3-Methylphenol; CASRN 108-39-4

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR 3-Methylphenol

File First On-Line 08/22/1988

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I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — 3-Methylphenol
CASRN — 108-39-4
Primary Synonym — m-Cresol
Last Revised — 08/22/1988

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of
substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

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<th>Experimental Doses*</th>
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<td>90-Day Oral Subchronic Neurotoxicity Study in Rats</td>
<td>LOAEL: 150 mg/kg/day</td>
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*Conversion Factors: None

I.A.2. Principal and Supporting Studies (Oral RfD)


In a 90-day subchronic toxicity study (U.S. EPA, 1986), 30 Sprague-Dawley rats/sex/dose were gavaged daily with 0, 50, 150, or 450 mg/kg/day m-cresol. The following parameters were evaluated: body and organ weights, food consumption, mortality, clinical signs of toxicity, and clinical pathology. At sacrifice, animals were necropsied and tissues and organs were subjected to histopathological evaluation. At 450 mg/kg/day there was a 20 to 25% reduction in body weight gain in males, 10 to 15% reduction in females; food intake was reduced by 10 to 15% in males, and there was a pronounced increase in the incidence of salivation, tremors and urination. At the 150 mg/kg/day dose, weight gain was reduced by 10 to 15% in males although no reduction was seen in females. At the 50 mg/kg/day level, there were no significant adverse effects.
In a 90-day neurotoxicity study (U.S. EPA, 1987), 10 Sprague-Dawley rats/sex/dose were gavaged daily with 0, 50, 150, or 450 mg/kg/day m-cresol. In addition to the parameters measured in the toxicity study (U.S. EPA, 1986), the following were monitored for signs of neurotoxicity: salivation, urination, tremor, piloerection, diarrhea, pupil size, pupil response, lacrimation, hypothermia, vocalization, exophthalmia, palpebral closure, convulsions (type and severity), respiration (rate and type), gait, positional passivity, locomotor activity, stereotypy, startle response, righting reflex, performance on a wire maneuver, forelimb strength, positive geotropism, extensor thrust, limb rotation, tail pinch reflex, toe pinch reflex, and hind limb splay. The lowest dose of m-cresol, 50 mg/kg/day, caused clinical signs of CNS-stimulation post dosing such as salivation, rapid respiration, hypoactivity, which were low in incidence and sporadic in nature. The highest dose (450 mg/kg/day) produced significant neurological events such as increased salivation, urination, tremors, lacrimation, palpebral closure, and rapid respiration. High-dose animals also showed abnormal patterns in the neurobehavioral tests. The NOAEL based on systemic toxicity was 50 mg/kg/day in rats.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — 10 for interspecies and 10 for intraspecies variability and 10 for uncertainty in extrapolation of subchronic data to levels of chronic effects.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

In a series of subchronic inhalation studies, Uzhdavine et al. (1972) exposed rats and guinea pigs to o-cresol at a concentration of 9.0 (plus or minus 0.9) mg/cu.m. No effect was seen in guinea pigs. In rats, the authors reported various hematopoietic effects, respiratory tract irritation, and sclerosis of lungs. Uzhdavine et al. (1972) also reported that humans exposed to 6 mg/cu.m cresol (duration unspecified) experienced nasopharyngeal irritation. Other studies support the findings (effects) reported in this study. Based on a review and assessment of the available literature, primarily Uzhdavine et al. (1972), NIOSH (1978) recommended a TLV-TWA of 10 mg/cu.m (0.05 mg/kg/day). An RfD of 0.05 mg/kg/day can be derived from this value; this lends support to the RfD derived from the subchronic toxicity studies (U.S. EPA, 1986, 1987).
I.A.5. Confidence in the Oral RfD

Study — High
Database — Medium
RfD — Medium

Confidence in the study is high because the critical studies provided adequate toxicological endpoints that included both general toxicity and neurotoxicity. The database is medium because there are adequate supporting subchronic studies. Thus, until additional chronic toxicity studies and reproductive studies are available, medium confidence in the RfD is recommended.

