4-Methylphenol; CASRN 106-44-5

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 4-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 — 4-Methylphenol
CASRN — 106-44-5

The Oral Rfd for 4-methylphenol was withdrawn on 08/01/1991 as a result of further review. A new Rfd summary is in preparation by the Rfd/RfC Work Group.


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 4-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.

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).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — 4-Methylphenol
CASRN — 106-44-5

The health effects data for 4-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 additional 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 4-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.

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II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 4-Methylphenol
CASRN — 106-44-5
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, dichlorooctane, 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 C3H1OT1/2 (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 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 4-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 — 4-Methylphenol
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VI.A. Oral RfD References

Not available at this time.

VI.B. Inhalation RfC References


VI.C. Carcinogenicity Assessment References


VII. Revision History

Substance Name — 4-Methylphenol
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VIII. Synonyms

Substance Name — 4-Methylphenol
CASRN — 106-44-5
Last Revised — 08/22/1988

- 106-44-5
- Phenol, 4-methyl-
- Cresoles [Spanish]
- Cresols (o-,m-,p-)
- Cresols [French]
- HSDB 1814
- NSC 3696
- p-Cresol
- p-CRESYLYC ACID
- p-HYDROXYTOLUENE
- p-KRESOL
- p-METHYLHYDROXYBENZENE
- p-METHYLPHENOL
- p-OXYTOLUENE
- p-TOLUOL
- p-TOLYL ALCOHOL
- para-cresol
- PARAMETHYL PHENOL
- 1-HYDROXY-4-METHYLBENZENE
- 1-METHYL-4-HYDROXYBENZENE
- 4-cresol
- 4-HYDROXYTOLUENE
- 4-Methylphenol