FOREOWRD INTRODUCTION

M/P-CRESOL CATEGORY

m/p-Cresol CAS N°:15831-10-4

m-Cresol CAS No: 108-39-4

p-Cresol CAS No: 106-44-5

SIDS Initial Assessment Report

For

SIAM 16

Paris, France, 27 – 30 May 2003

1.	**Category Name:**	m/p-Cresol
2.	**CAS Numbers:**	m/p-Cresol Category: m-Cresol CAS No: 108-39-4 p-Cresol CAS No: 106-44-5 m/p-Cresol CAS No: 15831-10-4
3.	**Sponsor Country:**	Germany Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn-Bad Godesberg
4.	**Shared Partnership with:**	
5.	**Roles/Responsibilities of the Partners:**	
•	Name of industry sponsor /consortium	Bayer AG, Germany Contact person: Dr. Burkhardt Stock D-51368 Leverkusen Gebäude 9115
•	Process used	see below
6.	**Sponsorship History**	
•	How was the chemical or category brought into the OECD HPV Chemicals Programme ?	
7.	**Review Process Prior to the SIAM:**	last literature search (update): 01.06.2002 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 15.05.2002 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search terms
8.	**Quality check process:**	As basis for the SIDS-Report the IUCLID was used. All data have been checked and validated by BUA.
9.	**Date of Submission:**	19 February 2003
10.	**Date of last Update:**	

11. Comments:

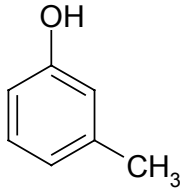
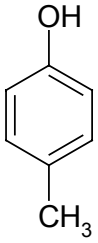
OECD/ICCA - The BUA* Peer Review Process

Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:

- a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET
- Review of data and assessment of the quality of data
- Review of data evaluation
- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications
- Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications (if original reports are missing: reliability (4), i.e. reliability not assignable)
- Review of validity of structure-activity relationships
- Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)
- In case of data gaps, review of testing plan or rationale for not testing

* BUA (GDCh-Beratergremium für Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)

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 capacity 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.

SIDS Initial Assessment Report

1 IDENTITY

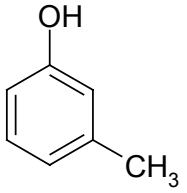
1.1 Identification of the Substance

Chemical Names: m-Cresol
p-Cresol
m-/p-Cresol mixtures

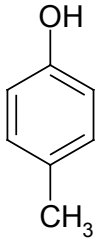
CAS Numbers: m-Cresol CAS No: 108-39-4
p-Cresol CAS No: 106-44-5
m/p-Cresol CAS No: 15831-10-4

Molecular Formula: C_7H_8O

Structural Formula:



m-Cresol



p-Cresol

Molecular Weight: 108.14 g/mol

m-Cresol, p-cresol and mixtures of both isomers are discussed in one SIAR because of their similar properties in physico-chemical data, environmental fate, ecotoxicity, and toxicity. Both isomers as well as their mixture are products of technical importance.

o-Cresol was subject of previous work in the OECD HPVC Programme. The Screening Information Data Set (SIDS) has been published by OECD in 1998 (OECD 1998). Data for o-cresol are therefore generally not included in this assessment.

Table 1 Identification of the 3 Cresol Products of Technical Importance

Substance	Synonyms	CAS-No.	Composition
m-Cresol	3-Methylphenol	108-39-4	Purity > 99 %
p-Cresol	4-Methylphenol	106-44-5	Purity approximately 99.9 %
m/p-Cresol mixtures		15831-10-4	60 - 75 % m-Cresol, 25 - 40 % p-Cresol

1.2 Physico-Chemical properties

The physico-chemical properties of the technical products are presented in table 2 (for references cf. SIDS Dossiers).

Table 2: Summary of Physico-Chemical Properties of Cresols

Substance	m-Cresol	p-Cresol	m/p-Cresol
Melting point [°C]	11.8	35.5	ca.10
Boiling point (1013 hPa) [°C]	202.2	201.9	ca. 200
Density (20°C) [g/cm3]	1.0336	1.0178	ca. 1.035
Vapour pressure (25°C) [hPa]	0.147	0.147	
Log Kow (exp.)	1.96	1.94	1.94 - 1.96
Water solubility (25°C) [g/l]	22.7	21.5	24.4
Dissociation constant pKa	10.09	10.26	

Of particular importance for environmental behaviour and ecotoxicity are the values for partition coefficient (log Kow), vapour pressure and water solubility. Water solubility, vapour pressure and log Kow were experimentally determined for both isomers. The values are nearly identical for the pure isomers, so the isomer mixture can be assessed as well.

Cresols are weak acids. The pKa values of 10.09 and 10.26 for m- and p-cresol resp. indicate that at environmental relevant pH values (5-9) the substances are largely non-dissociated in aqueous solution.

1.3 Category Justification

The category justification is presented in the Annex.

2 GENERAL INFORMATION ON EXPOSURE

About 40 % (decreasing tendency) of the world-wide required cresols are isolated from the natural sources coal tar and spent refinery caustics. The separation of phenolics is essentially a recovery, purification, and fractional operation (Ullmann 2002).

The most important processes to obtain synthetic cresol mixtures with an usable content of the m- and p-isomers are

- alkaline chlorotoluene hydrolysis (higher m-cresol content)
- sulfonation of toluene and alkali fusion (higher p-cresol content)
- cleavage of cymene hydroperoxide (higher m/p- and low o-cresol content) (Ullmann 2002).

Only o-cresol can be separated directly from the crude cresol-mixtures by distillation. The m/p-isomer mixture cannot be separated into the isomers by conventional distillation technology because of the low difference in the boiling points of this two isomers. There are different industrial methods to separate the m- and p-isomers:

- by distillation using an adsorption column process,
- butylation of the mixture, distillation and debutylation of the separated butylkresols,
- using a separation process via urea-cresol- adducts (Ullmann 2002).

Table 3: Estimated Capacities and Their Locations

Region	m/p-Mixture [1]		Pure m-Cresol [2]		Pure p-Cresol [2]	
WORLD	128,000 t	100 %	28,500 t	100 %	59,500	100 %
SE-ASIA	58,000 t	45 %	14,500 t	51 %	31,000	52 %
W-EUROPE	30,000 t	23 %	8,000 t	28 %	13,000 t	22 %
N-AMERICA	18,000 t	14 %	6,000 t	21 %	12,500 t	21 %
OTHER	20,000 t	16 %			3000 t	5 %
E-EUROPE	2000 t	2 %				

(Srour; 1 = stage October 2001, 2 = stage July 2000)

The largest part of cresols is used as intermediates in chemical processes:

Pure m-cresol (total processing in 1999 21,000 t) is mainly used as an intermediate for the following products: for synthetic vitamin E (39 %), and in the synthesis of pesticides (insecticides, herbicides, 29 %), fragrances and antioxidants (15 %), disinfectants and preservatives (12 %) and other chemicals (5 %) (Srour 2000) (e.g. photographic chemicals and explosives, ATSDR 1992; HSDB 1993).

Pure p-cresol (production and demand in 1999 31,400 t) is used in chemical synthesis for the antioxidant BHT (49 %), other antioxidants (17 %), anisaldehyde (18 %), and other intermediates (16 %) which are used for production of pharmaceuticals, plant protection agents and dyestuffs (Srour 2000).

These figures for m- and p-cresol show that the actual production and demand is much below the estimated capacities given in Table 3.

m/p-Isomer mix is used to produce antioxidants (e.g. BHT, about 15,000 t/a) and arylphosphates (approximately 6000 t/a), the latter are used as plasticizers, flame retardants or special catalysts (Srour 2001).

m/p-Isomer mix is used as a solvent in the wire enamels business (49,000 t) (Srour 2000). In a closed process the solvent, which evaporates during the drying of the wires, is burned. The burning heat is used for heating the drying unit. Due to the waterfree process significant releases into the hydrosphere can be excluded. The emissions of cresols into the atmosphere from the application wire enamels is controlled by national authorities in the EC (EC 1999).

Furthermore some direct uses of cresols are known (< 1 % of production):

- m-Cresol is used by professionals as bactericide in the biotechnological processing of pharmaceuticals (Bayer AG 2003)
- m-Cresol is used as a preservative in pharmaceutical articles (injection solutions of insulin, somatropin) (Rote Liste 2002)
- m-Cresol is used as a pesticide for the treatment of the stems of fruit trees and plants: This is a registered application and exclusively performed by professionals (HSDB 1993).
- Cresols (all isomers) are used as disinfectants, preservatives or stabilizers in cleaning/washing agents, surface treatment products, paints, solvents, adhesives, binding agents and fillers (hardener), corrosion inhibitors, and impregnation materials. (Danish, Swedish, and Swiss Product Register 2002)

10,000 to 50,000 t/a cresol isomer mixture is produced at Bayer AG. Separation of the o-isomer results in a m/p-cresol mixture yielding about 70 % m-cresol. More than 90 % of this product is processed inside the company to produce pure m-cresol (5000 – 10,000 t/a by butylation process), microbicides (chlorination), aroma stuffs (alkylation), plasticizers and pesticides. Production and processing take place in closed systems. About 15 % of the raw cresol mixture ex Bayer AG are sold as m/p-cresol mixture or as pure m-cresol.

Cresols occur widely in nature (many plants, cheese flavor and some other foods, petroleum, coal tar [in the carbolic oil fraction and in carbolineum (Roempp 1999);], crude oil, wood tars [e.g. in Juniper tar oil, birch oils], volcanic actions, putrefaction). Pulich et al. (1975) mention cresols as an ingredient of crude and fuel oils with an concentration of less than 1 %. They are emitted from municipal incinerators, during coal and wood combustion, with vehicle exhaust, and cigarette smoke [e.g. component of the phenol fraction, which makes up 1 - 4 % of the smoke]. Cresols are also products of the photooxidation of toluene in the atmosphere (Howard 1989).

In automotive exhaust m-cresol concentrations of 1.18 - 1.49 mg/m^3 were detected (Kuwata et al. 1981). With 13 m^3 exhaust gas per kg gasoline and a gasoline consumption of 56.5 Mio t/year for Germany m-cresole emissions to the environment of 867 to 1094 t/year via automotive exhaust are calculated.

p-Cresol is an endogenous metabolite of the amino acid tyrosine and a normal constituent of human urine with levels of excretion ranging from 16 to 74 mg/24 hours (Bone et al. 1976; Renwick et al. 1988)**.** Based on this data a p-cresol emission to the environment of 467 to 2160 t/year can be calculated for the population of Germany (80 Mio).

The exhaust from production and processing of cresols in Germany are connected to exhaust purification plants. Following the last Official German Emission Declaration in 2000 only 81 kg/a Cresols were emitted into the atmosphere (Bayer AG 2000)

The emissions of cresols into the atmosphere from the application wire enamels is controlled by national authorities in the EC (EC 1999).

In a special program the effluent of the waste water treatment plant at Bayer AG was monitored for m-/p-cresols. All values of 22 effluent measurements were below the detection limit of 50 µg/l. For the receiving water a PEC of < 7.1 x 10^{-2} µg/l is calculated taking into account the 10 percentile of the river flow, the dilution factor, and the 90 percentile of the analysis measurements (Bayer AG 2003).

Recent monitoring data for cresols in the environment are not readily available. Older literature shows data for areas which were mostly particularly polluted (Howard 1989). These data cannot be used for a current evaluation.

Exposure to the environment may occur due to the use of cresol as a pesticide and other minor uses. However, at present no quantification of the release is possible.

2.1 Environmental Exposure and Fate

2.1.1 Distribution

As the main physico-chemical properties of the cresol isomers are in the same order of magnitude, the environmental distribution behaviour is expected to be similar.

The distribution of cresols in a ”unit world” was calculated according to the Mackay fugacity model level I (Bayer AG 2002a, b) based on the physico-chemical properties listed in table 1.2. For both,

m-cresol and p-cresol the main target compartment was estimated to be water (96.3 %) (Calculated distribution between environmental compartments: m-cresol resp. p-cresol: air: 2.33 / 2.46 %, water: 96.32 / 96.26 %, soil: 0.69 / 0.66 %, bottom sediment: 0.65 / 0.62 %, suspended sediment: 0.001 / 0.001 %, biota: 0.0004 / 0.0004 %). The distribution of cresols between aqueous solution and air is described by the Henry's law constant. Experimentally determined values of 0.09 Pa m^3/mol for m-cresol (Altschuh et al. 1999) and 0.10 Pa m^3/mol for p-cresol (Gaffney et al. 1987) are available. Both values indicate a low volatility from aqueous solution according to the criteria of Thomas (1990).

The distribution between the organic phase of soil solids and water was determined in batch equilibrium experiments similar to the OECD Guideline 106. For a clay loam soil Boyd (1982) determined Koc values of 34.58 for m-cresol and 48.66 for p-cresol indicating a low sorption potential for the cresol isomers according to the criteria of Blume and Ahlsdorf (1993).

2.1.2 Abiotic Degradation

With regard to its chemical structure m-cresols and p-cresols are not expected to hydrolyse under environmental conditions.

Several investigations are available about the indirect photolysis by OH-radicals in the atmosphere. In his critical review Atkinson (1994) recommended values for the reaction constant kOH at room temperature of 6.4 x 10-11 cm3 molecule-1 s-1 for m-cresol and 4.7 x 10-11 cm3 molecule-1 s-1 for p-cresol. Based on a tropospheric OH radical concentration of 5 x 105 molecules cm-3 corresponding half-lives of 6.0 h for m-cresol and 8.2 h for p-cresol can be calculated. Semadeni et al. (1995) determined the temperature dependency of the reaction constants in a smog chamber experiment: the calculated half-life is 3.8 h both for m-cresol (299 K) and p-cresol (301 K).

Because of the presence of a chromophore cresols are expected to undergo photolytical degradation in the hydrosphere. Scully and Hoigne (1987) determined the rate constants for the reaction of p-cresol with singlet oxygen in a laboratory experiment. Solutions of p-cresol (<10-4 M) in 0.05 M phosphate buffer were irradiated in a merry-go-round reactor, 5 mg/l rose bengal was used as a sensitizer. The authors estimated a half-life of 21 d in surface water under noon summer sunlight and the latitude of Switzerland.

However, under environmental conditions longer half-lives should be expected since the solar irradiation is considerably weakened due to light absorption and dispersion at greater water depths, cloudiness and the diurnal fluctuations of light intensity.

2.1.3 Biodegradation

Aerobic

Several standard tests on the aerobic biodegradation of the cresol isomers are available. Table 4 presents an overview of the results:

Table 4: Standard Tests on Aerobic Biodegradation of Cresols

Method	Duration	m-Cresol	p-Cresol	Reference
OECD 301 D	28 d	65 - 90 %		Bayer AG (2002c)
OECD 301 C	40 d	80 - 95 %	80 - 95 %	Desai et al. (1990)
OECD 302 B	10 d	96 %	100 %	Wellens (1990)
	5 d	95.5 %	96 %	Pitter (1976)

A Closed-Bottle-Test (OECD 301 D) using m-cresol as test substance in two concentrations (0.8 mg/l and 2.4 mg/l) was performed (Bayer AG 2002c). While in two parallel experiments at a m-cresol concentration of 0.8 mg/l nearly 90 % degradation was determined after 28 days incubation, at the test concentration 2.4 mg/l about 65 % degradation was achieved in two parallel vessels. At both concentrations the pass level of 60 % was reached within 28 days. The 10d- window was fulfilled in all but one parallel tests indicating that m-cresol can be considered as readily biodegradable.

Desai et al. (1990) determined the Monod kinetics of m- and p-cresol using an electrolytic respirometry test comparable to OECD guideline 301 C. Activated sludge from a wastewater treatment plant receiving predominantly domestic sewage was used as inoculum in a concentration of 30 mg/l. Within an incubation period of 40 days degradation of both cresol isomers (initial concentration 100 mg/l) was in the range of 80 % to 95 %. The specific oxygen uptake curves of the cresols are not reported. However, the authors state that all test compounds revealed the same pattern: the lag phase, biodegradation phase and the plateau region within a period of 10 days. Therefore, it can be concluded from this test that m- and p-cresol are readily biodegradable. The first order degradation constants ln(k) [h-1] were determined to be –5.77 (m-cresol) and –5.87 (p-cresol). From these values half-lives of 9.3 d resp. 10.3 d can be calculated.

The inherent degradability of two cresol isomers was studied by Wellens (1990). In a test according to the OECD guideline 302 B, m-cresol and p-cresol degraded to 95 % resp. 100 % within 10 days after lag-periods of 2 days. Using a 5 days incubation period, Pitter observed that removal of each 96 % of both compounds occurred with the same initial degradation rate of 55 mg COD g-1 h-1.

Van Veld and Spain (1983) demonstrated that p-cresol is rapidly degraded in different parts of an aquatic estuary system. From a river estuary, each 3 samples were taken from water, sediment and intact eco-cores having an aerobic layer of detritus overlying anaerobic sediment. Water and water/sediment samples were incubated in the laboratory with 14C-labelled p-cresol and shaken in flasks at 18 °C in the dark. Based on HPLC and 14CO2 measurements, half-lives between 9.4 and 43 h for p-cresol in water and between 5.9 and 11 h in water/sediment systems were determined. In intact eco-cores, p-cresol degraded with half-lives between 3.0 and 16 h.

The Closed-Bottle-Test (Bayer AG 2002c) reveals that m-cresol is readily biodegradable. As demanded by the OECD guideline, the oxygen consumption was above 60 % after 10 and 28 days. Desai et al. (1990) determined the degradation of both m- and p-cresol and found similar rate constants for both isomers. From this study it can be concluded that both m- and p-cresol are readily biodegradable.

Anaerobic:

The anaerobic degradation properties of a substance are important for the assessment of the substance's fate during secondary digesting of sewage sludge and the fate in anaerobic sediment layers. A number of investigations on the anaerobic degradability of cresols is available. The most

extensive study was conducted by Shelton and Tiedje (1981). Primary anaerobic sludges from 12 treatment plants receiving mainly domestic waste water were diluted to 10% in a mineral salt medium and incubated with 30 mg cresol/l. Triplicate samples were incubated for 8 weeks. Degradation was related to the theoretical CH4 and CO2 production. With m-cresol as the test substance, no degradation was observed in 4 sludges, while in 6 sludges the degradation ranged from 55 to 103 % after lag-periods of 4-6 weeks. For the experiments with 2 sludges the data were insufficient. In tests with p-cresol a degradation in the range of 62-101% was observed after lag-periods of 2 - 5 weeks (data for 1 sludge were insufficient). No explanation for the high variability of degradation results is given by the authors (Most of the results of this extensive study were also published in a journal; Shelton and Tiedje 1984). Monitoring the formation of methane and carbon dioxide, Battersby and Wilson (1989) obtained about 75 % of the theoretical yield of methane and carbon dioxide from m-cresol during a > 60 days incubation period including a lag phase of 40 days. For p-cresol the theoretical yield was 96 % during the same incubation period including a lag phase of 7 days.

As concluded above, m- and p-cresol can be considered as being readily biodegradable under aerobic conditions, thus it is unlikely that cresols released into waste waters or into surface waters will reach the anaerobic zones. Therefore the anaerobic degradation is expected to be of minor importance for the hazard assessment of cresols.

2.1.4 Bioaccumulation

Freitag et al. (1985) determined bioconcentration factors (BCF) of 14C-labelled m-cresol in fish (Leuciscus idus melanotus). The fish were exposed to a 0.05 mg/l solution of the tests compound. After the test period of 3 days radioactivity was measured in water medium and fish. A substance-specific analysis was not applied. BCF values of 20 were obtained.

In the same study BCF-values of 40 and 4900 for algae are reported without explanation for the difference. Higher BCF values with algae may be obtained due to adsorption of test substance to the surface of the algae and due to the high surface-volume ratio in the test. Thus the algal data were not used in the assessment of the bioaccumulation potential.

The low BCF value for fish is supported by a BCF, estimated on the basis of the log Kow. Based on the equation log BCFfish = 0.85. log Kow – 0.70 (EC 1996), a bioaccumulation factor (BCF) of 9.3 is calculated from the log Kow of 1.96 (m-cresol).

Experimental data for p-cresol are not available. Because of the similar log Kow, a similar accumulation behaviour is expected. For m-, p-cresols and the mixture the bioaccumulation potential is considered to be low.

2.2 Human Exposure

2.2.1 Occupational Exposure

The primary occupational exposure during manufacture and processing is via skin contact and, to a lesser extent, through inhalation of the vapours. No information is readily available on the total number of sites, which manufacture, process, or use cresols.

In Germany the workplace limit concentration is 22 mg/m³ (= 5 ppm) as TWA for the sum of all cresol isomers (TRGS 900, 2002). The German exposure limit value is in accordance with that of the other European countries limit values and with the US-TLV value.

Investigations on cresols at the workplace have to be performed according to German regulations (TRGS 402). This includes regular surveys on exposure levels at different workplaces and appropriate control measurements.

At Bayer AG, 27 measurements of the workplace concentration were made between 1996 and 2001. All values were below 2.0 mg/m³. The measurements were performed at different workplaces during production, processing, sampling, and filling/drumming of m/p-cresols. 11 measurements are short time values (mostly during sampling), the others are total shift values.

To protect workers from exposure to cresols at workplace, several different precautionary and protective measures are taken including engineering controls, periodical personnel training and appropriate personal protection equipment for different work situations. Sampling takes place in an automated manner with exhausting device. Filling/drumming is totally automated. In special situations (e.g. maintenance/repair work) special personal protection equipment has to be worn (e.g. self-contained breathing apparatus, full chemical protective clothing)

For on-site processing the m/p-cresols are transported in pipelines. For normal transport to customers m/p-cresols are transported in road tank trucks or rail tank wagons. Less then 10 % are filled in special rolling channel drums.

Down stream professional users of cresols are informed by way of a material safety data sheet on the recommended safety measures, including personal protective equipment (such as goggles, face shields, gloves, aprons, personal respirators), and local and/or general ventilation systems. No exposure measurements were available for workers involved in down-stream uses of m-Cresol, p-Cresol, and m/p-Cresol mixtures.

2.2.2 Consumer Exposure

The general public can be exposed to all isomers of cresol from air inhalation, food and beverage ingestion and dermal contact.

Cresols (mixed isomers) are widespread in nature, occuring, for instance, in many plants, petroleum, coal tar, crude oil and, volcanic actions. Foods, such as tomatoes, ketchup, asparagus, cheeses, butter, bacon, and smoked foods, as well as beverages, such as red wine, raw and roasted coffee and black tea, contain mixed cresols. Concentrations in spirit beverages were found to be within the range of 0.01 -0.2 mg/l (IPCS 1995). They are emitted from municipal incinerators, during coal and wood combustion, with vehicle exhaust, from oil refineries, and cigarette smoke (ATSDR 1992). The amount in tobacco smoke is approximately 75 µg in a nonfilter cigarette (IPCS, 1995), and exposure to m/p-cresol from environmental tobacco smoke has been estimated to 0.41 µg/m³ in adult Californian non-smokers (Miller et al. 1998). Cresols are also products of the photooxidation of toluene (Howard 1989). m-Cresol and p-cresol were identified, but not quantified, in the ambient outdoor air in the US (Shah and Singh, 1988). Combined m-/p-isomers were detected in the ambient air of Portland/USA at a reported mean concentration of $1.3*10^{-7}$ µg/m³ (0.03 ppb) (Grossjean 1991) and at a mean concentration of 1.4 µg/m³ (0 - 4.1 µg/m³) in the US (Kelly et al. 1993). Combined m-/p-isomers were detected at a concentration of 0.04 µg/m³ in Switzerland (Tremp et al. 1988). m/p-Cresols were found in USA outdoor air in concentrations of 0.038 - 0.411 µg/m³ in Minneapolis (MN) and of 0.053 - 0.408 µg/m³ in Salt Lake City (UT) in the winter months. The range shows the different influence of residential wood burning and of traffic (Hawthorne et al. 1992). 3.9×10^{-4} µg/m³ (88 ppb) were found near a shale oil wastewater facility (Hawthorne and Sievers 1984).

m/p-Cresol isomers were detected in cloud water in the Vosges mountains/France (altitude about 800 - 1000 m) at concentrations of 0.47 - 2.23 mg/m³ and at 0.11 - 1.21 mg/m³ in the rain (Levsen

et al. 1993). m/p-Cresol was found in rainfall in Switzerland at a concentration of 4.5 mg/m³ (Tremp et al. 1988).

The lack of adequate monitoring data, however, makes quantitative estimates of daily intakes of cresol from these sources practically impossible.

m-Cresol and p-cresol are permitted for direct addition to food for human consumption as flavouring substances (EU 1999), and are used as perfumes and aromatic raw materials in cosmetic products (SCCNFP 2000). m-Cresol is also used as preservative in cosmetics (BgVV 2001).

Exposure of humans is possible through the use of m-cresol as a preservative in pharmaceutical injection solutions (e.g. insulin injection solution 1.6 - 3 mg/ml) (Rote Liste 2002).

p-Cresol is used in cleaning/washing agents and in surface treatment products at concentrations up to 2 % (Danish Product Register 2002).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

All cresol isomers are absorbed across the respiratory and gastrointestinal tract and through the intact skin (Pereima 1977, Bray et al. 1950, Mandel 1971, DeBruin 1976, Roberts et al. 1977, IPCS 1995). Limited data indicate that cresols are widely distributed throughout the body after uptake (IPCS 1995). Cresols are mainly conjugated with glucuronic acid and inorganic sulfate and excreted as conjugates with the urine (Bray et al. 1950). Minor pathways include hydroxylation of the benzene ring (all isomers) and, for p-cresol, side-chain oxidation to p-hydroxybenzoic acid (Bray et al. 1950). For p-cresol, oxidation to a reactive quinone methide intermediate was also found in rat liver *in vitro* (IPCS 1995, Thompson et al. 1996).

At physiological pH, the conjugated metabolites are ionized to a greater extent than the parent compound, which reduces renal reabsorption and increases elimination with the urine (Mandel 1971). In addition to urinary excretion, cresols are excreted in the bile, but the most part undergoes enterohepatic circulation (IPCS 1995, Deichmann and Keplinger 1981, Scheline 1973). There are known species differences in the specific conjugation reactions of cresol isomers and the relative amounts of glucuronide and sulfate conjugates therefore differ between species and also vary with dose (Mandel 1971, Scheline 1973, IPCS 1995).

p-Cresol is an endogenous product of protein breakdown in humans. The anaerobic microflora of the ileum reportedly produces this isomer from the amino acid tyrosine (Bone et al., 1976). p-Cresol is a normal constituent of human urine with levels of excretion ranging from 16 to 74 mg/24 hours (Bone et al. 1976, Renwick et al. 1988, Schaltenbrand and Coburn 1985).

Conclusion:

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*.

3.1.2 Acute Toxicity

There are no studies with m-, p-, or m/p-cresol mixtures according to the current OECD Test guidelines, but there are studies which are adequately documented and are considered of sufficient quality to allow an evaluation of this endpoint:

Oral

m-Cresol:

LD_{50} (male rat): 242 mg/kg bw (undiluted). Until 4 hours post application the animals showed hypoactivity, tremors, convulsions, salivation and prostration. Gross autopsy revealed inflammation of the gastrointestinal tract, and hyperemia of lungs, liver and kidneys only in the decedents whereas the survivors showed no significant findings at the end of the 14 day observation period (BioFax 1969a). Given as 10 % olive oil solution the LD_{50} (rat) was 2020 mg/kg bw (Deichmann and Witherup 1944).

p-Cresol:

Application of 100 - 316 mg/kg bw undiluted substance to 5 male rats/dose resulted in an LD_{50} of 207 mg/kg bw. As signs of intoxications were observed hypoactivity, tremors, lacrimation, dyspnea, cyanosis, hemorrhagic rhinitis, convulsions, prostration and finally death occurred. Gross autopsy revealed inflammation of the gastrointestinal tract in the survivors at the end of the 14 d observation period. Haemorrhage of gastrointestinal tract, hyperemia of lungs, liver and kidneys were reported from decedents (BioFax 1969b). Given as 10 % olive oil solution the LD_{50} (rat) was 1800 mg/kg bw (Deichmann and Witherup 1944).

m/p-Cresol:

There are no studies available using a m/p-cresol mixture.

Conclusion:

Following oral application the LD_{50} of undiluted m-cresol in rats was 242 mg/kg bw; and the LD_{50} of undiluted p-cresol was 207 mg/kg bw. Thus, it can be assumed that the LD_{50} of m/p-cresol mixtures is slightly above 200 mg/kg bw. Clinical signs included hypoactivity, salivation, tremors, and convulsions.

Inhalation

m-Cresol:

In an 8 hour inhalation study rats were exposed to saturated vapour which was generated at room temperature. No mortality occurred and no signs of intoxication were observed (Mellon Inst. Ind. Res. 1949). These observations were in accordance with the inhalation study reported by BioFax (1969a): 6 male rats were exposed to 710 mg/m^3 for 1 hour and then observed for 14 days. No rat died and no signs of intoxication were observed. From gross autopsy, no pathological findings were reported. From a study in which m-cresol aerosols were used, the mean lethal concentration in rats was reported to be 58 mg/m^3 (exposure time not mentioned).. Clinical signs of toxicity included irritation of mucous membranes, neuromuscular excitation and convulsions. Haematuria was reported at very high concentrations (Pereima 1975).

p-Cresol

The exposure of 6 male rats to 710 mg/m^3 p-cresol for 1 hour caused no mortality, and no signs of intoxication. From gross autopsy no significant findings were reported (BioFax 1969b). From a

study in which p-cresol aerosols were used, the mean lethal concentration in rats was reported to be 29 mg/m³. Clinical signs of toxicity included irritation of mucous membranes, neuromuscular excitation and convulsions. Haematuria was reported at very high concentrations (Pereima 1975).

m/p-Cresol:

There are no data available using a m/p-cresol mixture.

Conclusion:

No mortality nor clinical signs of toxicity were seen following exposure to the 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 of toxicity included irritation of mucous membranes, excitation and convulsions. Haematuria was reported at very high concentrations.

Dermal

m-Cresol:

1000 - 3160 mg/kg bw undiluted m-cresol was applied to the skin of 5 rabbits per dose (exposure time not mentioned, observation time: 14 days) yielding an LD_{50} of 2050 mg/kg bw. From 4 hours post application up to 12 hours the animals showed lacrimation, salivation, hypersensitivity, convulsions and hypoactivity; the treated skin showed severe erythema and burns. At gross autopsy, the decedents showed hyperemia of lungs and kidneys whereas survivors showed no significant findings. (BioFax 1969a). This result is in accordance with the results of another study, in which 24 hr exposure to the neat material was followed by a 14-day observation period. The LD_{50}(rabbit) was reported to be 2830 mg/kg bw (Vernot et al. 1977).

p-Cresol:

215 - 681 mg/kg bw undiluted p-cresol was applied to the skin of 5 rabbits per dose (exposure time not mentioned, observation time: 14 days) yielding an LD_{50} of 300 mg/kg bw. From 4 hours post application up to 12 hours the animals showed tremors, salivation, sedation and finally died. At the application site severe subdermal hemorrhaging and severe erythema were observed. At gross autopsy, the decedents showed inflammation of the kidneys whereas survivors showed no significant findings (BioFax,1969b). This result is in accordance with the results of another study, in which 24 hr exposure to the neat material was followed by a 14-day observation period. The LD_{50}(rabbit) was calculated to be 300 mg/kg bw (Vernot et al. 1977).

m/p-Cresol:

There is no study available using m/p-cresol-mixtures.

Conclusion:

Following dermal application in rabbits the LD_{50} of undiluted m-cresol was 2050 mg/kg bw and the LD_{50} of p-cresol was 300 mg/kg bw. It can be assumed that the LD_{50} of m/p-cresol mixtures is between 300 and 2000 mg/kg bw.

3.1.3 Irritation

Skin Irritation

There is no study according to the current OECD Test guideline, but the available studies are adequately documented and are considered of sufficient quality to allow an evaluation of this endpoint:

m-Cresol:

Application of 0.5 ml of the undiluted liquid to the intact or abraded skin of each of 6 rabbits caused within 24 hours severe erythema and edema in each rabbit, which did not disappear within the 72 hours observation time (mean score value: 8.00/8.00) (BioFax 1969a). Using semi-occlusive dressing for 4 hours, the visible tissue damage was indicative of corrosive effects (Vernot et al. 1977).

p-Cresol:

Application of 0.5 ml of the undiluted liquid to the intact or abraded skin of each of 6 rabbits caused within 24 hours severe erythema and edema in the skin of each rabbit, which did not disappear within the 72 hours observation time (mean score value: 8.00/8.00) (BioFax 1969b). Using semi-occlusive dressing for 4 hours, the visible tissue damage was indicative of corrosive effects (Vernot et al. 1977).

Application of 0.5 % p-cresol to the skin for 6 weeks resulted in permanent depigmentation of the skin and hair in black and agouti mice (Shelley 1974).

m/p-Cresol:

Undiluted m/p-cresol mixture was applied to the clipped intact skin of three male and female rabbits for four hours covered by semiocclusive dressing and evaluated as corrosive because necrosis with severe edema was noted 4 hours post application and eschar formation developed within 24 hours (Younger Lab 1974).

Conclusion:

m-Cresol, p-cresol and m/p-cresol mixtures are corrosive to the skin.

Eye Irritation

m-Cresol:

0.1 ml of the undiluted liquid caused highly irritating effects in the cornea, iris and conjunctivae of all 6 treated rabbits. There was no recovery during the 72 hours observation period, and the mean irritation score at 72 hours was 87.3/110 (BioFax 1969a).

p-Cresol

0.1 ml of the undiluted liquid caused highly irritating effects in the cornea, iris and conjunctivae of all 6 treated rabbits. The effects did increase in severity during the 72 hours observation period, and the mean irritation score at 72 hours was 93.0/110 (BioFax 1969b).

m/p Cresol:

There is no study available using a m/p-Cresol-mixture.

Conclusion:

The instillation of undiluted m- or p-cresol into the rabbit eye according to the Draize method resulted in extreme irritation with the risk of serious eye damage.

3.1.4 Sensitisation

m-Cresol:

There is no study available using m-cresol.

p-Cresol:

A modified Draize test was performed on 10 guinea pigs (males and females). Preliminary irritation studies were performed to determine the suitable concentrations: the intradermal injection challenge concentration was a 0.1 % solution and the application challenge concentration was a 10 % solution. p-cresol did not induce sensitization in guinea pigs (Sharp 1978).

Human data:

A maximization test was conducted on 25 volunteers using a 4 % concentration of p-cresol in petrolatum. The maximization test involved an induction phase of 5 consecutive 48-hr covered patch tests, sometimes separated by 24-hr periods of treatment with a mild irritant, followed 10 - 14 days later by a 48-hr challenge patch using the same concentration. There were no sensitization reactions in any of the volunteers (Kligman 1972).

m/p-Cresol:

In a study in which a 7.5 % solution of a mixture of m- and p-cresol in acetone was repeatedly applied to the skin of guinea pigs, sensitization was not observed (DECOS, 1998).

Conclusion:

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 (Deichmann and Keplinger 1981).

3.1.5 Repeated Dose Toxicity

Oral application

Regenerative changes in the nasal epithelia as a result of the irritant effects were the predominant signs of toxicity following repeated dosing of rats and mice with p-cresol or with the 60:40 m/p-cresol with the feed in 28-day and 13-week studies. At minimum effect levels of 1000 ppm in the diet (mouse, ca. 200 mg/kg bw/day) and 3000 ppm in the diet (rat, ca. 250 mg/kg bw/day), the liver was the target organ for the toxic action of m-cresol, p-cresol and the 60:40 m/p-cresol mixture. A dose-dependent increase in liver weight was observed, but histopathological effects or changes of parameters indicative of liver toxicity were seen with p-cresol at high doses only. In the 13-week feeding study with m/p-cresol transitory increases in serum total bile acids, alanine aminotransferase and sorbitol dehydrogenase near the start of the study suggested that hepatocellular injury with a decrease in hepatocellular function may have occurred and regressed in the course of the study. Kidney weights were increased in male mice after feeding p-cresol for 28 days at 3000 ppm (469 mg/kg bw/day), and lengthened estrous cycles were noted in rats fed with the m/p-cresol at 7500 ppm (509 mg/kg bw/day) in the 13-week study. In feeding studies bone

marrow hypoplasia was found in rats after exposure to p-cresol at ≥ 3000 ppm (256 mg/kg bw/day), with m/p-cresol at 15,000 ppm, and in mice after exposure to p-cresol and m/p-cresol at 30,000 ppm.

Increased colloid within thyroid follicles in female rats were observed with m/p-cresol only at ≥ 509 mg/kg bw/day, but the biological significance of this observation is uncertain.

Based on the data from the subacute and subchronic studies there is no evidence to suggest that a significant increase in toxicity occurs with longer exposures

In a poorly documented neurotoxicity study in rats with m-cresol and p-cresol, convulsions were seen only in the groups treated with ≥ 450 mg/kg bw/day. Hypoactivity, rapid labored respiration and excessive salivation were observed sporadically at doses of ≥ 50 mg/kg bw/day. In spite of the observed clinical signs, few significant changes were found in performance on neurobehavioural test batteries, no brain weight changes were noted, and no gross or histopathological lesion in the brain or other nervous tissues were found for any isomer (TRL 1986 as cited in IPCS 1995).

