slide was then placed on a prewarmed microscope stage for viewing. When viewed, the numbers of motile and nonmotile spermatozoa were counted for five fields per slide; each of the fields selected contained 30 or fewer spermatozoa.

Sperm concentration: Following sperm motility estimates, each right epididymal tail was placed in physiologically buffered saline solution (0.9%). Tails were gently minced with razors and remained in the saline solution for 15 minutes. Remaining clumps of tissue were removed and the solution was gently mixed followed by heat-fixing at 65° C. Sperm counts were then performed microscopically with the aid of a hemacytometer.

Vaginal cytology: Beginning twelve days prior to sacrifice, the vaginal vaults of ten females of each species were lavaged (followed by aspiration) with physiological saline solution to obtain cytology samples for estrus-cycle stage determinations. The aspirated lavage fluid and cells were air-dried on frosted microscope slides. The prepared slides were stained with Toluidine Blue 0 and coverslips were applied for viewing. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial sheets were identified microscopically and used to ascertain the stages of the estrus cycle: diestrus, proestrus, estrus, and metestrus.

RESULTS

o-Cresol: In male rats, statistically significant effects were not observed for changes in reproductive tissue weights or spermatozoal characteristics (Table A1). Female rats exhibited a trend toward increased estrus cycle length with increased dose, although this was not statistically significant (Table A2). A significant, dose-related decrease in epididymal tail weights occurred in male mice at the high dose (Table A3). A statistically significant increase in the length of the estrus cycle occurred in female mice receiving the high dose (Table A4). Though body weight reductions in high-dose females contribute to longer estrus cycles, previous data suggest that weight loss alone is not responsible for increased cycle length (Morrissey *et al.*, 1988a). Estrus cycle lengthening occurred in females of both species in this study and suggests that further study may reveal possible effects of *o*-cresol on female reproductive function and fertility.

m/p-Cresol: A biologically insignificant decrease (4%) in mean sperm motility values occurred in male rats receiving the high dose (Table A5). Although this decrease occurred in high-dose males, it is

doubtful that any significant toxic change existed. In female rats, however, a dose-related increased estrus cycle length did occur in the 7,500 ppm and 30,000 ppm groups (Table A6). Because cycle length was increased at all doses, and at doses not showing corresponding effects in body weight, a toxic effect in female rats appears evident for the cresol mixture. This suggests that further study is warranted to examine and ascertain the effects of the mixture on reproductive function and fertility. In mice, there were no identifiable adverse reproductive effects in either sex. The apparent increase and statistical significance seen in sperm concentration at the high dose results from aberrantly low control group values; the normal range for sperm density in mice is 800 to 100 million spermatozoa per gram of cauda epididymis and technical error is likely. Studies in mice have shown that sperm motility is unaffected by weight loss up to 30% of the total body weight (Morrissey *et al.*, 1988b).

Table A1
Summary of Reproductive Tissue Evaluations in Male Rats in the 13-Week Feed Studies of *o*-Cresol

Study Parameters[a]	Number Animals	Body and Reproductive Tissue Weights and Spermatozoal Data for Control and Dosed Groups			
		0 ppm	1,880 ppm	7,500 ppm	30,000 ppm
Weights (g)					
Total body weight	10	392 ± 7	382 ± 7	383 ± 6	328 ± 6**
R. testicle	10	1.553 ± 0.031	1.530 ± 0.046	1.554 ± 0.021	1.487 ± 0.031
R. epididymis	10	0.480 ± 0.008	0.470 ± 0.011	0.480 ± 0.007	0.459 ± 0.011
R. epididymal tail	10	0.181 ± 0.006	0.191 ± 0.007	0.185 ± 0.006	0.186 ± 0.006
Spermatozoal measurements					
% motility	10	74 ± 1	75 ± 1	75 ± 2	73 ± 2
Concentration (10^6/g)	10	503.89 ± 30.30	463.15 ± 23.89	475.53 ± 28.16	498.43 ± 32.73

** Significantly different ($P \leq 0.01$) from the control group by Dunn's or Shirley's test
[a] Data presented as mean ± standard error

Table A2
Summary of Estrus Cycle Characterization in Female Rats in the 13-Week Feed Studies of *o*-Cresol

Study Parameters[a]	Number Animals	Vaginal Cytology Data for Control and Dosed Groups			
		0 ppm	1,880 ppm	7,500 ppm	30,000 ppm
Terminal body weight (g)[b]	10	211 ± 4	208 ± 4	206 ± 4	179 ± 3**
Estrus cycle length (days)[b]	10	4.9 ± 0.2	4.7 ± 0.2	5.1 ± 0.2[c]	5.3 ± 0.2[d]
Estrus stages as % of cycle					
% diestrus	10	40.0	35.7	32.9	41.4
% proestrus	10	14.3	17.1	20.0	18.6
% estrus	10	21.4	27.1	30.0	20.0
% metestrus	10	24.3	20.0	17.1	20.0

** Significantly different ($P \leq 0.01$) from the control group
[a] Terminal body weight data were analyzed for significance by Dunn's or Shirley's test; vaginal cytology data by multivariate analysis of variance (MANOVA).
[b] Data presented as mean ± standard error
[c] For 2/10 animals at 7,500 ppm, estrus cycle length exceeded 7 days.
[d] For 2/10 animals at 30,000 ppm, estrus cycle length was not determined or exceeded 7 days.

Table A3
Summary of Reproductive Tissue Evaluations in Male Mice in the 13-Week Feed Studies of *o*-Cresol

Study Parameters[a]	Number Animals	Body and Reproductive Tissue Weights and Spermatozoal Data for Control and Dosed Groups			
		0 ppm	1,250 ppm	5,000 ppm[b]	20,000 ppm
Weights (g)					
Total body weight	10	32.5 ± 0.8	31.9 ± 0.8	31.1 ± 0.7	27.7 ± 0.9**
R. testicle	10	0.117 ± 0.002	0.120 ± 0.004	0.116 ± 0.002	0.115 ± 0.003
R. epididymis	10	0.051 ± 0.001	0.051 ± 0.002	0.047 ± 0.001	0.048 ± 0.002
R. epididymal tail	10	0.018 ± 0.001	0.018 ± 0.001	0.016 ± 0.001	0.014 ± 0.001**
Spermatozoal measurements					
% motility	10	73 ± 1	74 ± 1	70 ± 2	71 ± 2
Concentration (10^6/g)	10	890.46 ± 61.27	828.69 ± 66.61	792.61 ± 85.46	950.17 ± 101.61

** Significantly different ($P \leq 0.01$) from the control group by Dunn's or Shirley's test
[a] Data presented as mean ± standard error
[b] Statistical evaluation not performed for reproductive tissues in this group

Table A4
Summary of Estrus Cycle Characterization in Female Mice in the 13-Week Feed Studies of *o*-Cresol

Study Parameters[a]	Number Animals	Vaginal Cytology Data for Control and Dosed Groups			
		0 ppm	1,250 ppm	5,000 ppm	20,000 ppm
Terminal body weight (g)[b]	10	26.9 ± 0.4	26.5 ± 0.7	26.1 ± 1.0	21.9 ± 0.3**
Estrus cycle length (days)[b]	10	4.2 ± 0.1	4.2 ± 0.1	4.1 ± 0.1	4.8 ± 0.2**
Estrus stages as % of cycle					
% diestrus	10	25.7	24.3	28.6	18.6
% procstrus	10	22.9	21.4	17.1	22.9
% estrus	10	28.6	31.4	32.9	35.7
% metestrus	10	22.9	22.9	21.4	22.9

** Significantly different ($P \leq 0.01$) from the control group
[a] Terminal body weight data were analyzed for significance by Dunn's or Shirley's test; vaginal cytology data by multivariate analysis of variance (MANOVA).
[b] Data presented as mean ± standard error

Table A5
Summary of Reproductive Tissue Evaluations in Male Rats in the 13-Week Feed Studies of *m/p*-Cresol

Study Parameters[a]	Number Animals	Body and Reproductive Tissue Weights and Spermatozoal Data for Control and Dosed Groups			
		0 ppm	1,880 ppm	7,500 ppm	30,000 ppm
Weights (g)					
Total body weight	10	368 ± 7	355 ± 6	366 ± 6	310 ± 6**
R. testicle	10	1.525 ± 0.014	1.500 ± 0.026	1.559 ± 0.034	1.531 ± 0.018
R. epididymis	10	0.480 ± 0.006	0.476 ± 0.014	0.464 ± 0.013	0.469 ± 0.008
R. epididymal tail	10	0.164 ± 0.005	0.161 ± 0.007	0.159 ± 0.007	0.170 ± 0.006
Spermatozoal measurements					
% motility	10	72 ± 1	70 ± 1	71 ± 1	68 ± 1**
Concentration (10^6/g)	10	543.96 ± 31.70	535.78 ± 27.03	540.36 ± 28.47	582.66 ± 37.60

** Significantly different (P≤0.01) from the control group by Dunn's or Shirley's test
[a] Data presented as mean ± standard error

Table A6
Summary of Estrus Cycle Characterization in Female Rats in the 13-Week Feed Studies of *m/p*-Cresol

Study Parameters[a]	Number Animals	Vaginal Cytology Data for Control and Dosed Groups			
		0 ppm	1,880 ppm	7,500 ppm	30,000 ppm
Terminal body weight (g)[b]	10	201 ± 3	200 ± 3	198 ± 2	175 ± 3**
Estrus cycle length (days)[b]	10	4.5 ± 0.2	4.7 ± 0.2	5.1 ± 0.2*	5.1 ± 0.2*[c]
Estrus stages as % of cycle					
% diestrus	10	38.6	35.7	32.9	47.1
% proestrus	10	17.1	18.6	20.0	18.6
% estrus	10	24.3	25.7	24.3	18.6
% metestrus	10	18.6	20.0	22.9	15.7
% uncertain diagnosis	10	1.4	0	0	0

* Significantly different (P≤0.05) from the control group
** P≤0.01
[a] Terminal body weight data were analyzed for significance by Dunn's or Shirley's test; vaginal cytology data by multivariate analysis of variance (MANOVA).
[b] Data presented as mean ± standard error
[c] For 2/10 females at 30,000 ppm, one showed length of estrus exceeding 7 days and one showed no cycle.

Table A7
Summary of Reproductive Tissue Evaluations in Male Mice in the 13-Week Feed Studies of *m/p*-Cresol

Study Parameters[a]	Number Animals	Body and Reproductive Tissue Weights and Spermatozoal Data for Control and Dosed Groups			
		0 ppm	625 ppm	2,500 ppm	10,000 ppm
Weights (g)					
Total body weight	10	31.4 ± 0.8	31.8 ± 0.7	31.8 ± 0.9	29.7 ± 0.4
R. testicle	10	0.115 ± 0.002	0.116 ± 0.002	0.116 ± 0.002	0.118 ± 0.003
R. epididymis	10	0.050 ± 0.002	0.049 ± 0.001	0.050 ± 0.003	0.047 ± 0.002
R. epididymal tail	10	0.018 ± 0.001	0.018 ± 0.001	0.018 ± 0.001	0.017 ± 0.001
Spermatozoal measurements					
% motility	10	52 ± 8	45 ± 8	27 ± 9	46 ± 8
Concentration (10^6/g)	10	391.13 ± 118.54	309.69 ± 95.12	486.84 ± 141.07	748.83 ± 104.63*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Data presented as mean ± standard error

Table A8
Summary of Estrus Cycle Characterization in Female Mice in the 13-Week Feed Studies of *m/p*-Cresol

Study Parameters[a]	Number Animals	Vaginal Cytology Data for Control and Dosed Groups			
		0 ppm	625 ppm	2,500 ppm	10,000 ppm
Terminal body weight (g)[b]	10	26.6 ± 0.6	26.2 ± 0.4	25.9 ± 0.6	25.0 ± 0.4*
Estrus cycle length (days)[b]	10	4.0 ± 0.0	3.9 ± 0.1	4.1 ± 0.1	4.0 ± 0.0[c]
Estrus stages as % of cycle					
% diestrus	10	27.1	20.0	20.0	31.4
% proestrus	10	24.3	18.6	24.3	15.7
% estrus	10	20.0	25.7	30.0	27.1
% metestrus	10	25.7	27.1	20.0	24.3
% uncertain diagnosis	9	2.9	8.6	5.7	1.5

* Significantly different ($P \leq 0.05$) from the control group
[a] Terminal body weight data were analyzed for significance by Dunn's or Shirley's test; vaginal cytology data by multivariate analysis of variance (MANOVA).
[b] Data presented as mean ± standard error
[c] For 1/10 animals at 10,000 ppm, length of estrus exceeded 7 days.

APPENDIX B
FEED AND COMPOUND CONSUMPTION IN THE 13-WEEK FEED STUDIES

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TABLE B1
Feed and Compound Consumption by Male Rats in the 13-Week Feed Studies of *o*-Cresol[a]

Week	0 ppm		1,800 ppm			3,750 ppm			7,500 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	17.0	153	16.2	151	202	16.3	157	391	15.4	148	781
2	18.1	197	17.6	193	171	18.1	200	339	17.1	188	683
3	18.0	225	17.9	222	151	18.3	229	300	17.5	215	613
4	18.1	251	18.4	252	137	18.5	258	269	17.4	238	549
5	17.9	274	18.8	276	128	18.4	281	245	17.1	259	495
6	18.9	290	18.8	290	122	17.9	293	229	18.2	277	494
7	17.5	293	14.8	268	104	17.5	293	224	18.6	291	480
8	19.0	313	19.1	302	119	18.9	319	222	19.1	305	469
9	18.0	323	18.5	314	110	19.1	332	216	18.6	317	440
10	18.7	342	17.5	339	97	18.7	350	201	18.7	335	418
11	19.0	362	19.4	352	103	18.9	365	195	19.8	350	424
12	20.0	378	19.5	367	100	19.3	379	191	20.4	366	418
13	19.7	388	19.2	377	96	19.3	383	189	18.4	377	366
14	20.1	384	19.6	377	98	20.0	394	190	21.3	379	421
Mean	18.5	291	18.1	285	126	18.4	295	247	18.2	282	510

TABLE B1
Feed and Compound Consumption by Male Rats in the 13-Week Feed Studies of *o*-Cresol (continued)

Week	0 ppm		15,000 ppm			30,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	17.0	153	13.8	148	1406	8.1	141	1713
2	18.1	197	17.2	184	1404	16.6	169	2933
3	18.0	225	17.4	211	1240	17.1	193	2662
4	18.1	251	17.6	238	1111	17.1	217	2363
5	17.9	274	17.7	260	1021	17.1	237	2166
6	18.9	290	18.9	277	1022	17.2	252	2044
7	17.5	293	18.5	286	969	17.4	259	2017
8	19.0	313	18.9	301	942	17.8	276	1934
9	18.0	323	17.7	306	867	17.1	285	1797
10	18.7	342	17.2	327	787	16.1	299	1617
11	19.0	362	19.1	343	834	17.9	310	1732
12	20.0	378	19.1	357	802	18.3	320	1716
13	19.7	388	19.9	366	816	18.2	326	1674
14	20.1	384	19.7	369	800	17.6	327	1615
Mean	18.5	291	17.9	277	1017	16.6	253	2028

[a] Feed consumption given in grams of feed consumed per animal per day

TABLE B2
Feed and Compound Consumption by Female Rats in the 13-Week Feed Studies of *o*-Cresol[a]

Week	0 ppm		1,800 ppm			3,750 ppm			7,500 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	12.4	125	11.9	122	183	12.0	123	367	11.3	121	699
2	12.7	144	12.0	138	163	12.7	142	335	11.9	137	649
3	12.2	155	11.5	150	144	11.9	154	288	11.7	149	589
4	12.5	171	12.1	162	140	12.7	166	288	11.9	160	558
5	12.6	177	12.1	170	134	12.1	174	260	11.8	168	527
6	12.3	177	11.8	176	126	11.6	178	244	12.0	173	520
7	11.1	182	11.2	179	117	11.2	182	231	11.3	178	477
8	12.2	192	12.4	187	124	12.2	190	240	11.7	185	475
9	11.9	198	11.5	192	113	12.1	195	233	11.5	188	459
10	12.1	203	11.4	196	110	11.3	201	210	10.9	193	423
11	12.2	209	11.6	204	107	11.9	206	218	11.3	198	427
12	12.0	212	11.7	208	106	12.1	212	214	12.1	204	444
13	11.4	212	11.7	211	104	11.5	213	202	11.5	204	422
14	13.7	204	13.0	203	121	13.4	206	245	13.7	200	514
Mean	12.1	181	11.8	177	129	11.9	180	256	11.6	174	513

TABLE B2
Feed and Compound Consumption by Female Rats in the 13-Week Feed Studies of *o*-Cresol (continued)

Week	0 ppm		15,000 ppm			30,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	12.4	125	10.7	122	1316	6.0	112	1608
2	12.7	144	12.5	139	1348	11.5	126	2751
3	12.2	155	11.6	151	1151	11.3	137	2473
4	12.5	171	11.8	159	1118	11.1	146	2280
5	12.6	177	11.5	166	1043	10.9	152	2153
6	12.3	177	11.6	170	1026	10.6	154	2076
7	11.1	182	11.0	174	951	10.5	159	1990
8	12.2	192	11.4	181	945	11.0	166	1978
9	11.9	198	11.1	182	919	10.4	168	1862
10	12.1	203	10.4	188	829	9.6	173	1667
11	12.2	209	11.3	190	891	10.2	175	1752
12	12.0	212	11.3	194	871	10.4	179	1749
13	11.4	212	11.3	198	858	10.4	181	1720
14	13.7	204	13.2	190	1040	12.1	174	2092
Mean	12.1	181	11.3	170	1021	10.3	156	2004

[a] Feed consumption given in grams of feed consumed per animal per day

TABLE B3
Feed and Compound Consumption by Male Rats in the 13-Week Feed Studies of *m/p*-Cresol[a]

Week	0 ppm		1,800 ppm			3,750 ppm			7,500 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	14.5	152	14.4	151	180	15.1	151	374	14.0	149	706
2	16.8	194	17.0	192	166	17.1	193	332	16.5	189	656
3	18.0	222	17.4	218	151	17.6	221	299	16.9	216	589
4	17.9	250	17.0	243	132	17.5	248	265	17.1	239	538
5	17.4	272	17.3	264	123	17.8	267	251	17.3	260	499
6	18.6	283	17.9	268	125	18.0	279	243	17.7	271	490
7	18.8	301	17.9	286	117	17.9	300	223	17.9	293	458
8	18.2	311	17.4	300	109	17.7	313	213	17.8	304	439
9	17.3	325	17.3	315	103	17.6	328	202	18.1	321	423
10	17.6	333	17.3	316	103	18.1	337	202	17.9	328	409
11	17.1	341	17.0	327	98	16.7	346	182	16.9	338	374
12	17.9	356	18.0	342	99	17.3	361	180	17.5	351	373
13	18.0	360	17.2	348	93	17.2	368	175	17.4	359	365
14	18.5	371	18.6	357	98	18.0	375	180	18.2	364	376
Mean	17.5	285	17.2	275	123	17.4	285	241	17.2	278	486

TABLE B3
Feed and Compound Consumption by Male Rats in the 13-Week Feed Studies of *m/p*-Cresol (continued)

