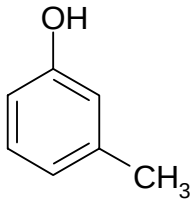
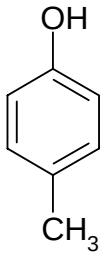
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-39-4	106-44-5	15831-10-4
Chemical Name	m-Cresol	p-Cresol	m/p-Cresol mixtures
Structural Formula	 m-Cresol	 p-Cresol	

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

m-Cresol, p-cresol and mixtures of both isomers can be considered as a single category because of their similarity in physico-chemical properties, distribution between environmental compartments, degradation, ecotoxicity, and toxicology.

Human Health

m-Cresol, p-cresol and m/p-cresol mixtures are absorbed across the respiratory and gastrointestinal tracts and through the skin, and are distributed throughout the body. The primary metabolic pathway for all cresol isomers is conjugation with glucuronic acid and inorganic sulfates. All isomers are mainly eliminated by renal excretion in form of conjugates. For p-cresol, oxidation to a reactive quinone methide intermediate was found in rat liver *in vitro*. The oral LD50 of undiluted m-cresol in rats was 242 mg/kg bw; and the LD50 of undiluted p-cresol was 207 mg/kg bw. Thus, it can be assumed that the LD50 of m/p-cresol mixtures is slightly above 200 mg/kg bw. Clinical signs included hypoactivity, salivation, tremors, and convulsions. No mortality nor clinical signs of toxicity were seen following exposure to saturated vapour concentration of either m-cresol or p-cresol. Inhalation of aerosols may however cause death, and mean lethal concentrations in rats were reported to be 29 mg/m³ for p-cresol and 58 mg/m³ for m-cresol. Clinical signs included irritation of mucous membranes, excitation and convulsions. Haematuria was reported at very high concentrations. Following dermal application in rabbits the LD50 of undiluted m-cresol was 2050 mg/kg bw and the LD50 of p-cresol was 300 mg/kg bw. It can be assumed that the LD50 of m/p-cresol mixtures is between 300 and 2000 mg/kg bw.

m-Cresol, p-cresol and m/p-cresol mixtures are corrosive to the skin and may cause serious damage to the eyes. There is no indication of a sensitizing effect of p-cresol and m/p-cresol from a limited guinea pig study and a limited human study. No sensitization test was available for m-cresol. In a survey article hypersensitivity reactions of some individuals to cresol (isomer unspecified) have been mentioned.

In 28-day and 13-week feeding studies, m-cresol, p-cresol and m/p-cresol (60:40) had a very similar pattern of toxicity in rats and mice with minimal effect levels of 1000 – 3000 ppm in the diet for increases in liver weight (rat, mouse) and kidney weight (mouse, p-cresol). No increase in relative kidney weight was found for m-cresol. Atrophy and regenerative changes in the nasal epithelia and forestomach were seen after exposure to p-cresol and m/p-cresol, presumably as direct result of the irritant effects of the chemicals. The no observed adverse effect levels (NOAELs)

for m-cresol, p-cresol and m/p-cresol were generally ≥ 50 mg/kg bw/day in rats and mice.

In vitro, m-cresol and p-cresol did not induce gene mutations in bacterial and mammalian cell systems and m/p-cresol mixture did not induce gene mutations in bacteria. m-Cresol was negative for clastogenic activity *in vitro*, and *in vivo*. p-Cresol was clastogenic *in vitro*, but has not been adequately tested in somatic cells *in vivo*. p-Cresol was, however, negative for dominant lethal mutations in germ cells in male mice at clearly toxic exposure levels. A 60:40 m/p-cresol mixture did not increase the frequency of micronucleated erythrocytes in the peripheral blood erythrocytes of mice. *In vitro*, it is possible that m- and p-cresol and m/p-cresol mixture have the potential to interact with DNA either directly or indirectly via metabolites.

As for o-cresol, there are no adequate data available to assess the carcinogenic potential of m-cresol, p-cresol or m/p-cresol mixtures. From tumour promotion studies in mice there are some indications that cresols may act as promoters. Currently, the U.S. National Cancer Institute is performing a carcinogenicity feeding study on mice and rats with cresols (mixture of ortho-, meta- and para-) within the National Toxicological Program (NTP).

Despite general toxicity (hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration, perioral wetness) fertility was not affected by treatment with m-cresol or p-cresol (NOAEL, rat: 450 mg/kg bw/day). The NOAELs for general toxicity were determined as 30 mg/kg bw/day. Fertility effects including a 20% reduction in pup survival as well as reductions in the weights of male reproductive organs were found following treatment of mice with m/p-cresol mixture in a continuous breeding study at systemically toxic dose levels (reduced food consumption and reduced body weights, increases in liver and kidney weights) (NOAEL, fertility and general toxicity: 0.25 % in feed (ca. 375 mg/kg bw/day).

In developmental toxicity studies with m-cresol in rats and rabbits, no toxic effects on the developing organism could be found despite of the toxic effects on the dams as evidenced by hypoactivity, ataxia, tremor, twitches, prone positioning, audible respiration, perioral wetness, and a reduction in food consumption in rats, and audible respiration, and ocular discharge in rabbits (NOAELs: 175 mg/kg bw (maternal toxicity) and 450 mg/kg bw (developmental toxicity) for rats, and 5 mg/kg bw (maternal toxicity) and 100 mg/kg bw (developmental toxicity) for rabbits, respectively. p-Cresol caused fetotoxicity (delayed ossification, decreased fetal body weight) at maternally toxic dose levels in rats, but not in rabbits (NOAEL, rat, maternal toxicity, developmental toxicty: 175 mg/kg bw/day). Based on the available data, it can be assumed that m/p-cresol mixtures may have the potential to induce fetotoxicity in the presence of maternal toxicity.