Results of repeated dose oral toxicity studies with m-cresol, p-cresol and m/p-cresol (60:40) are summarized in the following tables:

Table 5: m-Cresol: Repeated Dose Toxicity Rat/Mouse

Study-Description	NOAEL	Effects	Reference
Rat			
5 rats/sex/dose, 28 d, feeding 0, 300, 1000, 3000, 10,000, 30,000 ppm (m: 0, 25, 85, 252, 870, 2470 mg/kg bw/day; f: 0, 25, 82,252, 862, 2310 mg/kg bw/day),	3000 ppm (252 mg/kg bw/day)	No mortality, no clinical signs of toxicity 30,000 ppm, m, f: decreased body weight gain and final body weight, decreased food consumption, minimal to mild uterine atrophy in 4/5 females; no histopathological changes in other organs ≥ 10,000 ppm: increased rel liver weights	NTP 1991
30 rats/sex/dose, 13 w gavage 0, 50, 150, 450 mg/kg bw/day in corn oil	Males: 50 mg/kg bw/day Females: 150 mg/kg bw/day	450 mg: 1 male died (gavage error), lethargy, tremor, hunched posture, dyspnoe, reduced body weight gain, decreased food consumption (m); no histopathological changes 150 mg: reduced bw gain (m)	Microbiological Associates Inc 1988a
10 rats/sex/dose, 13 w gavage 20 rats/sex as control 0, 50, 150, 450 mg/kg bw/day in corn oil neurotoxicity study available as summary only	*	450 mg: reduced food consumption (m,f) convulsions, death of 1 female, urination ↑ (f) ≥ 50 mg: clinical signs as salivation, urine wet abdomen, hypoactivity, rapid and labored respiration, myoclonus, hyperreactivity	TRL 1986
Mouse			
5 mice/sex/dose, 28 d feeding 0, 300, 1000, 3000, 10,000, 30,000 ppm (m: 0, 53, 193, 521,1730, 4710 mg/kg bw; f: 0, 66, 210, 651, 2080, 4940 mg/kg bw)	1000 ppm (m: 193 mg/kg bw/day), < 300 ppm (f, 66 mg/kg bw/day)	Mortality: 1/5 control male; 30,000 ppm: 2/5 f, 2/5 m; 10,000 ppm: 1/5 f 30,000 ppm, m,f: reduced body weight gain, and final body weight, decreased food consumption, thin appearance, lethargy, tremor, hypothermia (f only), in females atrophy of mammary gland, ovaries, uterus; no histopathological changes in liver and kidneys ≥ 10,000 ppm, m,f: hunched posture, rough hair coat, laboured breathing(only f) ≥ 3000 ppm: increased rel liver weight (m) ≥ 300 ppm: increased rel liver weight (f)	NTP 1991

* due to limitations in the study documentation, NOAELs were not derived

Table 6: p-Cresol: Repeated Dose Toxicity: Rat/Mouse

Study Description	NOAEL	Effects	Reference
Rat			
5 rats/sex/dose, 28 d feeding 0, 300, 1000, 3000, 10,000, 30,000 ppm (m:0, 25, 87, 256, 835, 2180 mg/kg bw/day; f: 0, 25, 83, 242, 769, 2060 mg/kg bw/day)	Systemic: 1000 ppm (m: 87 mg/kg bw/day, f: 83 mg/kg bw/day) and 1000 ppm (local)	No mortality 30,000 ppm,m,f: decreased feed consumption, decreased bw gain and final bw; hunched posture, rough hair coat, increased rel. liver and kidney weight, uterus atrophy in 3 of 5 females; no histopathological changes in liver or kidney. ≥10,000 ppm: increased rel liver, mild bone marrow hypocellularity, in males increased rel kidney weight, ≥3000 ppm: effects in nasal cavity indicative of irritation; mild bone marrow hypocellularity in 1 of 5 males, increased rel liver weight in females	NTP 1991
30 rats/sex/dose, 13 w gavage 0, 50, 175, 600 mg/kg bw/day in corn oil	50 mg/kg bw/day	600 mg: in females death of 3 animals, lethargy, salivation, tremor, convulsion, decreased body weight gain, decreased food consumption (m), increased SGPT (f) and SGOT (f), decreased ovary weight, increased rel. liver weight (m) and increased rel kidney weight, effects on trachea indicative of irritation ≥175 mg : decreased body weight gain (m), increased serum protein (m), decreased red blood cell count, Hb-, hematocrit-values (f) chronic nephropathy in all male animals, including the controls	Microbiological Associates Inc 1988b
10 rats/sex/dose, , 13 w gavage 20 rats/sex as control 0, 50, 175, 600 mg/kg bw/day in corn oil neurotoxicity study available as summary only	*	600 mg: increased mortality (4m and4f; due to aspiration), reduced body weight gain (m), reduced food consumption, reduced locomotor activity ≥ 50 mg: clinical signs as salivation, tremor, urine wet abdomen, hypoactivity, myoclonus, rapid and labored respiration, hyperreactivity	TRL 1986
Mouse			
5 mice/sex/dose, 28 d feeding 0, 300, 1000, 3000, 10,000, 30,000 ppm (m.: 0, 50, 163, 469, 1410, n.d.* mg/kg bw/day; f.: 0, 60, 207, 564, 1590,n.d.* mg/kg bw/day) * not determined	1000 ppm (systemic; 163/207 mg/kg bw/day) 300 ppm (local; m) < 300 ppm (local, f)	30,000 ppm: death of all dosed mice: renal and hepatic necrosis, bone marrow hypocellularity and renal tubular necrosis and liver cell necrosis; in females hunched posture, rough hair coat, lethargy, hypothermia, laboured breathing, paleness 10,000 ppm: 1 m died, in males hunched posture, rough hair coat, lethargy, hypothermia, laboured breathing, paleness, lowered bw gain and final bw, depressed food consumption at the beginning; rel. liver- and heart-weight increased, in females depressed food consumption ≥3000 ppm, in females rel. liver weight increased, in males rel. kidney weight increased	NTP 1991

		≥300 ppm, f and ≥1000 ppm, m: nasal lesions indicative of irritation	

* due to limitations in the study documentation, NOAELs were not derived

Table 7: m/p-Cresol (60:40): Repeated Dose Toxicity: Rat

Study Description	NOAEL	Effects	Reference
Rat			
5 rats/sex/dose, 28 d, feeding 0, 300, 1000, 3000, 10,000, 30,000 ppm (m: 0, 26, 90, 261, 877, 2600 mg/kg bw/day f: 0, 27, 95, 268, 886,2570 mg/kg bw/day)	Systemic: 1000 ppm (m;90 mg/kg bw/day; f; 95 mg/kg bw/day) 300 ppm (local)	No mortality 30,000 ppm, m, f: reduced bw gain, reduced food consumption, thin appearance, bone marrow hypocellularity, no histopathological changes in liver or kidney ≥ 10,000 ppm,f: increased rel. liver and kidney weight, local effects at forestomach (m) ≥ 3000 ppm: slightly increased rel. liver weight, (m,f) increased colloid within follicles of the thyroid gland. effects on oesophagus and forestomach (f only) indicative of irritation ≥ 1000 ppm (f) and ≥ 3000 ppm (m): effects in the nasal cavity indicative of irritation	NTP 1991
20 rats/sex/dose, 13 week feeding 0, 1880, 3750,7500, 15,000, 30,000 ppm, (m: 0, 123, 241, 486, 991, 2014 mg/kg bw/day; f: 0, 131, 254, 509, 1024, 2050 mg/kg bw/day)	Males: 1880 ppm females: 3750 ppm (systemic, 123/254 mg/kg bw/day) < 1880 ppm (local)	No mortality 30,000 ppm: rough hair coat , urine stained fur, and thin appearance (f only), reduced feed consumption, increased rel kidney weights (f), bone marrow hypocellularity (f), decreased 5'Nucleotidase, increased serum bile acids; no histopathological changes in liver or kidney ≥ 15,000 ppm reduced terminal body weight and decreased body weight gain(f only), increased rel testes weight, bone marrow hypocellularity (m), uterus atrophy, increased colloid within thyroid follicles ≥7500 ppm: increased rel liver weight and kidney weight (m), increased colloid within thyroid follicles (f only), lengthened oestrous cycle ≥3750 ppm: increased abs. liver weight (m) ≥1880 ppm: histological changes in nasal epithelium indicative of irritation	NTP 1991

Table 8: m/p-Cresol (60:40): Repeated Dose Toxicity: Mouse

Study Description	NOAEL	Effects	Reference
Mouse			
5 mice/sex/dose, 28 d feeding 0, 300, 1000, 3000, 10,000, 30,000 ppm (m: 0, 50, 161, 471, 1490, 4530 mg/kg bw/day; f: 0, 65, 200, 604, 1880, 4730 mg/kg bw/day)	Males: 300 ppm females: 1000 ppm (systemic; 50/200 mg/kg bw/day) Males: 3000 ppm. Females: 1000 ppm (local)	No mortality 30,000 ppm: alopecia, dehydration, hunched posture, hypothermia, lethargy, rough hair coat, thin appearance, reduced food consumption, weight loss, minimal changes in lung, oesophgus and forestomach indicative of local irritation, hypocellularity of the bone marrow, in females atrophy of ovaries and uterus; no histopathological changes in other organs ≥ 10,000 ppm (m) and 30,000 ppm (f): reduced body weight gain ≥ 1000 ppm (m) and ≥ 3000 ppm (f): increased rel. liver weights ≥ 3000 ppm (f) and ≥ 10000 ppm (m): effects in the nasal cavity indicative of irritation	NTP 1991
10 mice/sex/dose, 13 week feeding 0, 625, 1250, 2500, 5000, 10,000 ppm (m: 0, 96, 194, 402, 776, 1513 mg/kg bw/day; f: 0, 116, 239, 472, 923, 1693 mg/kg bw/day)	Systemic: 5000 ppm (m, 776 mg/kg bw/day), 2500 ppm (f, 472 mg/kg bw/day) 2500 ppm (local)	No mortality 10,000 ppm: rough fur (f), decreased food consumption, reduced terminal body weight; no histopathological changes in liver and kidney ≥ 5000 ppm (m) and 10000 ppm (f): increased liver weights ≥ 5000 ppm (m) and ≥ 2500 ppm (f): effects in the nasal cavity indicative of irritation	NTP 1991

Inhalation Route

In two studies, rats were administered the cresol isomers (isomers not specified) by the inhalation route for 3 - 4 months at concentrations ranging from 0.05 to 10 mg/m³. In each study a decrease in body weight gain, and histological changes in the liver and kidney were reported. Because of the limited documentation regarding exposure methods, number of animals and results, these studies cannot be adequately evaluated (IPCS 1995).

Dermal Route

No data available.

Conclusion:

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 (ca. 200 mg/kg bw/day in mice, ca. 250 mg/kg bw/day in rats) for increases in liver weight (rat, mouse) and of 3000 ppm for increases in kidney weight (p-cresol; mouse, ca. 469 mg/kg bw/day). 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 these chemicals.

The no observed adverse effect levels (NOAELs) for m-cresol, p-cresol and m/p-cresol (28d- and 90d-studies) were generally ≥ 50 mg/kg bw/day in rats and mice:

Table 9: NOAEL Values for Systemic Toxicity From Repeated Dose Toxicity Studies

NOAELs	m-Cresol	p-Cresol	m/p-Cresol
Rat(m, f):			
28d, feeding,	252 mg/kg bw/day (m, f)	87 mg/kg bw/day (m) 83 mg/kg bw/day (f)	90 mg/kg bw/day (m), 95 mg/kg bw/day (f)
13 w, feeding			123 mg/kg bw/day (m) 254 mg/kg bw/day (f)
13 w gavage	50 mg/kg bw/day (m) 150 mg/kg bw/day (f)	50 mg/kg bw/day(m, f)	
Mouse (m, f)			
28 d feeding	193 mg/kg bw/day (m) 66 mg/kg bw/day (f; LOEL: increase in relative liver weight without histopathological correlate)	163 mg/kg bw/day (m) 207 mg/kg bw/day (f)	50 mg/kg bw/day (m) 200 mg/kg bw/day (f)
13 w feeding			776 mg/kg bw/day (m) 472 mg/kg bw/day (f)

The NOAEL for repeated dose (90d-study) of o-cresol was 50 mg/kg bw/day for mice and rats (UNEP 1998).

3.1.6 Mutagenicity

in vitro

(A) Gene mutation

m-Cresol

m-Cresol was tested negative in several Ames tests with various *Salmonella typhimurium* strains and using preincubation or standard methodology (e.g. Haworth et al. 1983, Pool and Lin 1982). The studies gave no indication of gene mutation with and without metabolic activation.

In addition, there is a mouse lymphoma assay with a negative result (with and without S9-mix, Hazleton Lab. Am. 1988a).

p-Cresol

p-Cresol was tested negative in several Ames tests with various *Salmonella typhimurium* strains and using preincubation or standard methodology (e.g. Haworth *et al*., 1983, Pool and Lin, 1982). The studies gave no indication of gene mutation with and without metabolic activation.

In addition, there is a mouse lymphoma assay (with and without S9-mix) with a negative result (Hazleton Lab. Inc. 1988e).

m/p-Cresol

An Ames test was performed without S9-mix and with S9-mix from rat and hamster livers. The studies gave no indication of gene mutations (NTP 1991).

Conclusion:

In vitro, m-,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, both in the presence or absence of metabolic activation.

(B) Cytogenicity

m-Cresol:

There is a study on cytogenicity (Chromosome aberration) using Chinese Hamster Ovary (CHO) cells in vitro which corresponds to the current OECD guideline 473 (Hazleton Lab. Am. 1988b). The study gave no indication of any clastogenic activity of the substance.

In addition, there is a mouse lymphoma assay (Hazleton Lab. Am. 1988a) with a negative result. In a Sister Chromatid Exchange (SCE) test on human fibroblasts without metabolic activation no increases in exchange rates were seen (Cheng and Kligerman 1984).

p-Cresol

There is a study on cytogenicity (Chromosome aberration) using Chinese Hamster Ovary (CHO) cells in vitro which corresponds to the current OECD guideline 473 Incubated without metabolic activation the assay was positive in all doses. The metabolic activated cultures which were incubated for 10 hours yielded negative results and those which were incubated for 20 hours yielded positive results (Hazleton Lab. Inc. 1988f). In addition, there is a mouse lymphoma assay with a negative result both in the presence or absence of metabolic activation (Hazleton Lab. Inc. 1988e).

In a Sister Chromatid Exchange (SCE) tests with human lymphocytes using a treatment time of up to 90 hours (Jansson et al. 1986) and with human fibroblasts incubated with p-cresol for two hours (Cheng and Kligerman 1984), no increases in exchange rates were seen.

m/p-Cresol

There are no cytogenetic assays in vitro with a m/p cresol mixture.

Conclusion:

m-Cresol did not induce chromosomal aberrations in vitro, whereas p-cresol had clastogenic activity in CHO cells in both the presence or absence of S-9 mix. It is therefore possible that m/p-cresol mixture has the potential to induce chromosomal aberrations in vitro. Neither m- nor p-cresol did increase SCE in vitro.

(C) Indicator test

m-Cresol

No induction of Unscheduled DNA Synthesis (UDS) was found in rat primary hepatocytes m (Hazleton Lab. Am. Inc. 1988c). In contrast, UDS was induced in SHE cells, but only in the presence of a metabolic activation system (Hamaguchi and Tsutsui 2000).

p-Cresol

p-Cresol inhibited both UV-induced DNA repair synthesis and semiconservative DNA synthesis as evidenced by a reduction in radiolabelled thymidine incorporation (Daugherty and Frank 1986). Induction of UDS was reported in Human Lung fibroblasts (Crowley and Margard 1978).

In vitro activation of p-cresol with either horseradish peroxidase or PB-induced rat liver microsomes followed by incubation with calf-thymus DNA resulted in DNA adducts which are the same as that produced by the quinone methide of p-cresol (Gaikwad and Bodell 2001).

m/p-Cresol

There are no data available using a m/p-cresol mixture.

Conclusion:

In vitro, p-cresol may induce unscheduled DNA synthesis, and the in vitro metabolite quinone methide can form DNA adducts. Contradictory results for UDS induction were reported with m-cresol from two studies both suffering from deficiencies. Thus, it is possible that m- and p-cresol and m/p-cresol mixtures have the potential to interact with DNA either directly or indirectly via metabolites.

in vivo

(A) Gene mutation

m-Cresol

There are no data available

p-Cresol

A *Drosophila melanogaster* SLRL test was negative following oral feeding of adult males with 0, 60, 300 or 600 µg/ml for three days (Hazleton Lab. Am. 1989).

m/p-Cresol

There are no data available using a m/p-cresol mixture.

Conclusion

p-Cresol did not induce gene mutations in *Drosophila melanogaster*.

(B) Cytogenicity

m-Cresol:

There is a study on cytogenicity (chromosome aberration) in 5 mice/sex/group following single oral application by gavage (0, 96, 320 and 960 mg/kg bw in corn oil) according to OECD guideline 475. Signs of toxicity were observed for the two highest dose groups and included scruffy coats, squinty eyes and difficulties in breathing. 3 male mice of the 960 mg-group were found dead during the study observation. m-Cresol revealed no clastogenic activity in bone marrow cells (Hazleton Lab. Am. 1988d).

p-Cresol

To determine the potential of p-cresol to induce dominant lethal mutations in germ cells male mice received single oral doses by gavage of 0, 100, 275 or 650 mg/kg bw suspended in corn oil. Because of the excessive toxicity within the first week after dosing high dose animals were

removed from the study and 550 mg/kg bw was assigned as the new high dose to be evaluated. p-Cresol did not induce dominant lethal mutations in the germ cells of male mice (Hazleton 1989a)

Single intraperitoneal injection of 0.75 mg/kg bw dissolved in sunflower oil was given to 2 or 3 intact or hepatectomized male mice. Negative and positive controls received sunflower oil (intact and hepatectomized mice) and cyclophosphamid (intact mice), respectively. p-Cresol did not induce significant increases in SCE frequencies in any of the cell types examined (Cheng and Kligerman 1984).

m/p-Cresol

Groups of 10 mice/dose were given 0, 625, 1250, 2500, 1000 and 10,000 ppm of a m/p-cresol mixture (60:40). The mean test substance intake was 0, 96, 194, 402, 776, 1513 mg/kg bw/day for males and 0, 116, 239, 472, 923, 1693 mg/kg bw/day for females, respectively. To determine the frequency of micronuclei in peripheral blood erythrocytes smears were prepared from blood samples obtained by cardiac puncture of dosed and control mice at the termination of the 13 week study. No significant elevation in the frequency of micronucleated erythrocytes was observed in either male or female mice (NTP 1991).

Conclusion:

In vivo, m-cresol showed no clastogenic activity in mouse bone marrow cells, even at clearly toxic dose levels (up to 960 mg/kg bw by gavage). p-Cresol did not induce dominant lethal mutations in germ cells of mice after single oral doses that elicited marked toxicity (up to 550 mg/kg bw by gavage). The sister chromatid exchange rate was not increased in mice after intraperitoneal injection of 0.75 mg p-cresol/kg). m/p-Cresol mixture (60:40) did not elevate the frequency of micronucleated erythrocytes in peripheral blood of mice fed for 13 weeks with up to 10,000 ppm.

Overall evaluation

In vitro, m- 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 mixtures have the potential to interact with DNA either directly or indirectly via metabolites.

Table 10: Results of Mutagenicity Tests

		m-Cresol	**p-Cresol**	**m/p-Cresol**
Geno-toxicity	In vitro	negative	negative	negative
	In vivo		negative	
Clasto-genicity	In vitro	negative	positive	
	In vivo	negative	negative	negative

o-Cresol can induce chromosomal aberrations and increase SCE in vitro but not in vivo (UNEP 1998).

3.1.7 Carcinogenicity

m-Cresol

There is no study available to assess the carcinogenic potential of m-cresol.

The promoting ability of m-cresol was investigated in the mouse skin painting model. The treatment did induce an increase in skin papillomas, but not in carcinomas. The presence of benzene, which was used as vehicle, did not appear to affect the results, since no papillomas were found in benzene treated controls (Boutwell and Bosch 1959).

m-Cresol did not induce cell transformations in BALB/c-3T3 cells (Hazleton 1988g,h).

p-Cresol

There is no study available to assess the carcinogenic potential of p-cresol.

The promoting ability of p-cresol was investigated in the mouse skin painting model. The treatment did induce an increase in skin papillomas, but not in carcinomas. The presence of benzene, which was used as vehicle, did not appear to affect the results, since no papillomas were found in benzene treated controls (Boutwell and Bosch 1959).

p-Cresol induced cell transformations in an in vitro cell transformation assay using mouse BALB/c-3T3 cells without a metabolic activation system (Hazleton 1988g, h).

m/p-Cresol

There is no study available to assess the carcinogenic potential of a m/p-cresol mixture.

Conclusion:

As for o-cresol, there are no adequate data available to assess the carcinogenic potential of m- or p- or m/p-cresol mixture. 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 o/m/p-cresol mixture within the National Toxicological Program (NTP).

3.1.8 Toxicity for Reproduction

m-Cresol

Reproductive toxicity was examined in a two-generation study on Sprague-Dawley rats given 0, 30, 175 or 450 mg/kg bw/day in corn oil by gavage (BRRC 1989).

Effects on reproductive function or on morphology of reproductive tissues were not detected even at doses producing overt toxicity in adult rats (hypoactivity, ataxia twitches, tremors, prostration urine stains, audible respiration and perioral wetness). The NOAEL (fertility) was 450 mg/kg bw/day. The NOAEL toxicity was 30 mg/kg bw/day.

In F1 and F2, litter size, sex ratio, and litter viability was unaffected by treatment. In F1 the female pups had reduced body weights in the highest dose tested, but pup survival was not affected. In F2, pup body weight, pup body weight gain and pup lactational index were reduced and pup mortality was increased at the highest dose. Thus, the NOAEL (developmental effects) was 175 mg/kg bw/day.

In the 13 week gavage study (0, 50, 50, 450 mg/kg bw/day in corn oil) with rats no effects on reproductive organs were reported, neither in males nor in females (Microbiological Association 1988a).

p-Cresol

Reproductive toxicity was examined in a two-generation test on Sprague-Dawley rats given 0, 30, 175 or 450 mg/kg bw/day in corn oil by gavage (BRRC 1989).

Reproductive function was not affected in either of the two generations even at doses producing overt toxicity in adult rats (hypoactivity, ataxia twitches, tremors, prostration urine stains, audible respiration and perioral wetness). NOAEL (fertility): 450 mg/kg bw/day. NOAEL (toxicity): 30 mg/kg bw/day. p-Cresol caused increased stillbirths in the F1 and F2 generations: in F1 pups at 175 (but not 450 mg/kg bw/day) and in F2 pups at 30 and 450 (but not at 175) mg/kg bw/day. There was some variability in the number of stillborn in control groups in the F1 and F2 generation (2 versus 0) and there was no clear dose-dependent effect in both generations (control/low/mid/high dose: F1 pups: 2/4/13/6; F2 pups:0/7/4/9). In F2 (but not F1) live birth indices were reduced at 30 and 450 (not 175) mg/kg bw/day. Without any other effects, especially in the 30 mg/kg bw/day-group, it is unclear whether the effects on live birth indices were substance related. Pup survival indices in both generations were not affected by treatment. A developmental NOAEL could therefore not be determined from this study.

At 600 mg/kg bw/day a decrease in ovary weights and an increase in testes weights was observed in a 13-week gavage study with rats (Microbiological Associated 1988a).

m/p-Cresol

Male and female Swiss CD-1 mice were exposed to m/p-cresol (60:40) in the diet to assess reproduction and fertility using the NTP continuous breeding protocol (RTI 1992):

Groups of 20 breading pairs received 0, 0.25, 1 and 1.5 % in feed for 7 days prior to cohousing and for 98 days of continuous breeding. 40 breeding pairs received food only. The average daily intake is calculated to be 0, 375, 1500 and 2250 mg/kg bw/day.

m-/p-Cresol mixture did not significantly affect most measures of reproductive competence in the F0-generation, including initial fertility, the proportion of pups born alive or the sex of pups born alive. Adjusted live pup weight and the number of live pups per litter were decreased by 5 and 20 %, respectively and cumulative days to the fifth litter were increased by almost 3 days in the high dose group compared to controls. Therefore the NOAEL (F0, fertility) was 1 % (approximately 1500 mg/kg bw/day).

F0 body weight and feed consumption were decreased at the 1.0 and 1.5 % dose levels, especially in delivering and lactating dams. At the 1.5 % level decreased body weight and increased kidney and liver weights of F0 animals were noted. Toxicity to reproductive organs at the 1,5 % dose level was observed in form of decreased epididymal and seminal vesicle weights by 10 and 21 %, respectively, with no changes in testes weight, sperm parameters or testicular and epididymal histopathology. The NOAEL (F0, general toxicity) was 0.25 % (approximately 375 mg/kg bw/day).

In F1 animals of the high dose group, birth weights were decreased (5 %), and decreased preweaning growth by 26 % and postweaning survival by 39 % were noted. Treatment related clinical signs were reduced size, dehydratation, lethargy and rough coat in the high dose group. At both, 1.0 and 1.5 % dose level male body and reproductive organ weights (prostate, seminal vesicle, testes) were decreased and relative liver and kidney weights were increased but there were no effects on sperm parameters or histology. Female terminal body weights were reduced at the two highest dose levels as was the ovarian weight in all three dosed groups while liver and kidney

weights were increased in all dosed groups. There was no effect of treatment on estrous cyclicity or ovarian, liver or kidney histopathology. NOAEL (F1, general toxicity): 0.25 % (approximately 375 mg/kg bw/day).

In F1, m/p-cresol mixture had no effect of mating index, fertility index, pregnancy index. Number of live F2 pups per litter, proportion of F2 pups born alive, and sex ratio of F2 pups was not affected. Only live F2 pup weights and the adjusted live F2 pup weights of the 1.5 % dose group was significantly reduced. Thus, the NOAEL (F1, fertility) was 1 % (approximately 1500 mg/kg bw/day).

No effects on sperm motility and concentration, and on oestrus cycle and vaginal cytology were found following 13 weeks of feeding, groups of 10 mice/sex doses of up to 10,000 ppm (1513 mg/kg bw/day for males and 1693 mg/kg bw/day for females, respectively) (NTP 1991).

Following 13 weeks of feeding groups of 10 rats/sex doses up to 30,000 ppm (ca. 2014 mg/kg bw/day for males and 2050 mg/kg bw/day for females) the only finding in males was a biologically insignificant decrease (4 %) in mean sperm motility values which occurred at the high dose level. In females, a dose-related increase in oestrous cycle length was observed at 7500 ppm (approximately 509 mg/kg bw/day) and 30,000 ppm; slight uterine atrophy was noted at 15,000 ppm (NTP 1991).

Conclusion

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-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)).

3.1.9 Developmental toxicity/Teratogenicity

m-Cresol

Developmental toxicity was examined in Sprague-Dawley rats and New Zealand White rabbits (BRRC 1988a, b).

m-Cresol was given to 25 pregnant rats/group by gavage on gestation day 6 - 15 at doses of 0, 30, 175 or 450 mg/kg bw/day dissolved in corn oil. At 450 mg/kg bw/day, there was a significant reduction in periodic maternal body weights and weight gain during the dosing period. Clinical signs of toxicity at 450 mg/kg bw/day included hypoactivity, ataxia, tremor, twitches, prone positioning, audible respiration, perioral wetness, and a reduction in food consumption. m-Cresol did not induce fetotoxicity or malformations at any dose level tested. The NOEL for maternal toxicity was 175 mg/kg bw/day and the NOEL for developmental toxicity was 450 mg/kg bw/day.

No fetotoxicity and no treatment-related effects on the incidence of any malformation (external, visceral, skeletal) was found in the progeny of 14 rabbits/group, dosed by gavage on gestation day 6 - 18 with doses of 0, 5, 50, 100 mg/kg bw/day dissolved in corn oil. Clinical signs of toxicity were observed at 50 mg/kg bw/day (audible respiration and ocular discharge). The NOEL for maternal toxicity was 5 mg/kg bw/day and the NOEL for developmental toxicity was 100 mg/kg bw/day.

p-Cresol

Developmental toxicity was examined in Sprague-Dawley rats and New Zeeland White rabbits (BRRC 1988a, b).

p-Cresol was given to 25 pregnant rats/ group by gavage on gestation day 6 - 15 at doses of 0, 30, 175 or 450 mg/kg bw/day dissolved in corn oil. At 450 mg/kg bw/day, there was a significant reduction in maternal body weight gain during the dosing period. Clinical signs of toxicity at 450 mg/kg bw/day included hypoactivity, ataxia, tremors, twitches, prone positioning, audible respiration, and peroral wetness. p-Cresol caused fetotoxicity at 450 mg/kg/day, as evidenced by reduced ossification in three skeletal districts. In addition, fetal body weight was reduced at 450 mg/kg/day. There was no treatment-related increase in the incidence of malformations (external, visceral, skeletal) at any dose level. Gestational parameters which were unaffected by treatment included number of ovarian corpora lutea, number of total, nonlive or live implants and sex ratio per litter. Thus, the NOEL for maternal toxicity and developmental toxicity was 175 mg/kg bw/day.

No treatment-related effects on the incidence of any malformations (external, visceral, skeletal) was found in the progeny of 14 rabbits / group, dosed by gavage on gestation day 6 - 18 with 0, 5, 50, 100 mg/kg bw/day dissolved in corn oil. Clinical signs of toxicity were observed at 50 and 100 mg/kg bw/day (audible respiration and ocular discharge, hypoactivity, gasping and cyanosis). There were no treatment-related effects on food consumption and no treatment-related lesions in does or any changes in maternal organ weights. Gestational parameters were unaffected by treatment (no treatment related abortions, early deliveries or resorptions, and no changes in total, nonlive or live implants per litter or fetal body weight per litter). Thus, the NOEL for maternal toxicity was 5 mg/kg bw/day and the NOEL for developmental toxicity was 100 mg/kg bw/day.

m/p-Cresol

There is no study available using a m/p-cresol-mixture.

Conclusion:

In developmental toxicity in rats and rabbits, no toxic effects on the developing organism could be found despite of the toxic effects of m-cresol 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 (NOELs: 175 mg/kg bw/day (maternal toxicity) and 450 mg/kg bw/day (developmental toxicity) for rats, and 5 mg/kg bw/day (maternal toxicity) and 100 mg/kg bw/day (developmental toxicity) for rabbits, respectively).

p-Cresol caused fetotoxicity (delayed ossification, decreased fetal body weight) at maternally toxic dose levels in rats (NOAEL maternal toxicity, developmental toxicity: 175 mg/kg bw/day). In rabbits, p-cresol caused no developmental effects even at doses that were maternally toxic (NOEL maternal toxicity, developmental toxicity: 175 mg/kg bw/day).

Based on the available data it can be assumed that the m-/p-cresol mixtures may have the potential to induce fetotoxicity in the presence of maternal toxicity.

3.1.10 Other relevant information

Experience with human exposure

The effects of (intentional or accidental) oral intake of cresols (all isomers) are described in several case reports. The effects comprise 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 (Bruce et al. 1976, Cote et al. 1984, Minami et al. 1990, DECOS 1998).

Skin contact has also resulted in effects on the nervous system, liver and kidneys, and caused human fatalities (DECOS 1998). A cresol solution, unintentionally poured over the trunk, caused gross haematuria, gastrointestinal bleeding, hypertension and septic shock with severe jaundice and renal failure (Lin and Yang 1992).

Accidental dermal exposure of both legs and face of a 47 old man to m-cresol resulted in corrosion of 15 % of his body surface and he developed acute polyuric renal failure (Evers et al. 1994).

Skin depigmentation (chemical leukoderma) has been reported after local exposure to cresols (NTP 1991).

No data on systemic effects following acute and short-term occupational exposure to cresol vapours or aerosol were located (DECOS 1998). 7 workers who were exposed to unknown concentrations of cresol vapour for 1½ to 3 years, suffered from frequent headaches, nausea and vomiting. Four of the workers had high blood pressure, impaired renal function, abnormal blood calcium levels an marked tremor (DECOS 1998).

No epidemiological studies or case reports on occupationally exposure to cresols were found containing adequate details on exposure levels. Anomalous menstrual cycles and hormonal disorders were reported for women who were employed in the production of enamelled wire or of tricresyl phosphate and were exposed in the process to a variety of compounds, including chlorobenzenes and phosphoryl chloride. It was claimed that the incidence of perinatal child death was increased and that developmental disorders were frequent among the new-born babies. Since no data on exposure levels and duration of exposure are given, and data on controls were not provided, a relationship between the described effects and cresol exposure cannot be deduced (DECOS 1998).

The human lethal dose (LD) is reported to be 50 - 500 mg/kg bw (Gleason et al. 1969).

The development of tumours in persons who had been exposed occupationally to cresol (unspecified isomer) has been reported, and two cases of transitional cell bladder carcinoma were described after long-term exposure to cresol (Garrett 1975). Another case involved a worker in an oil refinery who was exposed to cresol, dichlorooctane and chromic acid for a long period and who developed a squamous epithelial carcinoma of the vocal cords (DECOS 1998). Since no information on exposure levels are available, and since co-exposure to other substances cannot be excluded, a carcinogenic potential of the cresol isomers cannot be deduced from these case reports (DECOS 1998).

According to the results of studies in cancer patients, endogenous p-Cresol does not contribute significantly to the development of human bladder cancer (32 patients vs 32 age/sex-matched controls, Renwick 1988) or large bowl cancer (18 patients versus 10 normal healthy persons, Bone et al. 1976).

Conclusion:

In humans, the accidental oral uptake of cresols can induce 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 tumor 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.

3.2 Initial Assessment for 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 or clinical signs of toxicity were seen following exposure to the 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.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

For the effects assessment of cresols on aquatic organisms their ready biodegradability in aqueous solutions has to be taken into account. In static tests with analytical monitoring Falk-Petersen et al. (1985) found less than 10 % loss of the test substance after 4 days, thus short term tests without analytical monitoring can be accepted as valid.

Fish

Valid tests on acute toxicity to fish are available for 14 freshwater and 1 marine species. An overview is presented in table 4.1.

A flow-through test on the acute toxicity of p-cresol to Pimephales promelas was conducted by Geiger et al. (1986). The fish were exposed in Lake Superior water to 5 test substance concentrations. Analytical measurements revealed that the cresol concentrations were stable during the test period. Based on measured concentrations a 96h-LC50 of 16.5 mg/l was obtained. The affected fish lost schooling behaviour, swam near the tank surface, were hyperactive and overreactive to external stimuli, they had increased respiration and lost equilibrium prior to death.

DeGraeve et al. (1980) conducted flow-through bioassays on the toxicity of m- and p-cresol to Pimephales promelas and Oncorhynchus mykiss. The fish were exposed in well-water to 7 concentrations of the test substances and one control. O. mykiss was the more sensitive species with LC50 values of 8.9 mg/l for m-cresol and 7.9 mg/l for p-cresol; the LC50 values for P. promelas were 55.9 mg/l for m-cresol and 28.6 mg/l for p-cresol. All effect values are based on measured concentrations.

Table 11: Toxicity of m- and p-Cresol to Fish in Short-term Tests

Species	Test type	Exposure period	Effects [mg/l]		Reference
			m-Cresol	**p-Cresol**	
Pimephales promelas	**flow through**	**96 h**		**EC50 = 16.5 (e)**	**Geiger et al. (1986)***
	flow through	**96 h**	**LC50 = 55.9 (e)**	**LC50 = 28.6 (e)**	**DeGraeve et al. (1980) ***
	static	96 h		LC50 = 15.5 (n)	Howland (1969)
	static	96 h		LC50 = 19 (n)	Mattson et al. (1976)
Oncorhynchus mykiss	**flow through**	**96 h**	**LC50 = 8.9 (e)**	**LC50 = 7.9 (e)**	**DeGraeve et al. (1980) ***
	flow through	96 h		LC50 = 7.5 (e)	Hodson et al. (1984)
	static	96 h	LC50 = 8.6 (n)	LC50 = 7.4 (n)	Howland (1969)
Brachydanio rerio	static	96 h	LC50 = 15.9 (n)		Wellens (1982)
Lepomis macrochirus	static	96 h		LC50 = 7.1 (n)	Howland (1969)
Leuciscus idus	static	48 h	LC50 = 17 (n)	LC50 = 11 (n)	Ruebelt et al. (1982)
Salmo trutta	**static**	**96 h**	**LC50 = 8.4 (n)**	**LC50 = 4.4 (n)**	**Howland (1969) ***
Salvelinus fontinalis	**static**	**96 h**	**LC50 = 7.6 (n)**	**LC50 = 5.8 (n)**	**Howland (1969) ***
Poecilia reticulata	semistatic	96 h	LC50 = 23.1 (n)		Saarikoski andViluksela(1982)
Cyprinus carpio	static	96 h		LC50 = 13.3 (n)	Howland (1969)
Gadus morrhua (eggs)	static	96 h	EC50 > 30 (e)	EC50 = 5.0 (e)	Falk-Petersen et al. (1985)
Ictalurus melas	static	96 h		LC50 = 57.5 (n)	Howland (1969)
Ictalurus punctatus	static	96 h		LC50 = 39.7 (n)	Howland (1969)
Perca flavescens	static	96 h		LC50 = 10.0 (n)	Howland (1969)
Gambusia affinis	static	96 h		LC 50 =33 (n)	Sangli and Kanabur (2000)
Lepidocephalichthys guntea	semistatic	96 h		LC50 = 14.0 (n)	Kanabur and Sangli (1998)

(n): nominal concentration * : studies which are flagged as key studies
(e): effective concentration

The most sensitive fish species in acute toxicity tests belong to the salmonids. Howland (1969) conducted static tests on the toxicity of m-cresol to three trout species and of p-cresol to 9 fish species. Among the tests with m-cresol Salvelinus fontinalis was most sensitive exhibiting a LC50 of 7.6 mg/l, while with p-cresol as the test substance the lowest LC50 was found for Salmo trutta (4.4 mg/l).

The effect values from tests on m- and p-cresols indicate toxicity in the same order of magnitude, with p-cresol being slightly more toxic.

A chronic toxicity test (early life stage) with P. promelas was conducted with p-cresol over a period of 32 days. A NOEC of 1.35 mg/l was obtained. This is a nominal concentration (Barron and Adelman 1984). It has to be regarded that Pimephales promelas was not the fish species being most sensitive in short-term tests.

Invertebrates

The acute toxicity of m-cresol to Daphnia magna was determined in a static immobilization test after an exposure period of 24 h. Duplicate samples with each 10 individuals of 24 h old daphnids were exposed to the test solutions. Analytical control was not performed. The nominal EC50 was reported to be 25 mg/l (graphically determined) (Bringmann and Kühn 1982).

A comparable test was conducted with p-cresol. Kühn et al. (1988, 1989a) exposed each 20 daphnids in 4 replicates to p-cresol, the nominal EC50 was graphically determined to 4.9 mg/l.

The 3 valid test results, available for the short-term toxicity of m- and p-cresol on Daphnia magna, allow a comparison of the acute toxicity of both substances on this species. The results demonstrate a similar toxicity of both isomers.

Long-term tests to invertebrates are only available for p-cresol. In a semi-static test with *Daphnia magna*, each 20 individuals (24 h old) in 4 replicates were exposed to p-cresol in a concentration range of 0.003 - 10 mg/l. The test solutions were renewed 3 times per week, their stability was controlled by analytical monitoring. After 21 days of exposure a NOEC of 1 mg/l was determined (Kühn et al. 1988, 1989a).

Aquatic Plants

The cell multiplication inhibition of p-cresol on the alga *Scenedesmus subspicatus* was tested by Kühn and Pattard (1990). The algae were exposed to concentrations between 0.8 and 100 mg/l. Analytical control was not performed. Based on nominal concentrations a 48 h-EC_{50} of 21 mg/l and an EC_{10} of 4.6 mg/l (both related to growth rate) were determined.

In a study with macrophytes (Nobel 1983) NOEC-values for the endpoint photosynthesis (oxygen production) of 0.22 mg/l to 1.08 mg/l for m-cresol and < 0.22 mg/l to 1.08 mg/l for p-cresol are reported and provide a hint towards higher sensitivity of macrophytes to cresols. However, as no information is given about substance application, test design (no. of plants per vessel and replication) and control performance, the study is considered invalid and is not used for the PNEC derivation.

Table 12: Tests on Acute Toxicity of m-and p-Cresol to Invertebrates

Species	Test type	Exposure period	Effects [mg/l]		Reference
			m-Cresol	p-Cresol	
Daphnia magna	**Static**	**24 h**		**EC50 = 4.9 (n)**	**Kühn et al. (1988, 1989a) ***
	Static	48 h		EC50 = 7.7 (n)	Kühn et al. (1989b)
	Static	24 h	EC50 =19.2 (n)	EC50 =12.4 (n)	Devillers et al. (1987, 1988)
	static	**24 h**	**EC50 = 25 (n)**		**Bringmann and Kühn (1982) ***
	static	**24 h**	**EC50 = 8.9 (n)**		**Bringmann and Kühn (1977a) ***
Daphnia pulicaria	**flow through**	**48 h**	**EC50 > 99.5 (e)**	**EC50 = 22.7 (e)**	**DeGraeve et al. (1980) ***

(n): nominal concentration

(e): effective concentration

*: studies which are flagged as key studies

Table 13: Tests on Long-term Toxicity of m-and p-Cresol to Fish and Invertebrates

Species	Test type	Exposure period	Effects [mg/l]		Reference
			m-Cresol	p-Cresol	
Pimephales promelas	**Early life stage**	**32 d**		**NOEC = 1.35 (n)**	**Barron and Adelmann (1984)***
Daphnia magna	**semistatic**	**21 d**		**NOEC = 1.0 (n)**	**Kühn et al. (1988, 1989a) ***
Dugesia tigrina (aquatic flatworm)	semistatic	80 d		LC10 =2.0 (n) LC0 = 1.0 (n)	Solski and Piontek (1987)

(n): nominal concentration

(e): effective concentration

*: studies which are flagged as key studies

Table 14: Toxicity of m- and p-Cresol to Aquatic Plants

Species	**Exposure period**	**Effects [mg/l]**		**Endpoint**	**Reference**
		m-Cresol	**p-Cresol**		
Scenedesmus subspicatus	**48 h**		**E_bC10 = 2.3 (n)** **E_rC10 = 4.6 (n)** **E_bC50 = 7.8 (n)** **E_rC50 = 21 (n)**	**Biomass** **Growth rate**	**Kühn and Pattard (1990) ***
Chlorella pyrenoidosa	72 h	EC50 = 127 (n)	EC50 = 116(n)	Chlorophyll content	Huang and Gloyna (1968)

(n): nominal concentration

(e): effective concentration

*: studies which are flagged as key studies

Summary of aquatic effects:

The available ecotoxicity data for m- and p-cresol show that the toxicity of the two isomers is in the same order of magnitude within the uncertainty range of laboratory effect tests. Long-term tests are only available for p-cresol. However, from the similarity in acute toxicity testing, it can be expected that the long-term toxicity of both isomers is similar as well. For the isomeric mixture m/p-cresol no ecotoxicity data are available. However, it is expected that the toxicity of the isomeric mixture is covered by the data for m- and p-cresol. Therefore, for the hazard assessment of this category, all available ecotoxicity tests are considered together, independent from the isomer for which they were determined.

Determination of PNECaqua

Results from long-term tests 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). Applying an assessment factor of 10 to the lower value, the Predicted No Effect Concentration (PNEC) for the aquatic compartment is determined for m- and p-cresol and the isomeric mixture m/p-cresol: **PNECaqua = 0.1 mg/l.**

QSAR estimations using ECOSAR for phenolic compounds result in the following values:

fish: 30d-NOEC = 2.216 mg/l

90d-NOEC = 0.121 mg/l

daphnia: 21d-NOEC = 1.571 mg/l

The values for the 30d fish test and the 21d daphnia test are in good agreement with the experimentally determined values. Therefore, it cannot be excluded that a prolongation of the exposure period in fish tests would result in a NOEC that is about an order of magnitude below the available NOEC of 1.35 mg/l. This would have also consequences for the PNECaqua.