Week	0 ppm		15,000 ppm			30,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	14.5	152	12.3	146	1268	6.1	137	1349
2	16.8	194	16.7	180	1387	15.4	161	2875
3	18.0	222	16.9	205	1236	16.4	182	2692
4	17.9	250	16.7	232	1081	16.0	205	2340
5	17.4	272	16.8	252	1000	16.1	226	2139
6	18.6	283	17.3	259	1003	16.3	238	2062
7	18.8	301	18.7	278	1006	17.0	250	2041
8	18.2	311	18.3	290	948	17.1	259	1983
9	17.3	325	17.4	305	854	16.7	271	1844
10	17.6	333	16.9	316	801	16.7	281	1779
11	17.1	341	16.7	324	775	16.7	289	1736
12	17.9	356	16.9	332	765	16.6	296	1679
13	18.0	360	17.0	338	756	16.8	302	1663
14	18.5	371	17.8	346	772	16.7	308	1625
Mean	17.5	285	16.8	266	991	15.7	238	2014

[a] Feed consumption given in grams of feed consumed per animal per day; dose given in mg compound (60% *m*-cresol/40% *p*-cresol) per kg body weight per day

TABLE B4
Feed and Compound Consumption by Female Rats in the 13-Week Feed Studies of *m/p*-Cresol[a]

Week	0 ppm		1,800 ppm			3,750 ppm			7,500 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	10.8	112	11.1	113	185	11.5	111	387	10.9	113	729
2	11.4	134	11.8	135	165	12.1	135	337	11.7	134	654
3	11.7	143	12.0	146	154	11.9	145	307	11.5	145	597
4	11.3	155	11.4	156	137	10.7	156	258	10.9	156	527
5	11.3	165	11.8	168	132	11.2	166	253	11.3	165	515
6	11.8	167	11.8	166	134	11.2	168	250	11.4	166	514
7	12.0	176	11.3	174	123	10.9	174	236	11.1	175	476
8	11.6	178	11.6	177	123	11.1	178	234	11.1	175	473
9	11.0	182	11.2	181	116	10.8	185	218	10.8	182	447
10	11.1	188	11.5	187	116	11.2	188	224	11.0	185	444
11	11.2	190	11.1	191	109	10.2	192	199	10.4	187	416
12	11.2	196	11.0	195	106	10.9	197	209	10.7	193	415
13	11.0	199	11.0	197	105	10.4	200	196	10.5	193	408
14	11.0	202	11.1	199	105	10.5	203	194	11.0	197	420
Mean	11.3	168	11.4	168	131	11.1	169	254	11.0	167	509

TABLE B4
Feed and Compound Consumption by Female Rats in the 13-Week Feed Studies of *m/p*-Cresol (continued)

Week	0 ppm		15,000 ppm			30,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	10.8	112	9.8	111	1316	5.2	106	1475
2	11.4	134	11.4	130	1307	10.8	120	2707
3	11.7	143	11.2	141	1195	11.0	125	2627
4	11.3	155	10.6	151	1053	10.6	138	2315
5	11.3	165	10.8	160	1009	10.6	149	2129
6	11.8	167	11.3	160	1056	10.8	150	2151
7	12.0	176	10.9	166	991	10.6	155	2047
8	11.6	178	11.3	170	995	11.1	160	2089
9	11.0	182	10.5	175	897	10.4	163	1914
10	11.1	188	10.7	178	907	10.5	167	1884
11	11.2	190	10.4	181	861	9.9	169	1769
12	11.2	196	11.0	186	892	10.2	173	1758
13	11.0	199	10.4	187	833	10.5	176	1788
14	11.0	202	10.6	191	830	10.4	177	1757
Mean	11.3	168	10.8	161	1024	10.2	150	2050

[a] Feed consumption given in grams of feed consumed per animal per day; dose given in mg compound (60% *m*-cresol/40% *p*-cresol) per kg body weight per day

TABLE B5
Feed and Compound Consumption by Male Mice in the 13-Week Feed Studies of *o*-Cresol[a]

Week	0 ppm		1,250 ppm			2,500 ppm			5,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	4.2	21.3	3.8	22.3	212	3.9	21.2	464	3.2	21.7	739
2	4.1	22.6	4.1	23.1	223	4.0	22.9	437	3.8	22.3	847
3	4.6	23.3	4.5	24.1	234	4.9	23.8	517	4.9	23.5	1036
4	4.2	24.5	4.1	25.0	203	4.2	24.6	427	4.5	24.2	929
5	4.3	25.7	4.4	25.7	213	4.0	25.0	405	3.9	24.8	782
6	4.3	26.4	4.5	26.4	211	4.3	26.0	413	4.1	25.1	820
7	4.1	26.8	4.3	26.9	201	4.3	27.1	397	4.1	25.9	791
8	4.2	28.3	4.2	28.0	187	4.0	27.5	365	3.8	26.0	737
9	4.3	29.7	4.2	28.9	180	4.2	28.6	365	3.9	27.6	706
10	4.2	29.2	4.1	29.2	175	3.9	28.9	333	3.8	27.8	685
11	4.4	29.8	4.6	29.7	192	4.2	29.3	359	4.3	27.8	770
12	4.5	30.5	4.5	30.1	185	4.4	29.6	373	4.4	28.6	773
13	4.4	31.6	4.4	30.9	177	4.3	30.8	347	4.2	29.7	709
Mean	4.3	26.9	4.3	26.9	199	4.2	27.0	400	4.1	26.0	794

TABLE B5
Feed and Compound Consumption by Male Mice in the 13-Week Feed Studies of *o*-Cresol (continued)

Week	0 ppm		10,000 ppm			20,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	4.2	21.3	2.9	21.7	1341	1.4	22.4	1223
2	4.1	22.6	3.7	22.5	1623	3.1	19.6	3185
3	4.6	23.3	3.5	22.9	1542	3.4	21.9	3140
4	4.2	24.5	3.5	23.8	1471	3.1	22.6	2755
5	4.3	25.7	3.9	24.6	1596	3.3	22.9	2887
6	4.3	26.4	3.8	25.8	1483	3.0	23.2	2578
7	4.1	26.8	4.0	26.1	1518	3.4	23.5	2877
8	4.2	28.3	3.5	26.6	1329	3.3	24.4	2685
9	4.3	29.7	3.9	28.9	1337	3.6	25.4	2812
10	4.2	29.2	3.8	28.2	1349	3.2	26.0	2469
11	4.4	29.8	4.2	28.8	1471	3.8	25.9	2900
12	4.5	30.5	4.5	29.8	1513	3.9	26.5	2963
13	4.4	31.6	4.3	30.8	1407	3.9	26.7	2928
Mean	4.3	26.9	3.8	26.2	1460	3.3	23.9	2723

[a] Feed consumption given in grams of feed consumed per animal per day

TABLE B6
Feed and Compound Consumption by Female Mice in the 13-Week Feed Studies of *o*-Cresol[a]

Week	0 ppm		1,250 ppm			2,500 ppm			5,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	4.8	17.1	3.6	16.7	270	3.4	17.3	486	3.3	16.6	985
2	5.1	18.9	3.9	18.2	266	3.9	19.1	514	3.8	18.3	1045
3	6.0	20.4	4.3	19.8	271	4.9	20.6	601	4.3	19.5	1091
4	4.8	21.0	4.9	20.6	297	4.8	21.4	555	4.5	20.7	1088
5	4.5	22.1	4.1	21.2	241	4.4	22.4	486	3.8	21.2	905
6	4.8	22.8	4.4	22.3	246	4.5	23.4	485	3.9	22.2	884
7	4.5	23.3	4.0	22.6	222	4.3	23.9	449	4.4	22.9	959
8	4.6	25.0	4.4	23.7	231	4.4	24.5	449	4.2	23.4	889
9	4.7	25.5	4.2	24.8	211	4.3	25.7	417	4.0	24.2	820
10	5.0	25.6	4.1	25.0	203	3.7	25.4	364	3.9	24.3	809
11	4.6	25.9	4.2	25.2	207	4.5	25.8	439	4.5	24.6	911
12	4.9	26.6	4.4	25.3	217	4.6	25.7	447	4.6	24.9	918
13	4.3	27.4	4.2	26.3	202	4.3	26.8	400	4.4	25.8	848
Mean	4.8	23.2	4.2	22.8	237	4.3	23.9	469	4.1	20.9	935

TABLE B6
Feed and Compound Consumption by Female Mice in the 13-Week Feed Studies of *o*-Cresol (continued)

Week	0 ppm		10,000 ppm			20,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	4.8	17.1	2.6	17.4	1491	1.4	16.8	1668
2	5.1	18.9	3.3	18.0	1851	3.0	15.3	3921
3	6.0	20.4	3.5	18.9	1840	3.3	17.0	3886
4	4.8	21.0	3.5	19.8	1779	2.7	17.8	3013
5	4.5	22.1	3.6	21.1	1705	3.1	18.4	3332
6	4.8	22.8	3.6	22.1	1617	2.8	18.3	3065
7	4.5	23.3	3.9	22.0	1760	3.1	18.8	3341
8	4.6	25.0	3.5	22.8	1546	3.1	19.9	3134
9	4.7	25.5	3.6	24.2	1472	3.2	20.5	3124
10	5.0	25.6	3.5	24.0	1449	3.1	21.2	2927
11	4.6	25.9	4.1	23.9	1729	3.5	21.3	3308
12	4.9	26.6	4.2	24.2	1730	3.7	21.8	3365
13	4.3	27.4	4.1	24.8	1644	3.9	21.7	3582
Mean	4.8	23.2	3.6	21.8	1663	3.1	19.4	3205

[a] Feed consumption given in grams of feed consumed per animal per day

TABLE B7
Feed and Compound Consumption by Male Mice in the 13-Week Feed Studies of *m/p*-Cresol[a]

Week	0 ppm		1,250 ppm			2,500 ppm			5,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	3.5	21.6	3.7	21.4	107	3.4	21.3	200	3.7	21.4	428
2	3.7	22.8	3.5	23.0	96	3.5	22.7	191	3.7	22.8	401
3	4.2	24.2	4.5	24.3	116	4.5	24.0	236	4.7	23.7	494
4	4.7	23.8	4.3	24.9	107	4.6	25.2	229	4.6	23.9	485
5	4.3	25.2	3.9	25.1	96	4.2	26.0	200	4.2	25.6	410
6	4.3	25.8	4.0	25.8	98	4.3	26.3	204	4.2	26.1	406
7	4.4	26.8	4.4	26.3	104	4.3	26.9	201	4.3	26.6	402
8	4.1	27.4	4.5	27.3	103	4.3	27.7	196	4.3	27.3	390
9	4.2	28.3	4.2	27.9	93	4.2	28.5	185	4.2	27.9	372
10	4.0	29.1	4.0	28.6	86	4.1	28.2	181	4.2	28.4	367
11	4.1	29.8	3.9	29.4	83	4.2	29.7	177	4.3	29.0	370
12	4.0	30.8	3.8	30.2	79	4.1	30.8	165	4.3	30.2	358
13	3.9	31.2	4.2	30.8	85	4.1	31.6	160	4.3	31.1	345
Mean	4.1	26.7	4.1	26.5	96	4.1	26.8	194	4.2	26.5	402

TABLE B7
Feed and Compound Consumption by Male Mice in the 13-Week Feed Studies of *m/p*-Cresol (continued)

Week	0 ppm		10,000 ppm			20,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	3.5	21.6	3.7	21.5	857	3.3	21.1	1540
2	3.7	22.8	3.7	23.3	791	3.4	22.2	1537
3	4.2	24.2	4.5	24.2	929	4.1	23.0	1776
4	4.7	23.8	4.4	23.9	921	3.9	23.0	1710
5	4.3	25.2	4.0	25.1	803	3.7	24.3	1541
6	4.3	25.8	4.2	26.1	799	3.7	24.7	1506
7	4.4	26.8	4.4	27.0	812	4.1	25.8	1577
8	4.1	27.4	4.1	27.0	765	4.2	26.3	1582
9	4.2	28.3	4.0	28.6	704	3.9	27.1	1451
10	4.0	29.1	3.9	28.4	691	3.8	26.7	1407
11	4.1	29.8	4.0	29.1	692	3.8	27.5	1385
12	4.0	30.8	3.9	29.9	654	3.6	28.5	1266
13	3.9	31.2	4.1	30.9	670	3.9	28.4	1388
Mean	4.1	26.7	4.1	26.5	776	3.8	25.3	1513

[a] Feed consumption given in grams of feed consumed per animal per day; dose given in mg compound (60% *m*-cresol/40% *p*-cresol) per kg body weight per day

TABLE B8
Feed and Compound Consumption by Female Mice in the 13-Week Feed Studies of *m/p*-Cresol[a]

Week	0 ppm		1,250 ppm			2,500 ppm			5,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	3.3	17.8	3.5	17.5	125	4.1	17.5	291	3.5	17.4	509
2	3.9	19.0	3.7	18.8	124	4.2	18.7	279	3.6	18.4	491
3	4.7	20.6	4.9	20.4	150	4.5	20.3	279	5.3	20.6	649
4	5.5	21.4	4.8	21.8	138	4.8	21.5	280	4.8	21.3	565
5	4.5	22.4	4.1	21.7	119	4.3	22.3	240	4.3	22.2	482
6	4.3	22.8	4.2	22.4	118	4.4	23.0	237	4.1	22.8	448
7	4.8	23.4	4.3	23.4	114	4.4	23.6	232	4.4	23.4	473
8	4.5	24.3	4.5	24.3	115	4.5	23.9	237	4.3	24.0	448
9	4.4	24.7	4.4	24.4	112	4.3	24.3	220	4.0	24.3	413
10	4.2	25.4	4.0	24.4	102	4.2	24.9	212	4.1	24.6	418
11	4.2	25.9	4.0	25.4	99	4.2	25.5	207	4.2	25.3	410
12	4.3	26.1	4.0	25.7	97	4.2	25.9	203	4.0	25.0	405
13	4.2	26.8	4.1	26.0	99	4.0	26.2	193	4.3	25.4	423
Mean	4.4	23.1	4.2	22.8	116	4.3	22.9	239	4.2	22.7	472

TABLE B8
Feed and Compound Consumption by Female Mice in the 13-Week Feed Studies of *m/p*-Cresol (continued)

Week	0 ppm		10,000 ppm			20,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	3.3	17.8	3.6	17.7	1010	3.1	17.2	1775
2	3.9	19.0	3.7	19.0	961	3.2	18.5	1708
3	4.7	20.6	4.8	20.7	1152	4.0	19.6	2055
4	5.5	21.4	4.4	21.4	1022	3.9	21.1	1845
5	4.5	22.4	4.2	22.3	939	3.8	21.9	1724
6	4.3	22.8	4.1	22.9	897	3.7	22.1	1664
7	4.8	23.4	4.4	23.7	927	4.0	22.8	1739
8	4.5	24.3	4.4	24.4	908	4.1	23.3	1745
9	4.4	24.7	4.3	24.4	879	3.9	23.9	1612
10	4.2	25.4	4.3	24.7	870	3.7	23.7	1573
11	4.2	25.9	4.0	25.2	801	3.7	24.0	1540
12	4.3	26.1	4.0	25.6	782	3.5	24.5	1430
13	4.2	26.8	4.4	25.7	849	4.0	25.0	1594
Mean	4.4	23.1	4.2	22.9	923	3.7	22.1	1693

[a] Feed consumption given in grams of feed consumed per animal per day; dose given in mg compound (60% *m*-cresol/40% *p*-cresol) per kg body weight per day

APPENDIX C
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

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TABLE C1
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 28-Day Feed Studies of *o*-Cresol[a]

Organ	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Male						
Necropsy body wt	247 ± 5	263 ± 8	254 ± 12	244 ± 6	252 ± 5	223 ± 8
Brain						
Absolute	1.87 ± 0.01	1.86 ± 0.02	1.82 ± 0.03	1.75 ± 0.05	1.83 ± 0.02	1.84 ± 0.04
Relative	7.57 ± 0.16	7.09 ± 0.17	7.19 ± 0.21	7.20 ± 0.20	7.29 ± 0.13	8.26 ± 0.25
R. Kidney						
Absolute	0.99 ± 0.02	1.09 ± 0.05	1.06 ± 0.05	1.02 ± 0.02	1.14 ± 0.01**	1.17 ± 0.07*
Relative	4.00 ± 0.01	4.12 ± 0.07	4.19 ± 0.08	4.20 ± 0.06*	4.53 ± 0.05**	5.24 ± 0.16**
Liver						
Absolute	10.89 ± 0.23	11.81 ± 0.48	11.52 ± 0.64	11.56 ± 0.39	13.62 ± 0.31**	14.26 ± 0.89**
Relative	44.1 ± 0.3	44.9 ± 0.7	45.3 ± 0.8	47.4 ± 0.6**	54.1 ± 0.7**	63.9 ± 2.5**
Female						
Necropsy body wt	161 ± 2	164 ± 4	157 ± 2	166 ± 6	155 ± 5	142 ± 4**
Brain						
Absolute	1.71 ± 0.03	1.73 ± 0.03	1.72 ± 0.03	1.71 ± 0.03	1.70 ± 0.05	1.65 ± 0.02
Relative	10.6 ± 0.1	10.6 ± 0.2	11.0 ± 0.1	10.4 ± 0.2	11.0 ± 0.2	11.7 ± 0.2**
R. Kidney						
Absolute	0.69 ± 0.02	0.70 ± 0.03	0.70 ± 0.02	0.68 ± 0.02	0.66 ± 0.03	0.68 ± 0.02
Relative	4.28 ± 0.09	4.28 ± 0.09	4.48 ± 0.06	4.08 ± 0.07	4.27 ± 0.09	4.79 ± 0.03
Liver						
Absolute	6.13 ± 0.14	6.24 ± 0.18	6.48 ± 0.20	6.71 ± 0.33	7.13 ± 0.24**	7.44 ± 0.11**
Relative	38.0 ± 0.8	38.1 ± 0.8	41.3 ± 1.1	40.5 ± 0.7	46.1 ± 0.7**	52.5 ± 1.3**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error), n=5 for all groups.

TABLE C2
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 28-Day Feed Studies of *m*-Cresol[a]

Organ	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Male						
Necropsy body wt	258 ± 7	262 ± 5	256 ± 6	264 ± 6	257 ± 5	222 ± 12*
Brain						
Absolute	1.83 ± 0.02	1.81 ± 0.03	1.82 ± 0.03	1.86 ± 0.03	1.83 ± 0.02	1.82 ± 0.04
Relative	7.13 ± 0.23	6.92 ± 0.13	7.12 ± 0.15	7.07 ± 0.08	7.14 ± 0.12	8.27 ± 0.26*
R. Kidney						
Absolute	1.12 ± 0.03	1.09 ± 0.03	1.11 ± 0.05	1.12 ± 0.03	1.19 ± 0.03	1.11 ± 0.05
Relative	4.36 ± 0.09	4.14 ± 0.08	4.31 ± 0.13	4.26 ± 0.04	4.64 ± 0.10	5.04 ± 0.10*
Liver						
Absolute	11.64 ± 0.53	11.66 ± 0.40	11.87 ± 0.33	12.55 ± 0.40	13.54 ± 0.36**	13.04 ± 0.79
Relative	45.0 ± 1.0	44.5 ± 1.0	46.3 ± 0.5	47.5 ± 0.8	52.8 ± 0.8**	58.8 ± 1.1**
Female						
Necropsy body wt	174 ± 3	160 ± 6	167 ± 2	166 ± 4	165 ± 3	146 ± 2**
Brain						
Absolute	1.80 ± 0.01	1.68 ± 0.05*	1.75 ± 0.03	1.74 ± 0.04	1.73 ± 0.01	1.70 ± 0.03*
Relative	10.3 ± 0.1	10.5 ± 0.2	10.5 ± 0.1	10.5 ± 0.2	10.5 ± 0.2	11.6 ± 0.2**
R. Kidney						
Absolute	0.75 ± 0.02	0.67 ± 0.02*	0.71 ± 0.01	0.71 ± 0.04	0.71 ± 0.02	0.73 ± 0.02
Relative	4.34 ± 0.08	4.20 ± 0.07	4.25 ± 0.06	4.27 ± 0.14	4.31 ± 0.03	5.00 ± 0.08*
Liver						
Absolute	7.11 ± 0.23	6.29 ± 0.24	6.90 ± 0.11	7.02 ± 0.17	7.55 ± 0.23	7.16 ± 0.09
Relative	40.9 ± 1.0	39.3 ± 0.4	41.5 ± 0.9	42.3 ± 0.9	45.7 ± 1.0*	49.0 ± 0.6**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error), n=5 for all groups.