I.A.6. EPA Documentation and Review of the Oral RfD


The Health and Environmental Effects Profile has received an Agency-wide review with the help of two external scientists.


Verification Date — 08/13/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for 3-Methylphenol conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).
I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — 3-Methylphenol  
CASRN — 108-39-4  
Primary Synonym — m-Cresol

The health effects data for 3-methylphenol were reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for the derivation of an inhalation RfC. For information on the health effects of this chemical, interested parties are referred to the documentation listed below.


Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for 3-Methylphenol conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

EPA Contacts:

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).
II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 3-Methylphenol  
CASRN — 108-39-4  
Primary Synonym — m-Cresol  
Last Revised — 09/01/1990

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — C; possible human carcinogen

Basis — Based on an increased incidence of skin papillomas in mice in an initiation-promotion study. The three cresol isomers produced positive results in genetic toxicity studies both alone and in combination.

II.A.2. Human Carcinogenicity Data

Inadequate. Only anecdotal data available. Garrett (1975) reported two cases of multifocal transitional cell carcinoma of the bladder following chronic occupational exposure to cresol and creosote. Wodyka (1964, as cited in U.S. EPA., 1979) described a squamous cell carcinoma of the vocal cords in a petroleum refinery worker with a long history of exposure to cresol, dichloro-octane, and chromic acid.
II.A.3. Animal Carcinogenicity Data

Limited. Four skin application studies which had positive results are reported; however, the final two studies are of limited value due to the application of a mixture of chemicals. In a study by Boutwell and Bosch (1959), female Sutter mice (27-29/group; 2-3 months of age) received a single dermal application of 25 uL of 0.3% dimethylbenzanthracene (DMBA) in acetone as the initiator, followed 1 week later by 25 uL of 20% (v/v) o-, m- or p- cresol in benzene twice weekly for 12 weeks. Skin papillomas were evaluated at 12 weeks. Many of the cresol-treated mice died, presumably of cresol toxicity. There was no mortality or evidence of skin papillomas in the benzene control group (benzene weekly after DMBA initiation). The numbers of surviving mice that developed skin papillomas at 12 weeks were as follows: 10/17, o-cresol; 7/14, m-cresol; and 7/20, p-cresol. None of the 12 mice in the benzene control group died or developed skin papillomas.

In another experiment, groups of 20 mice received a single dose (25 uL) of 0.3% DMBA in acetone, followed by twice weekly applications of 5.7% m- cresol in benzene or 5.7% p-cresol in benzene for 20 weeks. No skin papillomas were observed in the 18 surviving benzene control mice; 4/17 m- cresol- and 4/14 p-cresol-treated mice developed skin papillomas (Boutwell and Bosch, 1959). These two experiments indicate that cresols can serve as tumor promoters of a polycyclic aromatic hydrocarbon.

Kaiser (1967), using spectroscopic and gas chromatographic analysis, showed that o-, m-, and p-cresol were present in a phenolic fraction isolated from tea. Two groups of 15 Swiss mice (age and sex not specified) received a single dermal application of 1% benzo[a]pyrene in acetone. On alternate days one group received dermal applications of tea (1g/155 ml water, dose unspecified). The type of housing used in these studies was not specified. At the end of 110 days (55 total treatments), 6/15 mice had epithelial cell carcinomas and 9/15 had developed precarcinogenic or carcinogenic stages of squamous-cell tumors. Control mice, which received only the initial benzo[a]pyrene treatment, developed no pathologic lesions. Bock et al. (1971) used steam distillation to isolate subfractions of an acid fraction of cigarette smoke condensate; this fraction was previously shown to be a tumor promoter (Bock et al., 1969). Phenolic compounds including o-, m-, and p- cresol were detected in the steam distillate subfraction. A synthetic distillate with the same composition was prepared. Groups of fifty 14-week- old Swiss mice (gender unspecified) were administered 0.2 ml of the nonvolatile fraction of the distillate, the distillate, the synthetic distillate, or acetone (for the control group) by dermal application, 5 times per week for 61 weeks. Approximately 45% of the mice survived in each group. Skin tumors developed with the following incidence: 4/23, 4/26, 2/21, and 14/21 for the control group, the distillate application group, the synthetic distillate application group, and the nonvolatile fraction group, respectively. (The tumor type was not specified.) These studies are of limited value in
determining the tumor-promoting activity of cresol, since both tea and cigarette smoke condensate contain numerous other compounds.