Microorganisms

In a respiration inhibition test using activated sludge according to OECD 209 with m-cresol as test substance, a 3 h-EC_{50} of 461.4 mg/l was obtained (Klecka and Landi 1985). In a similar test with p-cresol, the 2 h-EC_{50} was 439.5 mg/l (Chan et al. 1999). Tomlinson (1966) studied the inhibition of the first nitrification step (oxidation of NH_4 to NO_2) and obtained 4 h-EC_{75} values of 11.4 mg/l for m-cresol and 16.5 mg/l for p-cresol.

Table 15: Toxicity of Cresols to Microorganisms

Species	Exposure period	Effects [mg/l]		Endpoint	Reference
		m-Cresol	p-Cresol		
Domestic sewage sludge	**2 h**		**EC50 = 439.5**	**respiration**	**Chan et al. (1999) ***
	3 h	**EC50 = 461.4**		**respiration**	**Klecka andLandi (1985) ***
	4 h	**EC75 = 11.4**	**EC75 = 16.5**	**nitrification**	**Tomlinson (1966) ***
Nitrosomonas sp.	24 h	EC50 = 0.78 **	EC50 = 27	nitrification	Blum and Speece (1991)
Pseudomonas putida	16 h	EC3 = 53		cell multipl.	Bringmann and Kühn (1976)
Tetrahymena pyriformis (protozoa)	24 h		EC50 = 157	growth	Schultz et al. (1996)
	24 h		EC50 = 160	growth	Yoshioka et al. (1985)
Entosiphon sulcatum (protozoa)	72 h	EC5 = 31		cell multipl.	Bringmann (1978)
Chilomonas paramaecium (protozoa)	48 h	EC5 = 114		cell multipl.	Bringmann et al. (1980)
Uronema parduzci (protozoa)	20 h	EC5 = 62		cell multipl.	Bringmann and Kühn (1980)

(n): nominal concentration

(e): effective concentration

*: studies which are flagged as key studies

** This effect value has to be considered as invalid. The authors state that in the lower range (log IC50 < 1.5 µmol/l) the accuracy of the results are questionable.

4.2 Terrestrial Effects

The toxicity of m-cresol to *Lactuca sativa* according to the OECD-Guideline 208 was examined by Hulzebos et al. (1993). After an exposure period of 14 days, a nominal EC_{50} of 96 mg/kg soil (dw) was obtained. The authors state that during the test period, the soil concentrations of most tested phenols dropped to < 20 % of the initial soil concentration. It is not clear whether this is also true for m-cresol.

4.3 Other Environmental Effects

No reliable data available.

4.4 Initial Assessment for the Environment

Environmental behaviour:

According to a Mackay Level I model calculation both m- and p-cresol are mainly distributed to water (96.3 %). Experimentally determined values for the Henrys' law constant indicate slow volatilization from surface waters. The experimentally determined Koc values of 34.58 for m-cresol and 48.66 for p-cresol indicate a low sorption potential.

In the atmosphere, indirect photodegradation by hydroxyl radicals is expected with estimated half-lives of 6.0 – 8.2 hours.

With regard to its chemical structure m-cresols and p-cresols 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 all cresols is assumed to be low.

Environmental effects:

Ecotoxicity data are available for both m- and p-cresol. Effect values with the same tested species (fish and daphnids) indicate toxicity in the same order of magnitude, with p-cresol being slightly more toxic.

For the acute toxicity of cresols on aquatic species reliable experimental results from tests with fish, daphnia, algae and microorganisms are available. Long-term tests were conducted for all three trophic levels , the most sensitive species was *Daphnia magna* exhibiting a NOEC of 1 mg/l. Applying an assessment factor of 10, a PNECaqua of 0.1 mg/l for m-, p-cresols is obtained.

5 RECOMMENDATIONS

Environment

m-Cresol, p-cresol and m/p-cresol mixtures are currently of low priority for further work. The substances 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 levels, they should nevertheless be noted by chemical safety professionals and users.

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

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Hazleton Laboratories America Inc. (1988c) HLA Study No.10002-0-447 Mutagenicity test on meta-cresol in the rat primary hepatocyte unscheduled DNA synthesis assay. Kensington, USA, June 28, 1988 (at the request of CMA)

Hazleton Laboratories America Inc. (1988d) HLA Study No. 10002-0-451 Mutagenicity test on meta-cresol in a mouse bone marrow cytogenetic assay. Kensington, USA, January 31, 1989 (at the request of CMA)

Hazleton Laboratories America Inc. (1988e) HLA Study No. 10002-0-431 Mutagenicity test on meta-cresol in a mouse lymphoma mutation assay, Kensington, USA (at the request of CMA), EPA-OTS0517693

Hazleton Laboratories America Inc. (1988f) HLA Study No. 10002-0-437 Mutagenicity test on m-cresol in an in-vitro cytogenetic assay measuring chromosomal aberration frequencies in Chinese Hamster Ovary (CHO) cells. Kensington, USA, June 28, 1988 (at the request of CMA), EPA/OTS0517691

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ANNEX: CATEGORY JUSTIFICATION

Identity:

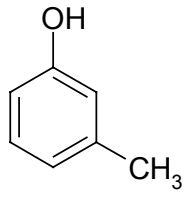
Chemical name: m-Cresol

p-Cresol

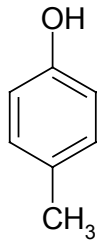
m/p-Cresol mixtures

Since o-cresol was assessed earlier within the OECD HPV program, it is not included here (UNEP (United Nations Environmental Program) (1998), Chemical Screening Information Data Sets (SIDS) for High Volume Chemicals: o-Cresol, Vol. 5/I)

Structural Formula:



m-Cresol



p-Cresol

Molecular Formula: C_7H_8O

Molecular weight: 108.14 g/mol

m-Cresol, p-cresol and mixtures of both isomers are considered as a category because of their similarity in physico-chemical properties, environmental fate, ecotoxicity and toxicity. Both isomers as well as their mixture are products of technical importance. m-Cresol, p-cresol and mixtures of both isomers are produced > 1000 t/y.

The 3 cresol products of technical importance considered here, are:

Substance	Synonyms	CAS-No.	Composition
m-Cresol	3-Methylphenol	108-39-4	Purity > 99 %
p-Cresol	4-Methylphenol	106-44-5	Purity approx. 99.9 %
m/p-Cresol mixtures		15831-10-4	60 - 75 % m-Cresol, 25 - 40 % p-Cresol

Category Justification

Environment

Of particular importance to environmental effects are the values for partition coefficient (log Kow), vapour pressure and water solubility.

Available Physico-Chemical Data for Cresols:

Substance	m-Cresol	p-Cresol	m/p-Cresol
Vapour pressure (25°C)	0.147 hPa	0.147 hPa	
Log Kow	1.96	1.94	1.94 -1.96
Water solubility (25°C)	22.7 g/l	21.5 g/l	24.4 g/l
Dissociation constant pKa	10.09	10.26	

Vapour pressure and log Kow were determined for both isomers, the water solubility for both isomers and the m/p-cresol mixture. The values are nearly identical for the pure isomers, so the isomer mixture can be assessed as well.

Cresols are weak acids. The pKa values of 10.09 and 10.26 resp. indicate that at environmentally relevant pH values (5 - 9) both substance are largely non-dissociated.

For the assessment of the removal in biological treatment plants and degradation in environmental compartments, results from biodegradation tests are crucial.

Available Data on Ready Biodegradability

Method	Duration	m-Cresol	p-Cresol	Reference
OECD 301 D	28 d	65 - 90 %		Bayer AG (1988)
OECD 301 C	40 d	80 - 95 %	80 - 95 %	Desai et al. (1990)

The OECD 301 D test reveals that m-cresol is readily biodegradable. As demanded by the OECD guideline, the oxygen consumption was above 60 % after 28 days and the 10d window was fulfilled.

In a test comparable to OECD 301 C test biodegradation in the range of 80 – 95 % for both compounds occurred. The oxygen uptake curves are not reported. However, the authors state that all test compounds revealed the lag phase, biodegradation phase and the plateau region within a period of 10 days. Therefore, it can be concluded from this test that m- and p-cresol are readily biodegradable. In addition, the rate constants for both m- and p-cresol were determined and found to be similar.

Available Ecotoxicity Data

For the acute toxicity of cresols on aquatic species a large number of experimental results from tests with fish, daphnids and algae are available. Long-term tests were conducted with fish, algae and invertebrates.

In the following table only those tests are reported where both isomers have been tested in parallel.

Toxicity of m - and p-cresol in Short-term Tests:

Species	Exposure period	Effects [mg/l]	
		m-Cresol	p-Cresol
Pimephales promelas			
	96 h	LC50 = 55.9 (e)	LC50 = 28.6 (e)
Oncorhynchus mykiss	96 h	LC50 = 8.9 (e)	LC50 = 7.9 (e)
	96 h	LC50 = 8.6 (n)	LC50 = 7.4 (n)
Leuciscus idus	48 h	LC50 = 17 (n)	LC50 = 11 (n)
Salmo trutta	96 h	LC50 = 8.4 (n)	LC50 = 4.4 (n)
Salvelinus fontinalis	96 h	LC50 = 7.6 (n)	LC50 = 5.8 (n)
Daphnia magna	24 h	EC50 =19.2 (n)	EC50 =12.4 (n)
Daphnia pulicaria	48 h	EC50 > 99.5 (e)	EC50 = 22.7 (e)
Chlorella pyrenoidosa	72 h	EC50 = 50 - 250 (n)	EC50 = 100 - 250 (n)

(n): nominal concentration (e): effective concentration

Effect values obtained from tests on both m- and p-cresol indicate a similar toxicity of both isomers, with p-cresol being slightly more toxic.

For long-term tests the toxicity cannot be compared directly, as no test performed with both isomers are available. However, from the similarity in acute toxicity testing, it can be expected that the long-term toxicity of both isomers is similar as well.

For the isomeric mixture m/p-cresol no ecotoxicity data are available. However, it is expected that the toxicity of the isomeric mixture is covered by the data for m- and p-cresol.

Available Toxicity Data (Human Health)

The available data indicate a very similar pattern of toxicity of m-cresol, p-cresol and of the m/p-cresol mixtures:

The following data were identified:

Substance		m-Cresol	p-Cresol	m/p-Cresol mixtures
Cas-No.		108-39-4	106-44-5	
Acute toxicity	oral	√/+	√/+	
	dermal	√/+	√/+	
	inhalation	√/+	√/+	
Irritation	skin	√/+	√/+	√/+
	eye	√/+	√/+	
Sensitization		√/-	√/-	√/-
Repeated dose toxicity		√/+	√/+	√/+
Genetic toxicity	in vitro	√/+	√/+	√/+
	in vivo	√/+	√/+	√/+
Carcinogenicity		X	X	
Effect on fertility		√/+	√/+	√/+
Developmental toxicity		√/+	√/+	

√/+ Adequate data available

√ information available

* evaluation based on human experience

X Testing being performed (o-/m-/p- isomer mixture)

All cresol isomers are well absorbed via all main exposure routes. The main metabolic pathway is hydroxylation of the benzene ring. p-Cresol can also be oxidized to hydroxybenzoic acid and, at least in vitro, to a reactive quinone methide. For m- and p-cresol, elimination occurs mainly as glucuronide and/or sulfate via urine, minor amounts via faeces.

The available acute toxicity data of the two isomers indicate similar toxicity profiles after oral exposure, and a lesser toxicity of m-cresol in experiments with dermal exposure. m-Cresol and p-cresol are corrosive substances.

There is no indication of a sensitizing effect of p-cresol from a limited guinea pig study and a limited human study. However, hypersensitivity reactions of some individuals to cresol (isomer unspecified) have been mentioned in the literature.

For both isomers, as well as for the mixture of the two the NOAELs in 28- and 90-d feeding studies are ≥ 50 mg/kg bw/day in rodents. At higher doses, there were indications of a transient impairment of liver function and a dose dependant increase in liver weight was observed for m-, p- and the mixture of cresols, but without histopathological correlate. Increases in kidney weight were observed with p-cresol and at higher doses with the m/p-cresol mixture.

p-Cresol exerted some clastogenic activity in vitro, but this activity was not reproduced in vivo. All isomers were consistently tested negative *in vivo*.

There is no adequate data available to assess the carcinogenic potential of m- and p-cresol. Limited studies gave an indication of a tumour promoting activity of m- and p-cresol. Carcinogenicity studies in two species with the o-/m-/p-isomer mixture are currently performed within the U.S. National Toxicology Program.

None of the isomers, and also not the mixture, was a reproductive toxicant. Mild developmental toxicity was only seen at maternally toxic doses of p-cresol; there was no indication of developmental effects with m-cresol. Hence, slight developmental toxicity at maternally toxic doses may also occur with the isomer mixture.

Based on the similarities in the results of studies on m-and p-cresol, inclusion of m/p-cresol mixture in this report is justified.

I U C L I D

Data Set

Existing Chemical	:	ID: 108-39-4
CAS No.	:	108-39-4
EINECS Name	:	m-cresol
EC No.	:	203-577-9
TSCA Name	:	Phenol, 3-methyl-
Molecular Formula	:	C7H8O

Producer related part

Company	:	Bayer AG
Creation date	:	11.01.1994

Substance related part

Company	:	Bayer AG
Creation date	:	11.01.1994
Status	:	
Memo	:	X AKTUELL EG / ICCA
Printing date	:	24.05.2004
Revision date	:	02.06.1994
Date of last update	:	24.05.2004
Number of pages	:	120
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type :
Name : ADCHEMCO Corporation
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2002

Type :
Name : American Chemistry Council Cresol Panel
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
27.07.2001

Type : cooperating company
Name : Bayer Corporation
Contact person :
Date :
Street : 100 Bayer Road
Town : PA 15205-9741 Pittsburgh
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
27.07.2001

Type : cooperating company
Name : Concord Chemical Company
Contact person :
Date :

Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
27.07.2001

Type : cooperating company
Name : Dakota Gasification Company
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
27.07.2001

Type : cooperating company
Name : Honshu Chemical Industry Company, Inc.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
27.07.2001

Type : cooperating company
Name : LaPorte (formerly Inspec Fine Chemicals)
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
27.07.2001

Type : cooperating company
Name : Merisol (Merichem-Sasol USA LLC)
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
01.08.2001

Type : cooperating company
Name : Mitsui Chemicals, Inc.
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
27.07.2001

Type : cooperating company
Name : Nippon Steel Chemical Company, Ltd.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
27.07.2001

Type : cooperating company
Name : PMC Specialties Group, Inc.
Contact person :
Date :
Street :

Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
27.07.2001

Type : cooperating company
Name : Sumiken Chemical Company, Ltd.
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
27.07.2001

Type : cooperating company
Name : Sumitomo Chemical Americas, Inc.
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
27.07.2001

Type : cooperating company
Name : Sumitomo Chemical Company, Ltd.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
27.07.2001

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : Organic
Physical status : Liquid
Purity : > 99
Colour :
Odour :

Flag : Critical study for SIDS endpoint
07.01.2003 (1)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1-HYDROXY-3-METHYLBENZOL

Flag : Critical study for SIDS endpoint

1-OXY-3-METHYLBENZOL

Flag : Critical study for SIDS endpoint

3-HYDROXYTOLUOL

Flag : Critical study for SIDS endpoint

3-KRESOL

Flag : Critical study for SIDS endpoint

3-METHYLPHENOL

Flag : Critical study for SIDS endpoint

M-HYDROXYTOLUOL

Flag : Critical study for SIDS endpoint

M-KRESOL

Flag : Critical study for SIDS endpoint

M-KRESYLSAEURE

Flag : Critical study for SIDS endpoint

M-OXYTOLUOL

Flag : Critical study for SIDS endpoint

M-TOLYLALKOHOL

Flag : Critical study for SIDS endpoint

PHENOL, 3-METHYL

Flag : Critical study for SIDS endpoint

1.3 IMPURITIES

Purity :
CAS-No : 106-44-5
EC-No : 203-398-6
EINECS-Name : p-cresol
Molecular formula :
Value : < 1 % w/w

15.01.2003 (1)

Purity :
CAS-No : 7732-18-5
EC-No : 231-791-2
EINECS-Name : water
Molecular formula :
Value : < .05

20.01.2003 (1)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : - tonnes produced in

Remark : 28,500 t in 2000, estimated world capacity
Flag : Critical study for SIDS endpoint
28.05.2002

1.6.1 LABELLING

Labelling	:	as in Directive 67/548/EEC
Specific limits	:	
Symbols	:	T, , ,
Nota	:	, ,
R-Phrases	:	(24/25) Toxic in contact with skin and if swallowed (34) Causes burns
S-Phrases	:	(36/37/39) Wear suitable protective clothing, gloves and eye/face protection (45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
Remark	:	19. Adaption, EC-Index-No. 604-004-00-9
Flag	:	Critical study for SIDS endpoint

1.6.2 CLASSIFICATION

Classified	:	as in Directive 67/548/EEC
Class of danger	:	toxic
R-Phrases	:	(24/25) Toxic in contact with skin and if swallowed
Specific limits	:	
Flag	:	Critical study for SIDS endpoint

16.11.2000

Classified	:	as in Directive 67/548/EEC
Class of danger	:	corrosive
R-Phrases	:	(34) Causes burns
Specific limits	:	
Flag	:	Critical study for SIDS endpoint

16.11.2000

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use	:	type
Category	:	Use in closed system
Flag	:	Critical study for SIDS endpoint

11.09.2000

Type of use	:	industrial
Category	:	Chemical industry: used in synthesis
Flag	:	Critical study for SIDS endpoint

16.11.2000

Type of use	:	use
Category	:	Intermediates

Flag : Critical study for SIDS endpoint
11.09.2000

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : MAK (DE)
Limit value : 22 mg/m3
Short term exposure limit value
Limit value : 22 mg/m3
Time schedule :
Frequency : times

Remark : all isomeres (CAS-Nr. 1319-77-3)
danger of cutaneous absorption
Source : TRGS 900 (DE)
Flag : Critical study for SIDS endpoint
24.05.2002

Type of limit : MAK (DE)
Limit value :

Remark : danger of cutaneous absorption
MAK list, canc. category 3A
27.05.2002 (2)

Type of limit : TLV (US)
Limit value : other: 5 ppm (= 22 mg/m³)

Remark : (TWA)
all isomers
danger of cutaneous absorption
Flag : Critical study for SIDS endpoint
19.09.2000

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 2 (water polluting)

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung (DE)
Substance listed : yes
No. in Seveso directive :

Remark : App. I, No. 2
17.07.2001

1.8.5 AIR POLLUTION

Classified by : TA-Luft (DE)
Labelled by :
Number : 3.1.7 (organic substances)
Class of danger : I

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered :
Date of search :

Remark : Toxicology: November 2002
Environmental aspects and ecotoxicology: January 2002
CAS number search in external and internal databases, e.g. HSDB, Aquire, Biosis, Embase, Toxline, Scisearch.
22.01.2003

1.13 REVIEWS

2.1 MELTING POINT

Value : 11.8 °C
Sublimation :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Remark : SRC (EPI Suite v 3.10) recommended value
Flag : Critical study for SIDS endpoint
10.05.2004

Value : 11.5 °C
Sublimation :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: m-cresol, purity > 95 % according to product specification on MSDS of Bayer

10.05.2004 (3) (4)

Value : 11 - 12 °C
Sublimation :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: m-cresol, no purity reported

10.05.2004 (5)

Value : 12 °C
Sublimation :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: m-cresol, no purity reported

10.05.2004 (6) (7)

Value : 12.2 °C
Sublimation :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: m-cresol, no purity reported

10.05.2004 (8)

2.2 BOILING POINT

Value : 202 °C at
Decomposition :
Method : other: no data available
Year : 1996

GLP : no data
Test substance : other TS: m-cresol, no purity reported

10.05.2004 (5) (7)

Value : 202.2 °C at 1013 hPa
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Remark : SRC (EPI Suite v 3.10) recommended value
Flag : Critical study for SIDS endpoint
10.05.2004 (8) (9)

Value : 203 °C at
Decomposition :
Method : other: no data available
Year : 1987
GLP : no data
Test substance : other TS: m-cresol, no purity reported

10.05.2004 (6)

2.3 DENSITY

Type :
Value : ca. 1.03 g/cm³ at 20 °C
Method :
Year :
GLP : no data
Test substance : other TS: m-cresol, purity > 95 % according to product specification on MSDS

10.05.2004 (3)

Type : density
Value : 1.0336 g/cm³ at 20 °C
Method :
Year :
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Flag : Critical study for SIDS endpoint
10.05.2004 (8)

Type : density
Value : 1.034 g/cm³ at °C
Method :
Year : 1987
GLP : no data
Test substance : other TS: m-cresol, no purity reported

10.05.2004 (9) (6) (5)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : .13 hPa at 20 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: m-cresol, purity > 95 % according to product specification on MSDS of Bayer

10.05.2004 (8) (3)

Value : .147 hPa at 25 °C
Decomposition :
Method : other (measured)
Year : 1989
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Remark : SRC (EPI Suite v 3.10) recommended value
Flag : Critical study for SIDS endpoint
10.05.2004 (10)

Value : .28 hPa at 30 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: m-cresol, no purity reported

10.05.2004 (8)

Value : 1.3 hPa at 50 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: m-cresol, purity > 95 % according to product specification on MSDS of Bayer

10.05.2004 (8) (3)

Value : 1.33 hPa at 52 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: m-cresol, no purity reported

10.05.2004 (6)

2.5 PARTITION COEFFICIENT

Partition coefficient :

Log pow : 1.96 at °C
pH value :
Method : other (measured)
Year :
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Remark : expertimental data, SRC (EPI Suite v 3.10) recommended value
Flag : Critical study for SIDS endpoint
10.05.2004 (11)

Partition coefficient :
Log pow : 1.96 at °C
pH value :
Method :
Year :
GLP : no data
Test substance : other TS: m-cresol, no purity reported

10.05.2004 (7)

Partition coefficient :
Log pow : 2.01 at °C
pH value :
Method :
Year :
GLP : no data
Test substance : other TS: m-cresol, no purity reported

10.05.2004 (7)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : 22.7 g/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
PKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: measured
Year : 1992
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Remark : SRC (EPI Suite v 3.10) recommended value (measured)
Flag : Critical study for SIDS endpoint
10.05.2004 (12)

Solubility in : Water
Value : 23.5 g/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :

PKa : at 25 °C
Description :
Stable :

10.05.2004 (7)

Solubility in : Water
Value : 24 g/l at 25 °C
pH value : 5
concentration : 20 g/l at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

07.05.2004 (3)

Solubility in : Water
Value : 58 g/l at 100 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

10.05.2004 (7)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : 86 °C
Type : closed cup
Method : other: DIN 51758
Year :
GLP :
Test substance : other TS: m-cresol, no purity reported

07.05.2004 (6) (5)

2.8 AUTO FLAMMABILITY

Value : 575 °C at
Method : other: DIN 51794
Year : 2000
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Remark : autoignition temperature
10.05.2004 (13)

Value : 558 °C at

Method : other: no data available
Year : 1987
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Remark : autoignition temperature
10.05.2004 (6)

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Remark : Explosive limits: lower: 1.0 % by volume (45 g/m3)
20.11.2000 (3)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

Acid-base constant : 10.1
Method : other: calculation
Year : 2002
GLP :
Test substance :

10.05.2004 (14)

Acid-base constant : 10.09
Method : other: measured and calculated
Year : 1968
GLP : no
Test substance : other TS: m-cresol, no purity reported

Method : Experimental data for cresols were taken from Kortuem G, Vogel W, and Andrussow K (1961) Dissociation Constants of Organic Acids in Aqueous Solution. Butterworths, London
Remark : For experimental data: Secondary literature
Result : Calculated result is pk = 10.1
Flag : Critical study for SIDS endpoint
10.05.2004 (15)

Acid-base constant : 10.49
Method : other: measured
Year : 1971
GLP : no
Test substance : other TS: m-cresol, no purity reported, but substance purified by distillation under reduced pressure

Method : Measured according to Bordwell FG and BD Cooper (1952) J. Am. Chem. Soc. 74, 1058
Remark : in 20 % water-ethanol (v/v) at 20 °C
10.05.2004 (16)

2.13 VISCOSITY

Test type : other
Test procedure :

Remark : .0169 Pa*s at 20 degrees C
18.10.2001 (3)

2.14 ADDITIONAL REMARKS

Remark : Maximum vapor concentration:
20 degrees Celsius: 0.58 g/m3
30 degrees Celsius: 1.2 g/m3
50 degrees Celsius: 5.2 g/m3
18.10.2001 (8)

Remark : Refraction index (nD):
1.5438 at 20 degrees Celsius
18.10.2001 (9)

Remark : Refraction index (nD): 1.5398 at 20 degrees C
18.10.2001 (5)

Remark : I. Threshold odor concentration in water: 0.800 ppm
II. Threshold taste concentration in water: 0.002 ppm
18.10.2001 (17)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm³
Rate constant	:	.00000000000873 cm³/(molecule*sec)
Degradation	:	50 % after 6 hour(s)
Deg. product	:	
Method	:	other (calculated): with SRC-AOPWIN, v1.90
Year	:	2003
GLP	:	
Test substance	:	
Remark	:	The calculated half-life is based on a mean OH radical concentration of 0.5E+6 OH radicals/cm3 given during the 24 hours/day as suggested in the EU-Technical Guidance Document
Reliability	:	(2) valid with restrictions Generally accepted calculation method
Flag	:	Critical study for SIDS endpoint

10.05.2004 (18)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (measured)
Year	:	1995
GLP	:	no data
Test substance	:	other TS: m-cresol, purity > 99 %
Method	:	Determination of the temperature-dependency of the OH-radical reaction under simulated tropospheric conditions
Remark	:	With a OH radical concentration of 1 000 000 molec cm-3 and a temperature of 299 K, the half-life is 3.8 h
Result	:	kOH = 5.17 x 10E-12 exp[(686+-231)/T] cm3 molec.-1 s-1 for a temperature range of 299-373 K
Test condition	:	test substance concentration 0.05-5 ppm reference compound (o-cresol) 0.05-2.3 ppm radical source methylnitrite 1.5-11 ppm together with NOx 2-70 ppm
Reliability	:	(1) valid without restriction Test procedure in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

11.05.2004 (19)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	

Method	:	other (measured): critical review
Year	:	1994
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	With a OH radical concentration of 1 000 000 molec/cm3, the half-life is 3.0 h at room temperature
Result	:	K[OH] = 64 [10E-12 cm3 molecule-1 s-1] K[NO3] = 9.74[10E-12 cm3 molecule-1 s-1] K[O3] = 1.9 [10E-19 cm3 molecule-1 s-1]
Reliability	:	(1) valid without restriction Critical review, evaluation of all available experimental data
Flag	:	Critical study for SIDS endpoint

11.05.2004 (20)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (measured)
Year	:	1990
GLP	:	no data
Test substance	:	other TS: m-cresol, purity > 99 % (obtained from Aldrich Chemical Company)
Method	:	smog chamber experiment with black light irradiation dry air pressure 735 Torr Temp. 296+-2 K irradiation time 4-20 min reference substance: propene OH radical concentration: (1-3) x 10E7 molecule cm-3
Result	:	k[OH] = 67.8 [10E-12 cm3 molecule-1 s-1]
Reliability	:	(1) valid without restriction Test procedure in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions

11.05.2004 (21)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (measured)
Year	:	1987
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Method	:	I. Smog chamber experiment II. Inkrement method
Result	:	I. observed: k[OH] = 57 [10E-12 cm3 molecule-1 s-1] II. calculated: k[OH] = 94 [10E-12 cm3 molecule-1 s-1]
Reliability	:	(1) valid without restriction Test procedure in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions

11.05.2004 (22)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (measured)
Year	:	1978
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Method	:	smog chamber Temp. 300 +-1 K reference substances: n-butane, neopentane initial concentration ca. 0.25 ppm for m-cresol OH radical concentration: (1-4)x10E6 molecule cm-3
Result	:	k[OH] = 67 [10E-12 cm3 molecule-1 s-1]
Reliability	:	(1) valid without restriction Test procedure in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions

11.05.2004 (23) (24)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	
Year	:	1989
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Result	:	K[OH] = 59 [10E-12 cm3 molecule-1 s-1] t[1/2] = 0.3 d
Reliability	:	(4) not assignable secondary literature

11.05.2004 (25)

Deg. product	:	
Method	:	other (measured)
Year	:	1985
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported, but in most cases purity exceeded 98 %
Method	:	substance adsorbed onto silica gel (100 ng/g) irradiated with UV lamp (290 nm) in a microphotoreactor
Result	:	degradation 33.3% of applied amount
Test condition	:	17 h at 15 degrees C
Reliability	:	(3) invalid Unsuitable test system

11.05.2004 (26)

3.1.2 STABILITY IN WATER

Remark	:	Based on the chemical structure of the compound hydrolysis is not expected under temperature and pH values occuring in

the environment.

Reliability : (2) valid with restrictions
Expert judgement

Flag : Critical study for SIDS endpoint

08.01.2003

3.1.3 STABILITY IN SOIL

Type	:	laboratory
Radiolabel	:	
Concentration	:	
Soil temperature	:	°C
Soil humidity	:	
Soil classification	:	
Year	:	
Deg. product	:	
Method	:	
Year	:	1990
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	Bench-scale experiments with contaminated soil. Determination of passive evaporation and biodegradation of cresols
Result	:	passive evaporation half-life 4.2 - 4.8 weeks biodegradation: after 4 days below detection limit
Test condition	:	Passive evaporation: plastic petri plates (88x18 mm) placed on canopy-covered table. Temp. 10-17 degrees C, humidity 75% Shake-flask biodegradation test: 8-25 g soil mixed with 50 ml buffer solution; shaken for 4 days
Reliability	:	(3) invalid Methodological deficiencies

07.05.2004 (27)

Type	:	laboratory
Radiolabel	:	yes
Concentration	:	
Soil temperature	:	°C
Soil humidity	:	
Soil classification	:	
Year	:	
Deg. product	:	
Method	:	other: see Method below
Year	:	1985
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Inocolum: subsurface microbial community of a pristine aquifer (Lula, Okla.) Soil: aquifer solid sample, unconsilated sand, from a depth of 4.5-5.6 m below surface All substances were radiolabeled. Incubation period: 8 months Determination of mineralization via 14CO2 evolution
Remark	:	The highest percent biodegradation achieved for nearly all the substances tested was 35% (e.g. anilin, which is the standard reference substance for all ready tests in OECD 301 achieved after 100 days only 15% biodegradation).

Result : - After 160 days and at a concentration of 39 ng/g m-cresol in soil, ca.15% mineralization was observed.
- The percent mineralized increased slowly and linearly with time.
- For the majority of the test compounds no adaptation period was observed.

Reliability : (3) invalid
No standard test procedure. Test design can only be used to assess degradation in soil of the pristine aquifer of Lula, Okla.

15.01.2003 (28)

3.2.1 MONITORING DATA

Type of measurement : other: contamination at a special working place
Media :
Concentration :
Method :

Remark : Combined m-/p-cresol isomers were detected among other chemicals in the indoor air at a shale oil wastewater facility at a concentration of 5.1 ppb.

Reliability : (2) valid with restrictions
Basic data given

20.01.2003 (29)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : volatility
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: measured
Year : 1999

Method : Thermodynamic column method of Brunner et al. 1990 applied [Brunner S, Hornung E, Santl H, Wolff E, Pringer OG, Altschuh J, Brueggemann R (1990) Henry´s law constants for polychlorinated biphenyls: Experimental determination and structure-property relationship. Environ Sci Technol 24, 1751 - 1754]:
- Aqueous solution of the TS produced in a generator column
- Solution is passed through gas liquid desorption column where it contacts a gas stream and the partition equilibrium is reached
- Gas and water are separated: water flows to the receiver dosing funnel, the gas is conducted into an absorption vessel where the TS is absorbed in organic solvent

Result : Henry's law constant (25 degrees C):
H = 3.5 E-5 calculated to
H = 8.67 E-2 Pa.m3.mol-1

Test condition : - Temperature 25 °C
- Gas phase: Nitrogen
- Liquid phase: Demineralized, distilled water
- Analysis: GC/ECD

Reliability : (2) valid with restrictions
basic data given
Flag : Critical study for SIDS endpoint
10.05.2004 (30)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: batch equilibrium method similar to OECD Guideline 106
Year : 1982

Remark : Koc value was determined for clay loam soil
Result : Koc=34.58
Test condition : Soil: Brookston clay loam soil, collected from top 15 cm,
air-dried, 5.10% organic matter, pH 5.7
soil/solution ratio 1:10
TS concentrations 5, 10, 20, 30, 50 mg/l, deoxygenated by purging with N2
triplicate samples, temp. 20+-1 degrees C, incubation period 24 h
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with general accepted scientific standards; sufficient documentation
Flag : Critical study for SIDS endpoint
10.05.2004 (31)

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level I
Year : 2001

Result : Calculated distribution between environmental compartments:
Air: 2.33 %
water: 96.32 %
soil: 0.69 %
bottom sediment: 0.65 %
suspended sediment: 0.001 %
biota: 0.0004 %
Test condition : data used in calculation
temperature (°C): 25
molar mass (g/mol): 108.14
vapor pressure (Pa): 14.7
water solubility (g/l): 22.7
log Kow: 1.96

volumes in unit world (m3)
air: 6 000 000 000
water: 7 000 000
soil: 45 000
sediment: 21 000
susp. sediment: 35
biota (fish): 7
Reliability : (2) valid with restrictions

generally accepted calculation method
Flag : Critical study for SIDS endpoint
11.12.2002 (32)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : predominantly domestic sewage
Concentration : .8 mg/l related to COD (Chemical Oxygen Demand)
related to
Contact time :
Degradation : = 90 (±) % after 28 day(s)
Result :
Kinetic of testsubst. : 7 day(s) = 45 - 80 %
14 day(s) = 70 - 90 %
21 day(s) = 75 - 70 %
28 day(s) = 90 - 90 %
%
Control substance : other: phenol, 0.8 mg/l
Kinetic : 28 day(s) = 73 %
%
Deg. product :
Method : OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year : 1988
GLP : no
Test substance : other TS: m-cresol pure

Result : 10-day window criteria is met
Test condition : Inoculum
- Type of sludge: activated sludge
- Source: treatment plant, receiving domestic sewage
- Sampling site: Odenthal
Concentration of control substance: 0.8 mg/l
Analytical parameter: Oxygen consumption
Test temperature: 20 degrees C
Test was performed in two paralleles.
Reliability : (2) valid with restrictions
Guideline Study
Flag : Critical study for SIDS endpoint
11.05.2004 (33)

Type : aerobic
Inoculum : predominantly domestic sewage
Concentration : 2.4 mg/l related to COD (Chemical Oxygen Demand)
related to
Contact time :
Degradation : = 65 (±) % after 28 day(s)
Result :
Kinetic of testsubst. : 7 day(s) = 55 - 58 %
14 day(s) = 58 - 66 %
21 day(s) = 61 - 65 %
28 day(s) = 65 - 65 %
%
Control substance : other: phenol, 2.4 mg/l
Kinetic : 28 day(s) = 69 %

%

Deg. product :
Method : OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year : 1988
GLP : no
Test substance : other TS: m-cresol pure

Remark : In two further tested concentrations (8 and 24 mg/l) the dissolved oxygen was completely emaciated within 7 days (concentration of control substance 8 and 24 mg/l for tests with 8 and 24 mg/l of test substance, respectively. Also i n these control experiments, oxygen was emaciated).
Result : Compared to the test with 0.8 mg/l the extent of degradation is lesser at 2.4 mg/l presumably due to the fact that most of the oxygen was used up at the high test substance concentration (10-day criteria met in only one of the two replicates)
Test condition : Inoculum / test organism
- Type of sludge: activated sludge
- Source: treatment plant, receiving domestic sewage
- Sampling site: Odenthal
Concentration of control substance: 2.4 mg/l
Analytical parameter: Oxygen consumption
Test temperature: 20 degrees C
Test was performed in two paralleles.