TABLE C3
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 28-Day Feed Studies of *p*-Cresol[a]

Organ	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Male						
Necropsy body wt	255 ± 8	260 ± 4	260 ± 9	247 ± 11	245 ± 6	180 ± 8**
Brain						
Absolute	1.84 ± 0.02	1.84 ± 0.03	1.81 ± 0.03	1.79 ± 0.07	1.84 ± 0.02	1.73 ± 0.02*
Relative	7.22 ± 0.16	7.06 ± 0.08	6.99 ± 0.18	7.26 ± 0.24	7.55 ± 0.22	9.70 ± 0.37*
R. Kidney						
Absolute	1.09 ± 0.04	1.06 ± 0.03	1.07 ± 0.05	1.10 ± 0.07	1.18 ± 0.05	0.93 ± 0.05
Relative	4.27 ± 0.07	4.06 ± 0.08	4.12 ± 0.09	4.44 ± 0.12	4.79 ± 0.11*	5.20 ± 0.14**
Liver						
Absolute	11.14 ± 0.50	11.81 ± 0.24	11.68 ± 0.66	11.36 ± 0.63	12.31 ± 0.40	9.77 ± 0.47
Relative	43.7 ± 1.0	45.4 ± 0.6	44.9 ± 1.1	45.9 ± 0.5	50.3 ± 0.8**	54.4 ± 1.1**
R. Testis						
Absolute	1.32 ± 0.05	1.32 ± 0.04	1.29 ± 0.02	1.30 ± 0.08	1.34 ± 0.03	1.12 ± 0.07
Relative	5.17 ± 0.06	5.08 ± 0.14	4.96 ± 0.13	5.26 ± 0.16	5.48 ± 0.12	6.25 ± 0.25*
Female						
Necropsy body wt	161 ± 6	171 ± 6	173 ± 6	173 ± 2	154 ± 5	135 ± 2*
Brain						
Absolute	1.68 ± 0.02	1.72 ± 0.03	1.75 ± 0.02	1.73 ± 0.02	1.68 ± 0.04	1.65 ± 0.02
Relative	10.5 ± 0.3	10.1 ± 0.3	10.2 ± 0.4	10.0 ± 0.1	11.0 ± 0.2	12.2 ± 0.3*
R. Kidney						
Absolute	0.69 ± 0.03	0.72 ± 0.03	0.69 ± 0.02	0.74 ± 0.02	0.69 ± 0.02	0.64 ± 0.02
Relative	4.29 ± 0.06	4.22 ± 0.09	4.02 ± 0.03	4.30 ± 0.09	4.47 ± 0.07	4.74 ± 0.11*
Liver						
Absolute	6.34 ± 0.28	6.62 ± 0.27	6.69 ± 0.26	7.33 ± 0.10*	6.78 ± 0.33	6.59 ± 0.26
Relative	39.3 ± 0.8	38.8 ± 0.8	38.7 ± 0.7	42.4 ± 0.3*	44.1 ± 1.3*	48.7 ± 1.2**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error), n=5 for all groups.

TABLE C4
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 28-Day Feed Studies of *m/p*-Cresol[a]

Organ	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Male						
Necropsy body wt	265 ± 5	266 ± 10	256 ± 7	254 ± 9	256 ± 6	217 ± 8**
Brain						
Absolute	1.87 ± 0.02	1.89 ± 0.01	1.86 ± 0.04	1.83 ± 0.03	1.87 ± 0.03	1.81 ± 0.02
Relative	7.04 ± 0.09	7.14 ± 0.24	7.28 ± 0.20	7.26 ± 0.29	7.31 ± 0.09	8.42 ± 0.31**
R. Kidney						
Absolute	1.12 ± 0.03	1.10 ± 0.06	1.13 ± 0.12	1.11 ± 0.05	1.20 ± 0.02	1.19 ± 0.06
Relative	4.23 ± 0.06	4.13 ± 0.11	4.39 ± 0.37	4.36 ± 0.06	4.71 ± 0.03*	5.50 ± 0.09**
Liver						
Absolute	10.93 ± 0.14	11.54 ± 0.59	11.18 ± 0.65	11.40 ± 0.56	12.70 ± 0.35*	11.85 ± 0.61
Relative	41.3 ± 0.5	43.3 ± 1.0	43.5 ± 1.4	44.8 ± 0.8*	49.7 ± 0.8**	54.6 ± 1.0**
R. Testis						
Absolute	1.35 ± 0.03	1.34 ± 0.03	1.27 ± 0.05	1.32 ± 0.04	1.35 ± 0.02	1.28 ± 0.04
Relative	5.08 ± 0.05	5.03 ± 0.09	4.96 ± 0.11	5.19 ± 0.10	5.28 ± 0.08	5.89 ± 0.10**
Female						
Necropsy body wt	155 ± 7	157 ± 3	160 ± 4	159 ± 0	157 ± 3	146 ± 3
Brain						
Absolute	1.67 ± 0.02	1.71 ± 0.01	1.71 ± 0.02	1.69 ± 0.02	1.72 ± 0.02	1.68 ± 0.03
Relative	10.9 ± 0.4	10.9 ± 0.3	10.7 ± 0.2	10.7 ± 0.1	11.0 ± 0.2	11.5 ± 0.1
R. Kidney						
Absolute	0.66 ± 0.03	0.67 ± 0.02	0.68 ± 0.03	0.69 ± 0.01	0.72 ± 0.01*	0.73 ± 0.02*
Relative	4.23 ± 0.03	4.28 ± 0.09	4.25 ± 0.11	4.37 ± 0.08	4.60 ± 0.09*	4.96 ± 0.09**
Liver						
Absolute	5.92 ± 0.27	6.26 ± 0.11	6.58 ± 0.23*	6.35 ± 0.25	7.27 ± 0.08**	7.42 ± 0.18**
Relative	38.2 ± 0.2	39.8 ± 0.7	41.0 ± 1.1*	40.0 ± 1.5*	46.3 ± 0.5**	50.8 ± 1.2**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error), n=5 for all groups.

TABLE C5
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 28-Day Feed Studies of *o*-Cresol[a]

Organ	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Male						
n	5	5	5	5	5	3
Necropsy body wt	24.1 ± 0.5	24.1 ± 0.5	24.9 ± 0.4	25.2 ± 0.5	22.9 ± 0.6	17.3 ± 0.6*
Brain						
Absolute	0.471 ± 0.016	0.472 ± 0.004	0.463 ± 0.009	0.463 ± 0.006	0.460 ± 0.008	0.437 ± 0.006
Relative	19.6 ± 0.6	19.6 ± 0.3	18.6 ± 0.4	18.4 ± 0.3	20.1 ± 0.7	25.3 ± 1.0
R. Kidney						
Absolute	0.252 ± 0.015	0.249 ± 0.008	0.268 ± 0.005	0.285 ± 0.011	0.268 ± 0.008	0.193 ± 0.008
Relative	10.5 ± 0.7	10.3 ± 0.3	10.8 ± 0.3	11.3 ± 0.3	11.7 ± 0.2*	11.2 ± 0.4
Liver						
Absolute	1.139 ± 0.012	1.144 ± 0.021	1.238 ± 0.031	1.305 ± 0.052	1.282 ± 0.069	0.990 ± 0.043
Relative	47.4 ± 1.1	47.5 ± 0.7	49.7 ± 0.7	51.8 ± 1.3**	55.9 ± 1.9**	57.3 ± 2.3**
Female						
n	5	5	5	5	5	4
Necropsy body wt	22.3 ± 0.6	21.2 ± 0.4	21.4 ± 1.0	21.1 ± 0.7	21.4 ± 0.7	15.2 ± 0.3**
Brain						
Absolute	0.472 ± 0.011	0.458 ± 0.005	0.466 ± 0.006	0.469 ± 0.006	0.468 ± 0.006	0.439 ± 0.003*
Relative	21.2 ± 0.3	21.6 ± 0.4	21.9 ± 0.8	22.3 ± 0.5	21.9 ± 0.7	29.0 ± 0.4**
R. Kidney						
Absolute	0.190 ± 0.004	0.180 ± 0.004	0.186 ± 0.007	0.192 ± 0.011	0.199 ± 0.013	0.153 ± 0.003*
Relative	8.5 ± 0.2	8.5 ± 0.2	8.7 ± 0.2	9.1 ± 0.3	9.3 ± 0.3*	10.1 ± 0.1**
Liver						
Absolute	1.070 ± 0.011	1.089 ± 0.039	1.122 ± 0.063	1.187 ± 0.071	1.294 ± 0.078	0.894 ± 0.050
Relative	48.2 ± 1.2	51.4 ± 1.6	52.3 ± 1.1	56.1 ± 1.7**	60.2 ± 1.6**	59.0 ± 3.4**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE C6
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 28-Day Feed Studies of *m*-Cresol[a]

Organ	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Male						
n	4	5	5	5	5	3
Necropsy body wt	25.4 ± 0.7	25.5 ± 0.8	25.0 ± 0.4	25.7 ± 0.2	23.5 ± 0.7	20.4 ± 1.3**
Brain						
Absolute	0.455 ± 0.007	0.459 ± 0.006	0.465 ± 0.005	0.463 ± 0.005	0.442 ± 0.006	0.435 ± 0.008
Relative	17.9 ± 0.5	18.0 ± 0.4	18.6 ± 0.2	18.0 ± 0.3	18.9 ± 0.4	21.5 ± 1.3**
R. Kidney						
Absolute	0.250 ± 0.009	0.261 ± 0.015	0.254 ± 0.008	0.274 ± 0.001	0.242 ± 0.009	0.194 ± 0.022
Relative	9.8 ± 0.1	10.2 ± 0.4	10.2 ± 0.2	10.7 ± 0.1*	10.3 ± 0.1	9.5 ± 0.7
Liver						
Absolute	1.28 ± 0.05	1.27 ± 0.06	1.27 ± 0.02	1.36 ± 0.02	1.39 ± 0.08	1.27 ± 0.14
Relative	50.1 ± 0.9	49.6 ± 1.2	50.7 ± 0.5	53.0 ± 0.9*	58.8 ± 1.6**	61.7 ± 3.2**
Female						
n	5	5	5	5	4	3
Necropsy body wt	22.6 ± 1.1	22.9 ± 0.9	23.9 ± 0.6	23.0 ± 0.7	21.9 ± 0.8	17.6 ± 1.2*
Brain						
Absolute	0.460 ± 0.010	0.463 ± 0.011	0.468 ± 0.004	0.471 ± 0.004	0.466 ± 0.006	0.432 ± 0.004
Relative	20.6 ± 0.9	20.3 ± 0.4	19.7 ± 0.4	20.6 ± 0.6	21.3 ± 0.8	24.8 ± 1.6
R. Kidney						
Absolute	0.189 ± 0.010	0.196 ± 0.012	0.186 ± 0.006	0.201 ± 0.007	0.193 ± 0.007	0.164 ± 0.013
Relative	8.4 ± 0.2	8.6 ± 0.2	7.8 ± 0.1	8.7 ± 0.1	8.8 ± 0.1	9.3 ± 0.2*
Liver						
Absolute	1.158 ± 0.058	1.216 ± 0.041	1.338 ± 0.053	1.315 ± 0.032	1.333 ± 0.063	0.985 ± 0.064
Relative	51.3 ± 0.4	53.2 ± 0.7*	56.0 ± 1.1**	57.3 ± 1.1**	60.8 ± 1.1**	56.4 ± 4.3**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE C7
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 28-Day Feed Studies of *p*-Cresol[a]

Organ	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Male						
n	5	5	5	5	4	0
Necropsy body wt	26.3 ± 0.7	26.2 ± 0.6	26.8 ± 0.7	26.4 ± 0.3	21.8 ± 0.9*	–[b]
Brain						
Absolute	0.452 ± 0.008	0.455 ± 0.008	0.456 ± 0.007	0.452 ± 0.007	0.438 ± 0.011	–
Relative	17.2 ± 0.4	17.4 ± 0.4	17.1 ± 0.2	17.1 ± 0.3	20.1 ± 0.4	–
Heart						
Absolute	0.130 ± 0.005	0.138 ± 0.004	0.139 ± 0.004	0.138 ± 0.003	0.119 ± 0.006	–
Relative	4.9 ± 0.2	5.3 ± 0.1	5.2 ± 0.1	5.2 ± 0.1	5.5 ± 0.1**	–
R. Kidney						
Absolute	0.262 ± 0.014	0.279 ± 0.006	0.287 ± 0.009	0.290 ± 0.010	0.242 ± 0.010	–
Relative	9.9 ± 0.3	10.7 ± 0.2	10.7 ± 0.2	11.0 ± 0.3*	11.1 ± 0.4*	–
Liver						
Absolute	1.34 ± 0.06	1.30 ± 0.04	1.46 ± 0.02	1.45 ± 0.06	1.28 ± 0.05	–
Relative	50.7 ± 1.4	49.6 ± 0..07	54.5 ± 1.0	54.9 ± 2.5	58.5 ± 0.6**	–
Female						
n	5	5	5	5	5	0
Necropsy body wt	21.9 ± 0.4	22.7 ± 0.5	21.6 ± 0.3	21.4 ± 0.8	21.1 ± 0.3	–[b]
Brain						
Absolute	0.467 ± 0.005	0.458 ± 0.002	0.451 ± 0.004*	0.455 ± 0.005*	0.448 ± 0.008*	–
Relative	21.4 ± 0.2	20.2 ± 0.5	20.9 ± 0.4	21.4 ± 0.8	21.2 ± 0.2	–
Heart						
Absolute	0.132 ± 0.013	0.120 ± 0.002	0.121 ± 0.004	0.120 ± 0.004	0.120 ± 0.003	–
Relative	6.0 ± 0.5	5.3 ± 0.2	5.6 ± 0.1	5.6 ± 0.1	5.7 ± 0.2	–
R. Kidney						
Absolute	0.186 ± 0.007	0.192 ± 0.005	0.179 ± 0.006	0.192 ± 0.013	0.182 ± 0.006	–
Relative	8.5 ± 0.3	8.5 ± 0.2	8.3 ± 0.2	9.0 ± 0.4	8.7 ± 0.3	–
Liver						
Absolute	1.14 ± 0.03	1.20 ± 0.03	1.17 ± 0.04	1.18 ± 0.03	1.32 ± 0.02**	–
Relative	52.1 ± 0.7	52.8 ± 1.5	54.0 ± 1.3	55.4 ± 0.7*	62.5 ± 2.0**	–

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] No data reported due to 100% mortality in this dose group.

TABLE C8
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 28-Day Feed Studies of *m/p*-Cresol[a]

Organ	0 ppm	300 ppm	1,000 ppm	3,000 ppm	10,000 ppm	30,000 ppm
Male						
Necropsy body wt	27.2 ± 0.6	25.7 ± 1.0	26.1 ± 0.6	25.5 ± 0.7	24.7 ± 1.4	19.7 ± 0.7**
Brain						
Absolute	0.471 ± 0.003	0.464 ± 0.009	0.468 ± 0.009	0.453 ± 0.009	0.459 ± 0.013	0.440 ± 0.005*
Relative	17.3 ± 0.3	18.1 ± 0.5	17.9 ± 0.1	17.8 ± 0.2	18.8 ± 0.8	22.4 ± 0.7**
R. Kidney						
Absolute	0.291 ± 0.010	0.269 ± 0.011	0.280 ± 0.012	0.285 ± 0.012	0.284 ± 0.018	0.220 ± 0.007**
Relative	10.7 ± 0.4	10.4 ± 0.2	10.8 ± 0.5	11.1 ± 0.2	11.5 ± 0.1	11.1 ± 0.2
Liver						
Absolute	1.307 ± 0.039	1.285 ± 0.059	1.354 ± 0.033	1.400 ± 0.062	1.539 ± 0.109	1.332 ± 0.080
Relative	48.0 ± 0.8	49.9 ± 0.4	51.9 ± 1.5*	54.9 ± 2.4*	62.1 ± 1.0**	67.3 ± 2.5**
R. Testis						
Absolute	0.113 ± 0.003	0.117 ± 0.003	0.112 ± 0.007[b]	0.110 ± 0.005	0.108 ± 0.006	0.101 ± 0.003
Relative	4.2 ± 0.1	4.5 ± 0.1	4.3 ± 0.2[b]	4.3 ± 0.1	4.4 ± 0.1	5.1 ± 0.1**
Female						
Necropsy body wt	21.7 ± 0.7	21.0 ± 0.5	22.3 ± 0.5	21.9 ± 0.7	21.6 ± 0.3	17.0 ± 0.6*
Brain						
Absolute	0.455 ± 0.015	0.455 ± 0.005	0.461 ± 0.005	0.462 ± 0.012	0.462 ± 0.004	0.429 ± 0.011*
Relative	21.0 ± 0.4	21.7 ± 0.6	20.7 ± 0.4	21.1 ± 0.2	21.4 ± 0.3	25.3 ± 0.3**
R. Kidney						
Absolute	0.190 ± 0.006	0.175 ± 0.005	0.188 ± 0.006	0.194 ± 0.009	0.200 ± 0.007	0.162 ± 0.007
Relative	8.8 ± 0.2	8.3 ± 0.2	8.5 ± 0.2	8.8 ± 0.2	9.3 ± 0.3	9.6 ± 0.2*
Liver						
Absolute	1.152 ± 0.024	1.125 ± 0.032	1.212 ± 0.037	1.276 ± 0.022*	1.506 ± 0.027**	1.213 ± 0.047*
Relative	53.2 ± 1.3	53.5 ± 0.7	54.4 ± 1.3	58.3 ± 1.3*	69.7 ± 1.9**	71.5 ± 0.9**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Weights are given in grams; organ weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error), n=5 for all groups except where noted.
[b] n=4

TABLE C9
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Studies of *o*-Cresol[a]