In an acute dermal toxicity study, technical grade o-, m-, and p-cresol caused severe skin damage on at least 2/6 shaved, female, albino New Zealand rabbits within 4 hours of application of 2000 mg/kg of technical grade cresol, 890 mg/kg of o-cresol, 2830 mg/kg of m-cresol, or 300 mg/kg p-cresol (Vernot et al. 1977).

II.A.4. Supporting Data for Carcinogenicity

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

In cell transformation assays using BALB/3T3 cells, a mixture of 3 cresol isomers was positive (Litton Bionetics, 1980d), and o-cresol was negative. Positive mutagenic responses were found at noncytotoxic doses (Litton Bionetics, 1980e). In another cell transformation assay using p-cresol, negative results were obtained with the mouse fibroblast cell line C3H10T1/2 (Crowley and Margard, 1978).

Cresols (o-, m- and p-) are not mutagenic for various strains of Salmonella typhimurium both in the presence and absence of mammalian liver homogenates (Crowley and Margard, 1978; Litton Bionetics, 1980a, 1981a; Florin et al., 1980; Douglas et al., 1980; Pool and Lin, 1982; Haworth et al., 1983).

A mixture of the three isomers was mutagenic in a mouse lymphoma forward mutation assay with mammalian liver homogenates, while o-cresol was not mutagenic both with and without liver homogenates (Litton Bionetics, 1980b, 1981b).

No isomer, when tested individually, induced sister chromatid exchanges (SCEs) in vivo, but the mixture of the three isomers induced SCEs in Chinese hamster ovary (CHO) cells in vitro (Litton Bionetics, 1980c). Only o-cresol induced SCEs in human lung fibroblasts (Cheng and Kligerman, 1984) and CHO cells (Litton Bionetics, 1981c).

In a screening test for putative carcinogens, infectious virus particles were produced from SV40-transformed weanling Syrian hamster kidney cells exposed to m-cresol (Moore and Coohill, 1983).
II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

None.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

None.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation


The Carcinogen Assessment Group's Preliminary Risk Assessment on Cresols: Type 1 - Air Program. Prepared by the Office of Health and Environment Assessment for the Office of Air Quality Planning and Standards, Washington, DC.


The 1985 Health and Environmental Effects Profile for Cresols is an external draft for review only and does not constitute Agency policy.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 07/11/1988, 10/05/1989

Verification Date — 10/05/1989

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for 3-Methylphenol conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.
II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — 3-Methylphenol
CASRN — 108-39-4
Primary Synonym — m-Cresol

VI.A. Oral RfD References


VI.B. Inhalation RfC References


VI.C. Carcinogenicity Assessment References


VII. Revision History

Substance Name — 3-Methylphenol  
CASRN — 108-39-4  
Primary Synonym — m-Cresol

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VIII. Synonyms

Substance Name — 3-Methylphenol  
CASRN — 108-39-4  
Primary Synonym — m-Cresol  
Last Revised — 08/22/1988

- 108-39-4  
- Phenol, 3-methyl-  
- Caswell No. 261A  
- EPA Pesticide Chemical Code 022102  
- HSDB 1815  
- m-Cresol  
- m-CRESYLIC ACID  
- m-HYDROXYTOLUENE  
- m-KRESOL  
- m-METHYLPHENOL
• m-OXYTOLUENE
• m-TOLUOL
• meta-cresol
• NSC 8768
• 1-HYDROXY-3-METHYLBENZENE
• 3-cresol
• 3-HYDROXYTOLUENE
• 3-Methylphenol