Reliability : (2) valid with restrictions
Guideline Study

11.05.2004 (33)

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : 100 mg/l related to Test substance
related to
Contact time :
Degradation : 80 - 95 (±) % after 40 day(s)
Result :
Deg. product :
Method : other: comparable to OECD Guide-line 301 C
Year : 1981
GLP : no
Test substance : other TS: m-cresol, purity > 99 %

Method : Initial sludge concentration: 30 mg d.w./l; aniline as reference compound
Remark : Incubation period: 20-40 days; no oxygen uptake curve given; degradation of reference substance aniline >/= 60 % within 28 days
Result : The oxygen uptake curves are not reported. However, the authors state that all test compounds revealed the lag phase, biodegradation phase and the plateau region within a period of 10 days, indicating that the 10-day window criteria is met.
First order biodegradation constant (hr-1): ln k = -5.77
maximum specific substrate uptake rate per unit biomass km = 17.3 / day (Aniline 16.1, Phenol 16.9).
m-Cresol is slightly better biodegradable than phenol and aniline.
Test condition : Inoculum /test organism
- Type of sludge: activated
- Source: municipal treatment plant, receiving predominantly domestic sewage
- Initial cell concentration: 30 mg/l
Test system
- Culturing apparatus: Sapromat
- Closed vessels used: yes

Initial test substance concentration: 100 mg/l
Duration of the test: 20-40 days
Test conditions
- Composition of synthetic medium: OECD
- Test temperature: 25 degrees C
Reference substance: aniline 100 mg/l

Reliability : (2) valid with restrictions
study comparable to OECD Guideline 301 C
Flag : Critical study for SIDS endpoint
11.05.2004 (34)

Type : aerobic
Inoculum : activated sludge, industrial
Contact time :
Degradation : 96 (±) % after 10 day(s)
Result :
Deg. product :
Method : OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year : 1990
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Result : 90% degradation during the log-phase (8 days)
Test condition : Test substance conc. 50-400 mg/l DOC, 200-1000 mg/l COD
acclimatization phase 2 days
Reliability : (2) valid with restrictions
Guideline study; basic data given
Flag : Critical study for SIDS endpoint
24.05.2004 (35)

Type : aerobic
Inoculum : activated sludge, adapted
Concentration : 200 mg/l related to COD (Chemical Oxygen Demand)
related to
Contact time :
Degradation : 95.5 (±) % after 5 day(s)
Result :
Deg. product :
Method : other: batch system (similar to OECD 302B "Zahn-Wellens Test")
Year : 1976
GLP : no
Test substance : other TS: m-cresol, no purity reported

Method : - Test compound was sole source of carbon
- Inoculum density: 100 mg dry matter/l; gradual increase of TS concentration during 20 days adaptation period
- With volatile substances a test without inocculum was done to differentiate the actual biological degradation from the losses due to mere volatilization
Result : Initial degradation rate: 55.0 mg COD/g/h
Test condition : 20 +- 3 degrees C; pH 7.2; mineral salts medium; dark; continuously stirred
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards;
basic data given
Flag : Critical study for SIDS endpoint
24.05.2004 (36)

Type : anaerobic

Inoculum : anaerobic sludge
Deg. product : yes
Method :
Year : 1981
GLP : no
Test substance : other TS: m-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Method : primary anaerobic sludge from 12 treatment plants receiving mainly domestic wastewater were diluted to 10 % in a mineral salts medium, test substance concentration: 30 mg/l; secondary anaerobic sludge from 2 treatment plants diluted to 10 % in a mineral salts medium, test substance: 50 mg/l; incubation for 8 weeks; triplicate samples
Result : primary sludges: no degradation was observed in 4 sludges; degradation ranged from 55 to 103 % in 6 sludges (lag times for approx 20 % of theoretical CH4 production: 4-6 weeks); insufficient data for 2 sludges. secondary sludge: degradation was 92% after 4 weeks with the first sludge and 90% after 5 weeks with the second (degradation related to theoretical methane and CO2 production)
Test condition : 35 degrees C, due to storage of sludges before incubation, lag phase of methanogenesis could be increased in some sludges
Reliability : (2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag : Critical study for SIDS endpoint
07.05.2004 (37)

Type : anaerobic
Inoculum : anaerobic sludge
Concentration : 50 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time : 56 day(s)
Degradation : (±) % after
Result :
Deg. product : yes
Method :
Year : 1984
GLP : no
Test substance : other TS: m-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Method : primary and secondary anaerobic sewage sludge from 9 treatment plants diluted to 10 % in a mineral salts medium; degradation measured as gas pressure increase
Remark : data have been published by the authors as a NTIS-study (previous data set)
Result : in 2 different secondary sludges >75% degradation in 9 different primary sludges degradation 0-103%
Test condition : incubation for 8 w at 35 degrees C
Reliability : (2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
Flag : Critical study for SIDS endpoint
07.05.2004 (38)

Type : anaerobic
Inoculum : anaerobic sludge
Concentration : 50 mg/l related to DOC (Dissolved Organic Carbon)
related to
Deg. product : yes
Method :
Year : 1988
GLP : no
Test substance : other TS: m-cresol, no purity reported (obtained from Aldrich Chemicals)
Deg. products : 74-82-8 200-812-7 methane

Method : primary anaerobic digesting sludge receiving a mixture of domestic and industrial wastewater
Result : lag time 40 days, accompanied with inhibition of gas production
net total gas production was 75 % +/- 15 % of the theoretical production (CH4+CO2)
Test condition : - medium 2-3 g dw/l sludge
- incubation for >= 60 d at 35 degrees C
- 3 replicates
- sterile controls for abiotic gas production
- gas production measured with hand-held pressure meter
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
Flag : Critical study for SIDS endpoint
07.05.2004 (39)

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : .05 mg/l related to Test substance
related to
Contact time :
Degradation : 35.6 (±) % after 5 day(s)
Result :
Deg. product :
Method : other: Activated sludge test
Year : 1985
GLP : no
Test substance : other TS: 14C-labelled m-cresol presumably > 98 % purity; no specific activity given

Remark : The bioaccumulation factor of the substance and its metabolites in activated sludge was 1100
Result : The readily biodegradable compounds methanol and phenol were about equally degraded like m-Cresol (41, 37 and 36 %)
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
24.05.2004 (26)

Type : aerobic
Inoculum : other bacteria: acclimatized mixed culture of pentachlorophenol-degrading bacteria
Concentration : 5 mg/l related to Test substance
related to
Contact time : 29 day(s)
Degradation : (±) % after

Result	:	
Kinetic of testsubst.	:	38 hour(s) 50 % 46 hour(s) 90 % % % %
Deg. product	:	
Method	:	other: Die-away Test
Year	:	1990
GLP	:	no
Test substance	:	other TS: gas chromatographic grade
Result	:	no lag phase
Reliability	:	(2) valid with restrictions No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

24.05.2004 (40)

Type	:	aerobic
Inoculum	:	other: denitrifying cultures from unadapted mixed wastewater
Concentration	:	.39 mg/l related to Test substance related to
Contact time	:	
Degradation	:	100 (±) % after 17 day(s)
Result	:	
Deg. product	:	
Method	:	other: measured
Year	:	1989
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Result	:	lag phase 3 days, completely degraded in 17 d
Test condition	:	inoculum prepared by mixing waste water samples from 12 denitrifying treatment plants incubated at 27 degrees C in the dark
Reliability	:	(2) valid with restrictions Study in accordance with generally accepted scientific standards and described in sufficient detail

24.05.2004 (41)

Type	:	anaerobic
Inoculum	:	other: municipal sewage sludge from primary anaerobic digesters
Concentration	:	50 mg/l related to Test substance related to
Contact time	:	56 day(s)
Degradation	:	100 (±) % after 49 day(s)
Result	:	
Deg. product	:	yes
Method	:	
Year	:	1983
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Deg. products	:	74-82-8 200-812-7 methane
Result	:	substance disappeared completely after 7 weeks net CH4 production >90% of theoretical value no transformation products observed
Test condition	:	mineral salt medium with 10% sludge Temperature 35 degrees C
Reliability	:	(2) valid with restrictions

No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (42)

Type : anaerobic
Inoculum : anaerobic sludge
Deg. product : yes
Method :
Year : 1983
GLP : no
Test substance : other TS: m-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Remark : sensitivity of acid formers and methanogenic consortia examined
Result : at <= 400 mg/l, m-cresol was not fermented and showed no inhibition of methane formation from degradable substrates as compared to control cultures; 1000 mg/l inhibited the methane production significantly (60 % of control values)
Test condition : screening optimized for mechanistic study
m-cresol concentration: 200, 400 or 1000 mg/l
incubation for 6 w at 37 degrees C
Reliability : (4) not assignable
No standard test procedure, but in accordance with generally accepted scientific standards; not relevant for purpose of HPV program

07.05.2004 (43)

Type : anaerobic
Inoculum : other: anaerobic sludge, adapted
Concentration : 300 mg/l related to Test substance
related to
Deg. product : yes
Method : other: see test condition
Year : 1986
GLP : no
Test substance : other TS: m-cresol, no purity reported (Aldrich chemicals) (methyl 14C-labelled from Pathfinder Lab.)
Deg. products : 74-82-8 200-812-7 methane

Result : Degradation: ca. 100 % after 9 days
Most of the methyl carbon of m-cresol (87 %) was converted to CH4.
Test condition : preincubation for 2-3 months
incubation for 20 d at 37 degrees C
Test substance : 14C-methyl labeled
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (44)

Type : anaerobic
Inoculum : anaerobic sludge
Concentration : 50 mg/l related to DOC (Dissolved Organic Carbon)
related to
Deg. product :
Method :
Year : 1982
GLP : no
Test substance : other TS: m-cresol, purity > 95 %

Deg. products : 74-82-8 200-812-7 methane

Method : - Sludge from 2 municipal plants
- Methane production monitored
- HPLC to monitor disappearance of substrate

Result : mineralization (related to theoretical methane and CO2 production) was 92% after 4 weeks with the first sludge and 90% after 5 weeks with the second

Test condition : incubation at 35 degrees C in the dark, 10 % sludge inoculum, duplicate tests

Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (45)

Type : anaerobic
Inoculum : other: anoxic lake sediment
Concentration : .1 mg/l related to Test substance
.8 mg/l related to Test substance
Deg. product :
Method :
Year : 1982
GLP : no
Test substance : other TS: m-cresol, purity > 95 %
Deg. products : 74-82-8 200-812-7 methane

Result : after 29 weeks no significant CH4 or CO2 formation observed
Test condition : incubation at 20 degrees C in the dark with occasional shaking
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (45)

Type : anaerobic
Inoculum : other bacteria: acclimatized mixed culture of pentachlorophenol-degrading bacteria
Concentration : 5 mg/l related to Test substance
related to
Contact time : 29 day(s)
Degradation : (±) % after
Result :
Kinetic of testsubst. : 144 hour(s) 10 %
197 hour(s) 50 %
236 hour(s) 90 %
%
%
Deg. product :
Method : other: Die-away Test
Year : 1990
GLP : no
Test substance : other TS: m-cresol, gas chromatographic grade

Result : 10-day window criteria is met
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (40)

Type : anaerobic
Inoculum : other: phenol-enriched methanogenic culture
Concentration : 100 mg/l related to Test substance
related to
Contact time :
Degradation : 100 (±) % after 58 day(s)
Result :
Deg. product : yes
Method :
Year : 1988
GLP : no
Test substance : other TS: m-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Result : lag time 42 d, complete disappearance after 58 d,
the CH4 production was 85 % of the theoretical production
Test condition : nominal test concentrations m-cresol 50, 100, 150, 250, 300, 400, 500, and 700 mg/l + phenol 200 mg/l
incubation at 35 °C with continuous shaking
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (46)

Type : anaerobic
Inoculum : other: shallow anaerobic alluvial sand aquifer
Deg. product : yes
Method :
Year : 1986
GLP : no
Test substance : other TS: m-cresol, no purity reported (obtained from Aldrich Chemical Co.)
Deg. products : 74-82-8 200-812-7 methane

Method : 2 sampling sites: 1 methanogenic, 1 sulfate-reducing
both aquifers receive leachate from a municipal landfill
Result : lag time 43 days under sulfate-reducing and 46-90 days under methanogenic conditions, no data for complete degradation given
Test condition : test medium: 50 g [wet weight] of aquifer solids and 50 ml of groundwater
incubation at room temperature in the dark, quadruplicates
preincubation 5 days, addition of 150 to 200 µM test substance
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (47)

Type : anaerobic
Inoculum : other: undefined methanogenic consortia from river sediment
Concentration : 54 mg/l related to Test substance
related to
Deg. product : yes
Method :
Year : 1989
GLP : no
Test substance : other TS: m-cresol, no purity reported

Deg. products	:	74-82-8 200-812-7 methane
Method	:	black anoxic mud collected from a river inoculated in a mineral medium (10% w/v)
Result	:	non-acclimated consortia: turnover rate 1.10 µmol/day/g sediment dw (lag-phase 16 d) acclimated consortia: turnover rate 2.37 µmol/day/g sediment dw (lag-phase 0 d, based on a 24-days-incubation period), the CH4 production was 96 % of the theoretically possible yield
Test condition	:	incubation at 28 degrees C in the dark cultures were refed with 60 mg/l test substance every 2-4 w for a total of 18 months
Reliability	:	(2) valid with restrictions No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (48)

Type	:	aerobic
Inoculum	:	
Concentration	:	10 mg/l related to Test substance related to
Contact time	:	3 day(s)
Degradation	:	26 - 100 (±) % after 3 day(s)
Result	:	
Deg. product	:	
Method	:	other: cultivation method
Year	:	1987
GLP	:	
Test substance	:	other TS: m-cresol, no purity reported in abstract
Result	:	biodegradation in river water = 100 % biodegradation in sea water = 26 % The authors assume the compound to be moderately to easily biodegradable
Reliability	:	(4) not assignable Japanese reference with short abstract in English

24.05.2004 (49)

Type	:	anaerobic
Inoculum	:	other: microcosm containing aquifer and ground water
Concentration	:	18 mg/l related to Test substance related to
Deg. product	:	yes
Method	:	
Year	:	1989
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Deg. products	:	74-82-8 200-812-7 methane
Result	:	lag time 110 days, disappearance after approx. 225 d (values taken from a graphics)
Test condition	:	methanogenic conditions in a microcosm
Reliability	:	(3) invalid Insufficient documentation

07.05.2004 (50)

Type	:	anaerobic
Inoculum	:	other: anoxic aquifer
Concentration	:	300 µmol/l related to Test substance related to

Deg. product	:	
Method	:	
Year	:	1990
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Method	:	anoxic aquifer slurries held under sulfate- and nitrate-reducing conditions
Result	:	m-cresol was largely degraded in less than 6 d degradation dependant on sulfate, inhibited by 1.0 mM molybdate, not influenced by bromoethanesulfonic acid
Reliability	:	(4) not assignable only abstract available

07.05.2004 (51)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species	:	Leuciscus idus melanotus (Fish, fresh water)
Exposure period	:	3 day(s) at °C
Concentration	:	.05 mg/l
BCF	:	20
Elimination	:	no data
Method	:	
Year	:	1985
GLP	:	no
Test substance	:	other TS: 14C-labelled m-cresol presumably > 98 % purity; no specific activity given
Remark	:	Determination of radioactivity includes possible metabolized and/or incorporated intermediates The authors report BCF in different tables with 17 or 20
Test condition	:	5 fish (2-4 g) were exposed in a closed system and concentrations determined by following radioactivity in fish and water; BCF values related to wet weight 20-25 degrees C; pH 7; hardness 100 mg CaO/l
Reliability	:	(2) valid with restrictions No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
Flag	:	Critical study for SIDS endpoint

12.05.2004 (26)

Species	:	other: Chlorella fusca (algae)
Exposure period	:	24 hour(s) at °C
Concentration	:	.05 mg/l
Elimination	:	no data
Method	:	
Year	:	1985
GLP	:	no
Test substance	:	other TS: 14C-labelled m-cresol presumably > 98 % purity; no specific activity given
Remark	:	In this study BCF-values of 40 and 4,900 for algae are reported without explanation for the difference.

It is a common observation that test substance adsorbes at the surface of the algae. Due to the high surface / volume ratio a high BCF could be obtained.

Test condition : 20-25 degrees C
Test substance : 14C-m-cresol
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (26)

Species : other: Activated Sludge
Exposure period : 5 day(s) at °C
Concentration :
BCF : 1100
Elimination :
Method :
Year : 1985
GLP : no
Test substance : other TS: 14C-labelled m-cresol presumably > 98 % purity; no specific activity given

Remark : Values of bioaccumulation factors range from 10 up to 42,800.
Esters and higher alcohols are placed in the intermediate range between 3,000 and 5,000. Sodium acetat with an accumulation factor of 29,100 is remarkable. In this ranking m-Cresol belongs to the group of compounds with low accumulation potential.
Correlation between accumulation factors and physico-chemical parameters was not practicable.
Test substance : 14C-m-cresol
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail.

12.05.2004 (26)

3.8 ADDITIONAL REMARKS

Memo : biodegradation under anaerobic conditions

Method : enrichment cultures prepared by addition of 3 g/l m-cresol once per week
initial concentration 200-300 mg/l test substance
incubation at 37 degrees C in the dark
Result : 1st step: incorporation of CO2 giving 4-hydroxy-2-methylbenzoic acid
2nd step:
2a: dehydroxylation to 2 methylbenzoic acid (not further metabolized) to a minor degree
2b: ring reduction, ring fission and beta-oxidation to acetate. Ring reduction appeared to be the rate-limiting step, because no subsequent intermediates accumulated
Test substance : 1. U-ring-14C m-cresol
2. methyl-14C m-cresol
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

11.12.2002 (52)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	8.9
Limit test	:	
Analytical monitoring	:	yes
Method	:	other: US EPA, Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians. Nat. Environm. Res. Center, Corvallis (1974)
Year	:	1980
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Method	:	Mean length/mean weight of fish: 7.9 cm/6.0 g
Result	:	sublethal effects: hyperactivity, rapid operculation, sensitive to disturbance and gathering at the surface
Test condition	:	DILUTION WATER - Source: well water - Hardness: 707.3 mg CaCO3/l - Conductance: 1212.3 µmhos/cm at 25 degrees C TEST SYSTEM - Concentrations: 1:2 dilution series - Number of replicates: 2 - fish per replicate: 10 - Test temperature: 14 degrees C - Dissolved oxygen: 6.5 mg/l (84.5% of saturation) - pH: 8.1 - Photoperiod: 16 h light, 8 h dark
Reliability	:	(1) valid without restriction Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

07.05.2004 (53)

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	55.9
Limit test	:	
Analytical monitoring	:	yes
Method	:	other: US EPA, Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians. Nat. Environm. Res. Center, Corvallis (1974)
Year	:	1980
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Method	:	Mean length/mean weight of fish: 4.9 cm/1.6 g
Result	:	sublethal effects: loss of equilibrium, erratic swiming and twitching at a test substance concentration of 49.8 mg/l
Test condition	:	DILUTION WATER - Source: well water - Hardness: 707.3 mg CaCO3/l - Conductance: 1212.3 µmhos/cm at 25 degrees C

TEST SYSTEM
- Concentrations: 1:2 dilution series
- Number of replicates: 2
- fish per replicate: 10
- Test temperature: 14 degrees C
- Dissolved oxygen: 6.5 mg/l (84.5% of saturation)
- pH: 8.1
- Photoperiod: 16 h light, 8 h dark

Reliability : (1) valid without restriction
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag : Critical study for SIDS endpoint
07.05.2004 (53)

Type : static
Species : Salmo trutta (Fish, fresh water, marine)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 8.4
Limit test :
Analytical monitoring : no
Method :
Year : 1969
GLP : no
Test substance : other TS: m-cresol, reported to be "purified grade"

Method : 10 acclimated fish exposed per concentration, 20 served as controls.
Result : LC50 (6 h) = 11.0 mg/l
LC50 (24 h) = 8.6 mg/l
LC50 (48 h) = 8.4 mg/l
Test condition : 12 degree C, reconstituted water
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
Flag : Critical study for SIDS endpoint
07.05.2004 (54)

Type : static
Species : Salvelinus fontinalis (Fish, estuary, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 7.6
Limit test :
Analytical monitoring : no
Method :
Year : 1969
GLP : no
Test substance : other TS: m-cresol, reported to be "purified grade"

Method : 10 acclimated fish exposed per concentration, 20 served as controls.
Result : LC50 (6 h) = 11.4 mg/l
LC50 (24 h) = 8.2 mg/l
LC50 (48 h) = 7.6 mg/l
at concentrations of 6 to 20 mg/l, the approximate incidences of surfacing were 20 %
Test condition : 12 degree C, reconstituted water

Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
Flag	:	Critical study for SIDS endpoint

07.05.2004 (54)

Type	:	static
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 8.6
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	other TS: m-cresol, reported to be "purified grade"
Method	:	10 acclimated fish exposed per concentration, 20 served as controls.
Result	:	LC50 (6 h) = 14.9 mg/l LC50 (24 h) = 10.4 mg/l LC50 (48 h) = 10.2 mg/l In an additional test under flow-through conditions a concentration of 10 mg/l caused total incapacitation in 15 of 20 fish within 11.5 min, after which a recovery to a higher level of activity was observed
Test condition	:	12 degree C, reconstituted water
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

07.05.2004 (54)

Type	:	semistatic
Species	:	Poecilia reticulata (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	23.12
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1982
GLP	:	no
Test substance	:	other TS: m-cresol, purity 99 % (BDH Chemicals)
Method	:	80 % of the test solution renewed at 12 h intervals
Test condition	:	25-27 degrees Celsius, pH 7
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

07.05.2004 (55)

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	11

LC50	:	15.9
LC100	:	22
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Pruefrichtlinie UBA (summer 1980)
Year	:	1982
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Test condition	:	pH 7.5 +- 0.3
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

07.05.2004 (56)

Type	:	static
Species	:	Gadus morrhua (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
EC50	:	> 30
Limit test	:	
Analytical monitoring	:	yes
Method	:	
Year	:	1985
GLP	:	no
Test substance	:	other TS: m-cresol, purity > 98 % as determined by GC (obtained from Merck)
Method	:	effect endpoints: death, pathology, inhibition of cleavage and differentiation, pigment defects
Result	:	parallel test with larvae (6 days after hatching) showed pigment effects at 10 and 30 mg/l
Test condition	:	5 degrees C
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

07.05.2004 (57)

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC0	:	10
LC50	:	17
LC100	:	22
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Test procedure of the Abwasserabgabengesetzentwurf (Deutscher Bundestag 1974)
Year	:	1982
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

07.05.2004 (58)

Type :
Species : Cyprinus carpio (Fish, fresh water)
Exposure period : 24 hour(s)
Unit : mg/l
LC50 : 25
Method :
Year : 1959
GLP :
Test substance : other TS: m-cresol, no purity reported

Remark : results from: Albersmayer and Erichsen: Z. Fisch. 8 (1/3), 29-66 (1959)
Reliability : (3) invalid
Study does not follow any guideline. No analytical monitoring, no information about the test substance. Further details are missing
07.05.2004 (59)

Type :
Species : Rutilus rutilus (Fish, fresh water)
Exposure period : 24 hour(s)
Unit : mg/l
LC50 : 23
Method :
Year : 1959
GLP :
Test substance : other TS: m-cresol, no purity reported

Remark : results from: Albersmayer and Erichsen: Z. Fisch. 8 (1/3), 29-66 (1959)
Reliability : (3) invalid
Study does not follow any guideline. No analytical monitoring, no information about the test substance. Further details are missing
07.05.2004 (59)

Type :
Species : Tinca tinca (Fish, fresh water)
Exposure period : 24 hour(s)
Unit : mg/l
LC50 : 21
Method :
Year : 1959
GLP :
Test substance : other TS: m-cresol, no purity reported

Remark : results from: Albersmayer and Erichsen: Z. Fisch. 8 (1/3), 29-66 (1959)
Reliability : (3) invalid
Study does not follow any guideline. No analytical monitoring, no information about the test substance. Further details are missing
07.05.2004 (59)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
LC50 : 6
Limit test :
Analytical monitoring : no

Method	:	other: Mann, H., Fischtest mit Goldorfen zur vergleichenden Pruefung der akuten Toxizitaet von Wasserinhaltsstoffen und Abwaessern, Praktische Erfahrungen aus 3 Ringtesten, Z. f. Wasser- u. Abwasser-Forschung 9, 103-109 (1976)
Year	:	1978
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Reliability	:	(4) not assignable Secondary literature not available (Mann 1976)

07.05.2004 (17)

Type	:	static
Species	:	other: Pleuronectes sp. (plaice)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	10 - 33
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1971
GLP	:	no
Test substance	:	other TS: cresol, isomer not specified
Test condition	:	15 degrees C
Reliability	:	(4) not assignable secondary literature

07.05.2004 (60)

Type	:	
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	10 - 13.6
Method	:	
Year	:	1971
GLP	:	
Test substance	:	other TS: m-cresol, no purity reported
Reliability	:	(4) not assignable secondary literature

12.05.2004 (61)

Type	:	
Species	:	Oryzias latipes (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	24
Method	:	
Year	:	1986
GLP	:	
Test substance	:	other TS: m-cresol, no purity reported
Reliability	:	(4) not assignable secondary literature, original source unknown

12.05.2004 (62)

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	48 hour(s)

Unit	:	mg/l
LC0	:	10
LC50	:	17 - 19
LC100	:	21 - 26
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische. DEV, L 15 (1976)
Year	:	1978
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Reliability	:	(4) not assignable Insufficient documentation

07.05.2004 (63)

Type	:	
Species	:	other: Agonus cataphractus (poacher)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	10 - 33
Method	:	
Year	:	1960
GLP	:	
Test substance	:	other TS: m-cresol
Reliability	:	(4) not assignable reference not available

12.05.2004 (64)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	13
EC50	:	25
EC100	:	50
Analytical monitoring	:	no
Method	:	other: immobilisation test according to Bringmann & Kühn: Z. Wasser Abwasser Forsch. 10, 162-166 (1977)
Year	:	1982
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	Exposure of 24 h old Daphnia (strain IRCHA); 10 individuals per concentration, duplicate samples
Result	:	effect values refer to nominal test substance concentrations
Test condition	:	20 degrees C; initial pH 8.0 +/-0.2; water saturated with oxygen; hardness: 16° d.h. (corresponding to 286 mg CaCO3/l)
Reliability	:	(1) valid without restriction Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

07.05.2004 (65)

Type	:	flow through
Species	:	Daphnia pulicaria (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	> 99.5
Analytical monitoring	:	yes
Method	:	other: US EPA, Methods for acute toxicity test with fish, macroinvertebrates, and amphibians. Nat. Environm. Res. Center, Corvallis (1974)
Year	:	1980
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Test condition	:	DILUTION AND TEST WATER - Source: well water - Hardness: 707.3 mg CaCO3/l - pH: 8.1 - Oxygen content: 6.5 mg/l (84.5% of saturation) - Conductance: 1212.3 µhos/cm at 25 degrees C - Number of replicates, individuals per replicate: 10 - Test temperature: 14 +- 1 degrees C - Photoperiod: 16 h light, 8 h dark
Reliability	:	(1) valid without restriction Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

07.05.2004 (53)

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	1.6
EC50	:	8.9
EC100	:	25
Analytical monitoring	:	no
Method	:	
Year	:	1977
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	Effect endpoint: immobilisation
Test condition	:	Hardness 16 degrees (German), pH 7.6-7.7, 20-22 degrees Celsius
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
Flag	:	Critical study for SIDS endpoint

07.05.2004 (66)

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	19.2
Analytical monitoring	:	no
Method	:	other: AFNOR (1974)
Year	:	1987

GLP	:	no data
Test substance	:	other TS: m-cresol, purity > 95 %
Remark	:	Effect endpoint: immobilisation
Result	:	Result is reported as 24h IC50 "0.178 mmol/l" (which equals 19.2 mg/l)
Test condition	:	Reconstituted hard water 200 mg/l CaCO3 pH 7.8-8.2 dissolved oxigen >25% of saturation
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
07.05.2004		(67) (68)
Type	:	other: not specified
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	18.8
Limit Test	:	no
Analytical monitoring	:	no data
Method	:	other: according to the method described by Parkhurst et al. 1977
Year	:	1979
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	Parkhurst BR, Gehrs CW, Rubin IB (1977): Proceedings of ASTM 2nd Annual Symposium on Aquatic Toxicology, 122-130
Test condition	:	Daphnia magna used in the test were adults. 100-ml test beakers were filled with 80 ml test solution and 4 daphnia. All the tests were run in triplicate. Temperature during the test: 25 +/- 0.5°C 12h light/dark cycle Test solution was prepared with filtered spring water (pH 7.8 alkalinity mg/l, hardness 140 mg/l) Control beakers were used 48h-EC50 values were obtained by PROBIT
Test substance	:	The test substance was obtained from an effluent
Reliability	:	(3) invalid Methodological deficiencies (method description is in the other reference from the same author). Age of daphnias used in the test is not clearly specified: test daphnias were "adults" (in the OECD guideline a 24h-old daphnia is suggested); temperature during the test was 25°C (in the guideline is suggested: 18-22°C); 12 daphnia were used for each test concentration (in the guideline 40 daphnias are suggested)
07.05.2004		(69)
Type	:	static
Species	:	Daphnia sp. (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
TT	:	28
Analytical monitoring	:	no
Method	:	
Year	:	1959
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	test organisms were reared from daphnids collected in surface water

Remark	:	TT = Toxicity threshold; test organisms were reared from daphnids collected in surface water
Test condition	:	river water, pH 7.5
Reliability	:	(3) invalid Experimental details missing. Study does not follow any guideline, concentrations tested were not reported, no information about the application method of the test substance is given. Neither O2/pH monitoring nor analytical monitoring were applied
12.05.2004		(70)

Type	:	
Species	:	other aquatic mollusc: Glossosiphonia complanata
Exposure period	:	
Unit	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: m-cresol, no purity reported
Result	:	perturbation level: 1.1 mg/l
Reliability	:	(4) not assignable Secondary literature
12.05.2004		(71)

Type	:	
Species	:	other aquatic arthropod: Limnoria tripunctata
Exposure period	:	100 hour(s)
Unit	:	mg/l
LC50	:	100
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: m-cresol
Reliability	:	(4) not assignable Reference not available
12.05.2004		(64)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus quadricauda (Algae)
Endpoint	:	biomass
Exposure period	:	8 day(s)
Unit	:	mg/l
TT	:	15
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Cell multiplication inhibition test
Year	:	1977
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	incubation of 10 ml test solution (algae in defined mineral salts medium)
Remark	:	TT (toxic threshold concentration) refers to nominal test substance concentration and was determined at 3 % effect compared to the control
Test condition	:	27 degrees C; initial pH 7.0

Reliability	:	(3) invalid It is unclear whether the algae are within the exponential growth throughout the whole exposure period of 8 days.
07.05.2004		(72)
Species	:	Chlorella pyrenoidosa (Algae)
Endpoint	:	other: chlorophyll content
Exposure period	:	72 hour(s)
Unit	:	mg/l
EC0	:	< 50
EC50	:	127
EC100	:	250
Limit test	:	no
Analytical monitoring	:	no
Method	:	
Year	:	1968
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Result	:	1000 mg/l: complete destruction of chlorophyll EC50 was not reported in the study, but it can be taken from the graph
Test condition	:	TEST ORGANISMS - Strain: Emerson strain - Test temperature: 25 +- 1 degrees C - pH: 7.0 - Photoperiod: continuous illumination TEST PARAMETER: chlorophyll
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
12.05.2004		(73)
Species	:	Microcystis aeruginosa (Algae, blue, cyanobacteria)
Endpoint	:	other: cell multiplication
Exposure period	:	8 day(s)
Unit	:	mg/l
TGK	:	13
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Modified DEV L9 (cell multiplication inhibition test)
Year	:	1975
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	TGK = Toxicity treshold, determined at 1% effect compared to control
Reliability	:	(3) invalid It is unclear whether the algae are within the exponential growth throughout the whole exposure period of 8 days.
07.05.2004		(74) (75)
Species	:	other aquatic plant: Potamogeton lucens
Endpoint	:	other: photosynthesis
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	.22
LOEC	:	.65
EC50	:	.65
EC100	:	> 1.08

Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1983
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	simulation of running water under summer climate conditions
Test condition	:	water hardness: 9° dH; conductivity: 300 uS; pH 7.8
Reliability	:	(3) invalid Methodological deficiencies. Most test conditions not indicated. No information about application mode, number of plants, controls, test concentrations, statistics, analytics.

07.05.2004 (76)

Species	:	other aquatic plant: Potamogeton coloratus
Endpoint	:	other: photosynthesis
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	1.08
LOEC	:	> 1.08
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1983
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	simulation of running water under summer climate conditions
Test condition	:	water hardness: 9° dH; conductivity: 300 uS; pH 7.8
Reliability	:	(3) invalid Methodological deficiencies. Most test conditions not indicated. No information about application mode, number of plants, controls, test concentrations, statistics, analytics.

07.05.2004 (76)

Species	:	other aquatic plant: Potamogeton crispus
Endpoint	:	other: photosynthesis
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	1.08
LOEC	:	> 1.08
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1983
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	simulation of running water under summer climate conditions
Test condition	:	water hardness: 9° dH; conductivity: 300 uS; pH 7.8
Reliability	:	(3) invalid Methodological deficiencies. Most test conditions not indicated. No information about application mode, number of plants, controls, test concentrations, statistics, analytics.

07.05.2004 (76)

Species	:	Agmenellum quadruplicatum (Algae)
Endpoint	:	
Exposure period	:	

Unit	:	
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	algae cells embedded in agar, test substance absorbed on discs (12.7 mm) which are placed directly on the agar surface incubation 5 to 8 days
Result	:	no effect with 0.5 mg test substance on the plate with 1 mg inhibition between 1 to 10 mm from the disc edge, with 10 mg complete killing within a zone of 36 mm
Reliability	:	(3) invalid Unsuitable test system

10.05.2004 (77)

Species	:	other algae: Chlorella autotrophica
Endpoint	:	
Exposure period	:	
Unit	:	
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	algae cells embedded in agar, test substance absorbed on discs (12.7 mm) which are placed directly on the agar surface incubation 5 to 8 days
Result	:	with 1 mg inhibition between 1 to 4 mm from the disc edge, with 2 mg 1nhibition between 3 to 35 mm from the disc edge
Reliability	:	(3) invalid Unsuitable test system

10.05.2004 (77)

Species	:	Scenedesmus quadricauda (Algae)
Endpoint	:	biomass
Exposure period	:	96 hour(s)
Unit	:	mg/l
TT	:	40
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Cell multiplication inhibition test
Year	:	1959
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	TT = toxicity treshold
Reliability	:	(3) invalid Methodological deficiencies

07.05.2004 (70)

Species	:	Ankistrodesmus falcatus (Algae)
Endpoint	:	biomass
Exposure period	:	10 day(s)
Unit	:	mg/l
MTL	:	100
Method	:	
Year	:	1976

GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	described in: Denson & Bold, The University of Texas Publication No. 6022, 72 (1960)
Remark	:	MTL = median tolerance limit
Result	:	sublethal concentration 100 mg/l lethal concentration 500 mg/l
Reliability	:	(4) not assignable Insufficient documentation

12.05.2004 (78)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	activated sludge, domestic
Exposure period	:	3 hour(s)
Unit	:	mg/l
EC50	:	461.4
Analytical monitoring	:	no
Method	:	OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year	:	1985
GLP	:	no
Test substance	:	other TS: m-cresol, reagent grade
Remark	:	synthetic sewage stock solution slightly different from OECD guideline; reference substance 1,5-dichlorophenol
Test condition	:	21 degrees C; continuous aeration with 0.5-10 l/min
Reliability	:	(1) valid without restriction Guideline study
Flag	:	Critical study for SIDS endpoint

07.05.2004 (79)

Type	:	aquatic
Species	:	activated sludge of a predominantly domestic sewage
Exposure period	:	
Unit	:	mg/l
EC75	:	11.4
Analytical monitoring	:	no
Method	:	other: inhibition of nitrification process
Year	:	1966
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	Quantitative determination of the nitrification rate (1st step, NH4 to NO2), colorimetric measurement of the NO2/NO3 concentration; static test system Pre-cleaned activated sludge in particle-free communal waste water (BOD5: 250 mg/l; NH4-N/l: 50-80 mg)
Remark	:	effect: inhibition of ammonia oxidation
Test condition	:	Exposure period: 2-4 h; 25 degree C; pH 7.6-7.8
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
Flag	:	Critical study for SIDS endpoint

07.05.2004 (80)

Type	:	aquatic
Species	:	other bacteria
Exposure period	:	
Unit	:	
Analytical monitoring	:	no
Method	:	other
Year	:	1985
GLP	:	no
Test substance	:	other TS: m-cresol, purity 99.5 %
Method	:	6 different pure bacteria cultures: 3 isolated from a laboratory activated sludge, 2 from activated sludge from a municipal plant receiving some industry wastewater, and 1 from a lake sediment Effect: 50 % resazurin reduction (determination of dehydrogenase activity)
Result	:	from laboratory sludges: EC50 = >500, 225, and 410 mg/l from activated sludges: EC50 = 360 and >500 mg/l from lake sediment: EC50 = >500 mg/l
Test condition	:	21 degrees C; incubation 30-60 min
Reliability	:	(2) valid with restrictions No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (81)

Type	:	aquatic
Species	:	other bacteria: Aerobic heterotrophic
Exposure period	:	49 hour(s)
Unit	:	mg/l
IC 50	:	440
Analytical monitoring	:	no
Method	:	
Year	:	1991
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	culture obtained from mixed liquor of a treatment plant
Remark	:	Effect: inhibition of respiration; prolonged incubation compared with ISO 8192
Test condition	:	25 and 35 degrees C
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

07.05.2004 (82)

Type	:	aquatic
Species	:	other bacteria: Methanogenic bacteria
Exposure period	:	96 hour(s)
Unit	:	mg/l
IC 50	:	890
Analytical monitoring	:	no
Method	:	other: Owen, W.F.: Bioassay for Monitoring Biochemical Methane Potential and Anaerobic Toxicity. Water Res. 13, 485 (1979)
Year	:	1991
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported

Remark	:	Effect: inhibition of gas production
Test condition	:	35 degrees C
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

07.05.2004 (82)

Type	:	aquatic
Species	:	Nitrosomonas sp. (Bacteria)
Exposure period	:	24 hour(s)
Unit	:	mg/l
IC 50	:	.78
Analytical monitoring	:	no
Method	:	other: Inhibition of nitrification, comparable to ISO/DIS 9509
Year	:	1991
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported

Method	:	culture obtained from mixed liquor of a treatment plant
Remark	:	Effect: inhibition of N-oxidation
Test condition	:	25 degrees C
Reliability	:	(3) invalid In principal the test is comparable to standard methods, but the authors state that the compounds with log IC50<1,5 umol/l had questionable accurate results, so that this effect value has to be considered invalid.