Organ	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male						
Necropsy body wt	392 ± 7	382 ± 7	396 ± 4	383 ± 6	369 ± 5*	328 ± 6**
Brain						
Absolute	2.00 ± 0.02	1.99 ± 0.02	1.99 ± 0.02	2.03 ± 0.02	2.00 ± 0.02	2.01 ± 0.05
Relative	5.11 ± 0.07	5.22 ± 0.08	5.03 ± 0.07	5.30 ± 0.10	5.43 ± 0.09*	6.13 ± 0.11**
Heart						
Absolute	1.20 ± 0.03	1.23 ± 0.02	1.25 ± 0.03	1.18 ± 0.03	1.16 ± 0.03	1.06 ± 0.04*
Relative	3.06 ± 0.05	3.23 ± 0.08	3.15 ± 0.06	3.08 ± 0.05	3.13 ± 0.06	3.22 ± 0.07
R. Kidney						
Absolute	1.42 ± 0.03	1.34 ± 0.02	1.46 ± 0.03	1.44 ± 0.02	1.44 ± 0.03	1.39 ± 0.04
Relative	3.61 ± 0.04	3.52 ± 0.05	3.67 ± 0.05	3.76 ± 0.05	3.90 ± 0.06**	4.22 ± 0.09**
Liver						
Absolute	14.18 ± 0.26	14.10 ± 0.35	14.85 ± 0.27	15.49 ± 0.30**	15.58 ± 0.28**	14.25 ± 0.43
Relative	36.2 ± 0.6	36.9 ± 0.5	37.5 ± 0.5	40.4 ± 0.7**	42.2 ± 0.7**	43.4 ± 0.7**
Lungs						
Absolute	2.17 ± 0.11	2.02 ± 0.11	2.20 ± 0.08	2.08 ± 0.08	2.01 ± 0.12	1.65 ± 0.06**
Relative	5.54 ± 0.27	5.27 ± 0.25	5.56 ± 0.18	5.42 ± 0.20	5.44 ± 0.29	5.02 ± 0.15
R. Testis						
Absolute	1.55 ± 0.03	1.53 ± 0.05	1.60 ± 0.04	1.55 ± 0.02	1.51 ± 0.02	1.49 ± 0.03
Relative	3.96 ± 0.06	4.00 ± 0.08	4.03 ± 0.08	4.06 ± 0.08	4.10 ± 0.08	4.53 ± 0.05**
Thymus[b]						
Absolute	324.10 ± 13.12	306.30 ± 10.76	372.50 ± 18.87	320.20 ± 11.40	349.60 ± 15.59	303.00 ± 10.37
Relative	0.83 ± 0.04	0.80 ± 0.03	0.94 ± 0.05	0.84 ± 0.03	0.95 ± 0.04*	0.92 ± 0.03*
Female						
Necropsy body wt	211 ± 4	208 ± 4	212 ± 3	206 ± 4	197 ± 3*	179 ± 3**
Brain						
Absolute	1.81 ± 0.04	1.84 ± 0.01	1.86 ± 0.02	1.79 ± 0.02	1.81 ± 0.02	1.83 ± 0.02
Relative	8.61 ± 0.16	8.84 ± 0.14	8.77 ± 0.11	8.73 ± 0.16	9.18 ± 0.11**	10.24 ± 0.20**
Heart						
Absolute	0.75 ± 0.02	0.75 ± 0.02	0.77 ± 0.02	0.72 ± 0.03	0.73 ± 0.02	0.61 ± 0.04**
Relative	3.54 ± 0.08	3.61 ± 0.06	3.63 ± 0.10	3.48 ± 0.09	3.69 ± 0.09	3.41 ± 0.22
R. Kidney						
Absolute	0.79 ± 0.02	0.81 ± 0.02	0.81 ± 0.02	0.76 ± 0.01	0.78 ± 0.01	0.75 ± 0.03
Relative	3.76 ± 0.06	3.87 ± 0.06	3.81 ± 0.07	3.70 ± 0.06	3.95 ± 0.06*	4.20 ± 0.14**
Liver						
Absolute	6.46 ± 0.14	6.37 ± 0.16	6.78 ± 0.11	6.94 ± 0.14**	6.93 ± 0.27*	6.69 ± 0.18
Relative	30.6 ± 0.4	30.7 ± 0.8	32.0 ± 0.4	33.7 ± 0.6**	35.1 ± 1.2**	37.3 ± 0.5**
Lungs						
Absolute	1.26 ± 0.04	1.42 ± 0.12	1.23 ± 0.05	1.23 ± 0.06	1.17 ± 0.04	1.09 ± 0.05*
Relative	5.97 ± 0.16	6.83 ± 0.56	5.80 ± 0.23	5.94 ± 0.22	5.94 ± 0.24	6.07 ± 0.19
Thymus[b]						
Absolute	271.20 ± 10.43	255.10 ± 10.90	269.20 ± 11.56	271.10 ± 9.70	254.60 ± 8.94	230.20 ± 9.59**
Relative	1.29 ± 0.05	1.23 ± 0.06	1.27 ± 0.06	1.32 ± 0.04	1.29 ± 0.05	1.28 ± 0.04

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Weights are given in grams except where noted; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error), n=10 for all groups.
[b] Thymus weights are given in milligrams.

TABLE C10
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Studies of *m/p*-Cresol[a]

Organ	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male						
Necropsy body wt	368 ± 7	355 ± 6	376 ± 4	366 ± 6	348 ± 6	310 ± 6**
Brain						
Absolute	2.02 ± 0.01	2.03 ± 0.01	2.03 ± 0.01	2.02 ± 0.02	2.02 ± 0.02	1.99 ± 0.02
Relative	5.50 ± 0.10	5.75 ± 0.11	5.41 ± 0.07	5.54 ± 0.09	5.81 ± 0.11	6.42 ± 0.07**
Heart						
Absolute	1.16 ± 0.02	1.11 ± 0.01	1.14 ± 0.03	1.10 ± 0.02	1.06 ± 0.02**	0.99 ± 0.02**
Relative	3.15 ± 0.07	3.14 ± 0.06	3.04 ± 0.09	3.00 ± 0.04	3.05 ± 0.05	3.19 ± 0.07
R. Kidney						
Absolute	1.25 ± 0.03	1.25 ± 0.02	1.33 ± 0.02*	1.32 ± 0.03	1.38 ± 0.03**	1.31 ± 0.03*
Relative	3.38 ± 0.07	3.52 ± 0.04	3.55 ± 0.06	3.60 ± 0.05*	3.98 ± 0.08**	4.24 ± 0.07**
Liver						
Absolute	13.11 ± 0.39	12.83 ± 0.22	13.91 ± 0.20*	14.51 ± 0.51*	15.57 ± 0.29**	14.92 ± 0.29**
Relative	35.5 ± 0.5	36.2 ± 0.4	37.0 ± 0.6	39.6 ± 0.9**	44.7 ± 0.5**	48.2 ± 0.8**
Lungs						
Absolute	1.73 ± 0.09	1.62 ± 0.09	1.58 ± 0.04	1.55 ± 0.05	1.47 ± 0.04*	1.28 ± 0.04**
Relative	4.69 ± 0.17	4.60 ± 0.26	4.22 ± 0.14	4.23 ± 0.15	4.22 ± 0.14	4.13 ± 0.09*
R. Testis						
Absolute	1.52 ± 0.01[b]	1.50 ± 0.03	1.56 ± 0.02	1.56 ± 0.03	1.56 ± 0.02	1.53 ± 0.02
Relative	4.16 ± 0.07[b]	4.23 ± 0.05	4.15 ± 0.07	4.26 ± 0.08	4.48 ± 0.08*	4.95 ± 0.08**
Thymus						
Absolute	0.30 ± 0.02	0.29 ± 0.01	0.31 ± 0.01	0.28 ± 0.01	0.27 ± 0.01	0.25 ± 0.01*
Relative	0.80 ± 0.05	0.82 ± 0.04	0.84 ± 0.03	0.76 ± 0.03	0.78 ± 0.03	0.80 ± 0.02
Female						
Necropsy body wt	201 ± 3	200 ± 3	203 ± 3	198 ± 2	192 ± 2*	175 ± 3**
Brain						
Absolute	1.84 ± 0.03	1.87 ± 0.01	1.85 ± 0.02	1.89 ± 0.02	1.86 ± 0.02	1.82 ± 0.02
Relative	9.18 ± 0.15	9.40 ± 0.16	9.11 ± 0.16	9.51 ± 0.09	9.70 ± 0.10**	10.42 ± 0.19**
Heart						
Absolute	0.72 ± 0.02	0.68 ± 0.01	0.71 ± 0.01	0.72 ± 0.01	0.68 ± 0.02	0.64 ± 0.02**
Relative	3.57 ± 0.10	3.43 ± 0.08	3.48 ± 0.05	3.61 ± 0.07	3.54 ± 0.07	3.63 ± 0.07
R. Kidney						
Absolute	0.73 ± 0.02	0.73 ± 0.01	0.75 ± 0.02	0.73 ± 0.02	0.73 ± 0.01	0.73 ± 0.01
Relative	3.65 ± 0.05	3.63 ± 0.05	3.69 ± 0.08	3.70 ± 0.09	3.81 ± 0.05	4.18 ± 0.09**
Liver						
Absolute	6.12 ± 0.11	6.26 ± 0.10	6.23 ± 0.17	6.50 ± 0.09*	6.73 ± 0.10**	6.78 ± 0.08**
Relative	30.5 ± 0.4	31.4 ± 0.4	30.6 ± 0.7	32.8 ± 0.4**	35.0 ± 0.3**	38.7 ± 0.5**
Lungs						
Absolute	1.12 ± 0.03	1.12 ± 0.04	1.16 ± 0.03	1.10 ± 0.04	1.01 ± 0.02*	1.00 ± 0.03*
Relative	5.59 ± 0.17	5.60 ± 0.20	5.69 ± 0.16	5.51 ± 0.17	5.24 ± 0.13	5.73 ± 0.19
Thymus						
Absolute	0.24 ± 0.01	0.24 ± 0.01	0.23 ± 0.01	0.24 ± 0.01	0.23 ± 0.01	0.19 ± 0.01**
Relative	1.22 ± 0.05	1.21 ± 0.05	1.12 ± 0.03	1.21 ± 0.04	1.21 ± 0.06	1.09 ± 0.06

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error), n=10 for all groups except where noted.
[b] n=9

TABLE C11
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Studies of *o*-Cresol[a]

Organ	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Male						
Necropsy body wt	32.5 ± 0.8	31.9 ± 0.8	32.4 ± 1.2	31.1 ± 0.7	31.9 ± 0.9	27.7 ± 0.9**
Brain						
Absolute	0.463 ± 0.003	0.469 ± 0.005	0.466 ± 0.006	0.459 ± 0.004	0.456 ± 0.005	0.457 ± 0.004
Relative	14.3 ± 0.4	15.0 ± 0.4	14.5 ± 0.5	14.8 ± 0.4	14.3 ± 0.3	16.6 ± 0.5**
Heart						
Absolute	0.157 ± 0.005	0.177 ± 0.006	0.159 ± 0.004	0.168 ± 0.005	0.160 ± 0.004	0.142 ± 0.003
Relative	4.9 ± 0.2	5.5 ± 0.1**	4.9 ± 0.2	5.4 ± 0.2	5.0 ± 0.1	5.2 ± 0.1
R. Kidney						
Absolute	0.290 ± 0.006	0.303 ± 0.011	0.296 ± 0.007	0.296 ± 0.016	0.294 ± 0.008	0.264 ± 0.012
Relative	9.0 ± 0.3	9.5 ± 0.2	9.2 ± 0.2	9.5 ± 0.4	9.2 ± 0.3	9.6 ± 0.4
Liver						
Absolute	1.390 ± 0.031	1.471 ± 0.052	1.570 ± 0.060**	1.459 ± 0.061	1.623 ± 0.030**	1.474 ± 0.060*
Relative	42.9 ± 0.7	46.0 ± 0.8*	48.5 ± 1.0**	46.8 ± 1.6**	51.2 ± 1.6**	53.2 ± 1.8**
R. Testis						
Absolute	0.117 ± 0.002	0.120 ± 0.004	0.122 ± 0.003	0.116 ± 0.002	0.121 ± 0.004	0.115 ± 0.003
Relative	3.6 ± 0.1	3.8 ± 0.1	3.8 ± 0.1	3.7 ± 0.1	3.8 ± 0.1	4.2 ± 0.1**
Thymus[b]						
Absolute	43.40 ± 4.16	42.70 ± 3.41	44.30 ± 1.26	47.80 ± 2.44	44.60 ± 2.80	47.50 ± 3.58
Relative	1.3 ± 0.1	1.3 ± 0.1	1.4 ± 0.1	1.5 ± 0.1	1.4 ± 0.1	1.7 ± 0.2*
Female						
Necropsy body wt	26.9 ± 0.4	26.5 ± 0.7	27.3 ± 0.5	26.1 ± 1.0	25.3 ± 0.7	21.9 ± 0.3**
Brain						
Absolute	0.466 ± 0.009	0.471 ± 0.004	0.477 ± 0.004	0.483 ± 0.006	0.468 ± 0.007	0.450 ± 0.003*
Relative	17.3 ± 0.4	17.9 ± 0.4	17.5 ± 0.3	18.7 ± 0.6*	18.6 ± 0.5	20.6 ± 0.3**
Heart						
Absolute	0.142 ± 0.004	0.140 ± 0.006	0.136 ± 0.003	0.135 ± 0.005	0.133 ± 0.003	0.115 ± 0.005**
Relative	5.3 ± 0.2	5.3 ± 0.2	5.0 ± 0.1	5.2 ± 0.1	5.3 ± 0.1	5.3 ± 0.2
R. Kidney						
Absolute	0.196 ± 0.004	0.193 ± 0.007	0.210 ± 0.006	0.198 ± 0.007	0.193 ± 0.007	0.170 ± 0.004**
Relative	7.3 ± 0.1	7.3 ± 0.1	7.7 ± 0.2	7.6 ± 0.1	7.6 ± 0.1	7.8 ± 0.1*
Liver						
Absolute	1.290 ± 0.028	1.289 ± 0.040	1.336 ± 0.038	1.354 ± 0.045	1.362 ± 0.040	1.171 ± 0.017
Relative	47.9 ± 0.8	48.6 ± 0.4	48.9 ± 1.1	52.0 ± 1.1**	53.8 ± 1.1**	53.6 ± 1.0**
Lungs						
Absolute	0.184 ± 0.007	0.182 ± 0.006	0.184 ± 0.004	0.181 ± 0.006	0.173 ± 0.004	0.158 ± 0.004**
Relative	6.8 ± 0.2	6.9 ± 0.2	6.8 ± 0.1	7.0 ± 0.3	6.9 ± 0.2	7.2 ± 0.2
Thymus[b]						
Absolute	52.20 ± 4.44	53.80 ± 2.06	59.60 ± 2.86	58.10 ± 3.22	58.40 ± 2.59	54.80 ± 2.24
Relative	1.9 ± 0.2	2.0 ± 0.1	2.2 ± 0.1	2.2 ± 0.1	2.3 ± 0.1	2.5 ± 0.1**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Weights are given in grams except where noted; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error), n=10 for all groups.
[b] Weights are given in milligrams

APPENDIX D
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS IN THE 13-WEEK FEED STUDIES

TABLE D1 Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *o*-Cresol 108
TABLE D2 Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *m/p*-Cresol 114
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Table D1
Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *o*-Cresol[a]

Analysis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male						
Hematocrit (%)						
Day 5	38.0 ± 0.5	38.6 ± 0.4	38.8 ± 0.5	39.4 ± 0.5	39.7 ± 0.5*	41.2 ± 0.6**
Day 21	43.8 ± 1.5	46.0 ± 0.8	46.7 ± 0.4*	46.8 ± 0.4*	46.4 ± 0.4*	46.8 ± 0.3*
Day 43	44.6 ± 0.5	45.6 ± 0.5[b]	45.8 ± 0.3	45.8 ± 0.9	45.5 ± 0.6	45.9 ± 0.4
Day 90	47.6 ± 0.8	46.4 ± 0.7	48.2 ± 0.6[b]	45.8 ± 0.7	47.5 ± 0.5	46.6 ± 0.5
Hemoglobin (g/dL)						
Day 5	13.5 ± 0.1	13.6 ± 0.1	13.7 ± 0.1	13.9 ± 0.1*	13.9 ± 0.1*	14.6 ± 0.2**
Day 21	15.3 ± 0.5	15.8 ± 0.2	16.0 ± 0.2	16.1 ± 0.1	16.0 ± 0.2	16.3 ± 0.1**
Day 43	16.0 ± 0.1	16.3 ± 0.1[b]	16.2 ± 0.1	16.2 ± 0.3	16.3 ± 0.2	16.6 ± 0.1**
Day 90	15.9 ± 0.1	15.9 ± 0.3	15.9 ± 0.1[b]	15.8 ± 0.3	15.7 ± 0.1	15.8 ± 0.1
Red blood cell ($10^6/\mu L$)						
Day 5	6.28 ± 0.09	6.39 ± 0.10	6.43 ± 0.11	6.46 ± 0.10	6.64 ± 0.09**	6.89 ± 0.14**
Day 21	7.47 ± 0.25	7.75 ± 0.13	7.89 ± 0.08	7.81 ± 0.08	7.76 ± 0.07	7.78 ± 0.06
Day 43	8.30 ± 0.10	8.40 ± 0.11[b]	8.43 ± 0.08	8.38 ± 0.16	8.32 ± 0.10	8.24 ± 0.09
Day 90	9.31 ± 0.13	8.85 ± 0.18	9.20 ± 0.14[b]	9.00 ± 0.16	9.06 ± 0.09	8.88 ± 0.10*
Mean cell volume (fL)						
Day 5	60.6 ± 0.7	60.5 ± 0.9	60.3 ± 0.4	61.0 ± 0.7	59.8 ± 0.4	59.9 ± 0.8
Day 21	58.6 ± 0.3	59.3 ± 0.4	59.1 ± 0.3	59.9 ± 0.2**	59.8 ± 0.4**	60.1 ± 0.4**
Day 43	53.8 ± 0.2	54.3 ± 0.2[b]	54.4 ± 0.2	54.6 ± 0.2*	54.7 ± 0.3**	55.8 ± 0.3**
Day 90	51.1 ± 0.2	51.8 ± 0.4*	52.4 ± 0.3**[b]	50.9 ± 0.2	52.4 ± 0.2**	52.5 ± 0.2**
Mean cell hemoglobin (pg)						
Day 5	21.6 ± 0.2	21.3 ± 0.3	21.2 ± 0.2	21.6 ± 0.3	20.9 ± 0.2	21.2 ± 0.3
Day 21	20.5 ± 0.1	20.4 ± 0.2	20.3 ± 0.1	20.6 ± 0.1	20.6 ± 0.1	20.9 ± 0.1*
Day 43	19.3 ± 0.1	19.4 ± 0.2[b]	19.3 ± 0.1	19.4 ± 0.1	19.6 ± 0.1	20.1 ± 0.2**
Day 90	17.1 ± 0.2	17.8 ± 0.2**	17.3 ± 0.2*[b]	17.5 ± 0.2*	17.4 ± 0.1*	17.8 ± 0.1**
Mean cell hemoglobin concentration (g/dL)						
Day 5	35.6 ± 0.3	35.3 ± 0.2	35.2 ± 0.3	35.3 ± 0.4	35.0 ± 0.3	35.4 ± 0.2
Day 21	34.9 ± 0.2	34.4 ± 0.3*	34.3 ± 0.2	34.4 ± 0.2	34.5 ± 0.2	34.8 ± 0.1
Day 43	35.9 ± 0.2	35.7 ± 0.2[b]	35.4 ± 0.1	35.5 ± 0.2	35.9 ± 0.1	36.1 ± 0.2
Day 90	33.4 ± 0.3	34.3 ± 0.4	33.0 ± 0.2[b]	34.4 ± 0.4	33.2 ± 0.2	33.9 ± 0.2
Platelets ($10^3/\mu L$)						
Day 5	1,050 ± 19	1,023 ± 18	996 ± 9	1,023 ± 26	1,028 ± 16	1,176 ± 41*
Day 21	746 ± 26	811 ± 18*	772 ± 17	747 ± 15	806 ± 25	841 ± 13**
Day 43	703 ± 14	682 ± 12[b]	709 ± 8	679 ± 14	707 ± 14	728 ± 13
Day 90	596 ± 27	591 ± 33	596 ± 14[b]	594 ± 26	610 ± 5	631 ± 14
Reticulocytes ($10^3/\mu L$)						
Day 5	421 ± 26	435 ± 45	398 ± 38	398 ± 21	275 ± 21**	223 ± 23**
Day 21	108 ± 8	114 ± 11	106 ± 5	109 ± 7	107 ± 8	98 ± 7
Day 43	140 ± 9	115 ± 13[b]	121 ± 7	116 ± 11	124 ± 10	119 ± 8
Day 90	168 ± 8	193 ± 19[b]	211 ± 15[b]	161 ± 13	173 ± 15	153 ± 15