In humans, the accidental oral uptake of cresols can induced irritation of mouth and throat, abdominal pains, vomiting, haemolytic anemia, increased heart rate, liver and kidney damage, headaches, facial paralysis, drowsiness, cramps, coma and death. Skin contact with cresols can result in corrosion, skin depigmentation, effects on the nervous system, liver and kidneys, gastrointestinal bleeding, and can cause human fatalities.

There are some case reports about tumour development in connection with probable exposure against cresol isomers. Since co-exposures to other substances cannot be excluded, no conclusion on a carcinogenic potential can be deduced from these case reports.

Environment

m-Cresol, p-cresol and m/p-cresol mixtures have a melting point of ca. 10 - 35°C, a water solubility in the range of 21.5 - 24.4 g/l (25°C), a density of about 1.03 g/cm³ (20°C), and a vapour pressure of 0.147 Pa (25°C). The experimentally determined log Kow are in the range of 1.94 - 1.96.

According to a Mackay Level I model calculation, the main target compartment for m-cresol and p-cresol is the hydrosphere (96.3%). In the atmosphere m-cresol and p-cresol are indirectly photodegradable by hydroxyl radicals with half–lives $t_{1/2}$ = 6.0 – 8.2 hours (OH concentration $5 \cdot 10^5$ molecules/cm³). The measured Henrys' law constants of 0.09 Pa·m³/mol (m-cresol) and 0.1 Pa·m³/mol (p-cresol) indicate slow volatilization from surface waters. Adsorption onto soils and sediments are low, according to experimentally determined Koc values of 34.58 for m-cresol and 48.66 for p-cresol.

With regard to the chemical structure m-cresol and p-cresol are not expected to hydrolyse under environmental conditions. Aerobic biodegradation is considered to be the major removal mechanism in the hydrosphere, leading to complete mineralization. From the available test results, m-cresol and p-cresol can be considered as being readily biodegradable under aerobic conditions. In surface waters and sediments half-lives in the range of some hours to a few days are expected. Photolytical degradation in surface waters as well as anaerobic degradation in lower sediment layers are expected to be of minor importance.

For m-cresol, a BCF of 20 was obtained in a laboratory tests on fish, indicating a low bioaccumulation potential. Because of the similarity of the log Kow the accumulation potential of m-cresol, p-cresol and m/p-cresol mixtures is assumed to be low.

For the acute toxicity of cresols on aquatic species experimental results with m-cresol and p-cresol from tests with fish, daphnids and algae are available. Long-term tests were conducted for p-cresol with fish, algae and invertebrates. Effect values with the same tested species indicate toxicity in the same order of magnitude, with p-cresol being slightly more toxic. Therefore, it is assumed that the long-term toxicity of both isomers is similar as well. No ecotoxicity tests are available for the isomeric mixture m/p-cresol. However, it is expected that the toxicity of the isomeric mixture is covered by the data for m- and p-cresol.

In acute toxicity tests the following results were obtained with either m-or p-cresol:

fish (15 species):	48 - 96 h LC_{50} = 4.4 - 57.5mg/l;
invertebrates (4 species):	24 - 48 h LC_{50} = 4.9 - > 99.5 mg/l;
algae (2 species):	48 – 72 h EC_{50} = 21 - 127mg/l.

Results from long-term tests for p-cresol are available for fish, invertebrates and algae, the most sensitive species being *Pimephales promelas* (NOEC = 1.35 mg/l), *Daphnia magna* (NOEC = 1 mg/l) and *Scenedesmus subspicatus* (ErC10 = 4.6 mg/l, EbC10 = 2.3 mg/l). Applying an assessment factor of 10 to the lower value, a Predicted No Effect Concentration (PNEC) for the aquatic compartment of 0.1 mg/l is determined for m- and p- cresol and the isomeric mixture m/p-cresol.

Exposure

Cresols (mixed isomers) are widespread in nature, occurring, for instance, in many plants, petroleum, coal tar, crude oil and, volcanic actions. They are emitted from municipal incinerators, during coal and wood combustion, with vehicle exhaust, from oil refineries and cigarette smoke. Cresols are also products of the photooxidation of toluene. p-Cresol is an endogenous metabolite of the amino acid tyrosine in humans and warm-blooded animals.

The world production figures amounts of about 28,500 tonnes for m-, 59,500 tonnes for p-, and 128,000 tonnes for the m/p-cresol isomeric mixture. The largest part of cresols are used as intermediates in chemical processes for the production of e.g. antioxidants, arylphosphates, synthetic Vitamin E and pesticides. m/p-Cresol isomeric mixture is used as a process solvent for the production of wire enamels.

Direct uses of cresols are as bactericide in biotechnological processing, pesticide and other minor, wide dispersive uses (< 1 % of worldwide production).

Information on releases into the environment from direct uses of cresols are not readily available.

RECOMMENDATION

The chemicals in this category are currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: m-Cresol, p-cresol and m/p-cresol mixtures possess properties indicating a hazard for human health. Based on data presented by the Sponsor country, adequate risk management measures are being applied. Countries may desire to check their own risk management measures to find out whether there is a need for measures beyond those which are being applied already. Cresols (mixed isomers of ortho-, meta- and para-) are being tested in carcinogenicity studies under the U.S. National Toxicology Program (NTP).

Environment: The chemicals possess properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute toxicity which may become evident only at very high exposure level, they should nevertheless be noted by chemical safety professionals and users.