07.05.2004 (82)

Type	:	aquatic
Species	:	anaerobic microorganisms
Exposure period	:	
Unit	:	
Analytical monitoring	:	yes
Method	:	
Year	:	1989
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported

Method	:	phenol-enriched methanogenic culture nominal concentrations 50, 100, 150, 250, 300, 400, 500, and 700 mg/l m-cresol + 200 mg/l phenol incubation at 35 degrees C
Result	:	m-cresol concentrations above 150 mg/l inhibited the anaerobic phenol degradation
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

07.05.2004 (46)

Type	:	aquatic
Species	:	Pseudomonas putida (Bacteria)
Exposure period	:	16 hour(s)
Unit	:	mg/l
TT	:	53
Analytical monitoring	:	no
Method	:	other: Cell multiplication inhibition test
Year	:	1977
GLP	:	no

Test substance : other TS: m-cresol, no purity reported

Remark : TT = Toxicity threshold; determined at 3 % effect compared to control
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
07.05.2004 (75) (72)

Type : aquatic
Species : other bacteria: Mixed marine bacteria culture
Exposure period : 16 hour(s)
Unit : mg/l
EC10 : 33.4
EC50 : 324 - 326
Analytical monitoring : no
Method : other: Static bioassay (determination of bacterial growth)
Year : 1989
GLP : no
Test substance : other TS: m-cresol, no purity reported

Remark : mixed culture of 13 unidentified bacterial strains isolated from sea water
Test condition : Incubation at 25-30 degrees Celsius, artificial saltwater
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (83) (84)

Type : aquatic
Species : Chilomonas paramaecium (Protozoa)
Exposure period : 48 hour(s)
Unit : mg/l
TT : 114
Analytical monitoring : no
Method : other: cell multiplication inhibition test
Year : 1980
GLP : no
Test substance : other TS: m-cresol, no purity reported

Remark : TT = Toxicity threshold; determined at 5 % effect compared to control
Test condition : 20 degrees C; initial pH 6.9
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (85)

Type : aquatic
Species : Entosiphon sulcatum (Protozoa)
Exposure period : 72 hour(s)
Unit : mg/l
TT : 31
Analytical monitoring : no
Method : other: cell multiplication inhibition test
Year : 1978
GLP : no

Test substance : other TS: m-cresol, no purity reported

Remark : TT = Toxicity threshold; determined at 5 % effect compared to control
Test condition : 25 degrees C; initial pH 6.9
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (86)

Type : aquatic
Species : Tetrahymena pyriformis (Protozoa)
Exposure period : 24 hour(s)
Unit : mg/l
LC100 : 375
Analytical monitoring : no
Method : other: Microtox
Year : 1978
GLP : no
Test substance : other TS: m-cresol, no purity reported

Test condition : 28 degrees C
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (87)

Type : aquatic
Species : Uronema parduzci (Protozoa)
Exposure period : 20 hour(s)
Unit : mg/l
TT : 62
Analytical monitoring : no
Method : other: cell multiplication inhibition test
Year : 1980
GLP : no
Test substance : other TS: m-cresol, no purity reported

Remark : TT = Toxicity threshold; determined at 5 % effect compared to control
Test condition : 25 degrees C; initial pH 6.9
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (88)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 5 minute(s)
Unit : mg/l
EC50 : 11
Analytical monitoring : no
Method : other: Microtox assay
Year : 1983
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Remark	:	effect: reduction of bioluminescence Secondary literature. Not enough information supplied for assessment. Although the author suggests that Microtox may lack reproductibility due to variations in bacterial cell suspensions, no information is supplied on the maintenance of the lyophilized bacteria, their age, duration of reconstitution and other important parameters.
Reliability	:	(3) invalid Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

07.05.2004 (89)

Type	:	aquatic
Species	:	Photobacterium phosphoreum (Bacteria)
Exposure period	:	15 minute(s)
Unit	:	mg/l
EC50	:	8
Analytical monitoring	:	no
Method	:	other: Microtox assay
Year	:	1987
GLP	:	no
Test substance	:	other TS: m-cresol, analytical grade (either from Merck or EGA Chemie)
Remark	:	Not enough information supplied for assessment of the test used (Test done according to Beckman manual). Although it is suggested that Microtox may lack reproducibility due to variations in bacterial cell suspensions [Bitton G (1983) Bacterial and Biochemical Tests for Assessing Chemical Toxicity in the Aquatic Environment: A Review. Crit Rev Environ Control 13: 51 -67], no information is supplied on the maintenance of the lyophilized bacteria, their age, duration of reconstitution and other important parameters.
Reliability	:	(3) invalid Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

07.05.2004 (90)

Type	:	aquatic
Species	:	other bacteria: Photobacterium (Vibrio) fischeri (marine)
Exposure period	:	5 minute(s)
Unit	:	mg/l
EC50	:	8.2
Analytical monitoring	:	no
Method	:	other: Microtox assay
Year	:	1981
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	Although it is suggested that Microtox may lack reproducibility due to variations in bacterial cell suspensions [Bitton G (1983) Bacterial and Biochemical Tests for Assessing Chemical Toxicity in the Aquatic Environment: A Review. Crit Rev Environ Control 13: 51 -67], no information is supplied on the maintenance of the lyophilized bacteria, their age, duration of reconstitution and other important parameters. In contrast to Bulich [Bulich AA (1977), Aquatic Toxicology: Second conference ASTM STP 667, American Society for Testing of Materials, Philadelphia, pp 98 - 106], pH not buffered.
Test condition	:	15 degrees C
Reliability	:	(3) invalid Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

07.05.2004 (91)

Type : aquatic
Species : Escherichia coli (Bacteria)
Exposure period : 19 day(s)
Unit :
Analytical monitoring : no
Method :
Year : 1983
GLP : no
Test substance : other TS: m-cresol, no purity reported

Method : Incubation in microcosms containing sterile sea water
Result : Number of viable cells remained constant
Number of culturable cells decreased, no plasmids were detected. Changes in membrane protein composition observed. After transfer into rich medium without test substance, growth resumed and plasmids were again detectable.
Test condition : Test concentration 1 µg/l, 18 degrees C
Reliability : (3) invalid
Tested organism not relevant for environment

07.05.2004 (92) (93)

Type : aquatic
Species : Pseudomonas putida (Bacteria)
Exposure period : 48 hour(s)
Unit :
Analytical monitoring : no
Method :
Year : 1989
GLP : no
Test substance : other TS: m-cresol, no purity reported

Method : in the culture medium absorbance at 660 nm was measured
Result : absorbance 0.46 with 0.5 g/l and 0.22 with 1 g/l
Test condition : 30 degrees C
Reliability : (3) invalid
Experimental details missing

07.05.2004 (94)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 30 minute(s)
Unit : mg/l
EC50 : 11.8
Analytical monitoring : no
Method : other: Microtox
Year : 1981
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Remark : Inhibition of bioluminescence
Secondary literature; not enough information for assessment of cited result
Test condition : 20 degrees C
Reliability : (3) invalid
Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals

12.05.2004 (95)

Type : aquatic

Species	:	other bacteria: gentechnologically constructed luminescent bacteria originating from wastewater treatment plant
Exposure period	:	30 minute(s)
Unit	:	mg/l
EC50	:	68 measured/nominal
Analytical monitoring	:	no
Method	:	other: Microtox assay
Year	:	1986
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	Inhibition of bioluminescence Modified microorganisms used which represent the metabolic potentials present in a wastewater treatment plant and some properties of a marine organism, but which are not identical to any known species in natural environments
Test condition	:	- Wastewater bacteria (Eschericia coli) which were obtained from a wastewater treatment plant - Bacteria obtained the luciferase operon of Vibrio fischeri by transfer from luminescent E. coli - Incubation at 20 °C - Result calculated from the difference of the luminescence between controls and test substance taking into account the light emissions at 0 and 20 °C
Reliability	:	(3) invalid Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

07.05.2004 (95)

Type	:	aquatic
Species	:	Escherichia coli (Bacteria)
Exposure period	:	2 hour(s)
Unit	:	mg/l
EC50	:	1000
Method	:	
Year	:	1954
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Result	:	endpoint related to growth inhibition no effect on cell size
Test condition	:	37 degrees C
Reliability	:	(3) invalid Methodological deficiencies

12.05.2004 (96)

Type	:	aquatic
Species	:	Escherichia coli (Bacteria)
Exposure period	:	
Unit	:	mg/l
TT	:	600
Analytical monitoring	:	no
Method	:	
Year	:	1959
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	test organisms isolated from river water endpoint: inhibition of glucose metabolism
Remark	:	TT = toxicity treshold; determined at 5 % effect compared to

control
Reliability : (3) invalid
Methodological deficiencies
07.05.2004 (70) (97)

Type : aquatic
Species : Pseudomonas fluorescens (Bacteria)
Exposure period :
Unit : mg/l
TT : 40
Analytical monitoring : no
Method :
Year : 1960
GLP : no
Test substance : other TS: m-cresol, no purity reported

Remark : TT = toxicity treshold; determined at 5 % effect compared to control
endpoint: inhibition of glucose metabolism
Reliability : (3) invalid
Methodological deficiencies
07.05.2004 (70)

Type : aquatic
Species : other bacteria: Pseudomonas Stamm Berlin 33/2
Exposure period :
Unit : mg/l
EC0 : 180
Analytical monitoring : no
Method : other
Year : 1982
GLP : no
Test substance : other TS: m-cresol, no purity reported

Remark : Effect endpoint: cell multiplication inhibition
Reliability : (4) not assignable
Insufficient documentation
07.05.2004 (58)

Type : aquatic
Species : Paramaecium caudatum (Protozoa)
Exposure period :
Unit :
Method :
Year :
GLP :
Test substance : other TS: m-cresol, no purity reported

Result : pertubation level 0.9 mg/l
Reliability : (4) not assignable
secondary literature
12.05.2004 (71)

Type : aquatic
Species : other protozoa: Vorticella campanula
Exposure period :
Unit :
Method :
Year :
GLP :

Test substance	:	other TS: m-cresol, no purity reported
Result	:	pertubation level 0.5 mg/l
Reliability	:	(4) not assignable secondary literature

12.05.2004 (71)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Species	:	other terrestrial plant: Lactuca sativa Ravel R2
Endpoint	:	growth
Exposure period	:	14 day(s)
Unit	:	mg/kg soil dw
EC50	:	96
Method	:	OECD Guide-line 208 "Terrestrial Plants, Growth Test"
Year	:	1993
GLP	:	no data
Test substance	:	other TS: m-cresol, purity >= 95 %
Method	:	analytical monitoring at start and end of test
Result	:	EC50 based on nominal concentration; for most of the examined phenols (including m-cresol) applied concentrations dropped but remained larger than 50 % of the nominal values. The 7-d EC50 was 69 mg/kg soil (original dimension µg/g soil).
Reliability	:	(2) valid with restrictions Guideline study; applied test concentrations not stable during the test period
Flag	:	Critical study for SIDS endpoint

07.05.2004 (98)

Species	:	Lactuca sativa (Dicotyledon)
Endpoint	:	emergence
Exposure period	:	3 day(s)
Unit	:	mg/l
EC50	:	53
Method	:	other: Seed germination test
Year	:	1978
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	As described by Reynolds 1975 (Characterization of osmotic restraints on lettuce fruit germination. Ann. Bot. 39, 791-796) and 1977 (Comparative effects of aliphatic com-pounds on inhibition of lettuce fruit germination. Ann. Bot. 41, 637-648) - Lettuce cultivar Great Lakes - Germination temperature 30 °C
Result	:	Result was reported as "0.49 mmol/l" which equals 53 mg/l

Reliability : (2) valid with restrictions
Basic data given
07.05.2004 (99)

Species : other terrestrial plant: Lactuca sativa Ravel R2
Endpoint : growth
Exposure period : 16 day(s)
Unit : mg/l
EC50 : 50
Method :
Year : 1993
GLP : no data
Test substance : other TS: m-cresol, purity >= 95 %

Method : semistatic test in nutrient solution, renewed 3 times/week
nutrient solution as described in Steiner, A.A.: Soilless culture. Proceedings, Sixth Colloqium of the International Potash Institute, Florence, Italy, 324-341 (1968);
analytical monitoring of TS at start and end of exposure and before renewal of test solution
Result : EC50 based on nominal concentration; TS concentration before renewal of test solution > 50% of initial concentration
Reliability : (3) invalid
unsuitable test system
07.05.2004 (98)

Species : Raphanus sativus (Dicotyledon)
Endpoint : other: germination and growth rate
Exposure period : 4 day(s)
Unit : g/l
Method :
Year : 1989
GLP : no
Test substance : other TS: m-cresol, special grade purity (obtained from Wako Pure Chemicals Industries, Ltd.)

Method : seeds exposed to test compounds dissolved in distilled water
24 degrees C, 10h light, 14 h dark
3 replicates of 20 seeds
Result : Concentr. Germination rate% Growth rate %

g/l	1 day	4 days	Radicle	Hypocotyl
10	0	0	-	-
1	0	5.3	2.0	-
0.1	82.6	95.0	80.8	104.7

Reliability : (3) invalid
Methodological deficiencies
07.05.2004 (100)

Species : Brassica rapa (Dicotyledon)
Endpoint : other: germination and growth rate
Exposure period : 4 day(s)
Unit : g/l
Method :
Year : 1989
GLP : no
Test substance : other TS: m-cresol, special grade purity (obtained from Wako Pure Chemicals Industries, Ltd.)

Method : seeds exposed to test compounds dissolved in distilled water

24 degrees C, 10h light, 14 h dark
3 replicates of 20 seeds

Result : Concentr. Germination rate% Growth rate %

g/l	1 day	4 days	Radicle	Hypocotyl
10	0	0	-	-
1	0	0	-	-
0.1	85.8	91.5	54.9	72.8

Reliability : (3) invalid
Methodological deficiencies

07.05.2004 (100)

Species : Brassica campestris var. chinensis (Dicotyledon)
Endpoint : other: germination and growth rate
Exposure period : 4 day(s)
Unit : g/l
Method :
Year : 1989
GLP : no
Test substance : other TS: m-cresol, special grade purity (obtained from Wako Pure Chemicals Industries, Ltd.)

Method : seeds exposed to test compounds dissolved in distilled water
24 degrees C, 10h light, 14 h dark
3 replicates of 20 seeds

Result : Concentr. Germination rate% Growth rate %

g/l	1 day	4 days	Radicle	Hypocotyl
10	0	0	-	-
1	0	0	-	-
0.1	100	100	86.5	77.1

Reliability : (3) invalid
Methodological deficiencies

07.05.2004 (100)

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

Species : other avian: Agelaius phoeniceus (red-winged blackbird)
Endpoint : mortality
Exposure period :
Unit : mg/kg bw
LD50 oral : 113
Method :
Year : 1983
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Test condition : birds pre-conditioned to captivity for 2 to 6 weeks
dosed by gavage with solution in propylene glycol or by pellets resp. gelatin capsules

Reliability : (2) valid with restrictions
Unsuitable test system

07.05.2004 (101)

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

Remark : In aquarium water of 12 species of freshwater fish 48 h after exposure to 3-15 mg/l m-cresol, cresyl sulphate (55-64% of 14C recovered) or m-hydroxybenzoic acid (0-39 %) were found
In bile of 11 species, cresyl glucuronide (63-74 %), cresyl sulphate (8-20 %) and m-hydrobenzoic acid (5-12 %) were found
Unchanged m-cresol detected in both aquarium water and bile
Test substance : m-[U-14C]cresol
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

17.10.2001 (102)

4.9 ADDITIONAL REMARKS

Memo : Sea urchin test

Remark : Strongylocentrotus droebachiensis (sea urchin):
static test, 5 degrees C
Determined effect endpoints: death, pathology, inhibition of cleavage and differentiation, pigment defects
EC50 (96 h): ca. 30 mg/l
Test substance : other TS: m-cresol, purity > 98 % as determined by GC (obtained from Merck)
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (57)

Memo : Tree neoplasms

Remark : m-cresol (1.5 % v/v) showed a toxicity rating from 3-4 (0 = no injury, 5 = complete kill within 14 d) in tomato crown gall tumors incited by Agrobacterium tumefaciens.
Test substance : other TS: m-cresol, no purity reported
Reliability : (3) invalid
Unsuitable test system

07.05.2004 (103)

Memo : Hela cell screening

Remark : In a rapid-cell culture assay with HeLa cells, m-cresol (4x10-5 to 4x10-3 M, 4 h incubation) showed a concentration-dependent inhibition of 3H labeled thymidine incorporation into DNA
incubation 4 h
Test substance : other TS: m-cresol, no purity reported
Reliability : (3) invalid

Unsuitable test system

07.05.2004 (104) (105)

Memo : Mollusc

Remark : Teredo diegensis (Mollusca):
LC50 (72 h): 100 mg/l

Test substance : other TS: m-cresol

Reliability : (4) not assignable
Reference not available

07.05.2004 (64)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo : In vivo
Type : Distribution
Species : dog
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : oral unspecified
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :

Result : Following oral exposure cresols in the body initially concentrate in the blood, liver, brain followed by more widespread distribution in the lungs, kidneys and other unspecified organs (no further details given)
Reliability : (4) not assignable
secondary literature

25.10.2002 (106)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : rabbit
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle : other: sodiumhydroxycarbonate
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other: see freetext ME
Year : 1949
GLP : no
Test substance : other TS: m-cresol, not specified further

Method : Approx. 200 mg/kg bw was administered to 10 rabbits (sex not mentioned) as single dose as solution in bicarbonate by gavage. Urine was collected over a period of 24-48 hours and the levels of free and conjugated cresol was estimated by the method of Folin O. and Ciocalteu V., J. biol. Chem. 73, 627 (1927). Metabolites were identified with the method described in

Bray et al., Biochem J. 41, 212 (1947) and 43, 561 (1948)

Result : absorption and excretion:
Within 24 hours 84 % of the m-Cresol dose was excreted in the urine indicating that at least this amount was absorbed through the gastrointestinal tract and urinary excretion was the main route of elimination.
metabolism:
The principal metabolic pathway was conjugation wit h glucuronic and sulphuric acids: 10% of the dose were discovered as ethereal sulphate and 60% of the dose as etheral glucuronide and 1% of the dose as free cresol. About 3 % of the dose was conjugated 2,5-dihydroxytoluene; conjugated 3,4-dihydroxytoluene was only discovered in traces.

Reliability : (2) valid with restrictions
no information on sex of rabbits used, no information on distribution in the tissue

Flag : Critical study for SIDS endpoint

06.02.2004 (107) (108)

In Vitro/in vivo : In vitro
Type : Absorption
Species : other: human skin
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle : water
Route of administration : dermal
Exposure time : 250 minute(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method :
Year :
GLP :
Test substance : other TS: m-cresol, not specified further

Method : The permeability of m-Cresol was measured across 2.5 cm2 epidermal membranes from human abdominal skin. The membranes were supported in a glass cell and the amount of m-Cresol passing to the receptor vessel measured spectrophotometrically. Each test was conducted at least in duplicate and at 25 Degree Celsius

Result : The permeability coefficient of m-Cresol was 2.54 x10 (exp)-4 cm/min and the lag time for a 0.4%w/v solution was 15 min. The threshold concentration for damage i.e. the aqueous concentration at which the permeability coefficient began to increase was 1.0 %w/v.

Reliability : (2) valid with restrictions
in vitro investigation

Flag : Critical study for SIDS endpoint

06.02.2004 (109)

In Vitro/in vivo : In vivo
Type :
Species : other: dogs and rabbits
Number of animals

Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : oral unspecified
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st.:
2nd.:
3rd.:
Toxic behaviour :
Deg. product :
Method :
Year :
GLP :
Test substance : other TS: m-cresol, not specified further

Remark : m-Cresol undergoes entero-hepatic circulation when administered orally to dogs and rabbits.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
06.02.2004 (110) (111)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : other
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year :
GLP :
Test substance : other TS: m-cresol, not specified further

Result : At physiological pH, the conjugated metabolites of phenolic compounds are ionized to a greater extent than the parent compound, which reduces renal reabsorption and increases elimination with the urine.
In addition to urinary excretion, cresols are excreted in the bile, but the most part undergoes enterohepatic circulation. There are known species differences in the specific conjugation reactions of cresol isomers and the relative amounts of glucuronide and sulfate conjugates therefore differ between species and also vary with dose.
Reliability : (2) valid with restrictions
basic information
Flag : Critical study for SIDS endpoint
06.02.2004 (110) (112) (113) (114)

In Vitro/in vivo : In vivo
Type : Absorption
Species : rat
Number of animals
Males :
Females :

Doses
Males :
Females : 10 mg/m3, 4 hrs a day for 100 d up to 4 months
Vehicle :
Route of administration : inhalation
Exposure time : 4 hour(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method :
Year :
GLP :
Test substance : other TS: m-cresol, not specified further

Result : Female rats were exposed to 10 mg/m3 m-cresol 4 hours per day, daily for 100 d up to 4 months. m-Cresol reached a concentration of 12.2 ug/g lung tissue; the neutral red sorption on day 3 resp d 39 was 133 % resp. 152 % of the control value as a marker for cytotoxicity. Full recovery did not occur.
Reliability : (2) valid with restrictions
information on absorption via lung, but study description suffer from deficiencies
Flag : Critical study for SIDS endpoint
06.02.2004 (115)

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : 242 mg/kg bw
Species : rat
Strain :
Sex : male
Number of animals : 5
Vehicle : other: none
Doses :
Method : other: 5 rats/dose group, 4 doses, undiluted liquid, time of recovery: up to 14 days
Year : 1969
GLP : no data
Test substance : other TS: m-cresol, purity not given, M.P.: 11-12 C, B.P.: 202,8 C

Result :

dosage mg/kg bw	onset of sympt. 0-4 hrs	mortality 0-4hrs	mortality day3	mortality day6	mortality day7	mortality cumulat.
147	S					0/5
215	S		1/5		1/5	2/5
316	S	3/5		1/5		4/5
464	S	4/5	1/5			5/5

S=signs of intoxication: Hypoactivity, tremors, convulsions, salivation, prostration
survivors: recovery within observation time, gross necropsy: no significant findings

decedents, gross necropsy: inflammation of the gastrointestinal tract, hyperemia of lungs, liver and kidneys

Reliability : (2) valid with restrictions
no information on strain used , no information on statistical evaluation given
Flag : Critical study for SIDS endpoint
06.02.2004 (116) (117)

Type : LD50
Value : = 2020 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 10
Vehicle : other: olive oil
Doses : 1500, 1700, 2000, 2200, 2400 mg/kg bw
Method : other: 5 rats/sex/dose, 6 doses, administration as a 10% solution in olive oil to non-fasted Wistar rats by gavage to give doses of 1500-2700 mg/kg bw, observation time was not reported, section was not performed
Year : 1944
GLP : no data
Test substance : other TS:m-cresol, purity: 96-98 %

Result : 1500 mg/kg: 0 % dead, 1700 mg/kg: 20 % dead, 2000 mg/kg: 40 % dead, 2200 mg/kg: 70 % dead, 2400 mg/kg: 70 % dead,
time of death not mentioned
signs of poisoning: twitching of isolated bundles of muscles and uncoordinated movement of the legs, irregular pulse and difficulties in breathing
Reliability : (2) valid with restrictions
post-exposure observation time not reported
Flag : Critical study for SIDS endpoint
06.02.2004 (118)

Type : LD50
Value : = 2010 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: oil
Doses : no data
Method : other: 10 % solution was used
Year : 1974
GLP : no data
Test substance : other TS: m-cresol, not specified further

Reliability : (4) not assignable
secondary citation
06.02.2004 (112) (119)

Type : LD50
Value : = 520 mg/kg bw
Species : rat
Strain :
Sex : male
Number of animals : 10
Vehicle : water
Doses :
Method : other: 10 rats/ dose were fed with a 10 % aqueous solution, 5 doses, observation period: 14 d, gross examination

Year : 1949
GLP : no
Test substance : other TS: purity no data

Remark : at the dosage level used the rats developed tremor within a few minutes, deaths occurred within a few hours
Reliability : (4) not assignable
Documentation insufficient for assessment

18.09.2002 (120)

Type : LD50
Value : = 828 mg/kg bw
Species : mouse
Strain :
Sex : no data
Number of animals :
Vehicle : other: oil
Doses :
Method : other: 10 % oil solution
Year : 1974
GLP : no data
Test substance : other TS: purity not mentioned

Reliability : (4) not assignable
secondary citation

17.12.2002 (112) (119)

Type : other: dose selection study for MNT
Value :
Species : mouse
Strain :
Sex : male/female
Number of animals : 6
Vehicle : other: corn oil
Doses : 400, 800, 1200, 1600, 2000 mg/kg bw (dose volumes: 5 ml/kg bw)
Method : other: 3 mice/sex and dose received one dose by gavage: 400,800,1200,1600,2000 mg/kg bw, post dose observation for 2 d for toxic effects and mortality
Year : 1989
GLP : yes
Test substance : other TS: Purity: 99.8 %

Remark : the study was performed in order to select doses for a mouse in vivo bone marrow cytogenetic assay (see chapter 5.6)
Result : 2000 mg/kg:immediately after dosing all mice showed convulsions, experienced difficulties in breathing, and were extremely lethargic; mortality: 6/6
1600, 1200 mg/kg: all mice showed convulsions 2-4 min. after dosing, experienced breathing difficulties and lethargy; mortality: 1600 mg/kg: 6/6; 1200 mg/kg: male 1/3, female 2/3, all other rats showed signs of recovery
800 mg/kg: all mice showed convulsions 4-5 min. after dosing with difficulty in breathing and lethargy, no rat died; all showed signs of recovery after 2 d
400 mg/kg: all mice apparently healthy
Reliability : (2) valid with restrictions
only 2 days post-exposure observation;
preliminary dose range finding study

10.01.2003 (121)

Type : other: LD

Value	:	= 1400 mg/kg bw
Species	:	rabbit
Strain	:	
Sex	:	no data
Number of animals	:	1
Vehicle	:	other: water
Doses	:	
Method	:	other: single oral gavage of a 20 % aqueous emulsion, 4 doses, time till death was recorded
Year	:	1944
GLP	:	no data
Test substance	:	other TS: purity not mentioned
Remark	:	620 and 940 mg/kg: no death; 1400 mg/kg: 8 hrs until death; 2100 mg/kg 90 min. till death
Reliability	:	(4) not assignable study reporting suffers from deficiencies

17.12.2002 (118)

Type	:	other: LD
Value	:	640 - 1000 mg/kg bw
Species	:	dog
Strain	:	
Sex	:	no data
Number of animals	:	2
Vehicle	:	no data
Doses	:	
Method	:	other: single application by gavage, no further data
Year	:	1907
GLP	:	no data
Test substance	:	other TS: no data on purity
Remark	:	640 mg/kg: transitional aggitation, staggering gait, sedation, recovery 1000 mg/kg: death within 30 min after application probably due to aspiration
Reliability	:	(4) not assignable study reporting suffers from deficiencies

17.12.2002 (111)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	> .71 mg/l
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	6
Vehicle	:	other: air
Doses	:	
Exposure time	:	1 hour(s)
Method	:	other: 6 rats exposed to 0.71 mg/l for 1 hr, room temperature, up to 14 d post exposure observation, gross necropsy
Year	:	1969
GLP	:	no data
Test substance	:	other TS: m-cresol, M.p.: 11-12 C; B.P.: 202.8 C
Result	:	Mortality. 0/6; signs of intoxication: none; gross autopsy: no significant findings
Reliability	:	(2) valid with restrictions

no information about strain used, exposure time : 1 hr, only one concentration

Flag : Critical study for SIDS endpoint

06.02.2004 (116)

Type : LC50
Value : = 58 mg/m³
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Exposure time :
Method : other: aerosol-exposure; no further data
Year : 1975
GLP :
Test substance : other TS: m-cresol, not specified further

Remark : the mean lethal concentration of m-cresol was measured. The original data are not published and no further experimental details are availabel from the citing literature
Result : Clinical signs of toxicity included irritation of mucous membranes, neuromuscular excitiation and convulsions; hematuria at very high concentrations (no further information)
Reliability : (2) valid with restrictions
Secondary citation from peer-reviewed data source
Flag : Critical study for SIDS endpoint

06.02.2004 (122)

Type : other: inhalation of mist
Value :
Species : rat
Strain :
Sex : no data
Number of animals : 6
Vehicle :
Doses :
Exposure time : 8 hour(s)
Method : other: mist was generated by holding the compound in a bath of 170 degree Celsius, observation period: 14 d
Year : 1949
GLP : no
Test substance : other TS: no data on purity

Result : all rats survived the exposure period; only 1/6 failed to gain weight during the observation period
Reliability : (4) not assignable
documentation suffers from significant deficiencies

18.09.2002 (120)

Type : other: inhalation of saturated vapour
Value :
Species : rat
Strain :
Sex : no data
Number of animals : 6
Vehicle : other: air
Doses :
Exposure time : 8 hour(s)

Method : other: exposure to saturated vapour produced at room temperature by bubbling air at 2.5 l/min, observation period 14 d
Year : 1949
GLP : no
Test substance : other TS: m-cresol, not specified further

Remark : m-Cresol did not affect rats in 8 h exposure periods, all of the rats gained weight during the observation period
Reliability : (2) valid with restrictions
description considered of sufficient quality to allow evaluation
Flag : Critical study for SIDS endpoint
06.02.2004 (120)

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Value : = 1100 mg/kg bw
Species : rat
Strain :
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Method : other: no data
Year : 1974
GLP : no data
Test substance : other TS: no data

Reliability : (4) not assignable
secondary citation
17.12.2002 (112) (119)

Type : LD50
Value : = 2050 mg/kg bw
Species : rabbit
Strain : no data
Sex : no data
Number of animals : 5
Vehicle : other: none
Doses : 1000, 1470, 2150, 3160 mg/kg bw
Method : other: 5 rabbits/dose, 4 doses, exposure time not mentioned, up to 14 days post exposure observation time
Year : 1969
GLP : no data
Test substance : other TS: m-cresol, M.P.: 11-12 C; B.P.: 202.8 C

Result : Dosage onset of symp. mortality mortality
mg/kg 4-12 hrs 12-24 hrs day3 cumulative

1000				0/5
1470				0/5
2150	S		4/5	4/5
3160	S	4/5		4/5

S = signs of intoxication from 4 hrs up to 12 hrs p.a.:
lacrimation, salivation,
hypersensitivity, convulsion, hypoactivity:
dermal
irritation: severely burned, severe edema

gross necropsy-survivors: no significant findings
gross necropsy-decedents: hyperemia of lungs and kidneys

Reliability : (2) valid with restrictions
no information about strain used, statistical evaluation not given

Flag : Critical study for SIDS endpoint

06.02.2004 (116)

Type : LD50
Value : = 2830 mg/kg bw
Species : rabbit
Strain :
Sex : female
Number of animals : 3
Vehicle : no data
Doses :
Method : other: see freetext ME
Year : 1977
GLP : no data
Test substance : other TS: m-cresol, not specified further

Method : The method used was essentially that of Smyth et al. 1962 (Am. Ind. Hyg. Ass. J. 23, 95-107) except three females/dose were tested 24 hr occlusive exposure to the neat material was followed by a 14-day observation period. the most probable LD50 value was determined by the method of Thompson 1947 (Bact. Rev.11, 115-145) of moving averages. Clinical signs and purity of the Ts are not reported.

Reliability : (2) valid with restrictions
no guideline study: Doses used, clinical signs and purity of Test substance are not reported

Flag : Critical study for SIDS endpoint

06.02.2004 (123)

Type : LD50
Value : = 1860 mg/kg bw
Species : rabbit
Strain :
Sex : male
Number of animals : 10
Vehicle : other: undiluted
Doses :
Method : other: application to the slipped trunk of rabbits for 24 hours under 'Vinylite' sheeting, gross examination
Year : 1949
GLP : no
Test substance : other TS: purity no data

Remark : original data: 1.80 ml/kg
severe necrosis and erythema of the skin and kidney damage (bloody urine in the urinary bladder), congested pancreas, mottled liver and abdominal wall hemorrhagia were noted

Reliability : (4) not assignable
documentation insufficient for assessment

18.09.2002 (120)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LD50
Value : = 168 mg/kg bw
Species : mouse
Strain :

Sex : no data
Number of animals :
Vehicle : no data
Doses :
Route of admin. : i.p.
Exposure time : unspecified
Method : other: no data
Year :
GLP : no
Test substance :

Reliability : (4) not assignable
unusual application route
18.09.2002 (124)

Type : other: LD
Value : = 100 mg/kg bw
Species : guinea pig
Strain :
Sex :
Number of animals :
Vehicle : no data
Doses :
Route of admin. : i.p.
Exposure time :

Reliability : (4) not assignable
unusual application route
18.09.2002 (124)

Type : other: LD
Value : = 900 mg/kg bw
Species : rat
Strain :
Sex : no data
Number of animals :
Vehicle : other: no data
Doses :
Route of admin. : s.c.
Exposure time :
Method : other: no data
Year :
GLP : no
Test substance : other TS: no data

Reliability : (4) not assignable
unusual application route
18.09.2002 (124)

Type : other: LD
Value : = 450 mg/kg bw
Species : mouse
Strain :
Sex : no data
Number of animals :
Vehicle : water
Doses :
Route of admin. : s.c.
Exposure time :
Method : othe: no data
Year : 1905

GLP : no
Test substance : other TS: no data

Reliability : (4) not assignable
unusual application route
18.09.2002 (125)

Type : other: LD
Value : = 500 mg/kg bw
Species : rabbit
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Route of admin. : s.c.
Exposure time :

Reliability : (4) not assignable
secondary literature
18.09.2002 (126)

Type : other: LD
Value :
Species : cat
Strain :
Sex : no data
Number of animals : 1
Vehicle : other: olive oil
Doses :
Route of admin. : s.c.
Exposure time :
Method : other subcoutaneous admininstration of a 10 % solution, 1 cat/dose 7 doses, hours till death were recorded
Year : 1944
GLP : no data
Test substance : other TS: 10 % in olive oil

Remark : hours until death:
80 and 120 mg/kg: no death; 180 mg/kg: 27 hours, 280 mg/kg: 4 hours; 420 mg/kg: 12 hours; 620 mg/kg: 7 hours; 940 mg/kg: 5.5 hours
Reliability : (4) not assignable
unusual application route
18.09.2002 (118)

Type : other: LD
Value : = 120 mg/kg bw
Species : cat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Route of admin. : s.c.
Exposure time :

Reliability : (4) not assignable
unusual application route
18.09.2002 (125)

Type : other: LD
Value : ca. 120 mg/kg bw
Species : cat
Strain :
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Route of admin. : s.c.
Exposure time :
Method : other: no data
Year : 1905
GLP : no
Test substance : other TS: no data

Reliability : (4) not assignable
unusual application route
18.09.2002 (125)

Type : other: LD
Value : = 300 mg/kg bw
Species : guinea pig
Strain :
Sex :
Number of animals :
Vehicle : no data
Doses :
Route of admin. : s.c.
Exposure time :

Reliability : (4) not assignable
unusual application route
18.09.2002 (124)

Type : other: LD
Value : = 250 mg/kg bw
Species : other: frog
Strain :
Sex : no data
Number of animals : 1
Vehicle : water
Doses :
Route of admin. : s.c.
Exposure time :
Method : other: no data
Year : 1905
GLP : no
Test substance : other TS: no data

Reliability : (4) not assignable
unusual application route
05.02.2004 (125)

Type : other: LD
Value :
Species : rabbit
Strain :
Sex :
Number of animals : 1
Vehicle : other: water
Doses :

Route of admin.	:	i.v.
Exposure time	:	
Method	:	other: intravenous injection to 1 rabbit per dose of an 0.5 % aqueous solution, 4 doses, time until death was recorded
Year	:	1944
GLP	:	no data
Test substance	:	other TS: purity no data
Remark	:	hours until death: 120 and 180 mg/kg: no death; 280 mg/kg: 15 hours; 420 mg/kg: 7 hours
Reliability	:	(4) not assignable unusual application route

18.09.2002 (118)

Type	:	other: LD
Value	:	= 150 mg/kg bw
Species	:	dog
Strain	:	
Sex	:	no data
Number of animals	:	
Vehicle	:	other: no data
Doses	:	
Route of admin.	:	i.v.
Exposure time	:	
Method	:	other: no data
Year	:	
GLP	:	no
Test substance	:	other TS: no data
Reliability	:	(4) not assignable unusual application route

18.09.2002 (124)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	.5 other: ml
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	
PDII	:	
Result	:	corrosive
Classification	:	
Method	:	other: see freetext ME
Year	:	1977
GLP	:	no data
Test substance	:	other TS: m-cresol, not specified further
Method	:	TS applied to the clipped backs or flanks of the rabbits. The material was covered by a surgical gauze two layers thick, gauze patches were held in place with strips of Elastoplast tape for 4 hours. After 4 hrs the patches were carefully removed and the test areas were evaluated for visible tissue destruction. evaluation criterias: When visible tissue destruction occurred in at least 2/6 rabbits, the test materials were classified as corrosive (no further details given).
Reliability	:	(2) valid with restrictions Limited documentation
Flag	:	Critical study for SIDS endpoint

06.02.2004 (123)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	no data
Exposure time	:	no data
Number of animals	:	6
Vehicle	:	
PDII	:	
Result	:	highly irritating
Classification	:	
Method	:	other: 0.5 ml undiluted TS was applied to the intact and to the abraded skin, time of observation: 24 and 72 hours
Year	:	1969
GLP	:	no data
Test substance	:	other TS: m-Cresol, M.P.:11-12 C; B.P.: 202.8 C
Result	:	intact skin, erythema. edema: 24 hr: Score 4 in 6/6; 72 hr: Score 4 in 6/6 abraded skin, erythema, edema: 24 hr: Score 4 in 6/6; 72 hr: Score 4 in 6/6 no tissue destruction and/or necrosis reported, no further details reported Summary: irritation score: 8.00/8.00
Reliability	:	(2) valid with restrictions limited documentation; no information on exposure time and conditions
Flag	:	Critical study for SIDS endpoint

06.02.2004 (116)

Species	:	rabbit
Concentration	:	other: see method
Exposure	:	no data
Exposure time	:	no data
Number of animals	:	5
Vehicle	:	
PDII	:	
Result	:	highly irritating
Classification	:	
Method	:	other: 0.01 ml on the skin of the rabbit belly: undiluted and 10 % solution in acetone
Year	:	1949
GLP	:	no
Test substance	:	other TS: no data on purity
Remark	:	undiluted m-cresol: necrosis of the skin (belly); 10 % solution in acetone: 2/5 severe erythema; 3/5 erythema and moderate oedema These reactions relegate to grade 6/10
Reliability	:	(4) not assignable documentation insufficient for assessment

18.09.2002 (120)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	
PDII	:	
Result	:	corrosive
Classification	:	
Method	:	other: conducted in accordance with Fed. Reg.37,No.57§173.240,1972; evaluated according to Draize, J.Pharm.Exp.Therap. 82, 1944
Year	:	1974

GLP	:	no data
Test substance	:	other TS: no data on purity
Reliability	:	(4) not assignable documentation insufficient for assessment
18.09.2002		(127)
Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	
Classification	:	
Method	:	other: see remarks
Year	:	
GLP	:	
Test substance	:	
Remark	:	Paper discs were soaked with 30 ul of m-cresol (dilutions 1:1 to 1:64) and kept secured on the shaved dorsal skin for 30 min. Then 6 ml/kg bw of a 1 % solution of Evan's blue were injected i.v.. After 10 min the rabbits were sacrificed, the dorsal skin was exfoliated, spread on glass plates, and lighted from behind. The paper discs were removed and the sites of application were examined. The lowest concentration causing dye exsudation was found at a dilution of 1:16 (6.25 %). The lowest concentration causing corrosion was found at a dilution of 1:2 (50 %).
Reliability	:	(4) not assignable unusual test method
18.09.2002		(128)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	unspecified
Comment	:	no data
Number of animals	:	6
Vehicle	:	
Result	:	highly irritating
Classification	:	
Method	:	other: undiluted 0.1 ml, time of reading: 24, 48 and 72 hours
Year	:	1969
GLP	:	no data
Test substance	:	other TS: m-cresol, M.P.: 11-12 C; B.P.: 202.8 C
Remark	:	after 24 hrs: cornea, iris, conjunctivae: 87.3 (mean score) mean score for cornea: 60, mean score for iris: 10, mean score for conjunctivae: 18) after 48 hrs: cornea, iris, conjunctivae: 87.3 (mean score) mean score for cornea: 60, mean score for iris: 10, mean score for conjunctivae: 18) after 72 hrs: cornea, iris, conjunctivae: 87.3 (mean score) mean score for cornea: 60, mean score for iris: 10, mean score for conjunctivae: 18)

summary: irritation score: 87.3/110

Reliability : (2) valid with restrictions
observation time should be longer to evaluate reversibility

Flag : Critical study for SIDS endpoint

06.02.2004 (116)

Species : rabbit
Concentration : other: see method
Dose :
Exposure time : unspecified
Comment :
Number of animals :
Vehicle :
Result : highly irritating
Classification :
Method : other: instillation of a 5 % solution and a 1 % solution, solvent: propylene glycol
Year : 1949
GLP : no
Test substance : other TS: no data on purity

Remark : 5 % solution: severe damage of the cornea
1.0 % solution: was harmless
result: Grade 9/10

Reliability : (4) not assignable
documentation insufficient for assessment

18.09.2002 (120)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type : Sub-acute
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 2 weeks (14 exposures)
Frequency of treatm. : 6 hrs/d, 7 d
Post exposure period : 2 weeks
Doses : target conc.: 20 ug/l of an 0.25 % solution in 1.6 % aquous glycerol
Control group : other: yes, water
Method : other: see freetext ME
Year : 2001
GLP : yes
Test substance : other TS: m-cresol, not specified further

Method : 6 rats/sex /group, nose-only exposure to an aerosol, target conc. 20 ug/l, target pulmonary dose: 504 ug/kg bw/day

observations for mortality, moribundity twice daily during exposure and during recovery, clinical observations (hematology, blood chemistry) within one hour of exposure during exposure and during recovery period, record of body weight prior to first exposure and weekly during exposure and during recovery period,
complete necropsy was performed on all animals at completion of exposure and recovery period including external and internal examination: body orifices, body cavities, external and cut surfaces, record of organ

weights at terminal and recovery necropsies: liver, kidneys, lungs, spleen, adrenal glands, thymus, testes, ovaries, organ weight to terminal body weight ratios were calculated.
Microscopic examination on respiratory tract (target tissue) of the first 5 rats/sex/group
statistical methods:
one way analyses of variance (ANOVA)

Result : observed concentration: 27 ug/l, achieved pulmonary dose level: 690 ug/kg bw
no animal died during the study,
no treatment related clinical signs; incidental observations in all treatment groups including control groupswere salivation, diarrhea, wet inguinal fur, red material around nose and eyes, alopecia, lesions and red material around nose seen sporadically and in low frequencies during recovery period.
Body weights, body weight gain, hematology, blood chemistry were not statistically different from control group.
terminal and recovery sacrifices:
no statistically differences in organ weights when compared to controls and no test-article related gross or histopathologic lesions. Observed minor inflammatory or degenerative changes observed in peribronchial, perivascular and subserosal regions were evaluated as incidental findings in rodent inhalation studies

Reliability : (4) not assignable
study suffers from deficiencies: only 1 dose used, solvent (aquous glycerol) was not the control, detailed data of the results were not presented, result description did not differ between phenol and m-cresol

06.02.2004 (129) (129)

Type : Sub-acute
Species : rat
Sex : male
Strain : no data
Route of admin. : oral feed
Exposure period : 28 d
Frequency of treatm. : daily
Post exposure period : no
Doses : 0, 20, 150, 500 mg/kg diet (approx. 0, 1.86, 13.95 or 45.8 mg/kg bw/d)
Control group : yes, concurrent no treatment
NOAEL : ca. 45.8 mg/kg bw
Method : other: 10 rats/group, TS was prepared as a 2.0 % corn oil solution and blended with the diet; diets were prepared fresh weekly. Control rats received basal diets containing 2 % corn oil, necropsy of all animals
Year : 1969
GLP : no data
Test substance : other TS: M.P.:11-12 C; B.P.: 202.8 C

Result : No deaths occurred during the study and no untoward behavioural reactions were noted.
At necropsy, no significant gross lesions were noted among the test animals, when compared to the control animals.