Table D1
Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *o*-Cresol (continued)

Analysis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male (continued)						
White blood cell ($10^3/\mu L$)						
Day 5	8.33 ± 0.23	8.64 ± 0.40	8.85 ± 0.54	9.04 ± 0.48	9.61 ± 0.43	10.92 ± 0.34**
Day 21	10.30 ± 0.66[b]	10.00 ± 0.33	9.04 ± 0.69	10.39 ± 0.58	10.99 ± 0.41	10.48 ± 0.43
Day 43	6.46 ± 0.39	5.79 ± 0.48[b]	6.38 ± 0.39	6.66 ± 0.53	6.06 ± 0.41	5.17 ± 0.31*
Day 90	8.51 ± 0.88	8.72 ± 1.06	9.28 ± 0.59[b]	7.49 ± 0.70	8.42 ± 0.66	8.73 ± 0.58
Segmented neutrophils ($10^3/\mu L$)						
Day 5	0.88 ± 0.08	0.87 ± 0.15	0.98 ± 0.09	1.08 ± 0.07	1.07 ± 0.13	1.02 ± 0.11
Day 21	1.18 ± 0.15[b]	0.89 ± 0.07	0.70 ± 0.06*	0.89 ± 0.16	1.14 ± 0.11	0.81 ± 0.07
Day 43	1.13 ± 0.11	1.13 ± 0.21[b]	1.00 ± 0.06	1.34 ± 0.13	1.25 ± 0.14	0.65 ± 0.06**
Day 90	1.01 ± 0.14	1.00 ± 0.16	1.22 ± 0.17[b]	0.88 ± 0.10	0.88 ± 0.17	1.26 ± 0.31
Lymphocytes ($10^3/\mu L$)						
Day 5	7.12 ± 0.27	7.30 ± 0.32	7.51 ± 0.47	7.62 ± 0.44	7.98 ± 0.36	9.48 ± 0.31**
Day 21	8.59 ± 0.53[b]	8.60 ± 0.31	7.90 ± 0.64	8.98 ± 0.53	9.26 ± 0.38	9.10 ± 0.39
Day 43	5.04 ± 0.28	4.39 ± 0.32[b]	5.12 ± 0.39	5.07 ± 0.44	4.51 ± 0.33	4.33 ± 0.25
Day 90	7.08 ± 0.72	7.33 ± 0.88	7.84 ± 0.50[b]	6.30 ± 0.58	7.26 ± 0.59	7.12 ± 0.38
Urea nitrogen (mg/dL)						
Day 5	18.8 ± 0.4	18.5 ± 0.5	18.1 ± 0.5	17.9 ± 0.4	18.1 ± 0.4	16.4 ± 0.6**
Day 21	20.0 ± 0.6	18.5 ± 0.7	19.2 ± 0.4	18.8 ± 0.6	18.9 ± 0.5	17.8 ± 0.6*
Day 43	21.6 ± 0.6[b]	21.2 ± 0.5	21.0 ± 0.5	21.4 ± 1.0	22.0 ± 0.7	18.2 ± 0.4**
Day 90	21.7 ± 0.8	21.8 ± 0.4	20.7 ± 0.9	21.7 ± 0.6	19.7 ± 0.4*	19.8 ± 0.4*
Creatinine (mg/dL)						
Day 5	0.63 ± 0.03	0.66 ± 0.02	0.66 ± 0.01	0.66 ± 0.01	0.67 ± 0.01	0.65 ± 0.01
Day 21	0.59 ± 0.02	0.59 ± 0.02	0.57 ± 0.01	0.59 ± 0.02	0.60 ± 0.01	0.56 ± 0.02
Day 43	0.56 ± 0.02[b]	0.60 ± 0.09	0.59 ± 0.05	0.63 ± 0.06	0.60 ± 0.04	0.50 ± 0.03
Day 90	0.84 ± 0.09	0.75 ± 0.05	0.78 ± 0.04[b]	0.77 ± 0.06	0.90 ± 0.08	0.77 ± 0.09
Alanine aminotransferase (IU/L)						
Day 5	36 ± 2	35 ± 1	37 ± 1	38 ± 1	46 ± 3**	41 ± 2**
Day 21	44 ± 2	42 ± 1	42 ± 3	42 ± 1	43 ± 1	40 ± 1
Day 43	45 ± 2	44 ± 2	44 ± 2	47 ± 4	48 ± 3	38 ± 2
Day 90	59 ± 5	70 ± 10	59 ± 6	55 ± 3	47 ± 2**	48 ± 2*[b]
Alkaline phosphatase (IU/L)						
Day 5	520 ± 12	520 ± 12	518 ± 17	533 ± 13	542 ± 20	487 ± 9
Day 21	421 ± 10	409 ± 12	401 ± 13	412 ± 9	425 ± 13	375 ± 13*
Day 43	299 ± 6	289 ± 9	293 ± 7	297 ± 6	317 ± 8	280 ± 7
Day 90	213 ± 6	220 ± 7	229 ± 7	222 ± 7	213 ± 5	215 ± 5
5′-Nucleotidase (IU/L)						
Day 5	18.8 ± 0.4	19.6 ± 0.5	19.3 ± 0.3	19.5 ± 0.5	19.4 ± 0.4	16.7 ± 0.3**
Day 21	18.0 ± 0.6	17.1 ± 0.4	17.5 ± 0.5	17.5 ± 0.6	17.9 ± 0.4	16.8 ± 0.7
Day 43	19.3 ± 0.7	20.3 ± 0.9	19.4 ± 0.4	19.9 ± 0.9	19.0 ± 1.1	18.0 ± 0.5
Day 90	22.1 ± 0.8	21.7 ± 0.4	22.0 ± 0.6	22.0 ± 0.6	22.0 ± 0.6	22.8 ± 1.2

Table D1
Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *o*-Cresol (continued)

Analysis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male (continued)						
Bile acids (μmol/L)						
Day 5	20.10 ± 5.25	18.90 ± 3.02	15.80 ± 3.48	15.60 ± 3.47	30.60 ± 6.18	62.10 ± 5.24**
Day 21	10.40 ± 1.73	13.50 ± 2.85	17.70 ± 3.64	11.90 ± 2.47	20.20 ± 4.76*	49.20 ± 9.32**
Day 43	7.40 ± 1.31	6.78 ± 0.78[b]	7.33 ± 0.62[b]	11.89 ± 2.77[b]	14.80 ± 4.21	26.30 ± 4.79**
Day 90	31.50 ± 9.90	17.78 ± 3.13[b]	35.33 ± 7.51[c]	18.30 ± 3.14	43.40 ± 6.91[d]	45.43 ± 4.85*[e]
Urine aspartate aminotransferase (IU/mL)						
Day 8	0.012 ± 0.001	0.012 ± 0.001[f]	0.013 ± 0.001[f]	0.018 ± 0.002[b]	0.015 ± 0.002[b]	0.012 ± 0.002[g]
Day 19	0.015 ± 0.001[b]	0.013 ± 0.001[b]	0.012 ± 0.002[f]	0.015 ± 0.002[b]	0.014 ± 0.001[b]	0.010 ± 0.001**[f]
Day 41	0.020 ± 0.001	0.017 ± 0.002[b]	0.019 ± 0.001	0.021 ± 0.002[h]	0.030 ± 0.002[g]	0.016 ± 0.002[f]
Day 90	0.021 ± 0.002	0.021 ± 0.002	0.017 ± 0.002[f]	0.020 ± 0.005[f]	0.015 ± 0.001*[b]	0.016 ± 0.001[b]
Urine N-acetyl β-glucose aminidase (IU/L)						
Day 8	16.73 ± 0.77	17.21 ± 0.72[f]	17.96 ± 1.31[f]	20.96 ± 0.95**[b]	19.67 ± 1.52*[b]	19.66 ± 1.08[f]
Day 19	14.96 ± 1.16[b]	12.02 ± 0.92[b]	11.41 ± 0.46[f]	10.89 ± 1.14*[b]	14.83 ± 1.12[b]	15.46 ± 1.02[f]
Day 41	17.86 ± 1.38	16.63 ± 1.46[b]	16.54 ± 1.14	21.47 ± 0.77[g]	25.73 ± 3.23*[e]	20.60 ± 2.12[f]
Day 90	18.80 ± 1.17	18.28 ± 1.42	18.06 ± 2.22[b]	15.39 ± 2.27[f]	16.28 ± 1.12[b]	21.82 ± 1.59[b]
Urine volume (mL/16 h)						
Day 8	3.30 ± 0.35[b]	3.20 ± 0.30[f]	3.15 ± 0.27[f]	2.27 ± 0.24*[b]	2.56 ± 0.36[b]	2.76 ± 0.30[f]
Day 19	3.96 ± 0.36[b]	4.30 ± 0.51[b]	4.58 ± 0.48[f]	4.08 ± 0.50[b]	3.22 ± 0.28[b]	3.91 ± 0.24[f]
Day 41	3.26 ± 0.37	4.24 ± 0.36[b]	4.12 ± 0.30	2.96 ± 0.54[d]	3.26 ± 0.46[e]	3.27 ± 0.28[e]
Day 90	3.99 ± 0.29	4.64 ± 0.62	4.99 ± 0.46[b]	4.99 ± 0.73[f]	4.60 ± 0.48[b]	3.76 ± 0.32[b]
Specific gravity						
Day 8	1.042 ± 0.003	1.045 ± 0.003[f]	1.043 ± 0.003[f]	1.051 ± 0.003*[b]	1.047 ± 0.004[b]	1.049 ± 0.003[f]
Day 19	1.036 ± 0.002[b]	1.032 ± 0.002[b]	1.032 ± 0.001[f]	1.032 ± 0.002[b]	1.034 ± 0.001[b]	1.036 ± 0.002[f]
Day 41	1.047 ± 0.003	1.045 ± 0.002[b]	1.043 ± 0.003	1.052 ± 0.005[g]	1.054 ± 0.007[e]	1.037 ± 0.004[f]
Day 90	1.048 ± 0.003	1.047 ± 0.004	1.039 ± 0.002[b]	1.040 ± 0.005[f]	1.044 ± 0.003[b]	1.047 ± 0.004[b]
Female						
Hematocrit (%)						
Day 5	42.9 ± 0.6	42.7 ± 0.6	42.5 ± 0.6	42.2 ± 0.2	42.4 ± 0.6	44.7 ± 0.5
Day 21	47.2 ± 0.4	46.8 ± 0.6[b]	47.4 ± 0.4	46.7 ± 0.4	46.7 ± 0.3	45.9 ± 0.4
Day 43	47.4 ± 0.5	46.7 ± 0.7[b]	47.2 ± 0.6	46.0 ± 0.4	46.6 ± 0.4	46.5 ± 0.4
Day 90	47.0 ± 0.3	45.8 ± 0.7[b]	46.7 ± 0.8	47.7 ± 0.5	45.6 ± 1.4	45.0 ± 0.5
Hemoglobin (g/dL)						
Day 5	14.6 ± 0.2	14.4 ± 0.2	14.4 ± 0.2	14.3 ± 0.1	14.4 ± 0.2	15.6 ± 0.1**
Day 21	15.9 ± 0.2	15.6 ± 0.2[b]	15.9 ± 0.1	15.8 ± 0.1	15.7 ± 0.1	15.6 ± 0.1
Day 43	16.4 ± 0.2	16.1 ± 0.2[b]	16.3 ± 0.2	16.1 ± 0.1	16.2 ± 0.1	16.5 ± 0.1
Day 90	16.1 ± 0.1	15.7 ± 0.2[b]	16.0 ± 0.2	16.2 ± 0.2	15.7 ± 0.5	15.7 ± 0.2
Red blood cell (10^6/μL)						
Day 5	7.12 ± 0.15	6.97 ± 0.12	7.00 ± 0.12	6.92 ± 0.07	7.05 ± 0.12	7.45 ± 0.09
Day 21	7.68 ± 0.08	7.58 ± 0.10[b]	7.67 ± 0.05	7.60 ± 0.06	7.66 ± 0.05	7.59 ± 0.08
Day 43	8.46 ± 0.09	8.27 ± 0.13[b]	8.40 ± 0.12	8.19 ± 0.07	8.31 ± 0.08	8.36 ± 0.08
Day 90	8.58 ± 0.07	8.27 ± 0.13[b]	8.48 ± 0.15	8.61 ± 0.11	8.35 ± 0.24	8.18 ± 0.09*

Table D1
Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *o*-Cresol (continued)

Analysis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Female (continued)						
Mean cell volume (fL)						
Day 5	60.3 ± 0.5	61.3 ± 0.4	60.8 ± 0.4	61.0 ± 0.4	60.2 ± 0.3	59.0 ± 1.0
Day 21	61.6 ± 0.3	61.7 ± 0.3[b]	61.8 ± 0.2	61.5 ± 0.2	61.0 ± 0.3	60.5 ± 0.1**
Day 43	56.1 ± 0.2	56.5 ± 0.1[b]	56.2 ± 0.1	56.2 ± 0.1	56.1 ± 0.1	55.7 ± 0.2
Day 90	54.8 ± 0.2	55.4 ± 0.3[b]	55.0 ± 0.2	55.4 ± 0.2	54.7 ± 0.2	55.0 ± 0.2
Mean cell hemoglobin (pg)						
Day 5	20.5 ± 0.2	20.7 ± 0.1	20.6 ± 0.2	20.7 ± 0.2	20.4 ± 0.1	20.9 ± 0.1
Day 21	20.7 ± 0.1	20.6 ± 0.1[b]	20.7 ± 0.1	20.7 ± 0.1	20.5 ± 0.1	20.6 ± 0.1
Day 43	19.4 ± 0.1	19.5 ± 0.1[b]	19.5 ± 0.2	19.7 ± 0.1	19.5 ± 0.1	19.7 ± 0.1*
Day 90	18.8 ± 0.1	19.0 ± 0.1[b]	18.8 ± 0.1	18.9 ± 0.1	18.8 ± 0.1	19.2 ± 0.1**
Mean cell hemoglobin concentration (g/dL)						
Day 5	34.0 ± 0.1	33.8 ± 0.2	33.9 ± 0.2	33.9 ± 0.2	33.9 ± 0.2	34.9 ± 0.2**
Day 21	33.6 ± 0.1	33.4 ± 0.1[b]	33.5 ± 0.1[b]	33.7 ± 0.1	33.7 ± 0.1	34.0 ± 0.2*
Day 43	34.6 ± 0.1	34.5 ± 0.2[b]	34.6 ± 0.3	35.0 ± 0.2	34.8 ± 0.1	35.4 ± 0.1**
Day 90	34.2 ± 0.2	34.2 ± 0.2[b]	34.2 ± 0.3	34.0 ± 0.2	34.3 ± 0.1	35.0 ± 0.2*
Platelets ($10^3/\mu L$)						
Day 5	948 ± 24	934 ± 40	1,031 ± 20*	967 ± 29	932 ± 34	1,057 ± 19**
Day 21	739 ± 15	768 ± 19[b]	762 ± 16	740 ± 13	753 ± 16	842 ± 24**
Day 43	668 ± 11	668 ± 8[b]	670 ± 12	655 ± 9	681 ± 16	702 ± 15
Day 90	643 ± 15	607 ± 26[b]	608 ± 32	634 ± 18	604 ± 20	645 ± 17
Reticulocytes ($10^3/\mu L$)						
Day 5	144 ± 18	93 ± 8	126 ± 20	103 ± 14	131 ± 9	99 ± 6
Day 21	95 ± 5	104 ± 9[b]	100 ± 7	92 ± 10	93 ± 9	92 ± 7
Day 43	103 ± 8	105 ± 6[b]	98 ± 5	93 ± 4	92 ± 4	94 ± 5
Day 90	164 ± 10	143 ± 12[b]	150 ± 8	153 ± 9	152 ± 10	151 ± 10
White blood cell ($10^3/\mu L$)						
Day 5	9.97 ± 0.37	10.32 ± 0.32	10.81 ± 0.55	10.49 ± 0.36	9.65 ± 0.30	12.63 ± 0.34**
Day 21	10.13 ± 0.26	9.99 ± 0.34[b]	10.03 ± 0.35	9.34 ± 0.28	9.96 ± 0.23	10.29 ± 0.28
Day 43	6.68 ± 0.37	7.59 ± 0.35[b]	6.93 ± 0.28	7.08 ± 0.28	6.85 ± 0.30	8.16 ± 0.36**
Day 90	8.49 ± 0.73	8.93 ± 0.88[b]	7.82 ± 0.75	8.99 ± 0.60	9.13 ± 0.49	9.12 ± 0.75
Segmented neutrophils ($10^3/\mu L$)						
Day 5	1.20 ± 0.15	1.29 ± 0.16	1.16 ± 0.12	1.31 ± 0.07	0.95 ± 0.11	1.56 ± 0.14
Day 21	0.80 ± 0.11	0.83 ± 0.09[b]	0.73 ± 0.10	0.78 ± 0.13	0.72 ± 0.11	0.92 ± 0.07
Day 43	0.91 ± 0.15	1.43 ± 0.14*[b]	1.18 ± 0.12	0.98 ± 0.14	0.92 ± 0.09	0.98 ± 0.15
Day 90	1.23 ± 0.15	1.03 ± 0.25[b]	1.14 ± 0.22	1.23 ± 0.19	1.40 ± 0.36	0.92 ± 0.11
Lymphocytes ($10^3/\mu L$)						
Day 5	8.25 ± 0.33	8.56 ± 0.22	9.14 ± 0.45	8.61 ± 0.34	8.17 ± 0.28	10.46 ± 0.31**
Day 21	9.04 ± 0.27	8.82 ± 0.29[b]	8.83 ± 0.39	8.14 ± 0.21	8.85 ± 0.23	9.07 ± 0.28
Day 43	5.47 ± 0.27	5.88 ± 0.30[b]	5.37 ± 0.20	5.78 ± 0.17	5.61 ± 0.29	6.79 ± 0.33*
Day 90	6.89 ± 0.62	7.52 ± 0.62[b]	6.50 ± 0.56	7.50 ± 0.48	7.47 ± 0.52	7.96 ± 0.66