Reliability : (4) not assignable
documentation insufficient for assessment

18.09.2002 (116)

Type : Sub-acute
Species : rat
Sex : male/female
Strain : other: F344/N
Route of admin. : oral feed
Exposure period : 28 days

Frequency of treatm.	:	continuously in diet
Post exposure period	:	no
Doses	:	0, 300, 1000, 3000, 10000 or 30000 ppm (see freetext RM)
Control group	:	yes
NOAEL	:	3000 ppm
Method	:	other: see freetext ME
Year	:	1991
GLP	:	yes
Test substance	:	other TS: purity > 98 %

Method :

SIZE OF STUDY GROUP:
5 male and 5 female mice per group
TIME HELD BEFORE STUDY: 13-15 days
METHOD OF ANIMAL DISTRIBUTION:
randomized for each sex on the basis of body weight into groups per sex
DIET: NIH-07 rat ration
ANIMAL ROOM ENVIRONMENT:
temperature: 72° +/-3° F, humidity: 50 % +/-15 %, Fluorescent light: 12 hrs/day, room air changes : 10-12 changes/hr
TYPE AND FREQUENCY OF OBSERVATION:
observed twice daily, body weight taken initially, weekly, and at termination, feed consumption by cage recorded twice weekly
NECROPSY AND HISTOLOGIC EXAMINATION:
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 aninmals 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, oesophagus, heart, kidney, large intestines (caecum, colon, rectum), liver, lungs, lymph nodes (mesenteric), mammary glands, nasal cavity and turbinates, oral cavity, ovaries, pancreas, parathyroids, pharynx, pituirary, preputial gland, prostate, salivary glands, scrotal sac, seminal vesicles, skin, small intestine (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: uterus and ovaries. Organ weights recorded for brain, liver, right kidney, thymus, heart, and lungs of all animals, and the right testis of all males.
STATISTICAL METHODS:
nonparametric multiple comparison test of Dunn and Shirley, Jonckheere's test

Remark : mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	25	25
1000 ppm	85	82
3000 ppm	252	252
10000 ppm	870	862
30000 ppm	2470	2310

Result : no mortallity; no clinical signs of toxicity were observed
and
30000 ppm: mean final body weight sign. decreased: male (p</=0.05), female (p</=0.01), sign. reduced mean body weight gains, males, females p</=0.01); reduced food
consumption in males and females during the first week of the study;
no gross lesions were noted at necropsy,

at study termination organ weights (w) were sign. increased:
liver: male, abs. w. at 10000 ppm (p</=0.01), rel. w. from 10000 ppm (p</=0.01), females, rel. w. from 10000 ppm (p</=0.05), right kidney: male, female, rel. w. at 30000 ppm (p</=0.05); brain, male, rel. w. at 30000 ppm, female, abs. w at 30000 ppm (p</=0.05),rel.w. at 30000 ppm (p</=0.01),
No histomorphologic changes were reported from these organs.
Histological evaluation , characterized by average severity score based on a scale of 1 to 4 (1=minimal, 2=mild, 3=moderate, 4= marked) revealed effects: uterine atrophy in 4/5 females at 30000 ppm
NOAEL = 3000 ppm (male, female)

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
30.04.2003 (130)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 13 w
Frequency of treatm. : once daily
Post exposure period : 1 w
Doses : 0, 50, 150 or 450 mg/kg bw/d in corn oil
Control group : yes, concurrent vehicle
NOAEL : = 50 mg/kg bw
Method : other: 30 rats/sex/dose, add.10 rats/sex for baseline clin. Pathol., interim kill at week 7, terminal kill at week 14, blood samples for hematology, clin.chemistry; urinalysis; gross and microsc. pathology; stat. anal.: Dunnett's t-t
Year : 1986
GLP : yes
Test substance : other TS: purity: 98.6 %

Method : Dose selection was based on the results of a range-finding study
30 rats/sex/dose,
additional 10 rats/sex/dose for baseline clinical pathology
interim kill at week 7.
Body weights were recorded on test day1 and weekly thereafter; individual food consumption data were collected weekly;
moribund/mortality check twice daily (moribund rats were killed and necropsied); physical examination weekly; ophthalmologic examination during quarantine period and in test week 13
HAEMATOLOGY
haemoglobin, haematocrit, protrombin time (PT), erythrocyte count, reticulocyte count, toal and differential leucocyte count, activated partial thromboplastin time (APTT)
CLINICAL CHEMISTRY
sodium, chloride, potassium, direct and total bilirubin, alkaline phosphatase, total cholesterol, albumin, CO2, SGPT, SGOT, glucose, BUN, globulin (calculated), total protein, creatinine, A/G ratio (calculated)
URINALYSIS
appearance, volume, colour, specific gravity, pH, protein, glucose, ketone, bilirubin, urobilinogen, haemoglobin, microscopic examination
PATHOLOGY
determination of weights of:
heart, liver, spleen, brain, kidneys (individually), gonads (individually, adrenals, thyroid/parathyroid
examination of all control rats and high dose rats at study termination as well as those that died during the study:
all gross lesions,
brain (3 levels), spleen, bone (with marrow), skeletal muscles, salivary

gland, mammary gland, thymus, thyroid (with parathyroid), lungs (with mainstem bronchi), trachea, liver, urinary bladder, testes, prostate, ovaries, corpus and cervix uteri, eye, pituitary gland, lymph node, spinal cord, heart, aorta, siatic nerve, pancreas, oesophagus, kidneys, small and large intestine, adrenals, stomach
STATISTICAL ANALYSIS
One-way Analysis of Variance tests with Dunnett's t-test

Result : MORTALITY/CLINICAL OBSERVATIONS:
450 mg/kg: one high dose male was found dead on day 5 (cause not evident),
signs of intoxication:
450 mg/kg bw, male, female:
lethargy, tremors, hunched posture, rough hair coats post dosing
BODY WEIGHT
was sign reduced (p</=0.05): male, week 2-5, 13 at 450 mg/kg bw and week 6-12, 14 from 150 mg/kg bw; female, week 11 at 450 mg/kg bw
body weight gain was reduced (p</=o.05): male, week 1-3 at 450 mg/kg bw and week 4-13 from 150 mg/kg bw; female, week 1 at 450 mg/kg bw
FOOD CONSUMPTION
was sign. reduced (p</=0.05): male: 50 mg/kg bw, week 1, 2, 9, 11, 12; 150 mg/kg bw week 3, 6, 8, 12, 13; 450 mg/kg bw week 1-4, 6-9, 11; female: 50 mg/kg bw, week 4, 150 mg/kg bw, week 4, 11, 450 mg/kg bw, week1, 4, 6
CLINICAL PATHOLOGY
clinical chemistry, haematology and urinalyses parameters were not affected by treatment
OPHTHALMOLOGY
treatment related lesions were not seen
ORGAN WEIGHTS
organ weights were not affected by treatment
PATHOLOGY
treatment-related gross and histomorphology lesions were not in evidence
NOAEL (female) = 150 mg/kg bw/day
NOAEL (male) = 50 mg/kg bw/day

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
05.02.2004 (131)

Type : Sub-acute
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 28 days
Frequency of treatm. : continuously in diet
Post exposure period : no
Doses : 0, 300, 1000, 3000, 10000 or 30000 ppm (see freetext RM)
Control group : yes
LOAEL : ca. 300 ppm
Method : other: see freetext ME
Year : 1991
GLP : yes
Test substance : other TS: m-cresol, purity > 98 %

Method : SIZE OF STUDY GROUP:
5 male and 5 female mice per group
TIME HELD BEFORE STUDY: 13-15 days
METHOD OF ANIMAL DISTRIBUTION:
randomized for each sex on the basis of body weight into groups per sex
DIET: NIH-07 mouse ration
ANIMAL ROOM ENVIRONMENT:

temperature: 72° +/-3° F, humidity: 50 % +/-15 %, Fluorescent light: 12 hrs/day, room air changes : 10-12 changes/hr
TYPE AND FREQUENCY OF OBSERVATION:
observed twice daily, body weight taken initially, weekly, and at termination, feed consumption by cage recorded twice weekly
NECROPSY AND HISTOLOGIC EXAMINATION:
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 aninmals 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, oesophagus, gallbladder, heart, kidney, large intestines (caecum, colon, rectum), liver, lungs, lymph nodes (mesenteric), mammary glands, nasal cavity and turbinates, oral cavity, ovaries, pancreas, parathyroids, pharynx, pituirary, preputial gland, prostate, salivary glands, scrotal sac, seminal vesicles, skin, small intestine (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: uterus and ovaries and mammary gland. Organ weights recorded for brain, liver, right kidney, thymus, heart, and lungs of all animals, and the right testis of all males.
STATISTICAL METHODS:
nonparametric multiple comparison test of Dunn and Shirley, Jonckheere's test

Remark : mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	53	66
1000 ppm	193	210
3000 ppm	521	651
10000 ppm	1730	2080
30000 ppm	4710	4940

Result : mortality:
0 ppm: 1/5 male; 10000 ppm: 1/5 females; 300000 ppm: 2/5 males, 2/5 females;
Signs of toxicty:
at 30000 ppm: male, female;
hunched posture, rough hair coat, thin appearance, lethargy and tremor,hypothermia (only females),
at 10000 ppm: males and females, hunched posture, rough hair coat, females only: laboured respiration lethaty, sunken eyes
final mean body weight reduced at 30000 ppm in males (p</=0.01) and in females (p</=0.05)
at study termination organ weights (w) were sign. increased:
liver: male rel. w. from 3000 pp. (p</=0.05), female, rel. w. from 300 ppm (p</=0.05); right kidney: male, rel. w. at 3000 ppm, female rel. w. at 30000 ppm (p</=0.05); brain: male, rel. w. at 30000 ppm (p</=0.01).
No histopathologic changes were reported from these organs.
histopathological evaluation,characterized by average severity score based on a scale of 1 to 4 (1=minimal, 2=mild, 3=moderate, 4=marked), revealed effects:
30000 ppm: female, moderate mammary gland atrophy, mild ovary atrophy and moderate uterus atrophy
LOAEL (female) = 300 ppm (66 mg/kg bw/day), based on the increase in relative liver weight
NOAEL (male) = 1000 ppm (193 mg/kg bw/day)

Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint
06.02.2004		(130)

Type	:	
Species	:	mouse
Sex	:	female
Strain	:	other: CBA/J
Route of admin.	:	dermal
Exposure period	:	6 w
Frequency of treatm.	:	3 times/week
Post exposure period	:	6 months
Doses	:	0.5 % in acetone
Control group	:	yes
Method	:	other: 5 rats, application of the substance to depilated or clipped lower back by mist spray; observation of the hair colour of the new hair regrowth were made weekly
Year	:	1974
GLP	:	no data
Test substance	:	other TS: no data on purity
Result	:	No depigmentations of the regrowthed hair were observed.
Reliability	:	(4) not assignable special study
18.09.2002		(132)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Sister chromatid exchange assay
System of testing	:	human lymphocytes
Test concentration	:	0 -1.0 mM
Cycotoxic concentr.	:	no data
Metabolic activation	:	no data
Result	:	negative
Method	:	other: see freetext ME
Year	:	1986
GLP	:	no data
Test substance	:	other TS: purity: 99.2 %
Method	:	Lymphocyte fraction from healthy donors were grown in Medium 199 with Earles salts. After 24 hrs of cultur m-Cresol diluted in DMSO was added for 88-90 hrs. Positive control: Styrene-7,8-oxide Statistical Method: Linear regression analysis
Remark	:	Results of the positive control or solvent control in comparison to p-cresol were not given.
Reliability	:	(2) valid with restrictions Study description suffers from deficiencies: no information about cytotoxicity and wether a metabolic activation system was used or not, only summary results given
05.02.2004		(133)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration	:	up to 2 mg/plate (solubility limit); vehicle: water
Cycotoxic concentr.	:	not cytotoxic
Metabolic activation	:	with and without
Result	:	

Method	:	other: according to Ames,Proc.Natl.Acad.Sci.70, 2281(1973); Mutat.Res.31,347(1975); Nestmann,Cancer Res.39.4412(1979); Environ.Mutagen.1,361(1979)
Year	:	1980
GLP	:	no data
Test substance	:	other TS: m-cresol from commercial source (Aldrich)
Remark	:	According to the authors the result was "presumably negative, but solubility did not allow the testing of the compound in amounts that result in bacterial toxicity" Metabolic activation: with and without (liver S-9 mix from Aroclor 1254 induced rats)
Reliability	:	(2) valid with restrictions limited documentation

17.12.2002 (134)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537
Test concentration	:	no data
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: according to Ames, Mutation Res. 31, 347 (1975)
Year	:	1980
GLP	:	no data
Test substance	:	other TS: no data on purity
Reliability	:	(4) not assignable documentation insufficient for assessment

20.09.2002 (135)

Type	:	Unscheduled DNA synthesis
System of testing	:	rat primary hepatocytes
Test concentration	:	502, 251, 100, 50.2, 25.1, 10.0, 5.02, 2.51, 1.0, 0.502 ug/ml in DMSO
Cycotoxic concentr.	:	concentration range: 502 - 25.1 ug/ml: excessive toxicity
Metabolic activation	:	without
Result	:	negative
Method	:	other: OECD Guide-line 482, see freetext ME with additional informations
Year	:	1988
GLP	:	yes
Test substance	:	other TS: m-cresol, purity: 99.8 %
Method	:	DOSE SELECTION: Doses were chosen following a preliminary experiment SOLVENT: DMSO CONTROLS: solvent and 1-acetylaminofluorene (2-AAF) served as negative and positive controls, respectively EVALUATION CRITERIA: a dose related increase of at least 6 grains per nucleus after subtraction of the concurrent negative control value
Result	:	m-Cresol was evaluated as not causing UDS in cultured rat hepatocytes. The positive control was functional.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

06.02.2004 (136)

Type	:	Sister chromatid exchange assay
System of testing	:	cultured male human fibroblasts
Test concentration	:	0, 0.08, 0.8, 4, 8 mM dissolved in ethanol; 10, 30 mM dissolved in Eagle's Minimal Essential Medium (MEM)
Cycotoxic concentr.	:	> 8 mM cytotoxic response
Metabolic activation	:	without

Result : negative
Method : other: see freetext ME
Year : 1984
GLP : no data
Test substance : other TS:m-cresol, purity: > 99 %

Method : m-Cresol was added to the cells and incubated, in triplicate, at 37 C for 2 hours. Following exposure, the cells were washed, reincubated in the absence of the test chemical for 48 hours, harvested and SCE frequency and cell-cycle kinetics analysed
SOLVENT: m-Cresol was dissolved in 95% ethanol at concentrations up to and including 8 mM and in Eagle's minimum essential medium (MEM) at concentrations above this.
CONTROLS: 95% Ethanol and mitomycin C were used as negative and positive controls respectively.
EVALUATION CRITERIA: positive if a dose-dependant significant incrase in SCE frequencies compared to control is observed..
STATISTICAL ANALYSIS: Dunnett's test
Remark : m-Cresol did not induce significant increases over the control SCE frequencies. The positive control was functional.
m-Cresol caused a small but statistically significant decrease in cell-cycle progression at 8 mM (864 mg/l) and above, indicative of a small cytotoxic response
Reliability : (2) valid with restrictions
only tested in the absence of metabolic activation and no information on GLP
Flag : Critical study for SIDS endpoint
06.02.2004 (137)

Type : other: DNA amplification
System of testing : SV40-transformed CHO cell
Test concentration : 5.0 mM in DMSO
Cycotoxic concentr. :
Metabolic activation : without
Result : negative
Method : other: cells were incub. for 4d with m-cresol, then viability of the cells was determined, SV40-DNA content was detected by hybridization according to Lavi,Proc.Natl.Acad.Sci. (USA)80,6144,1981;Winocour,Proc.Natl.Acad. Sci.(USA)77,48
Year : 1989
GLP : no data
Test substance : other TS: purity: 98 %

Reliability : (4) not assignable
special study
24.09.2002 (138)

Type : other: SV40 Mammilian Inductest
System of testing : Syrian hamster kidney cells (SV40)
Test concentration : 0.0001-0.0000001 ml
Cycotoxic concentr. :
Metabolic activation : without
Result : positive
Method : other
Year : 1983
GLP : no
Test substance : no data

Remark : Mammalian inductest
Reliability : (4) not assignable
special test

24.09.2002 (139)

Type : Ames test
System of testing : Salmonella typhimurium TA 100, TA 1530, TA 1535, TA 1538,TA 1950, TA 1951, TA 1952, G 46
Test concentration : 0.5 % in ethanol
Cycotoxic concentr. :
Metabolic activation : no data
Result : ambiguous
Method : other: according to Ames Mutat. Res. 31,347 (1975); Science 176, 47 (1972)
Year : 1975
GLP : no data
Test substance : other TS: no data on purity

Remark : a questionable effect was produced in the strain TA 1535
Reliability : (4) not assignable
documentation insufficient for assessment

20.09.2002 (140)

Type : other: SOS-Chromotest
System of testing : Escherichia coli PQ37
Test concentration : no data
Cycotoxic concentr. :
Metabolic activation : without
Result : positive
Method : other: After termination of the nitrosation of m-cresol with ammonium sulphamate, test was performed according to Quillardet, Mutat. Res. 147,65 (1985)
Year : 1989
GLP : no data
Test substance : other TS: no data

Reliability : (4) not assignable
documentation insufficient for assessment

24.09.2002 (141)

Type : other: Prophage induction assay
System of testing : Escherichia coli / Bacteriophage lambda
Test concentration :
Cycotoxic concentr. :
Metabolic activation :
Result : positive
Method :
Year :
GLP :
Test substance :

Reliability : (4) not assignable
abstract only

20.09.2002 (142)

Type : Cytogenetic assay
System of testing : Allium cepa
Test concentration :
Cycotoxic concentr. :
Metabolic activation : without
Result : negative
Method :
Year : 1948

GLP : no
Test substance : other TS: no data on purity

Remark : marginal effects
Reliability : (4) not assignable
documentation insufficient for assessment
20.09.2002 (143)

Type : Mouse lymphoma assay
System of testing : L 5178 Y (TK +/-) cells
Test concentration : with and without S9-mix: 52.0, 78.0, 104, 156, 260, 312, 416, 520 ug/ml in DMSO
Cycotoxic concentr. : with and without S9-mix: 520 ug/ml;
Metabolic activation : with and without
Result : negative
Method : other: similar to OECD Guideline 476, No differentiation between large and small colonies, see also freetext ME
Year : 1988
GLP : yes
Test substance : other TS: m-cresol, purity: 99.8 %

Method : S9-MIX of rat liver was used as metabolic activation system
SOLVENT: DMSO
CONTROL: DMSO and ethylmethane sulfonate, 3-methylcholantrene served as negative and positive cotrol, respectively
EVALUATION CRITERIA: a solitive response was indicated by a > two-fold increase of mutant frequency over the concurrent background frequencies
Result : m-cresol was evaluated as nonmutagenic in the mouse lymphoma cell system.
The positive controls were functional
Reliability : (2) valid with restrictions
no differentiation between small and large colonies, statistical evaluation not mentioned
Flag : Critical study for SIDS endpoint
06.02.2004 (144)

Type : Cytogenetic assay
System of testing : Allium cepa
Test concentration : 0, 0.015, 0.02 and 0.025 % in destilled water
Cycotoxic concentr. : no data
Metabolic activation : no data
Result : positive
Method : other: treatment period: 0: 3 hrs; 0.015 24 hrs; 0.02: 5 hrs; 0.025: 5 hrs
Year : 1965
GLP : no
Test substance : other TS: no data on purity

Reliability : (4) not assignable
documentation insufficient for assessment
20.09.2002 (145)

Type : Ames test
System of testing : Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration : 0, 0.5, 5, 50, 500, 5000 ug/plate dissolved in DMSO
Cycotoxic concentr. : 5000 ug/plate
Metabolic activation : with and without
Result : negative
Method : other: see freetext ME
Year : 1982
GLP : no data
Test substance : other TS: m-cresol, purity: 98 %

Method	:	Plate incorporation assay according to Ames, Mutation Res. 31, 347 (1975), S9-MIX: of Aroclor pretreated rat liver SOLVENT: DMSO CONTROL: DMSO and sodium azide, 2-nitrofluorene, 9-aminoacridine, 2-amino anthracene served as negative and positive control DATA EVALUATION: Significance level for positive dose-response effects were obtained with the Joncheere test STATISTICAL ANALYSIS: Joncheere test
Remark	:	The positive controls were functional
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

06.02.2004 (146)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537
Test concentration	:	0.0, 3.3, 10.0, 33.0, 100.0, 333.0 ug/plate in water as solvent
Cycotoxic concentr.	:	to select dose range the chemical was checked for toxicity to S. typh. TA 100 (details not given)
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: preincubation methodology according to Ames, Mutat. Res. 31,347 (1975) and Yahagi, Cancer Lett. 1,91 (1975); see also freetext ME
Year	:	1983
GLP	:	no data
Test substance	:	other TS: m-cresol, purity: 97 %

Method	:	SOLVENT: water S9-MIX: prepared from male Syrian Hamster liver anf from male sprague-Dawley rat liver, that were injected with Arocolor 1254: CONTROL: water and : 2-aminoanthracenen, 4-nitro-o-phenylene diamine, sodium azide, 9-aminoacridine served as negative and positive control; DATA EVALUATION: oisitive response was indicated by a reproducable, dose-related increase wether it be twofold over tthe background or not STATISTICAL METHODS: based on the models presented by Margolin
Remark	:	the positive controls were functional
Reliability	:	(2) valid with restrictions only 4 strains of Salmonella typhimurium were used
Flag	:	Critical study for SIDS endpoint

06.02.2004 (147)

Type	:	Cytogenetic assay
System of testing	:	Chinese Hamster Ovary (CHO) cells
Test concentration	:	without S9-mix: (1)+(2): 198, 297, 398, 495 ug/ml DMSO ; with S9-mix: (1)+(2): 250, 500, 749, 999 ug/ml, (3) 699, 749, 799, 898, 998, 1100 ug/ml DMSO
Cycotoxic concentr.	:	Preliminary rangefinding assays were performed with and without metabolic activation to determin cytotoxicity: >=898 ug/ml: toxic
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: preliminary range finding studies; in accordance with OECD Guideline 473, see also freetext ME
Year	:	1988
GLP	:	yes
Test substance	:	other TS:m-cresol, purity: 99.8 %

Method	:	Duplicate CHO cultures were incubated for 17.2 hrs with 198-495 ug/ml of the test substance in the nonactivation aberrations assay. The metabolic activation cultures were treated with 250-1100 ug/ml of the test substance for 2 hours

Solvent: DMSO
CONTROL: DMSO and Mitomycin C, cyclophosphamide served as negative and positive control, respectively
STATISTICAL ANALYSIS: Fisher's Exact Test with an adjustment for multiple comparisons

Remark : The positive controls were functional
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
06.02.2004 (148)

Type : Unscheduled DNA synthesis
System of testing : other: Syrian Hamster Embryo (SHE) cells
Test concentration : 1, 3, 10 uM, vehicle: medium
Cycotoxic concentr. : not determined
Metabolic activation : with and without
Result : positive
Method : other: according to OECD Guide-line 482: not tested up to cytotoxicity
Year : 2000
GLP : no data
Test substance : other TS: m-cresol, purity: >=98 %

Result : A dose-dependent positive result was only obtained when tested in the presence of a metabolic activation system. It was not tested up to cytotoxicity.
Reliability : (2) valid with restrictions
not tested up to cytotoxic concentration, no data on GLP, no positive or negative controls reported
Flag : Critical study for SIDS endpoint
06.02.2004 (149)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Cytogenetic assay
Species : other: mouse bone marrow cells
Sex : male/female
Strain : ICR
Route of admin. : gavage
Exposure period : once
Doses : 0, 96, 320, 960 mg/kg bw in corn oil
Result : negative
Method : other: in accordance with OECD Guideline 475, 5 mice/sex/dose, bone marrow cells, sacrifice 6,24,48 hrs post treatment, negative and positive controls, stat. method: Kruskal-Wallis test
Year : 1989
GLP : yes
Test substance : other TS: m-cresol, purity: 99.8 %

Remark : dose finding study: see chapter 5.1.1
CONTROL: corn oil and cyclophphamide served as negative and positive control
EVALUATION CRITERIA: positive response is indicated by statistically significant dose-related increase in the number of structural aberrattions at 3 dose levels
Result : The treatment did not increase the frequency of chromosomal aberrations, indicating that m-cresol was not clastogenic under the conditions of this assay. The positive control was functional
mortality: 3/5 male mice in the 960 mg-group
signs of toxicity:
960 mg-group: within 10 min after dosing: squinty eyes, scruffy coats, mild tonic convulsions and rapid breathing which ceased after 30 min.,

breathing difficulties
320 mg/kg bw: slightly scruffy coats within 22 hours after dosing
96 mg/kg bw: no signs of toxicity

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
06.02.2004 (150)

Type : Sister chromatid exchange assay
Species : mouse
Sex : male
Strain : DBA
Route of admin. : i.p.
Exposure period : single application
Doses : 0, 200 mg/kg bw dissolved in sunflower oil
Result : negative
Method : other: see freetext ME
Year : 1984
GLP : no data
Test substance : other TS: m-cresol, purity: 99 %

Method : m-Cresol was administered to 2 or 3 intact or hepatectomized male mice by single intraperitoneal injection. After 30 min, DNA labelling was initiated using BrdU. After a further 21 hr the animals were killed, cells isolated and harvested and sister chromatid exchange (SCE) frequency in bone marrow cells, alveolar macrophages and regenerating liver cells analysed. Some of the mice were partially hepatectomized to induce liver cell regeneration
NEGATIVE CONTROLS: 0.35 ml sunflower oil (4 intact and 5 hepatectomized male mice, bone marrow cells, alveolar macrophages, liver cells)
Positive Control: 5 mg cyclophosphamide/kg bw (2 intact male mice, bone marrow cells and alveolar macrophages)
STATISTICAL ANALYSIS: One way analysis of variance; Dunnett's test for comparison

Result : No increase in SCE frequencies in the intact mice as well as in the partially hepatectomized mice.
The dose tested was overtly toxic to the mice, causing lethargy, piloerection and lacrimation.
The positive control was functional

Reliability : (2) valid with restrictions
only one dose tested and no information on GLP
06.02.2004 (137)

5.7 CARCINOGENICITY

Species : mouse
Sex : female
Strain : other: Sutter
Route of admin. : dermal
Exposure period : 12 w (I) or 20 w (II)
Frequency of treatm. : twice weekly
Post exposure period : no
Doses : 25 ul of a 20 % (I) or 5.7 % (II) solution in benzene
Result :
Control group : yes, concurrent vehicle
Method : other: Initiation-promotion test (see remarks)
Year : 1959
GLP : no
Test substance : other TS: m-cresol, not specified further

Remark : Groups of 20-29 Sutter strain mice:

I. method: initiator: single dermal appl. of 0.3 % DMBA in acetone; m-cresol was applied as promotor to the back of each mouse

I. result: 14/29 mice (12/12 benzene control animals) survived and in 50 % (0 % in control animals) skin papillomas were found; no carcinomas were detected

II.method: initiator: 0.3 % DMBA in benzene; promotor: m-cresol was applied to the back of each mouse

II.result: 17/20 mice (18/20 benzene control animals) survived and in 24 % (0 % in control animals) skin papillomas were found; no carcinomas were detected

Result : m-cresol was evaluated as promotor
Reliability : (2) valid with restrictions
no data on purity, benzene a known carcinogen as solvent, high mortality rate
Flag : Critical study for SIDS endpoint
06.02.2004 (151)

Species : other: in vitro cell transformation assay
Sex :
Strain : other: mouse BALB/c-3T3 cells
Route of admin. :
Exposure period :
Frequency of treatm. :
Post exposure period :
Doses : 0.57 - 48 nl/ml culture medium
Result : negative
Control group : yes
Method : other: see freetext ME
Year : 1988
GLP : yes
Test substance : other TS: m-cresol, purity > 99 %

Method : 40CFR 795.285 (modified), preliminary clonal cytotoxicity test, performance of the test according to Kakunaga, Int. J. Cancer 12, 463, 1973, without metabolic activation, negative and positive controls
Result : Meta-cresol did not induce cell transformation in this assay; cytotoxicity: 48 nl/ml
Reliability : (2) valid with restrictions
non-validated test system
Flag : Critical study for SIDS endpoint
06.02.2004 (152)

Species : other: in vitro cell transformation assay
Sex :
Strain : other: mouse BALB/c-3T3 cell
Route of admin. :
Exposure period :
Frequency of treatm. :
Post exposure period :
Doses : 6 - 72 nl/ml culture medium
Result : negative
Control group : yes
Method : other: preliminary cytotoxicity test, performance of the test according to Kakunaga, Int. J. Cancer 12, 463, 1973, with metabolic activation
Year : 1988

GLP	:	yes
Test substance	:	other TS: m-cresol, purity > 99 %
Result	:	m-cresol did not produce significant increases in the number of transformed foci, cytotoxicty: 62 nl/ml
Reliability	:	(2) valid with restrictions non-validated test system
Flag	:	Critical study for SIDS endpoint

06.02.2004 (153)

Species	:	other: in vitro cell transformation assay
Sex	:	
Strain	:	other: Syrian Hamster embryo (SHE) cells
Route of admin.	:	
Exposure period	:	
Frequency of treatm.	:	
Post exposure period	:	
Doses	:	
Result	:	positive
Control group	:	
Method	:	other: no details reported
Year	:	1987
GLP	:	no data
Test substance	:	other TS: no data on purity
Remark	:	abstract only
Result	:	m-cresol induced cell transformation
Reliability	:	(4) not assignable abstract documentation insufficient for assessment

17.12.2002 (154)

5.8.1 TOXICITY TO FERTILITY

Type	:	Two generation study
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	27 w
Frequency of treatm.	:	once/d, 7 d/w
Premating exposure period		
Male	:	10 w
Female	:	10 w
Duration of test	:	29 w
No. of generation studies	:	
Doses	:	0, 30, 175 or 450 mg/kg bw/d in corn oil
Control group	:	yes, concurrent vehicle
NOAEL parental	:	30 mg/kg bw
NOAEL F1 offspring	:	ca. 175 mg/kg bw
Method	:	other: TSCA Health Effects Test Guideline for specific organ/tissue toxicity - Reproduction/Fertility effects (EPA, 1983), see also freetext ME
Year	:	1989
GLP	:	yes
Test substance	:	other TS: m-cresol, purity: 99.4 %
Method	:	25 rats/sex/dose (F0) were administered m-Cresol in corn oil. Exposure began 10 weeks prior to breeding and continued in the females throughout mating, gestation and lactation.

25 randomly selected F1 pups/sex/dose were gavaged with the appropriate concentration of m-cresol for 11 weeks and then bred to produce F2 litters (dosing was continued throughout mating, gestation and lactation)
F2 offspring was sacrificed at weaning.

reproductive indices: mating indices for males and females, fertility indices for males and females, gestational index, live birth index, 4-day survival index 7-day survival index, 21-day survival index, lactation index

Necropsy and pathology:
all F0 and F1 parental rats in all groups were subjected to a complete necropsy ; 25 male and 25 female adults from the controls and from the high dose groups were subjected to histopathology examination: pituitary, vagina, uterus, ovaries. testes, epididymides, seminal vesicles, prostate and other tissues with gross lesions identified as potentially treatment related; any of thze above organs or tissues showing gross alterations were also evaluated microscopically in other dose groups
A complete gross necropsy and histopathologic examination were conducted for any parental rat dying on test
Gross necropsy included examination of the external surfaces, all orificwes, cranila cavity, carcass, external and cut surfaces of the brain and spinal cord, the thoracic,abdominal and pelvic cavities and their viscera, cervical tissues and organs
a gross internal examination on any F1 and F2 pup appearing abnormal or dying on testA complete gross necropsy and histopathologic examinations were conducted for any animals dying on test.

statistical methods:
Levene's test,ANOVA, t-test corrected by Bonferroni method, Kruskal-Wallis test, Mann Whitney U-test, Fishers exact test

Result : F0: pre-breed dosing period:
450 mg/kg: f,m: significant reduced body weight, signs of toxicity: hypoactivity, ataxia, twitches, tremors, prostration, unkempt appearance(males), urine stains, audible respiration perinasal encrustration and perioral wetness; mortality: 7/25 m, 5/25 f;
175 mg/kg: sacrifice due to trauma 1/25 m
F0: breed period:
450 mg/kg: maternal gestat. and lactat. bw sign. reduced, mortality: 450 mg/kg:2/20 f; 175 mg/kg: 1/25 f;
reproductive parameters including gestational length were unaffected by treatment
F1:
litter size, sex ratio, litter viability, pup survival were unaffected by treatment; 450 mg/kg: reduced female pup bw
F1 pre-breed period:
slightly reduced bw in m (450, 175,30 mg/kg) and in f (450,30 mg/kg); signs of toxicity: 450 mg/kg bw: hypoactivity, ataxia twitches, tremors prostration urine stains, audible respiration and perioral wetness (also at 175 mg/kg
females); mortality: 450 mg/kg 3 m and 4 f;
F1 breed period:
450, 175, 30 mg/kg: reduced bw in m; maternal gestational and lactational bw reduced in 450 mg/kg f; mortality during gestation: 1 f each at control, 30, 175 mg/kg and 3 f at 450 mg/kg, mortality during lactation: 3 f at 450 mg/kg

Reproductive parameters including gestational parameters were unaffected by treatment
F2:
litter size and sex ratio unaffected; F2 pup lactational

index was reduced at 450 mg/kg
450 mg/kg: pup bw and pup bw gain was reduced and pup deaths increased.
Pathology:
all groups: there were no treatment related gross lesions or histologic lesions in F0, F1 and F2 rats which survived to scheduled sacrifice.
dead prior to schedule: F0,F1 m: lesions in brain , thymic regions, lungs, decrease in number of sperm in epididymides, atrophied seminal vesicles and coagulation glands, epididymitis; F0,F1 f: lesions in the brain, lungs
NOAEL (fertility): 450 mg/kg bw

The exact A/D ratio cannot be calculated. But it can be assumed that the A/D ratio would be less than 1 (<30.0 mg/kg bw/day/175.0 mg/kg bw) indicating no increased risk to offspring in the absence of parental toxicity.

A/D ratio: exposure level at which there were no observable effects in adults/the exposure level at which there were no observable effects in offspring

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
06.02.2004 (155)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	day 6 through day 15 of gestation
Frequency of treatm.	:	daily
Duration of test	:	until gd 21
Doses	:	0, 30, 175 or 450 mg/kg bw/d dissolved in corn oil
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	ca. 175 mg/kg bw
NOAEL teratogen.	:	ca. 450 mg/kg bw
Result	:	see freetext RS
Method	:	other: following the TSCA Health Effects Test guidelines for Specific Organ/Tissue Toxicity - Developmental Toxicity (EPA, 1984,1987)
Year	:	1988
GLP	:	yes
Test substance	:	other TS: m-cresol, purity: 99.4 %

Method :
Dose selection was based on the results of a range-finding study.
Solvence: corn oil
25 mated females/group, 50 control females, all females were weighed ond gd 0, 6, 11, 15, and 21, food consumption was measured throughout gestation, all females were examined daily for clinical signs, for mortality and morbidity
sacrifice on gd 21:
does were evaluated for body weight, liver and gravid uterine weight, number of corpora lutea and number of status of implantation sites (i.g. resorptions, dead fetuses, live fetuses)
live fetuses were dissected from uterus, counted and weighed, examined for external malformations and variations, and for visceral malformaltions and variations, and for soft tissue craniofacial malformations
statistical analysis:
Levene's test, ANOVA, pooled t-test, Kruskal-Wallis test, Mann-Whitney U-

test, Fisher's exact test

Result : maternal toxicity:
no deaths, no abortions or early deliveries
450 mg/kg:
significant reduced food consumption, reduced maternal body weights and weight gain during dosing period; reduced gestational weight gain (day 0-21);
clinical signs of toxicity: hypoactivity, ataxia, tremors, audible respiration, perioral wetness;
increased relative but not absolute liver weights no embryotoxicity or teratogenicity was observed at any
dosage level

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

06.02.2004 (156)

Species : rabbit
Sex : female
Strain : New Zealand white
Route of admin. : gavage
Exposure period : day 6 through day 18 of gestation
Frequency of treatm. : once daily
Duration of test : until day 29 of gestation
Doses : 0, 50, 150, 300 or 500 mg/kg bw/d
Control group : yes

Remark : 8 rabbits/dose
range-finding study

Result : 50 mg/kg: one doe aborted; ataxia, twitching, gasping, audible, labored and rapid respiration; increased relative liver weights
150 mg/kg: maternal mortality 2/8; reduced food consumption o gd 7-9; significantly depressed body weight gain for gd 6-12; cleft palace in 1 fetus
>= 300 mg/kg:reduced food consumption on gd 6-10; significantly elevated clinicals signs of toxicity (CNS and cardiopulmonary categories; see at 50 mg/kg)
300 mg/kg: maternal mortality 1/8; one doe aborted; reduced body weight on gd 12 and significantly depressed body weight gain on gd 6-12; increased preimplantation loss and increase in dead fetuses/litter; forelimb and pectoral girdle anomalies in 4 fetuses in 2 litters; cleft palate in 1 fetus; small tongue
500 mg/kg: maternal mortality 8/8

Reliability : (2) valid with restrictions
dose range finding study

12.11.2002 (157)

Species : rabbit
Sex : female
Strain : New Zealand white
Route of admin. : gavage
Exposure period : day 6 through day 18 of gestation
Frequency of treatm. : once daily
Duration of test : until day 29 of gestation
Doses : 0, 5, 50 or 100 mg/kg bw/day
Control group : yes, concurrent vehicle

NOAEL maternal tox.	:	ca. 5 mg/kg bw
NOAEL teratogen.	:	ca. 100 mg/kg bw
Method	:	other: following the TSCA Health Effects Test guidelines for Specific Organ/Tissue Toxicity - Developmental Toxicity (EPA, 1984,1987)
Year	:	1988
GLP	:	yes
Test substance	:	other TS: m-cresol, purity: 99.7 %
Method	:	Dose selection was based on the results of a range-finding study. 14 mated females/group, 28 control females, all females were weighed ond gd 0, 6, 12, 18, 24 and 29, food consumption was measured throughout gestation, all females were examined daily for clinical signs, for mortality and morbidity sacrifice on gd 29: does were evaluated for body weight, liver and gravid uterine weight, number of corpora lutea and number of status of implantation sites (i.g. resorptions, dead fetuses, live fetuses) live fetuses were dissected from uterus, counted and weighed, examined for external malformations and variations, and for visceral malformaltions and variations, and for soft tissue craniofacial malformations statistical analysis: Levene's test, ANOVA, pooled t-test, Kruskal-Wallis test, Mann-Whitney U-test, Fisher's exact test
Result	:	>= 50 mg/kg: audible respiration and ocular discharge No embryotoxicity or teratogenicity was observed at any dosage employed.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

06.02.2004 (158)

Species	:	rat
Sex	:	female
Strain	:	Wistar
Route of admin.	:	s.c.
Exposure period	:	day 7 through day 17 of gestation
Frequency of treatm.	:	daily
Duration of test	:	until post partum
Doses	:	90 mg/kg bw/d (30 ml/kg bw 0.3 %)
Control group	:	yes
Result	:	m-cresol was used as the solvent at a concentration of 0.3 %; no negative effects on F0- or F1-generation were observed when compared with control animals.
Reliability	:	(3) invalid application route is not relevant for the human situation

12.11.2002 (159)

Species	:	rat
Sex	:	female
Strain	:	Wistar
Route of admin.	:	s.c.
Exposure period	:	day 17 of gestation until 21 days after birth
Frequency of treatm.	:	daily
Duration of test	:	until 8 w post partum
Doses	:	90 mg/kg bw/d (30 mg/kg 0.3 %)
Control group	:	yes
Result	:	m-cresol was used as the solvent at a concentration of 0.3 %; no negative effects on F0-, F1- or F2-generation were observed when compared with controls (no fetotoxicity, normal postnatal development, normal behaviour and

fertility).
Reliability : (3) invalid
application route is not relevant for the human situation
12.11.2002 (160)

Species : Mouse
Sex : Female
Strain : other: ICR-SLC
Route of admin. : s.c.
Exposure period : day 6 through day 15 of gestation
Frequency of treatm. : Daily
Duration of test : until 5 w post partum
Doses : no data
Control group : Yes

Result : m-cresol was used as the solvent; no signs of fetotoxicity or teratogenicity, no maternal toxicity.
Reliability : (3) invalid
application route is not relevant for the human situation
12.11.2002 (161)

Species : Rabbit
Sex : Female
Strain : no data
Route of admin. : s.c.
Exposure period : day 6 through day 18 of gestation
Frequency of treatm. : Daily
Duration of test : until >= 12 d after exposure
Doses : 30 mg/kg bw/d (10 ml/kg 0.3 %)
Control group : Yes

Result : m-cresol was used as the solvent at a concentration of 0.3 %; decreased maternal food consumption and body weight gain after day 14 of gestation, increased average number of implantations and reduced mean body weights in male fetuses, no increase of anomalies.
Reliability : (3) invalid
application route is not relevant for the human situation
12.11.2002 (162)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type : Other
In vitro/in vivo : In vivo
Species : Rat
Sex : male/female
Strain : other: Fisher 344/N
Route of admin. : oral feed
Exposure period : 28 d
Frequency of treatm. : continuously in diet
Duration of test : 28 d
Doses : 0, 300, 1000, 3000, 10000, 30000 ppm
Control group : yes, concurrent no treatment
Result : see freetext RS
Method : other: the reproductive organs were examined as part of the 28-day study, see chapter 5.4
Year : 1991
GLP : Yes
Test substance : other TS: purity>98 %

Result	:	Histological evaluation , characterized by average severity score based on a scale of 1 to 4 (1=minimal, 2=mild, 3=moderate, 4= marked) revealed effects: uterine atrophy in 4/5 females at 30000 ppm
Reliability	:	(1) valid without restriction

10.07.2002 (130)

Type	:	Other
In vitro/in vivo	:	In vivo
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	28 d
Frequency of treatm.	:	continuously in diet
Duration of test	:	28 d
Doses	:	0, 300,1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
Result	:	see freetext RS
Method	:	other: the reproductive organs were examined as part of the 28 day study, see chapter 5.4
Year	:	1991
GLP	:	Yes
Test substance	:	other TS: purity>98 %

Result	:	Histopathological evaluation, characterized by average severity score based on a scale of 1 to 4 (1=minimal, 2=mild, 3=moderate, 4=marked), revealed effects: 30000 ppm: female, moderate mammary gland atrophy, mild ovary atrophy and moderate uterus atrophy
Reliability	:	(1) valid without restriction

10.07.2002 (130)

Type	:	Other
In vitro/in vivo	:	In vivo
Species	:	Rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	13 weeks
Frequency of treatm.	:	Daily
Duration of test	:	14 weeks
Doses	:	0, 50, 150, 450 mg/kg bw in corn oil
Control group	:	yes, concurrent vehicle
Result	:	no effects on reproductive organs were reported, neither in males nor in females
Method	:	other: the reproductive organs were examined as part of the 13 week study, see chapter 5.4
Year	:	1986
GLP	:	Yes
Test substance	:	other TS: m-cresol, purity: 98.6 %

Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

06.02.2004 (131)

5.9 SPECIFIC INVESTIGATIONS

Endpoint	:	Neurotoxicity
Study descr. in chapter	:	

Reference	:	
Type	:	other: subchronic
Species	:	Rat
Sex	:	male/female
Strain	:	other: CD
Route of admin.	:	Gavage
No. of animals	:	20
Vehicle	:	other: corn oil
Exposure period	:	90 day(s)
Frequency of treatm.	:	Daily
Doses	:	0, 50, 150, 450 mg/kg bw/day
Control group	:	yes, concurrent vehicle
Observation period	:	13 weeks during dosing
Result	:	see freetext RE
Method	:	other: see freetext ME
Year	:	1986
GLP	:	no data
Test substance	:	other TS: no data on purity

Method : 10 male and 10 female CD rats/treatment group received corn oil solutions of 50, 175 or 600 mg/kg bw /day by gavage once daily for 13 weeks. 20 male and 20 female CD rats received corn oil alond to serve as control.Rats were observed for body weight gain, food consumption, clinical signs.
Signs of neurobehavioral toxicity were documented during pretreatment, 1 and 6 hours after dosing on study day 1 and prior dosing on study days 2, 7, 14, 30, 60 and 90 including salivation, urination, tremors, piloerection, diarrhea, pupil size, pupil response, lacrimation, hypothermia, vocalization, exophthalmus, palpebral closure, convulsions (type and severity), respiration (rate and type), impaired gait, positional passivity, locomotor activity, stereotypy, startle response, righting reflex, performance on a wire maneuver, forelimb grip strength, positive geotropism, extensor thrust, limb rotation, tail pinch reflex, toe pinch reflex, hind limb splay.
gross and histopathologic examination

Result : Mortality: control: 1 female (2.5 %), 450 mg-gr: 1 female (5 %), gross and histopathologic examination: aspiration or inhalation of the TS, pulmonary edema
body weight gain comparable to control
mean food consumption, 450 mg-gr., males and females: significantly less than control during the initial portion of the study
clinical signs: dose related in incidence: salivation, myotonus, tremors, urine wet abdomen, hypoactivity, rapid respiration
neurobehavioral toxicity:
450 mg-group, males and females: initial part of the study: incidence of palpebral closure, rales, laboured respiration; at study termination, females: significantly increased urination.
Other differences from controls with regard to behavioral tests were evaluated as sporadic in nature by the authors (no further details given).
necropsy:
brain weights of treated animals comparable to controls; gross and microscopic examination of tissues revealed no lesions which were attributable to treatment

Reliability : (2) valid with restrictions
limited documentation (only study summary available)

Flag : Critical study for SIDS endpoint

05.02.2004 (163) (112) (164)

5.10 EXPOSURE EXPERIENCE

Remark : In humans, m-cresol may be excreted as a metabolite in urine after occupational exposure to phenols, cresols, xylenols, naphthalene and/or toluene.
Reliability : (4) not assignable
14.01.2003 (165) (166) (167) (168) (169) (170) (171)

Remark : The probable oral lethal dose for humans is 50-500 mg/kg.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
14.01.2003 (172)

Remark : In humans, insulin preparations with m-cresol resulted in an impaired leukocyte function (decreased killing capacity of human polymorphonuclear leukocytes (PMNL), expressed as the percentage of Staphylococcus aureus killed after 60 minutes of incubation). m-cresol is possibly implicated in the pathogenesis of local infections in continuous subcutaneous insulin infusion
Reliability : (4) not assignable
15.01.2003 (173)

Remark : Case report: A 44-y-old male was found unconscious after ingestion of 300 ml of 50 % cresol-soap solution. Endotracheal intubation, gastric lavage and activated charcoal reversed his conscious. He had dermal burns, oesophageal and gastric erosions, pneumonia, mixed metabolic acidosis and respiratory alkalosis, renal and liver function impairment, leucocytosis and dark urine. Acute renal failure and hemolysis developed, but recovered after hemodialysis and intensive supportive care.
Urine levels of p-,m-,o-cresol and phenol were resp. 2083, 2059, 125 and 68 mg/g creatinine at 7 h post ingestion.
The patient recovered.
Reliability : (4) not assignable
15.01.2003 (174)

Remark : case report: Accidental dermal exposure of both legs and face of a 47-year-old man resulted in corrosion of 15 % of his body surface and he developed acute polyuric renal failure. Serum levels of m-cresol after 1 h were above 30 mg/l.
After 5 hemodialysis procedures renal function recovered. Levels of m-cresol in the dialysate were less than 5 % of the levels in serum. Hemodialysis had no significant effect on the serum concentration time course of m-cresol.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
14.01.2003 (175)

Remark : The Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels (MLR) were developed to provide screening levels for health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites an releases. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a

specific duration of exposure:
m-cresol: MRL = 0.05 mg/kg bw/d acute oral exposure

Reliability : (4) not assignable
15.01.2003 (176)

Remark : It is reported that certain individuals are hypersensitive to cresol (isomer not specified, no further information)
Reliability : (4) not assignable
Flag : Critical study for SIDS endpoint
15.01.2003 (110)

Remark : Case reports: intentional or accidental oral intake of cresols (all isomers): irritation of mouth and throat, abdominal pain, vomiting, hemolytic anemia, increased heart ratem liver and kidney damage, headaches, facial paralysis, drowsiness, cramps coma and death
Reliability : (2) valid with restrictions
description suffers from deficiencies as the isomers are not specified
Flag : Critical study for SIDS endpoint
14.01.2003 (177) (178) (179) (180)

Remark : Skin depigmentation (chemical leukoderma has been reported after local exposure to cresols (isomer not specified)
Reliability : (4) not assignable
Flag : Critical study for SIDS endpoint
15.01.2003 (130)

Remark : It is reported that skin contact has alo resulted in effects on the nervous system, liver and kidneys and caused human fatalities.
Reliability : (4) not assignable
Flag : Critical study for SIDS endpoint
15.01.2003 (179)

Remark : A cresol solution, unintentionally poured over the trunk, caused gross hematuria, gastrointestinal bleeding, hypertension and septic shock with severe jaundice and renal failure.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
15.01.2003 (181)

Remark : The development of tumours in persons who had been exposed occupationally to cresol (unspecified isomer) has been reported, and two cases of transitional cell bladder carcinoma were described after longterm exposure to cresol. Since no information on exposure levels are available and since co-exposure to other substances cannot be excluded a carcinogenic potential of the cresol isomers cannot be deduced fron these cases.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
15.01.2003 (182)

Remark : Case report: a worker in an oil rafinery was exposed to cresol, dichlorooctane and chromic acid for a long period developed a squamous epithelial carcinoma of the vocal cords. Since no information on exposure levels is available and since co-exposure to other substances is included a

carcinogenic potential of the cresol isomers cannot be deduced from this case report.

Reliability : (4) not assignable
Flag : Critical study for SIDS endpoint
15.01.2003 (179)

Remark : Anomalous menstrual cycles were found and hormonal disorders were reported from women who were employed in ther production to enamelled wire or of tricresyl phosphate and were exposed to a variety of compounds, including chlorobenzenes and phosphoryl chloride. It was claimed that the incidence of perinatal child death was increased and that developmental disorders were frequent among new-born babies. since no data on exposure levels and duration of exposure are given and data on controls were not provided a relationship between the described effects and cresol exposure cannot be deduced.

Reliability : (4) not assignable
Flag : Critical study for SIDS endpoint
05.02.2004 (179)

5.11 ADDITIONAL REMARKS

Type : Cytotoxicity

Remark : m-cresol (test concentration: 0, 2, 5, 10, 20 or 50 ppm; test duration: 66 h) showed a concentration dependent decrease in growth rate and cell yield in L-M strain cells (CCL 1.2; derived from NCTC clone 939 mouse fibroblast line) in suspension culture. No effect was observed with 2 ppm.

Reliability : (4) not assignable
16.01.2003 (183)

Type : Cytotoxicity

Remark : Cytotoxicity assay, V79 cells: the growth of V79 cells was inhibited in a dose- and time-related manner, while DNA-, RNA- and protein-syntheses were inhibited in a dose-related fashion.

Reliability : (4) not assignable
16.01.2003 (184)

Type : Metabolism

Remark : In male Wistar rats, m-cresol was excreted as a metabolite in urine after a single i.p. injection of 0.12 ml 14C-toluene/rat.

Reliability : (4) not assignable
16.01.2003 (169)

Type : Metabolism

Remark : m-cresol was excreted as conjugated glucuronide in urine when adminstered orally to one rabbit in a dose of 2000 mg or one hen in a dose of 1000 mg.

Reliability : (4) not assignable
16.01.2003 (185)

Type : Metabolism

Remark : In female CFY rats, the excretion of m-cresol in urine was increased after exposure to xylene (4000 mg/m3/6 h).
Reliability : (4) not assignable
16.01.2003 (186)

Type : Metabolism

Remark : The retention of m-cresol in male Wistar rats after the oral administration of 25 ug/rat for 3 d (test period 7 d) was 0.2 % (percentage of applied dose).
Reliability : (4) not assignable
16.01.2003 (26)

Type : Metabolism

Remark : After an oral application of 10 g m-cresol within 3 days to one dog the substance was excreted unchanged in urine.
Reliability : (4) not assignable
16.01.2003 (187)

Type : Metabolism

Remark : In an in vitro study m-cresol was hydroxylated to 2,5-dihydroxytoluene and probably to the sulfate conjugate of m-hydroxybenzyl alcohol with rat liver homogenate and slices.
Reliability : (4) not assignable
16.01.2003 (188)

Type : Metabolism

Remark : in vitro: Metabolic cooperation assay for gap junctional intercellular communication with chinese hamster cells (V79): negative.
Reliability : (4) not assignable
16.01.2003 (189)

Remark : m-cresol inhibited the growth of chick embryo fibroblasts (incubation for 24 h), the sublethal dose was approx. 20 mg/l and the lethal dose > 20 < 50 mg/l.
Reliability : (4) not assignable
16.01.2003 (78)

Remark : m-cresol (0.5 or 1.0 ml) showed an inhibitory effect on the ATP-induced (50 ug) pulmonary vasoconstriction in isolated perfused rabbit lungs.
Reliability : (4) not assignable
16.01.2003 (190)

Remark : m-cresol (550 mg/m3) showed a ciliostasis index of 0.7 to 0.75 in isolated rabbit tracheal tissue.
Reliability : (4) not assignable
16.01.2003 (191)

Remark : In a neutral red (NR) cytotoxicity assay with Bluegill sunfish BF-2 cells, the NR50 was determined with 5.3 mM.

Reliability : (4) not assignable
16.01.2003 (192)

Remark : In male Sprague-Dawley rats no effect on oxygen consumption was observed after a single i.p. injection of 50-200 mg/kg bw.
Reliability : (4) not assignable
16.01.2003 (193) (194)

Remark : In vitro short term cytotoxicity tests:

I. method: inhibition of cell growth in ascites sarcoma BP8 cells (concentration 1mM, incubation for 48 hours)
I. result: the inhibitory effect was >= 30 <= 39 %
II. method: inhibition of oxidative metabolism in isolated brown fat cells (concentration 1mM, incubation for 5 min at 37 Grad C)
II. result: the inhibitory effect was >= 60 <= 69 %
III. method: plasma membrane damage in human diploid embryonic lung fibroblasts (MRC-5, leakage of a cytoplasmatic nucleotide marker from prelabelled cells, concentration 25 mM, incubation for 30 min at 37 Grad C)
III. result: the release was >= 30 <= 39 %
IV. method: ciliotoxicity (ciliostasis in tracheas of chicken embryos, concentration 5 mM, incubation at 37 Grad C)
IV. result: the ciliotoxicity was >= 70 <= 79 %

Reliability : (4) not assignable
16.01.2003 (195)

Remark : In vitro study:
in isolated heavy beef heart mitochondria (HBHM), m-cresol in a concentration of 3.6 x 10E-4 M was shown to stimulate the HBHM NADH-oxidase system. In the HBHM succinoxidase system, no effect was observed.
Reliability : (4) not assignable
16.01.2003 (196)

Remark : m-cresol showed no antimutagenic effect on MNNG-induced mutagenesis in E. coli WP2
Reliability : (4) not assignable
16.01.2003 (197)

Remark : Biochemistry: m-cresol at a concentration of 1 mM showed a stimulation of prostaglandin synthesis (max. percent increase: 268 +- 26), while a concentration of 10 mM showed an inhibition of prostaglandin synthesis (percent inhibition: 55 +-3.5).
Reliability : (4) not assignable
16.01.2003 (198)

Remark : Increasing concentrations of m-cresol produced increasing inhibition of thymidine incorporation in Hela cells.

Reliability : (4) not assignable
16.01.2003 (105)

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(in Japanese, engl. Abstract)

I U C L I D

Data Set

Existing Chemical	:	ID: 106-44-5
CAS No.	:	106-44-5
EINECS Name	:	p-cresol
EC No.	:	203-398-6
TSCA Name	:	Phenol, 4-methyl-
Molecular Formula	:	C7H8O

Producer related part

Company	:	Bayer AG
Creation date	:	11.01.2001

Substance related part

Company	:	Bayer AG
Creation date	:	11.01.2001
Status	:	
Memo	:	AKTUELL / ICCA (Category Cresols)
Printing date	:	24.05.2004
Revision date	:	
Date of last update	:	24.05.2004
Number of pages	:	122
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type : cooperating company
Name : ADCHEMCO Corporation
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

Type : lead organisation
Name : American Chenistry Council Cresol Panel
Contact person :
Date :
Street : 1300 Wilson Blvd.
Town : 22209 Arlington, VA
Country : United States
Phone : 703-741-5629
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
16.01.2001

Type : cooperating company
Name : Bayer Corporation
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
16.01.2001

Type : cooperating company
Name : Concord Chemical Company
Contact person :
Date :
Street :
Town :

Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
16.01.2001

Type : cooperating company
Name : Dakota Gasification Company
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
16.01.2001

Type : cooperating company
Name : Honshu Chemical Industry Company, Ltd.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

Type : cooperating company
Name : LaPorte (formerly Inspec Fine Chemicals, Inc.)
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
17.01.2001

Type : cooperating company
Name : Merisol (Merichem-Sasol USA LLC)
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
17.01.2001

Type : cooperating company
Name : Mitsui Chemicals, Inc.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

Type : cooperating company
Name : Nippon Steel Chemical Company, Ltd.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

Type : cooperating company
Name : PMC Specialties Group, Inc.
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :

Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
16.01.2001

Type : cooperating company
Name : Sumiken Chemical Company, Ltd.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

Type : cooperating company
Name : Sumitomo Chemical Americas, Inc.
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
16.01.2001

Type : cooperating company
Name : Sumitomo Chemical Company, Ltd.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : organic
Physical status : solid
Purity : ca. 99.9 % w/w
Colour :
Odour :

Flag : Critical study for SIDS endpoint
10.02.2003 (1)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1-Hydroxy-4-methylbenzene

01.05.1998

4-Cresol

01.05.1998

4-Hydroxytoluene

01.05.1998

4-Hydroxytoluol, 4-Methylphenol

19.05.1998

4-Methylfenol

06.03.1998

4-Methylphenol

01.05.1998

p-Cresol (8CI)

30.08.1996

p-Cresylic acid

01.05.1998

p-Hydroxytoluene

01.05.1998

p-Kresol

01.05.1998

p-Methylhydroxybenzene

23.05.2002

p-Methylphenol

01.05.1998

p-Oxytoluene

01.05.1998

p-Toluol

01.05.1998

p-Tolyl alcohol

23.05.2002

paracresol

01.05.1998

Phenol, 4-methyl-

01.05.1998

Phenol, 4-methyl- (9CI)

30.08.1996

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : - tonnes produced in

Remark : 59,500 tonnes in 2000, estimated world capacity
Flag : Critical study for SIDS endpoint
28.05.2002

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits :
Symbols : T, , ,
Nota : , ,
R-Phrases : (24/25) Toxic in contact with skin and if swallowed
(34) Causes burns
S-Phrases : (36/37/39) Wear suitable protective clothing, gloves and eye/face protection
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)

Remark : 19. Adaptation, EC-Index-No. 604-004-00-9
Flag : Critical study for SIDS endpoint
24.05.2002

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC
Class of danger : corrosive
R-Phrases : (34) Causes burns
Specific limits :

Flag : Critical study for SIDS endpoint
24.05.2002

Classified : as in Directive 67/548/EEC
Class of danger : toxic
R-Phrases : (24/25) Toxic in contact with skin and if swallowed
Specific limits :

Flag : Critical study for SIDS endpoint
24.05.2002

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Use in closed system

Flag : Critical study for SIDS endpoint
24.05.2002

Type of use : industrial
Category : Chemical industry: used in synthesis

Flag : Critical study for SIDS endpoint
24.05.2002

Type of use : use
Category : Intermediates

Flag : Critical study for SIDS endpoint
24.05.2002

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : MAC (NL)
Limit value : 22 mg/m3

Remark : Skin (all isomers).
22.03.2001

Type of limit : MAK (DE)
Limit value : 22 mg/m3
Short term exposure limit value
Limit value : 22 mg/m3
Time schedule :
Frequency : times

Remark : all isomers danger of cutaneous absorption
Source : TRGS 900 (DE)
Flag : Critical study for SIDS endpoint
24.05.2002

Type of limit : MAK (DE)
Limit value :

Remark : danger of cutaneous absorption
Mak list, canc. category 3A
27.05.2002 (2)

Type of limit : MAK (DE)
Limit value : 5 ml/m3
Short term exposure limit value
Limit value : 5 ml/m3
Time schedule :
Frequency : times

Remark : danger of cutaneous absorption
Source : TRGS 900 (DE)
Flag : Critical study for SIDS endpoint
24.05.2002

Type of limit : OES (UK)
Limit value : 22 mg/m3

Remark : Skin (all isomers).
Source : Synthetic Chemicals Ltd. Wolverhampton
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
16.05.1994

Type of limit : TLV (US)
Limit value : 5 other: ppm

Remark : Skin notation. Critical effects: dermatitis, irritation, CNS.
Flag : Critical study for SIDS endpoint
22.03.2001

Type of limit : TLV (US)
Limit value : 22 mg/m3

Remark : Skin notation. Critical effects: dermatitis, irritation, CNS.
Flag : Critical study for SIDS endpoint
22.03.2001

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 2 (water polluting)

24.05.2002

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung (DE)
Substance listed : yes
No. in Seveso directive : Appendix I, No. 2

24.05.2002

1.8.5 AIR POLLUTION

Classified by : TA-Luft (DE)
Labelled by :
Number : 3.1.7 (organic substances)
Class of danger : I

24.05.2002

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

Remark : Opmerkingen: Transportclassificering volgens RID/ADR: kl 6.1-27b / UN no. 2076
Source : B.V. CONSOLCO Amsterdam
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

06.03.1998

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered :
Date of search :

Remark : Toxicology: November 2002
Environmental aspects and ecotoxicology: January 2002
CAS number search in external and internal databases, e.g. HSDB, Aquire, Biosis, Embase, Toxline, Scisearch.

22.01.2003

1.13 REVIEWS

2.1 MELTING POINT

Value : 34.7 °C
Sublimation :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (3)

Value : 34.8 °C
Sublimation :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (4) (5)

Value : 35.3 °C
Sublimation :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (6)

Value : 35.5 °C
Sublimation :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Remark : SRC (EPI Suite v 3.10) recommended value
Flag : Critical study for SIDS endpoint
11.05.2004 (7) (8)

Value : ca. 34 °C
Sublimation :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported, but < 0.9 % of m-cresol

11.05.2004 (9)

2.2 BOILING POINT

Value : 201.9 °C at 1013 hPa
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Remark : SRC (EPI Suite v 3.10) recommended value
Flag : Critical study for SIDS endpoint
11.05.2004 (7)

Value : 201.9 °C at
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (3)

Value : 202 °C at
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (6) (4)

Value : ca. 202 °C at
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported, but < 0.9 % of m-cresol

11.05.2004 (9)

Value : 201.8 °C at 1013 hPa
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 179.4 °C at 267 hPa
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 140 °C at 133 hPa
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 117.7 °C at 53.3 hPa
Decomposition :

Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 102.3 °C at 26.7 hPa
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 88.6 °C at 13.3 hPa
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 76.5 °C at 6.58 hPa
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 53 °C at 1.32 hPa
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 85.7 °C at 13.3 hPa
Decomposition :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (5)

2.3 DENSITY

Type :
Value : 1.0178 g/cm³ at 20 °C
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Flag : Critical study for SIDS endpoint
11.05.2004 (5)

Type :
Value : 1.0341 g/cm³ at 20 °C
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (3) (8)

Type :
Value : 1.04 g/cm³ at 20 °C
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (4)

Type :
Value : 1.0185 g/cm³ at 40 °C
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (10)

Type :
Value : 1.039 g/cm³ at °C
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (6)

Type :
Value : ca. 1.034 g/cm³ at 20 °C
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported, but < 0.9 % of m-cresol

11.05.2004 (9)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : .053 hPa at 20 °C
Decomposition :
Method :
Year :
GLP : no data

Test substance : other TS: p-cresol, no purity reported

11.05.2004 (4)

Value : .1 hPa at 20 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (3)

Value : ca. .1 hPa at 20 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported, but < 0.9 % of m-cresol

11.05.2004 (9)

Value : .147 hPa at 25 °C
Decomposition :
Method : other (measured)
Year : 1989
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Remark : SRC (EPI Suite v 3.10) recommended value
Flag : Critical study for SIDS endpoint
11.05.2004 (11)

Value : .15 hPa at 25 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (4)

Value : .24 hPa at 30 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (3)

Value : 1.1 hPa at 50 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (3)

Value : ca. 1.1 hPa at 50 °C

Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported, but < 0.9 % of m-cresol

11.05.2004 (9)

Value : 1.3 hPa at 53 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (4)

Value : 6.58 hPa at 76.5 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 13.3 hPa at 85.7 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (5)

Value : 13.3 hPa at 88.6 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 26.7 hPa at 102.3 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 53.3 hPa at 117.7 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 133 hPa at 140 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : 267 hPa at 179.4 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

Value : ca. 1013 hPa at 202 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (8)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : 1.94 at °C
pH value :
Method : other (measured)
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Remark : experimental data, SRC (EPI Suite v 3.10) recommended value
Flag : Critical study for SIDS endpoint
11.05.2004 (12)

Partition coefficient : octanol-water
Log pow : = 1.94 at °C
pH value :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (4)

Partition coefficient : octanol-water
Log pow : 1.92 at °C
pH value :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

11.05.2004 (4)

Partition coefficient : octanol-water
Log pow : 1.92 - 1.99 at °C
pH value :
Method :
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Remark : 4 log Kow values in the range of 1.92 to 1.99 cited
11.05.2004 (13)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : 21.5 g/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: measured
Year : 1992
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Remark : SRC recommended value
Flag : Critical study for SIDS endpoint
11.05.2004 (14)

Solubility in : Water
Value : = 19.5 g/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: measured
Year : 1991
GLP : no data
Test substance : other TS: p-cresol, purity not noted

11.05.2004 (15)

Solubility in : Water
Value : ca. 21 g/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Deg. product :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, no purity reported, but < 0.9 % of m-cresol

11.05.2004 (9)

Solubility in : Water
Value : 24 g/l at 40 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, purity not noted

11.05.2004 (4)

Solubility in : Water
Value : 25 g/l at 50 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, purity not noted

11.05.2004 (8)

Solubility in : Water
Value : 50 g/l at 100 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: no data available
Year :
GLP : no data
Test substance : other TS: p-cresol, purity not noted

11.05.2004 (8)

Solubility in : Water
Value : 53 g/l at 100 °C

pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: no data available
Year	:	
GLP	:	no data
Test substance	:	other TS: p-cresol, purity not noted

11.05.2004 (4)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	86 °C
Type	:	closed cup
Method	:	other: DIN 51758
Year	:	
GLP	:	no data
Test substance	:	other TS: p-cresol, no purity reported, but according to Bayer MSDS < 0.9 % of m-cresol

11.05.2004 (9) (8) (6)

2.8 AUTO FLAMMABILITY

Value	:	558 °C at
Method	:	other: DIN 51794
Year	:	
GLP	:	no data
Test substance	:	other TS: p-cresol, no purity reported, but according to Bayer MSDS < 0.9 % of m-cresol
Remark	:	autoignition temperature

11.05.2004 (9) (6)

2.9 FLAMMABILITY

22.03.2001

2.10 EXPLOSIVE PROPERTIES

22.03.2001

2.11 OXIDIZING PROPERTIES

22.03.2001

2.12 DISSOCIATION CONSTANT

Acid-base constant : 10.2
Method : other: no data available
Year : 1987
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Remark : secondary citation
11.05.2004 (16)

Acid-base constant : 10.26
Method : other: measured and calculated
Year : 1968
GLP : no
Test substance : other TS: p-cresol, no purity reported

Method : Experimental data for cresols were taken from Kortuem G, Vogel W, and Andrussow K (1961) Dissociation Constants of Organic Acids in Aqueous Solution. Butterworths, Lon-don
Remark : For experimental data: Secondary literature
Result : Calculated result is pk = 10.32
Flag : Critical study for SIDS endpoint
11.05.2004 (17)

Acid-base constant : 10.70
Method : other: measured
Year : 1971
GLP : no
Test substance : other TS: m-cresol, no purity reported, but substance purified by distillation under reduced pressure

Method : Measured according to Bordwell FG and BD Cooper (1952) J. Am. Chem. Soc. 74, 1058
Remark : in 20 % water-ethanol (v/v) at 20 °C
11.05.2004 (18)

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Refraction index

Remark : Refraction index (nD): 1.5312 at 20 degrees C
11.05.2004 (10)

Memo : Refraction index

Remark : Refraction index (nD): 1.5395 at 20 degrees C
11.05.2004 (8)

Memo : Odor

Remark : Treshold odor concentration in water: 0.200 ppm
Treshold taste concentration in water: 0.002 ppm

11.05.2004 (19)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm³
Rate constant	:	.0000000000873 cm³/(molecule*sec)
Degradation	:	50 % after 8.2 hour(s)
Deg. product	:	
Method	:	other (calculated): with SRC-AOPWIN, v1.90
Year	:	2003
GLP	:	
Test substance	:	
Remark	:	The calculated half-life is based on a mean OH radical concentration of 0.5E+6 OH radicals/cm3 given during the 24 hours/day as suggested in the EU-Technical Guidance Document
Reliability	:	(2) valid with restrictions Generally accepted calculation method
Flag	:	Critical study for SIDS endpoint

10.05.2004 (20)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (measured)
Year	:	1995
GLP	:	no data
Test substance	:	other TS: p-cresol, purity > 99 %
Method	:	Determination of the temperature-dependency of the OH radical reaction under simulated tropospheric conditions
Remark	:	With a OH radical concentration of 1 000 000 molec cm-3 and a temperature of 301 K, the half-life is 3.8 h
Result	:	kOH = 2.21 x 10E-12 exp[(943+-449)/T] cm3 molec.-1 s-1 for a temperature range of 301-373 K
Test condition	:	test substance concentration 0.05-5 ppm reference compound (1,3-butadiene or o-cresol) 0.05-2.3 ppm radical source methylnitrite 1.5-11 ppm together with NOx 2-70 ppm
Reliability	:	(1) valid without restriction Test procedure in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

12.05.2004 (21)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (measured): critical review
Year	:	1994

GLP :
Test substance : other TS: p-cresol, no purity reported

Remark : With a OH radical concentration of 1 000 000 molec/cm3, the half-life is 4.1 h
Result : K[OH] = 4.7 [10E-11 cm3 molecule-1 s-1]
K[NO3] = 1.07 [10E-11 cm3 molecule-1 s-1]
K[O3] = 4.7 [10E-19 cm3 molecule-1 s-1]
Reliability : (1) valid without restriction
Critical review, evaluation of all available experimental data
Flag : Critical study for SIDS endpoint
07.05.2004 (22) (23) (24)

Type : water
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Conc. of substance : at 19 °C
Deg. product :
Method :
Year : 1987
GLP : no data
Test substance : other TS: p-cresol, no purity reported, but of highest commercial purity available

Method : Determination of rate constant for reaction with singlet oxigen
Result : INDIRECT PHOTOLYSIS:
- Rate constant: 1.1 E7 M-1 s-1 at pH 8.3
2.4 E7 M-1 s-1 at pH 8.8
1.6 E8 M-1 s-1 at pH 10
3.5 E8 M-1 s-1 at pH 11.5
- Half life t1/2: 500 h under noon summer sunlight (Switzerland) with 4E-14 M singlet oxygen

Test condition : - Test medium: aqueous solution containing 0.05M phosphate buffer and 5 mg/l rose bengal
- Test system: merry-go-round reactor
- Concentration of test substance: < 0.0001 M
Duration: < 2 hours
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail
Flag : Critical study for SIDS endpoint
10.05.2004 (16)

Type : air
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
INDIRECT PHOTOLYSIS
Sensitizer : OH
Conc. of sensitizer :
Rate constant : cm^3/(molecule*sec)
Degradation : % after
Deg. product :
Method : other (measured)
Year : 1990
GLP : no data
Test substance : other TS: p-cresol, purity > 99 % (obtained from Aldrich Chemical Company)

Method	:	smog chamber experiment with black light irradiation
Result	:	k[OH] = 4.84 +- 0.89 [10E-11 cm3 molecule-1 s-1]
Test condition	:	dry air pressure 735 Torr Temp. 296 +- 2 K irradiation time 4-20 min reference substance: propene OH radical concentration: (1-3) x 10E7 molecule/cm-3
Reliability	:	(1) valid without restriction Test procedure in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions

10.05.2004 (25)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	
Rate constant	:	cm^3/(molecule*sec)
Degradation	:	% after
Deg. product	:	
Method	:	
Year	:	1987
GLP	:	no data
Test substance	:	other TS: p-cresol, no purity reported

Method	:	I. Smog chamber experiment II. Inkrement method
Result	:	k[OH] = 44 [10E-12 cm3 molecule-1 s-1] both observed and calculated
Reliability	:	(1) valid without restriction Test procedure in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions

10.05.2004 (26)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	
Rate constant	:	cm^3/(molecule*sec)
Degradation	:	% after
Deg. product	:	
Method	:	other (measured)
Year	:	1978
GLP	:	no data
Test substance	:	other TS: p-cresol, no purity reported

Method	:	smog chamber Temp. 300 +-1 K reference substances: n-butane, neopentane initial TS concentration ca. 0.25 ppm for p-cresol OH radical concentration: (1-4) x10E6 molecule cm-3
Result	:	K[OH] = 52 +- 5 [10E-12 cm3 molecule-1 s-1]
Reliability	:	(1) valid without restriction

Test procedure in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions

10.05.2004 (27) (28)

Type : water
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product : not measured
Method : other (measured)
Year : 1995
GLP : no data
Test substance : other TS: p-cresol, purity commercial, vacuum distilled

Method : Determination of the photosensitized oxidation in water
- Merry-go-round photoreactor DEMA (Hans Mangels GmbH, Bornheim-roisdorf, Germany) Model 125
- Light source: 700 W Hanau TQ718 medium pressure mercury lamp, equipped with cut-off filter: lambda > 320 nm
- Temperature 25 °C
- Photon fluence density 1.7 mEinstein m-2 s-1 at 366 nm
- Chemical analysis by HPLC, quantification at 285 nm

Result : K = 0.0004 s-1
direct photolysis (in the absence of sensitizer) was negligible

Test condition : - Test system: merry-go-round photoreactor
- Concentration of test substance: 2.5 µM
- Concentration of sensitizer: humic acid (DOC = 1.65 mg/l)
- temperature: 25 degrees C

Reliability : (3) invalid
Quantification of environmental reaction rate not possible

10.05.2004 (29)

Type : water
Light source : Sun light
Light spectrum : 290 nm
Relative intensity : based on intensity of sunlight
Conc. of substance : 1 mg/l at °C
Deg. product :
Method : other (measured)
Year : 1978
GLP : no
Test substance : other TS: m-cresol, no purity reported by Choudry

Method : Determination of rate constants for photolysis in aqueous solution in the absence and presence of humic acids

Result : A photolysis halflife of 35 days was determined, while with addition of 9.5 ug/l humic acid the half-life was 3 days.

The authors report computer simulated estimated half-lives for different compartments (river: 200 d, eutrophic pond: > 400 d, eutrophic lake > 400 d, oligotrophic lake 100 d)

Test condition : Sunlight, in April (mostly overcast)
pure water, with and without humic acid (9.5 ug/ml)
tubes held in rack at 60 ° angle to the horizon

Reliability : (2) valid with restrictions
Basic data given

10.05.2004 (30) (31)

Type : water

Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Result	:	The rate constant of hydroxyl radicals reaction is 1.2 E10 1/M/sec
Reliability	:	(4) not assignable Secondary literature

02.10.2001 (32)

3.1.2 STABILITY IN WATER

Remark	:	Based on the chemical structure of the compound hydrolysis is not expected under temperature and pH values occuring in the environment.
Reliability	:	(2) valid with restrictions Expert judgement
Flag	:	Critical study for SIDS endpoint

09.01.2003

3.1.3 STABILITY IN SOIL

Type	:	laboratory
Radiolabel	:	
Concentration	:	
Soil temperature	:	°C
Soil humidity	:	
Soil classification	:	
Year	:	
Deg. product	:	
Method	:	
Year	:	1990
GLP	:	no
Test substance	:	other TS: p-cresol, no purity reported
Method	:	Bench-scale experiments with contaminated soil. Determination of passive evaporation and biodegradation of cresols
Result	:	passive evaporation half-life 4.2 - 4.8 weeks biodegradation: after 4 days below detection limit
Test condition	:	Passive evaporation: plastic petri plates (88x18 mm) placed on canopy-covered table. Temp. 10-17 degrees C, humidity 75% Shake-flask biodegradation test: 8-25 g soil mixed with 50 ml buffer solution; shaken for 4 days
Reliability	:	(3) invalid Methodological deficiencies

07.05.2004 (33)

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : volatility
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: measured
Year : 1987

Method : Data were taken from 2 sources
- Gaffney JS, Senum GI (1984) In: Newman L (ed.) Gas-Liquid Chemistry of Natural Waters. Brookhaven National Laboratory, Upton, NY, pp. 5-1 to 5-7
- Lind JA and Kok GLJ (1986) J. Geophys. Res. 91, 7889-7895

Result : Henry's law constant (25 degrees C):
H = 0.1 Pa.m3.mol-1
Reliability : (2) valid with restrictions
basic data given
Flag : Critical study for SIDS endpoint
10.05.2004 (34)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: batch equilibrium method, similar to OECD Guideline 106
Year : 1982

Remark : Koc determined for clay loam soil
Result : Koc = 48.66
Test condition : Soil: Brookston clay loam soil, collected from top 15 cm,
air-dried, 5.10% organic matter, pH 5.7
soil/solution ratio 1:10
TS concentrations 5, 10, 20, 30, 50 mg/l, deoxygenated by purging with N2
triplicate samples, temp. 20+-1 degrees C, incubation period 24 h
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with general accepted scientific standards; sufficient documentation
Flag : Critical study for SIDS endpoint
10.05.2004 (35)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: batch equilibrium method
Year : 1986

Remark : The authors presume that the high adsorption factors obtained in the study

for low OC soils could be attributed to H-bond interactions between phenolic hydroxyl and clay surfaces (clay-content in these soils: 68% and 86%).

This type of adsorption can't be applied to explain the adsorption phenomenon (correlation between OC-content and adsorption), which usually occures in standard soils.

Result : Koc = 3420 (Apison), 3350 (Fullerton), 115 (Dormont)
Test condition : 3 soils tested: Dormont (pH 4.2; OC 1.2%), Apison (pH 4.5; OC 0.11%), Fullerton (pH 4.4; OC 0.05%)
soil/water ratio 1:1 - 1:66
initial TS concentration 0.5 - 1.0 mg/l
incubation period 24 h
Reliability : (3) invalid
No standard soil was used in the test. Soils Apison and Fullerton have a very low OC-content.Suggested OC-content in OECD 106:0.6-3.5%; in 67/548/EEC C.18: >0.3%)).

10.05.2004 (36)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year :

Remark : the authors cite a log Koc of 2,70 (koc 501), but no details on the experiments are described nor the primary citation is given
Reliability : (4) not assignable
secondary literature, experimental details missing

15.01.2003 (37)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year :

Result : Neither Freundlich adsorption coefficients nor Koc values are reported in the article. The authors report the isotherms in graphic formate.
In the Chemfate database citation of this article Freundlich adsorption coefficients (K) are estimated from the isotherms at about 50 ppm: 0.50 E02 to 0.5 E01.
The corresponding Koc values can be calculated as 560 to 10000.
No explanation for the wide variety of the adsorpion coefficients is given.

Test condition : 5 soils were tested: Davidson (pH 6.4; OC 0.3%), Molokai (pH 6.2; 0.5%), Fanno (pH 7.0; OC 0.9%), Mohave (pH 7.8; OC 0.4%), Ava (pH 4.5; OC 0.4%)
200 ml deionized water were added to 10 g of soil
initial TS concentration 5 - 100 ppm
temperatur 22 °C
equilibration time 5 days
Reliability : (3) invalid

No standard soil was used in the test. The five soils have a very low OC-content (0.3-0.9 %).Suggested OC-content in OECD 106:0.6-3.5%; in 67/548/EEC C.18: >0.3%)).
The isotherms are reported in five graphs, but the logarithmic scale is not labeled correctly.