Table D1
Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *o*-Cresol (continued)

Analysis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Female (continued)						
Urea nitrogen (mg/dL)						
Day 5	21.5 ± 0.7	20.7 ± 0.6	20.1 ± 0.6	20.1 ± 0.4	19.9 ± 0.4	19.3 ± 0.6*
Day 21	22.7 ± 0.9	21.9 ± 0.9[b]	21.3 ± 0.8	23.8 ± 0.7	21.9 ± 0.6	22.7 ± 0.6
Day 43	21.4 ± 0.4	19.8 ± 0.5[b]	20.5 ± 0.6	21.4 ± 0.5	20.2 ± 0.5	21.0 ± 0.8
Day 90	18.4 ± 0.4	18.0 ± 0.7	18.5 ± 0.4	16.9 ± 0.5	18.6 ± 0.7	18.3 ± 0.6
Creatinine (mg/dL)						
Day 5	0.69 ± 0.02	0.60 ± 0.03**	0.66 ± 0.01	0.65 ± 0.02	0.66 ± 0.02	0.64 ± 0.01
Day 21	0.63 ± 0.01	0.60 ± 0.01[b]	0.62 ± 0.01	0.65 ± 0.01	0.61 ± 0.02	0.58 ± 0.01*
Day 43	0.51 ± 0.02	0.53 ± 0.02[b]	0.51 ± 0.01	0.56 ± 0.03	0.52 ± 0.03	0.51 ± 0.02
Day 90	0.49 ± 0.04	0.51 ± 0.05	0.45 ± 0.04	0.53 ± 0.05	0.46 ± 0.05	0.42 ± 0.03[b]
Alanine aminotransferase (IU/L)						
Day 5	32 ± 1	30 ± 1	30 ± 1	30 ± 1	33 ± 1	39 ± 2*
Day 21	33 ± 1	32 ± 2[b]	34 ± 2	35 ± 1	34 ± 1	36 ± 1
Day 43	36 ± 1	35 ± 1[b]	35 ± 2	37 ± 1	42 ± 2	39 ± 2
Day 90	47 ± 2	45 ± 3	43 ± 4	46 ± 3	49 ± 1	46 ± 1
Alkaline phosphatase (IU/L)						
Day 5	404 ± 14	410 ± 14	429 ± 10	388 ± 12	418 ± 22	417 ± 11
Day 21	343 ± 12	341 ± 10[b]	348 ± 12	339 ± 8	329 ± 14	340 ± 8
Day 43	237 ± 7	239 ± 8[b]	236 ± 9	238 ± 7	232 ± 5	264 ± 7*
Day 90	150 ± 10	149 ± 10	161 ± 8	155 ± 10	152 ± 5	180 ± 11
5′-Nucleotidase (IU/L)						
Day 5	24.7 ± 0.5	24.5 ± 0.6	22.9 ± 0.8	21.8 ± 0.4**	21.4 ± 0.6**	20.1 ± 0.5**
Day 21	21.7 ± 0.6	21.2 ± 0.6[b]	20.4 ± 0.4	20.8 ± 0.3	20.2 ± 0.4	17.6 ± 0.4**
Day 43	22.8 ± 0.7	21.0 ± 0.9[b]	19.3 ± 0.8**	20.7 ± 0.8*	20.2 ± 0.9*	19.6 ± 0.7**
Day 90	28.3 ± 0.7	28.3 ± 0.9[b]	27.0 ± 0.7	28.4 ± 0.7[b]	25.8 ± 0.8*	25.1 ± 0.9*[b]
Bile acids (μmol/L)						
Day 5	18.30 ± 2.56	18.10 ± 4.44	23.50 ± 3.27	18.70 ± 1.88	32.40 ± 3.05**	54.80 ± 8.13**
Day 21	12.17 ± 2.74[g]	18.14 ± 5.00[e]	11.17 ± 2.04[g]	15.78 ± 2.19[b]	31.86 ± 4.77*[e]	43.67 ± 19.10*[c]
Day 43	14.90 ± 2.37	18.78 ± 2.95[b]	14.90 ± 1.99	31.20 ± 6.33*	32.60 ± 5.43**	56.30 ± 4.56**
Day 90	15.38 ± 5.51[f]	15.75 ± 6.08[f]	20.50 ± 5.04	17.63 ± 2.21[f]	41.30 ± 7.21*	31.10 ± 4.70*
Urine aspartate aminotransferase (IU/mL)						
Day 8	0.011 ± 0.001[d]	0.014 ± 0.002[b]	0.019 ± 0.006[b]	0.009 ± 0.001[e]	0.016 ± 0.006[f]	0.036 ± 0.011[e]
Day 19	0.015 ± 0.002[e]	0.012 ± 0.001[f]	0.013 ± 0.002[c]	0.013 ± 0.002[d]	0.011 ± 0.001[f]	0.015 ± 0.004[f]
Day 41	0.016 ± 0.005[h]	0.038 ± 0.012[c]	0.015 ± 0.005[f]	0.024 ± 0.012[i]	0.017 ± 0.008[h]	0.008 ± 0.001[i]
Day 90	0.010 ± 0.001[b]	0.011 ± 0.001[b]	0.011 ± 0.002[e]	0.009 ± 0.001[f]	0.012 ± 0.002[b]	0.009 ± 0.001[b]
Urine N-acetyl β-glucose aminidase (IU/L)						
Day 8	10.81 ± 1.79[b]	11.22 ± 1.36[b]	9.81 ± 1.64	9.10 ± 1.14	10.41 ± 1.21	12.60 ± 1.33[b]
Day 19	9.63 ± 1.25	8.42 ± 1.27[b]	6.47 ± 1.08	7.33 ± 1.56	9.24 ± 1.21	9.55 ± 0.78
Day 41	16.91 ± 1.24	13.32 ± 3.33[b]	18.21 ± 0.99[b]	18.82 ± 1.97[f]	14.88 ± 1.01[b]	14.46 ± 1.26[b]
Day 90	11.76 ± 1.31[b]	11.04 ± 0.88[b]	10.87 ± 0.36[e]	11.67 ± 1.01[f]	12.63 ± 0.78[b]	14.20 ± 1.54[b]

Table D1
Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *o*-Cresol (continued)

Analysis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Female (continued)						
Urine volume (mL/16 h)						
Day 8	4.09 ± 0.76[b]	2.87 ± 0.34[b]	4.17 ± 0.53	3.90 ± 0.53	3.46 ± 0.45	2.80 ± 0.28[b]
Day 19	3.31 ± 0.47[b]	2.99 ± 0.78[b]	4.19 ± 0.52	4.79 ± 1.05[b]	2.68 ± 0.60	2.21 ± 0.25
Day 41	2.19 ± 0.17[b]	2.50 ± 0.57[b]	2.37 ± 0.35[b]	1.80 ± 0.37[f]	2.09 ± 0.31[b]	1.88 ± 0.18[b]
Day 90	2.94 ± 0.38[b]	3.39 ± 0.35[b]	3.69 ± 0.29[e]	3.25 ± 0.33[f]	2.67 ± 0.23[b]	2.84 ± 0.39[b]
Specific gravity						
Day 8	1.032 ± 0.003[b]	1.034 ± 0.002[b]	1.033 ± 0.003	1.031 ± 0.003	1.035 ± 0.003	1.039 ± 0.004[b]
Day 19	1.033 ± 0.004	1.034 ± 0.004[b]	1.025 ± 0.003	1.030 ± 0.005	1.036 ± 0.005	1.038 ± 0.004
Day 41	1.041 ± 0.003	1.030 ± 0.003[b]	1.041 ± 0.004[b]	1.048 ± 0.004[f]	1.041 ± 0.004[b]	1.043 ± 0.004[b]
Day 90	1.035 ± 0.004[b]	1.031 ± 0.001[b]	1.032 ± 0.001[e]	1.034 ± 0.003[f]	1.038 ± 0.002[b]	1.036 ± 0.003[b]

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error for groups of 10 animals, unless otherwise specified.
[b] n=9
[c] n=3
[d] n=5
[e] n=7
[f] n=8
[g] n=6
[h] n=4
[i] n=2

Table D2
Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *m/p*-Cresol[a]

Analysis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male						
Hematocrit (%)						
Day 5	41.7 ± 0.6	41.6 ± 0.7	41.0 ± 0.7	39.8 ± 1.3[b]	41.4 ± 0.8[b]	48.2 ± 1.3**
Day 21	45.1 ± 0.4	46.8 ± 0.5	46.0 ± 0.5	45.2 ± 0.4	45.6 ± 0.4	46.6 ± 0.3
Day 43	47.1 ± 0.4	48.5 ± 0.6	48.1 ± 0.5	47.6 ± 0.4	47.3 ± 0.6	47.5 ± 0.5
Day 90	45.8 ± 0.5	47.1 ± 0.3	45.2 ± 0.4	45.8 ± 0.6	45.6 ± 0.5	45.2 ± 0.5[b]
Hemoglobin (g/dL)						
Day 5	14.8 ± 0.1	14.8 ± 0.2	14.6 ± 0.2	14.3 ± 0.3[b]	14.6 ± 0.3[b]	16.7 ± 0.3**
Day 21	15.8 ± 0.1	16.2 ± 0.2	16.1 ± 0.1	15.7 ± 0.1	15.8 ± 0.1	16.3 ± 0.1
Day 43	16.3 ± 0.1	16.3 ± 0.1	16.4 ± 0.1	16.5 ± 0.1	16.3 ± 0.2	16.1 ± 0.1
Day 90	15.8 ± 0.2	16.2 ± 0.1	15.7 ± 0.1	15.8 ± 0.2	15.7 ± 0.1	15.6 ± 0.2[b]
Red blood cell ($10^6/\mu L$)						
Day 5	6.88 ± 0.11	6.85 ± 0.19	6.47 ± 0.24	6.28 ± 0.31[b]	6.78 ± 0.20[b]	8.20 ± 0.23**
Day 21	8.16 ± 0.08	8.44 ± 0.11	8.19 ± 0.11	8.01 ± 0.06	8.10 ± 0.10	8.51 ± 0.07*
Day 43	8.85 ± 0.07	9.00 ± 0.10	9.04 ± 0.10	8.95 ± 0.07	8.96 ± 0.09	8.78 ± 0.06
Day 90	8.93 ± 0.10	9.12 ± 0.09	8.84 ± 0.10	8.98 ± 0.15	9.00 ± 0.09	8.88 ± 0.11[b]
Mean cell hemoglobin (pg)						
Day 5	21.6 ± 0.2	21.7 ± 0.4	22.7 ± 0.5	23.0 ± 0.7[b]	21.6 ± 0.3[b]	20.5 ± 0.3
Day 21	19.3 ± 0.1	19.2 ± 0.2	19.7 ± 0.2	19.6 ± 0.1	19.6 ± 0.2	19.1 ± 0.1
Day 43	18.4 ± 0.1	18.1 ± 0.1	18.2 ± 0.1	18.4 ± 0.5	18.2 ± 0.4	18.4 ± 0.3
Day 90	17.7 ± 0.1	17.8 ± 0.1	17.8 ± 0.1	17.6 ± 0.1	17.4 ± 0.1	17.6 ± 0.1[b]
Platelets ($10^3/\mu L$)						
Day 5	1095 ± 31	1055 ± 50	1149 ± 50	1248 ± 69[b]	1208 ± 62[b]	1168 ± 42
Day 21	819 ± 11	811 ± 17	805 ± 13	810 ± 13	827 ± 15	910 ± 12**
Day 43	692 ± 7	683 ± 16	704 ± 7	733 ± 15	727 ± 10*	735 ± 13*
Day 90	634 ± 11	654 ± 8	629 ± 20	651 ± 18	643 ± 31	660 ± 10[b]
Reticulocytes ($10^3/\mu L$)						
Day 5	927 ± 366	428 ± 113	860 ± 203	1132 ± 177[b]	878 ± 219[b]	372 ± 164
Day 21	194 ± 13	187 ± 10	174 ± 6	182 ± 12	161 ± 11	193 ± 18
Day 43	131 ± 8	135 ± 10	129 ± 9	117 ± 6	127 ± 7	119 ± 10
Day 90	161 ± 10	161 ± 10	163 ± 13	176 ± 13	158 ± 12	151 ± 8[b]
White blood cell ($10^3/\mu L$)						
Day 5	7.67 ± 0.68	9.05 ± 1.12	20.45 ± 6.24	26.88 ± 10.36[b]	13.86 ± 3.74[b]	8.29 ± 0.44
Day 21	7.44 ± 0.45	8.54 ± 0.65	8.74 ± 0.51	8.53 ± 0.39	9.73 ± 0.48**	7.89 ± 0.48
Day 43	8.31 ± 0.66	9.72 ± 0.57	8.60 ± 0.62	9.20 ± 0.57	9.32 ± 0.48	8.68 ± 0.19
Day 90	7.41 ± 0.34	7.93 ± 0.60	8.46 ± 0.37	7.55 ± 0.53	7.90 ± 0.39	7.00 ± 0.53[b]
Lymphocytes ($10^3/\mu L$)						
Day 5	6.19 ± 0.56	7.79 ± 1.10	17.46 ± 5.64	8.74 ± 2.75[c]	11.79 ± 3.38[b]	7.19 ± 0.35
Day 21	6.11 ± 0.39	6.73 ± 0.51	7.03 ± 0.45	7.27 ± 0.45	8.27 ± 0.46*	6.25 ± 0.43
Day 43	6.69 ± 0.56	7.88 ± 0.49	7.05 ± 0.53	7.04 ± 0.37	7.20 ± 0.38	7.12 ± 0.18
Day 90	5.75 ± 0.31	6.39 ± 0.50	6.51 ± 0.24	5.80 ± 0.54	6.27 ± 0.40	5.49 ± 0.58[b]

Table D2
Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *m/p*-Cresol (continued)

Analysis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male (continued)						
Monocytes ($10^3/\mu L$)						
Day 5	0.05 ± 0.02	0.23 ± 0.05**	0.47 ± 0.20**	0.41 ± 0.17*[b]	0.20 ± 0.12*[b]	0.23 ± 0.04**
Day 21	0.17 ± 0.05	0.10 ± 0.02	0.23 ± 0.08	0.09 ± 0.05	0.12 ± 0.06	0.13 ± 0.04
Day 43	0.25 ± 0.05	0.30 ± 0.08	0.27 ± 0.04	0.38 ± 0.06	0.29 ± 0.06	0.22 ± 0.05
Day 90	0.26 ± 0.05	0.30 ± 0.04	0.47 ± 0.07	0.30 ± 0.05	0.36 ± 0.06	0.21 ± 0.05[b]
Eosinophils ($10^3/\mu L$)						
Day 5	0.03 ± 0.02	0.07 ± 0.02	0.03 ± 0.02	0.03 ± 0.02[c]	0.04 ± 0.02[c]	0.04 ± 0.02
Day 21	0.09 ± 0.02	0.09 ± 0.04	0.07 ± 0.03	0.05 ± 0.02	0.05 ± 0.02	0.06 ± 0.02
Day 43	0.09 ± 0.02	0.05 ± 0.02	0.06 ± 0.02	0.15 ± 0.03	0.05 ± 0.02	0.11 ± 0.03
Day 90	0.09 ± 0.02	0.01 ± 0.01*	0.09 ± 0.03	0.09 ± 0.02[b]	0.07 ± 0.02	0.09 ± 0.02[b]
Urea nitrogen (mg/dL)						
Day 5	18.5 ± 0.5	19.9 ± 0.6	20.1 ± 0.4	19.7 ± 0.4[b]	20.9 ± 0.8**	20.2 ± 0.5*[b]
Day 21	20.4 ± 0.8	19.3 ± 1.0	19.9 ± 0.8	20.4 ± 0.7	20.6 ± 0.6	20.0 ± 0.8
Day 43	23.1 ± 0.3	20.7 ± 0.7**	22.4 ± 0.3*	20.8 ± 0.5**	21.4 ± 0.6**	19.9 ± 0.4**
Day 90	24.0 ± 0.3	23.6 ± 0.4	22.9 ± 0.6	23.4 ± 0.6[b]	20.9 ± 0.5**	20.5 ± 0.7**
Alanine aminotransferase (IU/L)						
Day 5	37 ± 2	38 ± 2	37 ± 3	36 ± 2[b]	46 ± 3	55 ± 3**[b]
Day 21	38 ± 2	37 ± 1	34 ± 2	38 ± 3	39 ± 2	36 ± 2
Day 43	43 ± 2	40 ± 1	36 ± 2	38 ± 2	41 ± 2	39 ± 2
Day 90	49 ± 3	64 ± 6	60 ± 4[b]	54 ± 5[b]	70 ± 19[b]	44 ± 3
Alkaline phosphatase (IU/L)						
Day 5	404 ± 7	434 ± 17	435 ± 15	405 ± 16[b]	437 ± 20	366 ± 18[b]
Day 21	409 ± 6	417 ± 8	407 ± 8	395 ± 5	382 ± 8*	359 ± 5**
Day 43	312 ± 7	314 ± 8	306 ± 3	290 ± 9*	306 ± 5[b]	285 ± 7**
Day 90	193 ± 6	213 ± 9	205 ± 5	211 ± 7[b]	191 ± 3	177 ± 6
5′-Nucleotidase (IU/L)						
Day 5	17.8 ± 0.4	18.5 ± 1.2	20.5 ± 1.1	18.1 ± 0.7[b]	18.4 ± 0.8	15.0 ± 0.7*[b]
Day 21	18.2 ± 0.6	17.5 ± 0.4	16.6 ± 0.4*	16.1 ± 0.4**	16.0 ± 0.4**	14.8 ± 0.3**
Day 43	19.7 ± 0.5[b]	18.9 ± 0.4	19.4 ± 0.4	18.0 ± 0.4*	16.9 ± 0.5**	15.4 ± 0.3**
Day 90	19.8 ± 0.3	20.3 ± 0.6	21.6 ± 1.0	19.4 ± 0.4	20.9 ± 1.8	15.8 ± 0.4**
Sorbitol dehydrogenase (IU/L)						
Day 5	7 ± 1	9 ± 1	9 ± 1	11 ± 1*[b]	12 ± 1**	14 ± 1**[b]
Day 21	6 ± 1[b]	6 ± 1[b]	6 ± 0	8 ± 1	7 ± 1	7 ± 0
Day 43	7 ± 0	6 ± 1	6 ± 1	7 ± 0	8 ± 1	7 ± 1
Day 90	8 ± 1	12 ± 4	14 ± 3[b]	11 ± 2[b]	26 ± 11	9 ± 1
Bile acids ($\mu mol/L$)						
Day 5	12.44 ± 3.87[b]	11.00 ± 2.70	12.89 ± 2.00[b]	13.63 ± 1.95[c]	24.70 ± 5.26**	45.29 ± 9.21**[d]
Day 21	11.10 ± 2.25	14.20 ± 2.67	8.70 ± 1.86	15.90 ± 3.06	21.40 ± 4.86	55.40 ± 7.52**
Day 43	15.80 ± 3.07	10.10 ± 2.14	8.22 ± 1.29[b]	27.80 ± 6.48	29.30 ± 8.33	65.50 ± 8.55**
Day 90	9.63 ± 2.20[c]	6.00 ± 1.38[d]	31.80 ± 3.71**	8.20 ± 2.58[e]	42.70 ± 6.92**	33.67 ± 8.04**[f]

Table D2
Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *m/p*-Cresol (continued)

Analysis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Male (continued)						
Urine aspartate aminotransferase (IU/L)						
Day 8	11 ± 3[b]	9 ± 5[e]	9 ± 2[c]	14 ± 2[c]	9 ± 3	5 ± 2[b]
Day 19	15 ± 2[b]	23 ± 6[c]	12 ± 3[d]	18 ± 2[b]	16 ± 2[b]	10 ± 2[c]
Day 41	17 ± 3[b]	17 ± 2[c]	15 ± 1	25 ± 2**	33 ± 6**[b]	26 ± 7*[f]
Day 90	15 ± 1	14 ± 2	16 ± 1	20 ± 1**	27 ± 2**	27 ± 3**
Urine N-acetyl B-glucose aminidase (IU/L)						
Day 8	19.49 ± 1.30[b]	14.76 ± 1.38[e]	19.76 ± 1.47[b]	22.79 ± 0.91[c]	20.93 ± 2.02	16.88 ± 1.26[b]
Day 19	16.67 ± 1.09[b]	16.24 ± 1.13[c]	13.96 ± 0.72[d]	17.47 ± 0.74[b]	17.92 ± 0.79[b]	18.83 ± 0.84[b]
Day 41	14.93 ± 1.10[b]	14.72 ± 0.60[c]	16.51 ± 1.12	20.50 ± 1.22**	24.72 ± 3.41*[b]	29.35 ± 1.82**[f]
Day 90	13.58 ± 0.97	12.88 ± 1.05	14.10 ± 1.21	15.80 ± 1.69	22.43 ± 1.89**	27.31 ± 3.23**
Urine volume (mL/16 h)						
Day 8	2.07 ± 0.13[b]	3.20 ± 0.61[e]	2.79 ± 0.30[b]	2.09 ± 0.09[c]	2.04 ± 0.23[b]	2.76 ± 0.59[c]
Day 19	2.99 ± 0.20[b]	3.11 ± 0.41[c]	3.79 ± 0.32[d]	3.18 ± 0.24[b]	2.90 ± 0.35[b]	2.83 ± 0.20[b]
Day 41	3.56 ± 0.40[b]	3.49 ± 0.25[c]	3.60 ± 0.35	3.38 ± 0.23	2.89 ± 0.33[b]	2.13 ± 0.28**[f]
Day 90	6.05 ± 0.41	6.57 ± 0.57	5.21 ± 0.44	4.54 ± 0.40*	3.79 ± 0.43**	3.20 ± 0.42**[b]
Specific gravity						
Day 8	1.044 ± 0.003[b]	1.038 ± 0.003[e]	1.042 ± 0.004[b]	1.047 ± 0.002[c]	1.048 ± 0.005	1.041 ± 0.004[b]
Day 19	1.042 ± 0.002	1.044 ± 0.005[c]	1.034 ± 0.002[d]	1.039 ± 0.002	1.047 ± 0.005	1.042 ± 0.002
Day 41	1.041 ± 0.003[b]	1.040 ± 0.002[c]	1.045 ± 0.003	1.053 ± 0.002**	1.053 ± 0.005*[b]	1.054 ± 0.006*[f]
Day 90	1.032 ± 0.002	1.032 ± 0.002	1.035 ± 0.003	1.042 ± 0.003*	1.052 ± 0.003**	1.054 ± 0.005**
Female						
Hematocrit (%)						
Day 5	44.9 ± 0.6	44.3 ± 0.7	44.4 ± 0.5	44.4 ± 0.5	44.5 ± 0.7	46.2 ± 0.3*
Day 21	47.6 ± 0.3	47.7 ± 0.4	48.2 ± 0.5	47.6 ± 0.4	46.6 ± 0.3	49.6 ± 1.1
Day 43	47.6 ± 0.7	46.8 ± 0.4	47.7 ± 0.5	47.7 ± 0.6	45.7 ± 0.6*	45.7 ± 0.6*
Day 90	46.2 ± 0.5	46.4 ± 0.6	46.2 ± 0.3	45.4 ± 0.6	46.1 ± 0.5[b]	45.8 ± 0.5[c]
Hemoglobin (g/dL)						
Day 5	15.0 ± 0.2	15.1 ± 0.2	15.2 ± 0.1	15.2 ± 0.2	15.3 ± 0.2	16.2 ± 0.2**
Day 21	16.1 ± 0.1	16.2 ± 0.1	16.3 ± 0.2	16.1 ± 0.1	15.9 ± 0.1	16.9 ± 0.3
Day 43	16.2 ± 0.2	16.1 ± 0.1	16.3 ± 0.1	16.3 ± 0.1	16.0 ± 0.1	16.1 ± 0.1
Day 90	16.1 ± 0.1	16.0 ± 0.2	16.0 ± 0.1	15.7 ± 0.2	16.0 ± 0.1[b]	16.0 ± 0.1[c]
Red blood cell ($10^6/\mu L$)						
Day 5	7.23 ± 0.15	7.05 ± 0.19	7.24 ± 0.09	7.15 ± 0.12	7.35 ± 0.13	7.73 ± 0.07**
Day 21	8.23 ± 0.06	8.22 ± 0.08	8.37 ± 0.11	8.22 ± 0.06	8.18 ± 0.04	8.76 ± 0.14**
Day 43	8.67 ± 0.13	8.53 ± 0.09	8.72 ± 0.08	8.67 ± 0.11	8.47 ± 0.11	8.51 ± 0.11
Day 90	8.28 ± 0.09	8.36 ± 0.13	8.28 ± 0.04	8.16 ± 0.10	8.37 ± 0.10[b]	8.43 ± 0.11[c]
Mean cell volume (fL)						
Day 5	62.1 ± 0.7	63.1 ± 0.9	61.4 ± 0.4	62.2 ± 0.6	60.6 ± 0.4	59.8 ± 0.3**
Day 21	57.8 ± 0.2	58.1 ± 0.4	57.6 ± 0.3	57.9 ± 0.4	57.0 ± 0.2*	56.6 ± 0.5**
Day 43	54.8 ± 0.1	54.9 ± 0.2	54.8 ± 0.3	55.0 ± 0.3	53.9 ± 0.2**	53.7 ± 0.2**
Day 90	55.8 ± 0.1	55.5 ± 0.2	55.8 ± 0.2	55.6 ± 0.1	55.1 ± 0.1**[b]	54.3 ± 0.2**[c]

Table D2
Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *m/p*-Cresol (continued)

Analysis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Female (continued)						
Mean cell hemoglobin (pg)						
Day 5	20.8 ± 0.3	21.5 ± 0.4	21.0 ± 0.2	21.2 ± 0.3	20.9 ± 0.2	21.0 ± 0.2
Day 21	19.6 ± 0.1	19.8 ± 0.1	19.4 ± 0.1	19.6 ± 0.1	19.4 ± 0.1	19.2 ± 0.1*
Day 43	18.8 ± 0.1	18.9 ± 0.1	18.7 ± 0.1	18.8 ± 0.1	18.8 ± 0.1	18.9 ± 0.1
Day 90	19.4 ± 0.1	19.1 ± 0.2	19.3 ± 0.1	19.2 ± 0.1	19.2 ± 0.1[b]	19.1 ± 0.1*[c]
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.5 ± 0.3	34.1 ± 0.3	34.2 ± 0.3	34.1 ± 0.5	34.5 ± 0.3*	35.1 ± 0.3**
Day 21	33.9 ± 0.1	34.0 ± 0.2	33.7 ± 0.1	33.8 ± 0.1	34.0 ± 0.1	34.0 ± 0.3
Day 43	34.2 ± 0.2	34.5 ± 0.1	34.2 ± 0.2	34.1 ± 0.3	35.0 ± 0.3*	35.2 ± 0.3**
Day 90	34.8 ± 0.2	34.5 ± 0.2	34.7 ± 0.2	34.5 ± 0.2	34.8 ± 0.1[b]	35.0 ± 0.2[c]
Platelets ($10^3/\mu L$)						
Day 5	980 ± 31	976 ± 54	856 ± 30[b]	980 ± 57	928 ± 23	1,042 ± 55
Day 21	757 ± 14	767 ± 12	752 ± 16	813 ± 17*	829 ± 13**	847 ± 42*
Day 43	707 ± 14	723 ± 10	723 ± 17	721 ± 20	753 ± 19*	724 ± 20
Day 90	640 ± 25	658 ± 47	650 ± 29	686 ± 17	634 ± 37[b]	662 ± 50[c]
Reticulocytes ($10^3/\mu L$)						
Day 5	255 ± 52	241 ± 34[b]	189 ± 28	272 ± 60	132 ± 13*	123 ± 14**
Day 21	103 ± 7	103 ± 4	105 ± 6	102 ± 6	112 ± 7	103 ± 6
Day 43	127 ± 11	107 ± 4	127 ± 11	132 ± 11	114 ± 5	120 ± 8
Day 90	131 ± 6	131 ± 10	138 ± 11	129 ± 7	147 ± 10[b]	143 ± 12[c]
White blood cell ($10^3/\mu L$)						
Day 5	7.94 ± 0.46	8.71 ± 0.66	9.13 ± 0.66	7.75 ± 0.38	8.90 ± 0.52	8.70 ± 0.59
Day 21	7.68 ± 0.52	7.97 ± 0.31	7.51 ± 0.23	8.26 ± 0.49	8.38 ± 0.34	8.89 ± 0.69
Day 43	8.05 ± 0.39	8.87 ± 0.41	9.47 ± 0.59	8.88 ± 0.44	8.80 ± 0.45	8.60 ± 0.35
Day 90	8.13 ± 0.49	8.55 ± 0.47	8.93 ± 0.72	8.75 ± 0.57	7.62 ± 0.42[b]	7.93 ± 0.55[c]
Monocytes ($10^3/\mu L$)						
Day 5	0.12 ± 0.02[b]	0.32 ± 0.04*	0.24 ± 0.06	0.20 ± 0.04[b]	0.29 ± 0.06	0.22 ± 0.04
Day 21	0.26 ± 0.04	0.31 ± 0.05	0.26 ± 0.04	0.22 ± 0.04	0.27 ± 0.07	0.27 ± 0.06
Day 43	0.21 ± 0.05	0.21 ± 0.06	0.35 ± 0.09	0.33 ± 0.07	0.31 ± 0.06	0.22 ± 0.06
Day 90	0.33 ± 0.07	0.29 ± 0.06	0.28 ± 0.10	0.24 ± 0.04	0.27 ± 0.07[b]	0.11 ± 0.02*[c]
Eosinophils ($10^3/\mu L$)						
Day 5	0.03 ± 0.02	0.05 ± 0.02	0.06 ± 0.03	0.09 ± 0.03	0.04 ± 0.02	0.04 ± 0.02
Day 21	0.10 ± 0.02	0.06 ± 0.02	0.10 ± 0.02	0.12 ± 0.03	0.09 ± 0.02	0.12 ± 0.05
Day 43	0.09 ± 0.03	0.17 ± 0.04	0.15 ± 0.03	0.12 ± 0.03	0.13 ± 0.03	0.08 ± 0.02
Day 90	0.14 ± 0.03	0.10 ± 0.03	0.11 ± 0.03	0.09 ± 0.02	0.09 ± 0.03[b]	0.06 ± 0.02[c]
Urea nitrogen (mg/dL)						
Day 5	18.3 ± 0.7	19.3 ± 0.8	21.1 ± 1.1*	20.5 ± 1.0	22.1 ± 0.9**	21.2 ± 0.8**
Day 21	20.0 ± 0.8	21.6 ± 0.5	21.1 ± 0.7	21.4 ± 0.6	21.0 ± 0.7	20.8 ± 0.7
Day 43	22.8 ± 0.5	21.6 ± 0.5	20.4 ± 0.3**[b]	20.3 ± 0.7**	22.6 ± 0.6*	20.6 ± 0.7*
Day 90	19.4 ± 0.7	19.3 ± 0.5[b]	18.4 ± 0.5	19.6 ± 0.4	19.7 ± 0.7	19.0 ± 0.7[b]

Table D2
Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *m/p*-Cresol (continued)

Analysis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Female (continued)						
Alanine aminotransferase (IU/L)						
Day 5	31 ± 2	31 ± 2	33 ± 2	34 ± 2	38 ± 2*	42 ± 2**
Day 21	32 ± 2	28 ± 2	27 ± 2	29 ± 1	33 ± 2	40 ± 3
Day 43	37 ± 3	32 ± 2	32 ± 2	34 ± 2	39 ± 2	39 ± 2
Day 90	44 ± 2	46 ± 2[b]	43 ± 3	48 ± 3	47 ± 6	46 ± 1[c]
Alkaline phosphatase (IU/L)						
Day 5	391 ± 10	405 ± 15	413 ± 13	404 ± 19	394 ± 8	346 ± 14
Day 21	331 ± 11	342 ± 8	350 ± 7	321 ± 6	339 ± 11	259 ± 30
Day 43	277 ± 8	281 ± 7	279 ± 8	244 ± 11	271 ± 7	272 ± 9
Day 90	189 ± 8	184 ± 6[b]	176 ± 7	185 ± 6	179 ± 7	169 ± 7[b]
5′-Nucleotidase (IU/L)						
Day 5	23.6 ± 0.6	23.5 ± 0.6	23.1 ± 0.6	22.5 ± 0.8	20.4 ± 0.6**	17.1 ± 0.6**
Day 21	21.1 ± 0.5	21.0 ± 0.5	20.6 ± 0.6	18.5 ± 0.4**	18.4 ± 0.4**	14.7 ± 0.6**
Day 43	19.8 ± 0.7	19.9 ± 0.4	19.4 ± 0.5	18.1 ± 0.5*	17.1 ± 0.4**	15.3 ± 0.5**
Day 90	22.0 ± 0.5	21.3 ± 0.5[b]	19.8 ± 0.5**	20.5 ± 0.4**	18.2 ± 0.5**	15.7 ± 0.4**[b]
Sorbitol dehydrogenase (IU/L)						
Day 5	8 ± 0	10 ± 1	9 ± 1	8 ± 1	9 ± 0	11 ± 1
Day 21	8 ± 1	9 ± 1	8 ± 0	7 ± 1	6 ± 1	9 ± 1
Day 43	7 ± 1	9 ± 2	7 ± 1	8 ± 1	7 ± 1	10 ± 1
Day 90	8 ± 1	8 ± 1[b]	8 ± 1	8 ± 1	10 ± 2	10 ± 2[b]
Bile acids (μmol/L)						
Day 5	20.00 ± 4.71	42.50 ± 7.64	30.90 ± 6.17	27.80 ± 6.73	34.60 ± 8.05	42.30 ± 7.08
Day 21	12.30 ± 1.96	30.80 ± 4.12**	28.50 ± 4.75**	24.80 ± 3.35**	37.60 ± 4.89**	34.40 ± 6.04**
Day 43	19.90 ± 3.12	26.70 ± 4.56	26.30 ± 2.26	25.60 ± 3.68	46.40 ± 4.32**	57.30 ± 7.90**
Day 90	22.33 ± 4.11[b]	20.00 ± 4.53[b]	36.00 ± 7.44	35.50 ± 4.65	33.20 ± 5.53	52.33 ± 6.72**[b]
Urine aspartate aminotransferase (IU/L)						
Day 8	6 ± 2[b]	14 ± 5	19 ± 5	14 ± 4[b]	13 ± 3	4 ± 2[f]
Day 19	13 ± 4[d]	7 ± 1	9 ± 2[b]	6 ± 1[c]	16 ± 5	13 ± 6[d]
Day 41	11 ± 1[b]	9 ± 1[e]	6 ± 1**[b]	8 ± 1**[f]	7 ± 1**[b]	6 ± 1**[b]
Day 90	5 ± 1	2 ± 0[c]	4 ± 1[b]	5 ± 2[b]	7 ± 2	7 ± 2
Urine N-acetyl B-glucose aminidase (IU/L)						
Day 8	13.74 ± 1.15[b]	13.29 ± 0.54	14.08 ± 1.63	14.56 ± 1.27[b]	15.40 ± 2.01	14.40 ± 1.45[d]
Day 19	15.24 ± 1.40[d]	15.81 ± 1.12	14.28 ± 1.32[b]	12.81 ± 1.35[c]	15.68 ± 1.39	17.77 ± 1.26[d]
Day 41	13.54 ± 1.80[b]	14.22 ± 2.80[f]	8.13 ± 1.30[b]	11.44 ± 1.89[d]	10.94 ± 1.76[b]	17.36 ± 2.09
Day 90	15.01 ± 1.08	16.22 ± 2.73[b]	13.42 ± 1.42	13.63 ± 1.27[b]	16.37 ± 1.35	28.06 ± 3.95**
Urine volume (mL/16 h)						
Day 8	2.57 ± 0.36[b]	2.55 ± 0.23	2.50 ± 0.29	2.36 ± 0.18[b]	2.25 ± 0.38	2.77 ± 0.18[d]
Day 19	2.90 ± 0.54[d]	2.67 ± 0.24	3.13 ± 0.53[b]	2.79 ± 0.19[c]	2.22 ± 0.12[b]	2.41 ± 0.26[d]
Day 41	3.66 ± 0.39[b]	3.70 ± 0.45[f]	5.29 ± 0.70[c]	3.50 ± 0.52[d]	4.40 ± 0.66[b]	2.59 ± 0.39
Day 90	2.46 ± 0.25	2.58 ± 0.26[b]	3.10 ± 0.34	2.94 ± 0.29[b]	2.61 ± 0.41	2.20 ± 0.44

Table D2
Selected Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of *m/p*-Cresol (continued)

Analysis	0 ppm	1,880 ppm	3,750 ppm	7,500 ppm	15,000 ppm	30,000 ppm
Female (continued)						
Specific gravity						
Day 8	1.037 ± 0.003[b]	1.033 ± 0.001	1.035 ± 0.004	1.036 ± 0.003[b]	1.035 ± 0.004	1.036 ± 0.002[d]
Day 19	1.036 ± 0.005[d]	1.037 ± 0.003	1.033 ± 0.003[b]	1.031 ± 0.002[c]	1.033 ± 0.003	1.038 ± 0.004[d]
Day 41	1.031 ± 0.004[b]	1.029 ± 0.004[f]	1.022 ± 0.003[b]	1.025 ± 0.002[d]	1.024 ± 0.003[b]	1.032 ± 0.005
Day 90	1.035 ± 0.002	1.036 ± 0.004[b]	1.030 ± 0.002	1.031 ± 0.002[b]	1.035 ± 0.002	1.043 ± 0.006

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error for groups of 10 animals, unless otherwise specified.
[b] n=9
[c] n=8
[d] n=7
[e] n=5
[f] n=6

Table D3
Selected Hematology and Clinical Chemistry Data for Mice in the 13-Week Feed Studies of *o*-Cresol[a]

Analysis	0 ppm	1,200 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Male						
Hematocrit (%)						
Day 90	50.3 ± 0.5	50.6 ± 0.8	50.1 ± 0.6	50.7 ± 0.4	49.8 ± 0.4	49.0 ± 0.5
Hemoglobin (g/dL)						
Day 90	16.3 ± 0.1	16.3 ± 0.2	16.1 ± 0.2	16.1 ± 0.2	16.0 ± 0.1	15.6 ± 0.1**
Red blood cell (10^6/μL)						
Day 90	10.54 ± 0.12	10.51 ± 0.17	10.44 ± 0.12	10.52 ± 0.09	10.40 ± 0.09	10.27 ± 0.12
Mean cell volume (fL)						
Day 90	47.7 ± 0.2	48.2 ± 0.2	48.0 ± 0.2	48.2 ± 0.1	47.9 ± 0.2	47.7 ± 0.2
Mean cell hemoglobin (pg)						
Day 90	15.4 ± 0.1	15.5 ± 0.1	15.4 ± 0.1	15.3 ± 0.1	15.4 ± 0.1	15.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 90	32.3 ± 0.1	32.3 ± 0.2	32.1 ± 0.2	31.8 ± 0.2	32.1 ± 0.1	31.9 ± 0.2
Platelets (10^3/μL)						
Day 90	965 ± 17	960 ± 24	1015 ± 22	923 ± 30	1008 ± 14	931 ± 22
Reticulocytes (10^3/μL)						
Day 90	228 ± 18	232 ± 14	220 ± 20	237 ± 21	219 ± 15	283 ± 22
White blood cell (10^3/μL)						
Day 90	5.76 ± 0.50	4.54 ± 0.52	6.00 ± 0.35	3.94 ± 0.40*	6.08 ± 0.27	3.68 ± 0.37**
Lymphocytes (10^3/μL)						
Day 90	4.83 ± 0.42	3.72 ± 0.43	4.86 ± 0.36	3.35 ± 0.36	5.15 ± 0.24	3.09 ± 0.35*
Urea nitrogen (mg/dL)						
Day 90	48.5 ± 2.0	48.0 ± 3.2	34.3 ± 3.3**[b]	48.0 ± 3.8[c]	39.7 ± 1.8*[b]	39.7 ± 3.1*[c]
Creatinine (mg/dL)						
Day 90	1.03 ± 0.16[d]	1.29 ± 0.16	1.77 ± 0.70[e]	0.89 ± 0.18[d]	0.78 ± 0.16[f]	1.20 ± 0.13[b]
Alanine aminotransferase (IU/L)						
Day 90	153 ± 18[b]	143 ± 28	136 ± 29[d]	162 ± 15[c]	124 ± 19[b]	146 ± 21[b]
Alkaline phosphatase (IU/L)						
Day 90	54 ± 2	54 ± 2	60 ± 3[c]	51 ± 3[c]	54 ± 1[c]	56 ± 4[c]
5′-Nucleotidase (IU/L)						
Day 90	16.7 ± 0.8	16.0 ± 1.0	18.4 ± 0.8[g]	19.9 ± 1.5[c]	19.4 ± 0.8*[b]	18.4 ± 0.9[b]
Sorbitol dehydrogenase (IU/L)						
Day 90	37 ± 5	32 ± 3	29 ± 2[c]	24 ± 2**[c]	28 ± 3*[c]	28 ± 2*[c]
Bile acids (μmol/L)						
Day 90	6.00 ± 0.76[d]	3.90 ± 0.46	6.00 ± 2.08[h]	3.88 ± 0.83[b]	4.14 ± 1.08[d]	4.50 ± 1.00[b]

Table D3
Selected Hematology and Clinical Chemistry Data for Mice in the 13-Week Feed Studies of *o*-Cresol (continued)

Analysis	0 ppm	1,200 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Female						
Hematocrit (%)						
Day 90	50.2 ± 0.5	49.4 ± 0.8	48.8 ± 0.8	50.8 ± 0.8	49.3 ± 0.9	50.4 ± 0.8
Hemoglobin (g/dL)						
Day 90	17.1 ± 0.1	16.8 ± 0.2	16.8 ± 0.2	17.3 ± 0.1	16.7 ± 0.2	16.8 ± 0.2
Red blood cell ($10^6/\mu L$)						
Day 90	10.51 ± 0.11	10.37 ± 0.16	10.31 ± 0.15	10.60 ± 0.18	10.47 ± 0.14[c]	10.58 ± 0.22
Mean cell volume (fL)						
Day 90	47.8 ± 0.1	47.7 ± 0.2	47.3 ± 0.3	47.9 ± 0.1	47.6 ± 0.2	47.7 ± 0.5
Mean cell hemoglobin (pg)						
Day 90	16.3 ± 0.1	16.2 ± 0.1	16.3 ± 0.1	16.3 ± 0.2	16.2 ± 0.2	15.9 ± 0.3[e]
Mean cell hemoglobin concentration (g/dL)						
Day 90	34.1 ± 0.2	34.0 ± 0.4	34.5 ± 0.4	33.7 ± 0.2[c]	33.5 ± 0.4[c]	33.4 ± 0.4
Platelets ($10^3/\mu L$)						
Day 90	928 ± 34	937 ± 44	890 ± 32	939 ± 35	971 ± 43	1,002 ± 58
Reticulocytes ($10^3/\mu L$)						
Day 90	205 ± 17	198 ± 13	211 ± 9	228 ± 10	234 ± 25[c]	262 ± 17[e]
White blood cell ($10^3/\mu L$)						
Day 90	5.68 ± 0.26	5.28 ± 0.38	4.66 ± 0.38	5.46 ± 0.35	4.97 ± 0.43	6.84 ± 0.49
Lymphocytes ($10^3/\mu L$)						
Day 90	4.66 ± 0.23	4.34 ± 0.36[c]	4.01 ± 0.33	3.75 ± 0.47[f]	5.15 ± 0.24	5.58 ± 0.47[b]
Urea nitrogen (mg/dL)						
Day 90	25.0 ± 1.6[c]	28.5 ± 1.8[b]	28.7 ± 2.0	24.2 ± 2.4[c]	24.7 ± 3.2[b]	29.0 ± 1.8[f]
Creatinine (mg/dL)						
Day 90	0.80 ± 0.11[d]	0.68 ± 0.07[f]	0.87 ± 0.07[c]	0.60 ± 0.12[f]	0.79 ± 0.10[g]	0.36 ± 0.05[i]
Alanine aminotransferase (IU/L)						
Day 90	78 ± 8[c]	116 ± 9[d]	93 ± 8	108 ± 20[c]	80 ± 11[b]	176 ± 33[e,f]
Alkaline phosphatase (IU/L)						
Day 90	88 ± 2	87 ± 3[c]	90 ± 3	93 ± 6[c]	83 ± 2[c]	90 ± 3[d]
5′-Nucleotidase (IU/L)						
Day 90	39.6 ± 2.4[d]	37.3 ± 2.2[d]	39.2 ± 1.4	39.8 ± 3.5[b]	47.6 ± 1.9[e,d]	61.3 ± 1.9[e,f]

Table D3
Selected Hematology and Clinical Chemistry Data for Mice in the 13-Week Feed Studies of *o*-Cresol (continued)

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* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error for groups of 10 animals, unless otherwise specified. Bile acids were not measured in female mice.
[b] n=8
[c] n=9
[d] n=7
[e] n=2
[f] n=6
[g] n=5
[h] n=4
[i] n=2

Table D4
Selected Hematology and Clinical Chemistry Data for Mice in the 13-Week Feed Studies of *m/p*-Cresol[a]

Analysis	0 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male						
Hematocrit (%)						
Day 90	51.8 ± 0.6	50.7 ± 0.4	50.5 ± 0.6	52.0 ± 0.3	50.8 ± 0.5	50.3 ± 0.6
Hemoglobin (g/dL)						
Day 90	16.9 ± 0.2	16.6 ± 0.2	16.3 ± 0.2	16.8 ± 0.1	16.4 ± 0.2*	16.4 ± 0.2*
Red blood cell ($10^6/\mu L$)						
Day 90	10.49 ± 0.13	10.18 ± 0.10	10.10 ± 0.12	10.50 ± 0.06	10.26 ± 0.11	10.28 ± 0.15
Mean cell volume (fL)						
Day 90	49.3 ± 0.2	49.8 ± 0.2	50.0 ± 0.2*	49.6 ± 0.1	49.5 ± 0.2	49.2 ± 0.3
Mean cell hemoglobin (pg)						
Day 90	16.1 ± 0.1	16.2 ± 0.1	16.2 ± 0.1	16.0 ± 0.1	15.9 ± 0.1	16.0 ± 0.2
Mean cell hemoglobin concentration (g/dL)						
Day 90	32.7 ± 0.2	32.5 ± 0.2	32.4 ± 0.2	32.3 ± 0.1	32.1 ± 0.3	32.6 ± 0.3
Platelets ($10^3/\mu L$)						
Day 90	889 ± 39	969 ± 37	917 ± 17	922 ± 23	928 ± 17	952 ± 37
Reticulocytes ($10^3/\mu L$)						
Day 90	205 ± 15	210 ± 18	185 ± 8	183 ± 12	205 ± 18	209 ± 15
White blood cell ($10^3/\mu L$)						
Day 90	4.70 ± 0.28	4.52 ± 0.42	3.20 ± 0.38	3.72 ± 0.42	3.98 ± 0.36	4.88 ± 0.75
Urea nitrogen (mg/dL)						
Day 90	39.7 ± 2.2[b]	42.7 ± 2.3	41.3 ± 1.4[c]	42.0 ± 2.1	36.5 ± 1.6[d]	38.0 ± 2.2
Creatinine (mg/dL)						
Day 90	0.72 ± 0.03[b]	0.78 ± 0.07	0.70 ± 0.05[c]	0.82 ± 0.08	0.81 ± 0.12[d]	0.83 ± 0.06
Alanine aminotransferase (IU/L)						
Day 90	101 ± 12[b]	129 ± 31	90 ± 11[c]	103 ± 9	112 ± 11[d]	130 ± 15
Alkaline phosphatase (IU/L)						
Day 90	48 ± 1[b]	48 ± 1	47 ± 1[c]	46 ± 1	47 ± 1[d]	56 ± 5
5′-Nucleotidase (IU/L)						
Day 90	16.9 ± 0.5[b]	16.6 ± 0.3	16.9 ± 0.8[c]	16.4 ± 0.4	16.9 ± 0.8[d]	18.5 ± 1.2
Sorbitol dehydrogenase (IU/L)						
Day 90	26 ± 2[b]	23 ± 2	27 ± 2[c]	25 ± 1	31 ± 3[d]	48 ± 4**

Table D4
Selected Hematology and Clinical Chemistry Data for Mice in the 13-Week Feed Studies of *m/p*-Cresol
(continued)

Analysis	0 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Female						
Hematocrit (%)						
Day 90	50.0 ± 0.5	49.2 ± 0.7	48.5 ± 0.4	49.8 ± 0.3	49.5 ± 0.7	48.6 ± 0.5
Hemoglobin (g/dL)						
Day 90	16.4 ± 0.1	16.4 ± 0.3	15.9 ± 0.1*	16.2 ± 0.1	16.2 ± 0.3	16.0 ± 0.1*
Red blood cell (10^6/μL)						
Day 90	10.08 ± 0.10	10.07 ± 0.15	9.85 ± 0.10	10.03 ± 0.09	10.08 ± 0.14	9.81 ± 0.12
Mean cell hemoglobin (pg)						
Day 90	16.3 ± 0.1	16.2 ± 0.1	16.1 ± 0.1	16.2 ± 0.1	16.1 ± 0.1	16.3 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 90	32.8 ± 0.2	33.3 ± 0.3	32.7 ± 0.3	32.6 ± 0.1	32.7 ± 0.2	32.9 ± 0.2
Platelets (10^3/μL)						
Day 90	803 ± 20	806 ± 29	837 ± 16	837 ± 20	768 ± 54	851 ± 25
Reticulocytes (10^3/μL)						
Day 90	162 ± 10	142 ± 11	159 ± 10	162 ± 14	152 ± 12	170 ± 17
White blood cell (10^3/μL)						
Day 90	4.94 ± 0.19	4.66 ± 0.53	4.80 ± 0.43	4.48 ± 0.38	5.80 ± 0.57	6.04 ± 0.55
Urea nitrogen (mg/dL)						
Day 90	41.1 ± 3.3[c]	37.2 ± 1.4	36.6 ± 2.4[b]	41.6 ± 1.3	40.1 ± 1.9[d]	36.9 ± 1.8
Creatinine (mg/dL)						
Day 90	0.95 ± 0.08[c]	0.89 ± 0.07	0.77 ± 0.08[b]	0.90 ± 0.05	1.15 ± 0.23[e]	0.78 ± 0.07
Alanine aminotransferase (IU/L)						
Day 90	105 ± 14[d]	97 ± 12	152 ± 33[b]	74 ± 7[b]	80 ± 7[d]	98 ± 10
Alkaline phosphatase (IU/L)						
Day 90	74 ± 4[c]	77 ± 4	75 ± 3[b]	73 ± 2	62 ± 5[d]	73 ± 2
5′-Nucleotidase (IU/L)						
Day 90	36.8 ± 1.4[c]	34.5 ± 1.4	39.1 ± 1.8[b]	35.9 ± 1.0	42.7 ± 1.5*[d]	47.5 ± 2.2**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error for groups of 10 animals, unless otherwise specified.
[b] n=9
[c] n=8
[d] n=7
[e] n=6

APPENDIX E
GENETIC TOXICOLOGY

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TABLE E3 Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Exposed for 13 Weeks to *m/p*-Cresol 128

Table E1
Mutagenicity of *m/p*-Cresol in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9	+S9 (hamster) +10	+S9 (hamster) +30	+S9 (rat) +10	+S9 (rat) +30
TA100	0	140 ± 20.3	165 ± 2.9	150 ± 10.0	159 ± 5.5	173 ± 5.5
	10	129 ± 8.4				
	33	169 ± 2.7	160 ± 5.2		148 ± 5.9	
	100	178 ± 3.2	171 ± 2.3	157 ± 7.5	141 ± 16.0	176 ± 10.3
	333	160 ± 7.0	162 ± 5.5	188 ± 17.3	152 ± 12.8	179 ± 8.9
	1,000	165 ± 3.8	184 ± 3.7	178 ± 3.5	148 ± 8.6	176 ± 7.9
	3,333		88 ± 7.5[c]	167 ± 5.2	141 ± 4.1	128 ± 7.4
	6,666		95 ± 10.3		54 ± 11.0[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control[d]		961 ± 13.5	1,160 ± 25.2	900 ± 12.7	567 ± 6.4	620 ± 25.2
TA1535	0	9 ± 1.8	9 ± 1.9	7 ± 2.6	14 ± 0.6	12 ± 1.5
	10	8 ± 0.3				
	33	11 ± 1.7	8 ± 0.9	10 ± 2.3	12 ± 0.9	14 ± 3.2
	100	11 ± 1.8	10 ± 1.8	10 ± 0.6	13 ± 3.3	7 ± 2.3
	333	10 ± 1.2	9 ± 1.5	9 ± 1.0	8 ± 0.9	9 ± 1.3
	1,000	9 ± 1.0	12 ± 2.2	9 ± 1.9	12 ± 1.5	9 ± 0.6
	3,333		7 ± 1.0	4 ± 0.7	10 ± 2.0	7 ± 3.2
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		715 ± 67.9	79 ± 1.0	299 ± 49.9	126 ± 8.1	83 ± 11.1
TA97	0	169 ± 7.4	167 ± 7.9	169 ± 10.4	178 ± 8.2	217 ± 3.3
	10	180 ± 9.5				
	33	178 ± 3.5	179 ± 10.5	191 ± 12.6	202 ± 2.2	242 ± 35.1
	100	208 ± 13.4	222 ± 1.5	170 ± 3.2	216 ± 1.8	244 ± 4.8
	333	187 ± 1.8	192 ± 14.8	169 ± 11.9	211 ± 0.6	214 ± 13.5
	1,000	158 ± 9.0	192 ± 5.5	170 ± 9.6	176 ± 7.2	167 ± 10.8
	3,333		143 ± 17.5[c]	100 ± 2.0	149 ± 7.3	131 ± 7.9
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		546 ± 3.2	818 ± 19.8	549 ± 47.2	529 ± 39.3	360 ± 10.0
TA98	0	44 ± 2.8	33 ± 3.2	30 ± 1.3	38 ± 0.6	29 ± 3.0
	10	43 ± 3.2				
	33	27 ± 0.7	37 ± 2.0		46 ± 5.2	
	100	36 ± 2.6	39 ± 2.8	27 ± 4.6	47 ± 4.2	20 ± 4.5
	333	34 ± 4.7	33 ± 3.2	24 ± 0.6	39 ± 1.3	16 ± 1.5
	666	29 ± 1.8				
	1,000		36 ± 2.7	20 ± 1.8	46 ± 4.1	17 ± 1.9
	3,333		28 ± 8.3[c]	12 ± 1.7	30 ± 4.3	19 ± 2.7
	6,666					17 ± 1.8
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		695 ± 43.4	877 ± 25.0	525 ± 45.2	491 ± 23.7	102 ± 7.6

Table E1
Mutagenicity of *m/p*-Cresol in *Salmonella typhimurium* (continued)

[a] Study performed at Southern Research Institute (Birmingham, AL). The detailed protocol is presented in Zeiger *et al.* (1988). Cells and study compound or solvent (dimethylsulfoxide) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague-Dawley rat liver. High dose was limited by toxicity or solubility, but did not exceed 10 mg/plate; 0 μg/plate dose is the solvent control.
[b] Revertants are presented as mean ± standard error from 3 plates.
[c] Slight toxicity
[d] Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA97.

Table E2
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Exposed for 13 Weeks to *o*-Cresol[a]

Concentration (ppm)	Micronucleated PCE/1000 (mean ± standard error)	Micronucleated NCE/1000 (mean ± standard error)
Male		
0	2.24 ± 0.33	1.82 ± 0.17
5,000	2.20 ± 0.27	1.77 ± 0.09
10,000	1.80 ± 0.32	1.70 ± 0.10
20,000	1.28 ± 0.15	1.94 ± 0.07
Female		
0	1.41 ± 0.16	1.35 ± 0.08
5,000	1.12 ± 0.23	1.19 ± 0.05
10,000	1.77 ± 0.34	1.33 ± 0.10
20,000	1.34 ± 0.16	1.32 ± 0.09

[a] Smears were prepared from peripheral blood samples obtained by cardiac puncture of dosed and control animals at the termination of the 13 week study. Slides were stained with Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983). At least 2000 polychromatic erythrocytes (PCE) and 10,000 normochromatic erythrocytes (NCE) from each animal were scored for micronuclei. No significant elevation in the frequency of micronucleated erythrocytes was observed in either male or female mice.

Table E3
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Exposed for 13 Weeks to *m/p*-Cresol[a]

Concentration (ppm)	% Micronucleated Cells (mean ± standard error)
Male	
0	0.09 ± 0.01
625	0.08 ± 0.01
1,250	0.09 ± 0.01
2,500	0.08 ± 0.01
5,000	0.10 ± 0.01
10,000	0.10 ± 0.01
Female	
0	0.07 ± 0.01
625	0.06 ± 0.00
1,250	0.05 ± 0.01
2,500	0.06 ± 0.01
5,000	0.05 ± 0.01
10,000	0.05 ± 0.01

[a] Smears were prepared from peripheral blood samples obtained by cardiac puncture of dosed and control animals at the termination of the 13 week study. Slides were stained with Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983). At least 10,000 normochromatic erythrocytes from each animal were scored for micronuclei. No significant elevation in the frequency of micronucleated erythrocytes was observed in either male or female mice; n=10.