15.01.2003 (38) (39)

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level I
Year : 2001

Result : Calculated distribution between environmental compartments:
Air: 2.46 %
water: 96.26 %
soil: 0.66 %
bottom sediment: 0.62 %
suspended sediment: 0.001 %
biota: 0.0004 %

Test condition : data used in calculation
temperature (°C): 25
molar mass (g/mol): 108.14
vapor pressure (Pa): 14.7
water solubility (g/l): 21.5
log Kow: 1.94

volumes in unit world (m3)
air: 6 000 000 000
water: 7 000 000
soil: 45 000
sediment: 21 000
susp. sediment: 35
biota (fish): 7

Reliability : (2) valid with restrictions
Generally accepted calculation method
Flag : Critical study for SIDS endpoint
13.05.2003 (40)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : 100 mg/l related to Test substance
related to
Contact time :
Degradation : 80 - 95 (±) % after 40 day(s)
Result : readily biodegradable
Deg. product :
Method : other: comparable to OECD Guideline 301C
Year : 1981
GLP : no
Test substance : other TS: p-cresol, purity at least 99 % (obtained from Aldrich Chemical company)

Method : Initial sludge concentration 30 mg dw/l
reference compound aniline
Remark : Incubation period 20-40 days; no oxygen uptake curve given;
degradation of reference substance aniline >=60 % within 28 days
Result : The oxygen uptake curves are not reported. However, the authors state that all test compounds revealed the lag phase, biodegradation phase and the plateau region within a period of 10 days, indicating that the 10-day window criteria is met.
first order biodegradation constant (hr-1): ln k = -5.87
maximum specific substrate uptake rate per unit biomass km = 18.5 / day (Aniline 16.1, Phenol 16.9)
p-Cresol is slightly better biodegradable than phenol and aniline
Test condition : Inoculum /test organism
- Type of sludge: activated
- Source: municipal treatment plant, receiving predominantly domestic sewage
- Initial cell concentration: 30 mg/l
Test system
- Culturing apparatus: Sapromat
- Closed vessels used: yes
Initial test substance concentration: 100 mg/l
Duration of the test: 20-40 days
Test conditions
- Composition of synthetic medium: OECD
- Test temperature: 25 degrees C
Reference substance: aniline 100 mg/l
Reliability : (2) valid with restrictions
Study comparable to OECD Guideline 301C
Flag : Critical study for SIDS endpoint
11.05.2004 (41)

Type : aerobic
Inoculum : other: natural microorganism communities from water and sediment
Concentration : 200 µg/l related to Test substance
related to
Contact time :
Degradation : 50 - 100 (±) % after 43 hour(s)
Result :
Deg. product :
Method :
Year : 1983
GLP : no
Test substance : other TS: p-cresol, no purity reported [ring-U-14C] p-cresol

Method : Biodegradation in natural aquatic test systems:
1.shake-flasks with water, 2.shake flasks with water and sediment, 3.intact sediment-water cores (eco-cores)
3 sample sites in a river estuary
Result : First order half-lives:
water flasks: 9.5-43 h
sediment flasks: 5.9-11 h
eco-core: 3.0-16 h
Test condition : 1. shake flask tests with filtered water
2. shake flask tests with filtered water and 500 mg/l organic sediment (30-50% OC). Sediment collected from the top 5 cm of the sediment surface
3. Eco-core samples had an aerobic layer of detritus overlying anaerobic sediment.
All flasks incubated with radiolabelled TS and maintained at 18 degrees C in the dark
Analysis: water samples filtered and analysed by HPLC,

measurement of 14CO2 radioactivity
Reliability : (2) valid with restrictions
No standard procedure but in accordance with generally accepted scientific standards and described in sufficient detail
Flag : Critical study for SIDS endpoint
24.05.2004 (42)

Type : aerobic
Inoculum : activated sludge, industrial
Contact time :
Degradation : = 100 (±) % after 10 day(s)
Result : inherently biodegradable
Deg. product :
Method : OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year : 1990
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Result : 90 % degradation during the log-phase (8 days)
Test condition : Test substance conc. 50-400 mg/l DOC, 200-1000 mg/l COD
acclimatization phase 2 days
Reliability : (2) valid with restrictions
Guideline study, basic data given
Flag : Critical study for SIDS endpoint
24.05.2004 (43)

Type : aerobic
Inoculum : activated sludge, adapted
Concentration : 200 mg/l related to COD (Chemical Oxygen Demand)
related to
Contact time :
Degradation : = 96 (±) % after 5 day(s)
Result : inherently biodegradable
Deg. product :
Method : other: batch system (similar to OECD 302B "Zahn-Wellens-Test")
Year : 1976
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Method : - Test compound was sole source of carbon
- Inoculum density: 100 mg dry matter/l; gradual increase of TS concentration during 20 days adaptation period
- COD measured
- With volatile substances a test without inocculum was done to differentiate the actual biological degradation from the losses due to mere volatilization
Result : Initial degradation rate: 55.0 mg COD/g/h
Test condition : 20 +/-3 degree C; pH 7.2; mineral salts medium; dark; continuously stirred
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; basic data given
Flag : Critical study for SIDS endpoint
24.05.2004 (44)

Type : anaerobic
Inoculum : anaerobic sludge
Deg. product : yes
Method :

Year : 1981
GLP : no
Test substance : other TS: p-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Method : primary anaerobic sludge from 12 treatment plants receiving mainly domestic waste water were diluted to 10% in a mineral salts medium, test substance concentration 30 mg/l; secondary anaerobic sludge from 2 treatment plants diluted to 10% in a mineral salts medium, test substance 50 mg/l incubation for 8 weeks; triplicate samples
Result : primary sludges:
degradation ranged from 62 to 101% in 11 sludges (lag times for approx. 20% of theoretical CH4 production: 2-5 weeks; insufficient data for 1 sludge
secondary sludges:
degradation was 51% after 4 weeks lag-phase with the first sludge and 121% after 3 weeks lag-phase with the second (degradation related to theoretical methane and CO2 production)
Test condition : 35 degrees C, due to storage of sludges before incubation, lag phase of methanogenesis could be increased in some sludges
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag : Critical study for SIDS endpoint
07.05.2004 (45)

Type : anaerobic
Inoculum : anaerobic sludge
Concentration : 50 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time : 56 day(s)
Degradation : (±) % after
Result :
Deg. product : yes
Method :
Year : 1984
GLP : no
Test substance : other TS: p-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Method : primary and secondary anaerobic sewage sludge from 9 treatment plants diluted to 10% in a mineral salts medium; degradation measured as gas pressure increase
Remark : data have been published by the authors as a NTIS-study (previous data set)
Result : in 2 different secondary sludges >75% degradation
in 9 different primary sludges degradation 62-101%
Test condition : incubation for 8 w at 35 degrees C
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail
Flag : Critical study for SIDS endpoint
07.05.2004 (46)

Type : anaerobic
Inoculum : anaerobic sludge
Concentration : 50 mg/l related to DOC (Dissolved Organic Carbon) related to

Deg. product : yes
Method :
Year : 1988
GLP : no
Test substance : other TS: p-cresol, of highest purity available (obtained from Aldrich Chemical Co.)
Deg. products : 74-82-8 200-812-7 methane

Method : primary anaerobic digesting sludge receiving a mixture of domestic and industrial waste water
Result : lag time 7 days
net total gas production was 96 +/- 4.3 % of the theoretical production (CH4 + CO2)
Test condition : - medium 2-3 g dw/l sludge
- incubation for >= 60 d at 35 degrees C
- 3 replicates
- sterile controls for abiotic gas production
- gas production measured with hand-held pressure meter
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail
Flag : Critical study for SIDS endpoint
07.05.2004 (47) (48)

Type : aerobic
Inoculum : aerobic microorganisms
Contact time : 120 hour(s)
Degradation : (±) % after
Result :
Kinetic of testsubst. : 40 hour(s) ca. 50 %
70 hour(s) ca. 90 %
%
%
%
Deg. product : not measured
Method :
Year : 1982
GLP : no
Test substance : other TS: p-cresol, ring-U-14C-labelled

Method : Adaptation of natural microbial communities was measured in ecocore test systems filled with sediment and natural water collected at a river.
Parent compound disappearance and mineralization were monitored.
Remark : degradation values taken from a graphics
Result : Mineralization was rapid without a lag-phase. Pre-exposure did not accelerate degradation.
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
24.05.2004 (49)

Type : aerobic
Inoculum : other: marine bacteria
Deg. product : not measured
Method : other: batch culture study in seawater
Year : 1992
GLP : no
Test substance : other TS: p-cresol, purity >98%

Method : Seawater from California (USA) supplemented with 100, 500, and 1000 µg/l test substance. Analysis of subsamples with GC/MS
Result : t1/2 = 295 h (100 µg/l)
t1/2 = 215 h (500 µg/l)
t1/2 = 325 h (1000 µg/l)
Doubling time of population
85 h (100 µg/l)
40 h (500 µg/l)
31 h (1000 µg/l)
Test condition : Temp. 20+-2 degrees C
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

24.05.2004 (50)

Type : aerobic
Inoculum : other: mixed microbial cultures
Concentration : 1.6 mg/l related to Test substance
3.2 mg/l related to Test substance
Contact time : 8 day(s)
Degradation : (±) % after
Result :
Deg. product :
Method : other: APHA method (1980)
Year : 1988
GLP : no
Test substance : other TS: p-cresol, no purity reported

Method : BOD technique; determination of the degradation rate constant which is compared with those reported for natural waters
Result : Pseudo-first-order rate constants (1/h):
Degradation of p-cresol in BOD test solution 0.028
Degradation of p-cresol in 5 natural waters 0.025 - 0.106 (mean 0.063)
For comparison:
Degradation of phenol in BOD test solution 0.020
Degradation of phenol in 5 natural waters 0.046 - 0.110 (mean 0.075)
p-Cresol is nearly as biodegradable as phenol.
Test condition : 2.3 E8 cells/ml; 21 degrees C
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

10.05.2004 (51)

Type : aerobic
Inoculum : other: mixed microbial cultures
Concentration : 1.6 mg/l related to Test substance
3.2 mg/l related to Test substance
Deg. product :
Method : other: BOD technique
Year : 1989
GLP : no
Test substance : other TS: p-cresol, no purity reported

Method : study targets to determine the effect of inoculum density on biodegradation rate; BOD technique
Result : degradation rate was nearly independent on biomass concentration. First order rate constant 3.4 (+/- 0.24) x 10-1/day with 2.3

E4 cells/l and 4.0 (+/- 0.02) x 10-1/day with 2.3 E8 cells/l
Test condition : 21 +- 3 degrees C
5 inoculum concentrations between 2.3 E4 and 2.3 E8 cells/l
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (52)

Type : aerobic
Inoculum : other bacteria: natural aquatic microbial assemblages
Deg. product :
Method :
Year : 1986
GLP : no
Test substance : other TS: U-14C-labeled p-cresol

Method : Determination of degradation kinetics over a large concentration range
Tests performed in freshly collected water from a lake, a swamp surface, and seawater.
Result : Date Site TS Concentr.[µg/l] Vmax[µg/l/d]
June 1986 Lake 1-10000 11
Dec. 1986 Lake 1-100000 36
Febr. 1987 Lake 1-10000 1.3-176
Oct. 1986 Sea 1-500 0.06-0.8
Dec. 1986 Swamp 1-100000 40
Test condition : incubation at 25 degrees C
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (53)

Type : aerobic
Inoculum : other: groundwater microorganisms
Concentration : 2.1 mg/l related to Test substance
related to
Deg. product : no
Method :
Year : 1985
GLP : no
Test substance : other TS: p-cresol, no purity reported

Method : Degradation of TS in surficial groundwater
Result : Complete degradation within 5-8 days, lag phase 2 days
Test condition : pH 5.3; 20 degrees C
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
24.05.2004 (54)

Type : anaerobic
Inoculum : anaerobic sludge
Contact time :
Degradation : > 100 (±) % after 15 day(s)
Result : inherently biodegradable
Deg. product : yes
Method : other: Handbook
Year : 1983
GLP : no

Test substance : other TS: p-cresol, purity not noted
Deg. products : 74-82-8 200-812-7 methane

Remark : sensitivity of acid formers and methanogenic consortia examined
Result : Mineralization occurred after 15 days at a concentration of 100 ppm p-cresol. Duration of mineralization increased to 39 days at a concentration of 400 ppm p-cresol.
Test condition : TS concentrations: 200, 400, and 1000 mg/l incubation for 6 weeks at 37 degrees C
Reliability : (4) not assignable
No standard test procedure, but in accordance with generally accepted scientific standards, not relevant for purpose of HPV program

24.05.2004 (55)

Type : aerobic
Inoculum : other: acclimated mixed microbial culture
Concentration : .4 mg/l related to Test substance
3.2 mg/l related to Test substance
Contact time : 20 day(s)
Degradation : (±) % after
Result :
Deg. product :
Method : other: APHA 1980
Year : 1987
GLP : no
Test substance : other TS: p-cresol, no purity reported

Result : BOD (5 days) = 5.63 mmol O2/mmol TS
ThBOD = 8.50 mmol O2/mmol TS
Test condition : 21 +- 3 degrees C
Reliability : (4) not assignable
Documention insufficient for assessment

24.05.2004 (56)

Type : aerobic
Inoculum : other bacteria: Aufwuchs communitiy
Deg. product : not measured
Method :
Year : 1987
GLP : no
Test substance : other TS: p-cresol, purity at least 99 %

Method : Estimation of biotransformation kinetics in natural waters.
Aufwuchs colonized for 5 months on Teflon strips at 2 rivers and 2 ponds. Strips were returned to laboratory, and
fastened into a beaker containing autoclaved natural water.
Beakers spiked with 100 and 200 µg/l test substance at 20 degrees C. TS detected by HPLC.
Result : A great variability for the k values (for individual sample sites between -5.1 and -3388 h-1) was found. Mean values for the sites:
pond 1: k = -273.1 h-1
pond 2: k = -95.5 h-1
river 1: k = -1637.1 h-1
river 2: k = -70 h-1
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

11.05.2004 (57)

Type : aerobic

Inoculum : other bacteria: acclimatized mixed culture of pentachlorophenol-degrading bacteria
Concentration : 5 mg/l related to Test substance
related to
Contact time : 29 day(s)
Degradation : 90 (±) % after 36 hour(s)
Result :
Kinetic of testsubst. : 28 hour(s) = 50 %
36 hour(s) = 90 %
%
%
%
Deg. product :
Method : other: Die-away Test
Year : 1990
GLP : no
Test substance : other TS: p-cresol, gas chromatographic grade

Result : no lag phase
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail

24.05.2004 (58)

Type : anaerobic
Inoculum : other: anaerobic sludge of a wastewater treatment plant
Deg. product : no
Method :
Year : 1989
GLP : no
Test substance : other TS: p-cresol, no purity reported

Method : Simulation of anaerobic digestion of primary and secondary sludge; digesters fed with spiked sludge; analytical measurements in sludge feed, digester mixed liquor, and mixed-liquor centrate
Result : 6% of the TS were detected in waste water, 20% sorbed onto solids, and 74% were degraded
Test condition : sludge retention time 30 days; 35 +- 1 degrees C
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

11.05.2004 (59)

Type : anaerobic
Inoculum : other: anaerobic sludge from a municipal treatment plant
Deg. product :
Method : other: pilot plant study
Year : 1994
GLP :
Test substance : other TS: p-cresol, no purity reported

Method : Pilot scale anaerobic digester fed with sludge from a municipal treatment plant
Result : Overall removal 99.5%
Primary digester removal 96.6%
Secondary digester removal 85.7%
Secondary supernatant residual 0.1%
Secondary sludge residual 0.4%
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted

scientific standards and described in sufficient detail

07.05.2004 (60)

Type : anaerobic
Inoculum : anaerobic microorganisms
Concentration : 50 mg/l related to DOC (Dissolved Organic Carbon) related to
Deg. product : not measured
Method :
Year : 1995
GLP : no
Test substance : other TS: p-cresol, analytical grade
Deg. products : 74-82-8 200-812-7 methane

Method : Biodegradation under methanogenic conditions. Inoculi: anaerobically digested sludge from a treatment plant reveiving mainly domestic waste water, a freshwater swamp, and a marine sediment
Result : degradation 30-75% in sludge, >75% in swamp (lag time <5 weeks), 30-75% in sediment (lag time <10 weeks) resuts expressed as % of complete mineralization to CH4 and CO2
Test condition : incubation 56 days (slusge and swamp) resp. 96 days (sediment); 35 degrees C in the dark
Reliability : (2) valid with restrictions No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (61)

Type : anaerobic
Inoculum : anaerobic sludge
Concentration : 50 mg/l related to DOC (Dissolved Organic Carbon) related to
Deg. product : yes
Method :
Year : 1982
GLP : no
Test substance : other TS: p-cresol, purity > 95 %
Deg. products : 74-82-8 200-812-7 methane

Method : - Sludge from 2 municipal plants
- Methane production monitored
- HPLC to monitor dissapearance of substrate
Result : Mineralization (related to theoretical methane and CO2 production) was 51% after 4 weeks with the first sludge and 100 % after 3 weeks with the second. Experiment was also done with freshwater lake sediment but no degradation was observed within 29 weeks
Test condition : incubation at 35 degrees C in the dark, 10 % sludge inoculum, duplicate tests
Reliability : (2) valid with restrictions No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (62)

Type : anaerobic
Inoculum : other bacteria: acclimatized mixed culture of pentachlorophenol-degrading bacteria
Concentration : 5 mg/l related to Test substance related to

Contact time : 29 day(s)
Degradation : (±) % after
Result :
Kinetic of testsubst. : 144 hour(s) <= 10 %
166 hour(s) = 50 %
200 hour(s) = 90 %
%
%
Deg. product :
Method : other: Die-away Test
Year : 1990
GLP : no
Test substance : other TS: p-cresol, gas chromatographic grade

Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (58)

Type : anaerobic
Inoculum : anaerobic sludge
Concentration : 400 mg/l related to Test substance
800 mg/l related to Test substance
Deg. product : yes
Method :
Year : 1985
GLP : no
Test substance : other TS: p-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Method : Anaerobic batch study
Result : Complete metabolism was observed only after acclimation through repeated refeeding of substrate over a period of 5-8 months. The rates of substrate metabolism and gas production, however, was about equal in early (refed 3 or fewer times) and in acclimated (refed 4-8 times) cultures. After 35 days incubation the total gas production was 89% and the CH4 production 134% of the theoretical amount.
Test condition : 37 degrees C
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (63)

Type : anaerobic
Inoculum : other: anaerobic sludge, adapted
Concentration : 300 mg/l related to Test substance
related to
Contact time :
Degradation : 100 (±) % after 6 day(s)
Result :
Deg. product : yes
Method :
Year : 1986
GLP : no
Test substance : other TS: p-cresol, no purity reported (Aldrich Chemical Co.) (methyl 14C labelled from Pathfinder Lab.)
Deg. products : 74-82-8 200-812-7 methane

Result : Most of the methyl carbon of p-cresol (92 %) was oxidized to CO2.
Test condition : preincubation for 2-3 months

incubation for 20 d at 37 degrees C
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
12.05.2004 (64)

Type : anaerobic
Inoculum : other: municipal sewage sludge from primary anaerobic digesters
Concentration : 50 mg/l related to Test substance
related to
Contact time : 56 day(s)
Degradation : 100 (±) % after 21 day(s)
Result :
Deg. product :
Method :
Year : 1983
GLP : no
Test substance : other TS: p-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Result : substance disappeared completely after 3 weeks
net CH4 production >90% of theoretical value
no transformation products observed
Test condition : mineral salt medium with 10% sludge
Temp. 35 degrees C
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (65)

Type : anaerobic
Inoculum : other: phenol-enriched metanogenic culture
Concentration : 100 mg/l related to Test substance
related to
Contact time :
Degradation : ca. 100 (±) % after 192 hour(s)
Result :
Deg. product : yes
Method :
Year : 1988
GLP : no
Test substance : other TS: p-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Result : lag time 70 h, complete disappearance after 192 h, the CH4 production was 90% of the theoretical production
Test condition : nominal test concentrations p-cresol 50, 100, 150, 250, 300, 400, 500, and 700 mg/l + phenol 200 mg/l
incubation at 35 degrees C with continuous shaking
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (66)

Type : anaerobic
Inoculum : other: anoxic lake sediment
Concentration : .1 mg/l related to Test substance
.8 mg/l related to Test substance
Deg. product :

Method :
Year : 1982
GLP : no
Test substance : other TS: p-cresol, purity > 95 %

Result : after 29 weeks no significant CH4 or CO2 formation observed
Test condition : incubation at 20 degrees C in the dark with occasional shaking
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (62)

Type : anaerobic
Inoculum : other: aquifer from a river-groundwater infiltration site, adapted to m-xylene
Deg. product :
Method :
Year : 1987
GLP : no
Test substance : other TS: p-cresol, purity ar least 98 % (obtained from Fluka AG, Buchs, Switzerland)

Method : Laboratory aquifer column; analysis of influent and effluent by HPLC
Result : TS influent conc. 0.19 mM
TS effluentconc. <0.01 mM
Test condition : continuous flow, 30 degrees C, microorganisms adapted to m-xylene
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (67)

Type : anaerobic
Inoculum : other: shallow anaerobic alluvial sand aquifer
Deg. product : yes
Method :
Year : 1986
GLP : no
Test substance : other TS: p-cresol, no purity reported (obtained from Aldrich Chemical Co.)
Deg. products : p-hydroxybenzaldehyd
99-96-7 202-804-9 4-hydroxybenzoic acid

Method : 2 +sites: 1 methanogenic, 1 sulfate-reducing
both aquifers receive leachate from a municipal landfill
Result : lag time <10 days under sulfate-reducing and 46-90 days under methanogenic incubations, no data for complete degradation given. Degradation under sulfate reducing conditions postulated to stout with oxidation of methyl group
Test condition : test medium: 50 g [wet weight] of aquifer solids and 50 ml of groundwater
incubation at room temperature in the dark, quadruplicate samples, preincubation 5 days, addition of 150 to 200 µM test substance
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (68)

Type : anaerobic
Inoculum : other: undefined methanogenic consortia from river sediment

Concentration : 54 mg/l related to Test substance
related to
Deg. product : yes
Method :
Year : 1989
GLP : no
Test substance : other TS: p-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Method : black anoxic mud collected from a river inoculated in a mineral medium (10% w/v)
Result : non-acclimated consortia: turnover rate 3.00 µmol/day/g sediment dw (lag-phase 12 d)
acclimated consortia: turnover rate 6.00 µmol/day/g sediment dw (lag-phase 0 d, based on a 24 days incubation period), the CH4 production was 97% of the theoretically possible yield
Test condition : incubation at 28 degrees C in the dark
cultures were refed with 60 mg/l test substance every 2-4 w for a total of 18 months
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (69)

Type : anaerobic
Inoculum : other: unacclimated sediments
Concentration : 1 mmol/l related to Test substance
related to
Contact time :
Degradation : 100 (±) % after 30 day(s)
Result :
Deg. product : yes
Method :
Year : 1990
GLP : no
Test substance : other TS: p-cresol, no purity reported (obtained from Aldrich)
Deg. products : 123-08-0 204-599-1 4-hydroxybenzaldehyde
65-85-0 200-618-2 benzoic acid
74-82-8 200-812-7 methane
99-96-7 202-804-9 4-hydroxybenzoic acid

Method : Sediment samples from a freshwater pond; degradation tested under three reducing conditions: denitrifying, sulfidogenic, and methanogenic
Result : TS was completely utilized within 21 to 30 days in unacclimated sediment. p-Cresol degradation proceeded through p-hydroxybenzaldehyde and p-hydroxybenzoate under methanogenic and denitrifying conditions. Under methanogenic conditions, also dehydroxylation to benzoic acid took place
Test condition : 30 degrees C in the dark
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (70)

Type : anaerobic
Inoculum : other: acclimated sediments
Concentration : 1 mmol/l related to Test substance
related to
Contact time :
Degradation : 100 (±) % after 10 day(s)
Result :

Deg. product : yes
Method :
Year : 1990
GLP : no
Test substance : other TS: p-cresol, no purity reported (obtained from Aldrich)
Deg. products : 123-08-0 204-599-1 4-hydroxybenzaldehyde
65-85-0 200-618-2 benzoic acid
74-82-8 200-812-7 methane
99-96-7 202-804-9 4-hydroxybenzoic acid

Method : Sediment samples from a freshwater pond; degradation tested under three reducing conditions: denitrifying, sulfidogenic, and methanogenic
Result : TS was completely utilized within 6 to 10 days in acclimated sediment. p-Cresol degradation proceeded through p-hydroxybenzaldehyde and p-hydroxybenzoate under methanogenic and denitrifying conditions. Under methanogenic conditions, also dehydroxylation to benzoic acid took place
Test condition : - 30 degrees C in the dark
- head space gas in the methanogenogenic and sulfidogenic cultures: CO2/N2 (30 %/70 %)
- head space gas in the denitrifying cultures: argon
- cultures were acclimated to p-cresol by 2 - 3 feedings of p-cresol
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (70)

Type : aerobic
Inoculum : activated sludge, domestic, non-adapted
Concentration : 30 mg/l related to Test substance
100 mg/l related to Test substance
Contact time : 1.5 day(s)
Degradation : (±) % after
Result :
Kinetic of testsubst. : 2 day(s) = 100 %
%
%
%
%
Deg. product : yes
Method : other: Sapromat test
Year : 1972
GLP : no
Test substance : other TS: p-cresol, no purity reported

Reliability : (3) invalid
Insufficient documentation

07.05.2004 (71)

Type : aerobic
Inoculum : other: soil microorganisms
Contact time :
Degradation : 100 (±) % after 1 day(s)
Result :
Deg. product : no
Method :
Year : 1966
GLP : no
Test substance : other TS: p-cresol, no purity reported

Method : Inoculation in a 1% suspension of silt loam

TS analyzed photometrically
Reliability : (3) invalid
Unsuitable test system
24.05.2004 (72)

Type : anaerobic
Inoculum : other: microcosm containing aquifer and ground water
Concentration : 8 mg/l related to Test substance
related to
Deg. product : yes
Method :
Year : 1989
GLP : no data
Test substance : other TS: p-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Method : methanogenic conditions in a microcosm, presumably 10 °C
Result : lag time 100 days, disappearance after approx. 180 d (values taken from a graphics)
Reliability : (3) invalid
Insufficient documentation
24.05.2004 (73)

Type : aerobic
Inoculum : other: river water and sea water
Concentration : 10 mg/l related to Test substance
100 mg/l related to Test substance
Contact time : 3 day(s)
Degradation : 5 - 100 (±) % after 3 day(s)
Result :
Deg. product :
Method : other: cultivation method
Year : 1987
GLP :
Test substance : other TS: p-cresol, no purity reported in abstract

Result : The authors assume the compound to be easily biodegradable:
with 10 ppm: Biodegradation in river water = 100% (3 repl)
with 10 ppm: Biodegradation in sea water = 100% (3 repl)
with 100 ppm: Biodegradation in river water = 100% (1 repl)
with 100 ppm: Biodegradation in sea water = 5% (1 repl)
Reliability : (4) not assignable
Publication in Japanese, short abstract in English
24.05.2004 (74)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species : Oncorhynchus mykiss (Fish, fresh water)
Exposure period : 6 hour(s) at 11 °C
Concentration : 3.82 µg/l
Elimination : no
Method :
Year : 1985
GLP : no
Test substance : other TS: p-cresol, purity > 98 % (supplied by Pathfinder Laboratories, St. Louis)

Method : Determination of absorption rate across gills
Analytical measurements in inspired and expired water, calculation of gill uptake efficiency
Result : About 23% of the TS were taken up via the gills (value taken from a graphics)
Test condition : 1 fish per experiment
Reliability : (3) invalid
Only 1 fish tested, no BCF determined

07.05.2004 (75)

3.8 ADDITIONAL REMARKS

Memo : biodegradation under three different anaerobic (denitrifying, sulfidogenic, methanogenic) conditions

Method : biodegradation was studied with acclimated and unacclimated sedimet samples from a freshwater pond
Result : the proposed reaction pathway is: p-Cresol > p-hydroxybenzyl alcohol > p-hydroxybenzaldehyde > p-hydroxybenzoate for all three conditions. Under methanogenic conditions, p-hydroxybenzoate reacts to benzoate with subsequent ring fission. Under denitrifying and sulfidogenic conditions, p-hydroxybenzoate did not react to benzoate, immediate ring fission is postulated.
Test substance : other TS: p-cresol, no purity reported (Aldrich, Milwaukee, WI)
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.12.2002 (70)

Memo : biodegradation under anaerobic (sulfate-reducing) conditions

Method : acclimated aquifer slurries (alluvial sand) amended with either Na2MoO4, bromoethanesulfonic acid, or Na2SO4
HPLC measurements
Result : the proposed reaction pathway is: p-Cresol > p-hydroxybenzyl alcohol > p-hydroxybenzaldehyde > p-hydroxybenzoate
Test substance : other TS: p-cresol, no purity reported (obtained from Aldrich Chemical Co.)
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.12.2002 (68)

Memo : biodegradation under anaerobic (sulfate-reducing) conditions

Method : Ring-14C-labeled p-cresol incubated with bacteria enriched from the sulfate-reducing portion of an anoxic aquifer.
Periodical analysis of the enrichment by HPLC.
Result : the proposed reaction pathway is: p-Cresol > p-hydroxybenzyl alcohol > p-hydroxybenzaldehyde > p-hydroxybenzoic acid. The pathway diverges after p-hydroxybenzoic acid to form benzoic acid and phenol.
Test substance : Ring-14C-labeled p-cresol
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.12.2002 (76)

Memo	:	biodegradation pathway with activated sludge
Result	:	p-cresol is first hydroxylated to 4-methylcatechol and cleaved through meta-cleavage pathway.
Test substance	:	p-cresol, no purity reported in abstract
Reliability	:	(4) not assignable Publication in Japanese

12.05.2004 (77)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 16.5
EC50	:	= 16.5
Limit test	:	
Analytical monitoring	:	yes
Method	:	other
Year	:	1985
GLP	:	no
Test substance	:	other TS: p-cresol, purity at least 99 % (Aldrich Chemical Co.)
Method	:	Fish (28 d old; mean lenght: 20.9 mm; mean weight: 0.134 g) exposed in Lake Superior water; 5 TS concentrations in the range of 11.8 to 66.2 mg/l tested (plus control); number of dead fish recorded every 24 h; observations of fish behaviour and body morphology at regular intervals; TS analysis by GLC
Result	:	confidence limits (95%): LC50 = EC50 = 15.9 - 17.0 mg/l Affected fish lost schooling behaviour and swam near the tank surface. They were hyperactive and overreactive to external stimuli. They had increased respiration, convulsions, and rigid musculature. Some hemorrhaging was also apparent. They were deformed and lost equilibrium prior to death.
Test condition	:	24.1 degrees C; dissolved oxygen 7.0 mg/l; hardness 47.9 mg CaCO3/l; alkalinity 44.1 mg CaCO3/l; pH 7.79
Reliability	:	(1) valid without restriction Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

07.05.2004 (78)

Type	:	flow through
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 7.9
Limit test	:	
Analytical monitoring	:	yes
Method	:	EPA OPP 72-1
Year	:	1974
GLP	:	no data
Test substance	:	other TS: p-cresol, purity not noted
Remark	:	lethargic at 5.6 mg/l
Test condition	:	DILUTION WATER - Source: well water - Hardness: 707.3 mg CaCO3/l - Conductance: 1212.3 µmhos/cm at 25 degrees C TEST SYSTEM - Concentrations: 1:2 dilution series - Number of replicates: 2 - fish per replicate: 10

- Test temperature: 14 degrees C
- Dissolved oxygen: 6.5 mg/l (84.5% of saturation)
- pH: 8.1
- Photoperiod: 16 h light, 8 h dark

Reliability : (1) valid without restriction
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions

Flag : Critical study for SIDS endpoint
22.10.2001 (79)

Type : flow through
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 28.6
Limit test :
Analytical monitoring : yes
Method : EPA OPP 72-1
Year : 1974
GLP : no data
Test substance : other TS: p-cresol, purity not noted

Remark : Lethargic and loss of equilibrium at 22.7 mg/l
Test condition : DILUTION WATER
- Source: well water
- Hardness: 707.3 mg CaCO3/l
- Conductance: 1212.3 µmhos/cm at 25 degrees C

TEST SYSTEM
- Concentrations: 1:2 dilution series
- Number of replicates: 2
- fish per replicate: 10
- Test temperature: 14 degrees C
- Dissolved oxygen: 6.5 mg/l (84.5% of saturation)
- pH: 8.1
- Photoperiod: 16 h light, 8 h dark

Reliability : (1) valid without restriction
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions

Flag : Critical study for SIDS endpoint
22.10.2001 (79)

Type : static
Species : Salmo trutta (Fish, fresh water, marine)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 4.4
Limit test :
Analytical monitoring : no
Method :
Year : 1969
GLP : no
Test substance : other TS: p-cresol, purity of "practical grade"

Method : 10 acclimated fish exposed per concentration, 20 served as control
Result : LC50 (6 h) = 4.7 mg/l
LC50 (24 h) = 4.4 mg/l
LC50 (48 h) = 4.4 mg/l
Test condition : 12 degrees C; reconstituted water

Reliability	:	(2) valid with restrictions Study in accordance with generally accepted scientific standards and described in sufficient detail
Flag	:	Critical study for SIDS endpoint
07.05.2004		(80)
Type	:	static
Species	:	Salvelinus fontinalis (Fish, estuary, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 5.8
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	other TS: p-cresol, purity of "practical grade"
Method	:	10 acclimated fish exposed per concentration, 20 served as control
Result	:	LC50 (6 h) = 8.5 mg/l LC50 (24 h) = 6.3 mg/l LC50 (48 h) = 5.8 mg/l at concentrations of 6 to 20 mg/l, the approximate incidences of surfacing were 90% during the first 10 minutes
Test condition	:	12 degrees C; reconstituted water
Reliability	:	(2) valid with restrictions Study in accordance with generally accepted scientific standards and described in sufficient detail
Flag	:	Critical study for SIDS endpoint
07.05.2004		(80)
Type	:	static
Species	:	Cyprinus carpio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 13.3
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	other TS: p-cresol, purity of "practical grade"
Method	:	10 acclimated fish exposed per concentration, 20 served as control
Result	:	LC50 (24 h) = 22.0 mg/l LC50 (48 h) = 15.0 mg/l at concentrations of 15 to 23 mg/l, the approximate incidences of surfacing were 80% during the first 10 minutes
Test condition	:	12 degrees C; reconstituted water
Reliability	:	(2) valid with restrictions Study in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004		(80)
Type	:	static
Species	:	Ictalurus melas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 57.5

Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	other TS: p-cresol, purity of "practical grade"
Method	:	10 acclimated fish exposed per concentration, 20 served as control
Result	:	LC50 (24 h) = 120.0 mg/l LC50 (48 h) = 94.0 mg/l during the first 10 minutes the fish did not surface at any concentration
Test condition	:	12 degrees C; reconstituted water
Reliability	:	(2) valid with restrictions Study in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (80)

Type	:	static
Species	:	Ictalurus punctatus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 39.7
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	other TS: p-cresol, purity of "practical grade"
Method	:	10 acclimated fish exposed per concentration, 20 served as control
Result	:	LC50 (6 h) = 65.0 mg/l LC50 (24 h) = 58.0 mg/l LC50 (48 h) = 50.0 mg/l during the first 10 minutes the fish did not surface at any concentration
Test condition	:	12 degrees C; reconstituted water
Reliability	:	(2) valid with restrictions Study in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (80)

Type	:	static
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 7.1
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	other TS: p-cresol, purity of "practical grade"
Method	:	10 acclimated fish exposed per concentration, 20 served as control
Result	:	LC50 (24 h) = 7.9 mg/l LC50 (48 h) = 7.1 mg/l at concentrations of 14 to 16 mg/l, the approximate

incidences of surfacing were 30% during the first 10 minutes
Test condition : 12 degrees C; reconstituted water
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (80)

Type : static
Species : Oncorhynchus mykiss (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 7.4
Limit test :
Analytical monitoring : no
Method :
Year : 1969
GLP : no
Test substance : other TS: p-cresol, purity of "practical grade"

Method : 10 acclimated fish exposed per concentration, 20 served as control
Result : LC50 (6 h) = 11.4 mg/l
LC50 (24 h) = 9.2 mg/l
LC50 (48 h) = 8.4 mg/l
In an additional test under flow-through conditions, a concentration of 10 mg/l caused a total incapacitation of all tested 20 fish within 8.5 minutes
Test condition : 12 degrees C; reconstituted water
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (80)

Type : static
Species : Perca flavescens (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 10
Limit test :
Analytical monitoring : no
Method :
Year : 1969
GLP : no
Test substance : other TS: p-cresol, purity of "practical grade"

Method : 10 acclimated fish exposed per concentration, 20 served as control
Result : LC50 (6 h) = 19.5 mg/l
LC50 (24 h) = 12.3 mg/l
LC50 (24 h) = 10.0 mg/l
at concentrations of 12 to 18 mg/l, the approximate incidences of surfacing were 50% during the first 10 minutes
Test condition : 12 degrees C; reconstituted water
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (80)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)

Unit	:	mg/l
LC50	:	= 15.5
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	other TS: p-cresol, purity of "practical grade"
Method	:	10 acclimated fish exposed per concentration, 20 served as control
Result	:	LC50 (24 h) = 60.3 mg/l LC50 (48 h) = 50.8 mg/l at concentrations of 30 to 150 mg/l, the approximate incidences of surfacing were 30% during the first 10 minutes
Test condition	:	12 degrees C; reconstituted water
Reliability	:	(2) valid with restrictions Study in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (80)

Type	:	flow through
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 7.5
Limit test	:	
Analytical monitoring	:	yes
Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	other TS: p-cresol, purity not noted
Method	:	Bioassays were conducted at 0 (control), 10, 18, 32, 56, and 100% of the maximum test concentration. Ten fish were exposed at each concentration. The fish weighed between 1 and 4 g each. Bioassays were repeated 3 times. Chemicals were added to the water by a Hamilton Syringe pump to create the 100% concentration. Dilutions were done by a Mount-Brungs diluter. Each bioassay tank contained 14 liters of water and the flow per tank varied between tests from 21 to 111 ml/min, depending upon how much chemical was available. The tanks were not aerated, to reduce volatilization. The levels in water of most water-soluble test compounds were measured daily. The assay method was the measurement of the absorbance of the ultraviolet light by the test solutions in a quartz cell with a 1 cm path length. Concentrations were calculated by reference to standard curves of the chemical dissolved in the control tank water.
Reliability	:	(2) valid with restrictions Study in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (81)

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	
Limit test	:	
Analytical monitoring	:	no

Method	:	
Year	:	1984
GLP	:	no
Test substance	:	other TS: p-cresol, no purity reported
Method	:	Determination of sublethal endpoints with fish larvae
Result	:	concentrations up to 4.2 mg/l had no significant effect on larval survival or growth larval RNA, DNA and protein content, although reduced at 2.57 mg/l, was not significantly affected at any concentration
Test condition	:	Larval fish within 24 h of hatching, 25-35 per chamber medium: soft Lake Superior water 5 TS concentrations, range 0.4-4.2 mg/l
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; water chemistry data not reported

07.05.2004 (82)

Type	:	semistatic
Species	:	other: Lepidocephalichthys guntea (freshwater fish)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Limit test	:	
Analytical monitoring	:	no
Method	:	other: see test conditions
Year	:	1998
GLP	:	no
Test substance	:	other TS: p-cresol, analytical grade
Result	:	LC50 (24 h) = 21.0 (16.42 - 26.86) mg/l LC50 (48 h) = 18.0 (14.70 - 22.03) mg/l LC50 (72 h) = 16.0 (13.20 - 19.39) mg/l LC50 (96 h) = 14.0 (11.82 - 16.58) mg/l
Test condition	:	fish lenght 5.16 +- 0.38 cm, weight 1.46 +- 0.27 g 27-29 degrees C; pH 7.0-7.3; oxigen 7.0-7.2 mg/l; hardness 80-86 mg/l CaCO3 10 fish/concentration medium renewed daily
Reliability	:	(2) valid with restrictions Study in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (83)

Type	:	static
Species	:	Gadus morrhua (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
EC50	:	= 5
Limit test	:	
Analytical monitoring	:	yes
Method	:	
Year	:	1985
GLP	:	no
Test substance	:	other TS: p-cresol, purity > 98 % as determined by GC (obtained from Merck)
Method	:	Effect endpoints: death, pathology, inhibition of cleavage and differentiation, pigment defects
Result	:	parallel test with larvae (6 days after hatching) showed

pigment effects at 1 mg/l
Test condition : 5 degrees C
TS concentration stable during the test period
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (84)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 19
Limit test :
Analytical monitoring : no
Method :
Year : 1976
GLP : no
Test substance : other TS: p-cresol, no purity reported (obtained from Curtin Matheson Scientific Inc.)

Result : LC50 (1 h) = 30 mg/l
LC50 (24 h) = 26 mg/l
LC50 (48 h) = 21 mg/l
LC50 (72 h) = 21 mg/l
concentrations are nominal values
endpoint: complete immobilization, equated to death
O2 was =< 4 mg/l during the test
Test condition : Lake Superior Water; 18-22 degrees C
10 fish per concentration, fish 4-8 weeks old, length 1.1-3.1 cm
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (85)

Type : static
Species : Gambusia affinis (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 33 calculated
Limit test : no
Analytical monitoring : no
Method : other: see test conditions
Year : 2000
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Test condition : Test medium: dechlorinated one day old tap water, medium renewed daily.
3 replicates and control.
10 fish were exposed to each concentration from 30-40 mg/l.
Temperature: 25-27°C.
pH: 7.2-7.6.
Reliability : (2) valid with restrictions
Basic data given
07.05.2004 (86)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l

LC0	:	= 10
LC50	:	= 11
LC100	:	= 13
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Test Procedure of the Abwasserabgabengesetzentwurf (Deutscher Bundestag 1974)
Year	:	1982
GLP	:	no
Test substance	:	other TS: p-cresol, no purity reported
Reliability	:	(2) valid with restrictions Study in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (87)

Type	:	
Species	:	Leuciscus idus melanotus (Fish, fresh water)
Exposure period	:	4 hour(s)
Unit	:	
Method	:	other: DIN 38412 (20) (1981)
Year	:	1986
GLP	:	no
Test substance	:	other TS: p-cresol, no purity reported
Method	:	Endpoints: activity of the transaminases GOT and GPT
Result	:	acticity of both enzymes increased at concentrations of 5 mg/l, no change at 8 mg/l, increase at 10 and 12 mg/l
Reliability	:	(3) invalid No clear dose-response relationship

07.05.2004 (88)

Type	:	static
Species	:	other: Oreochromis mossambicus (freshwater fish)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	28
Limit test	:	no
Analytical monitoring	:	no
Method	:	other: see test conditions
Year	:	2001
GLP	:	no data
Test substance	:	other TS: p-cresol, no purity reported
Reliability	:	(3) invalid Insufficient documentation

07.05.2004 (89)

Type	:	
Species	:	Rutilus rutilus (Fish, fresh water)
Exposure period	:	24 hour(s)
Unit	:	mg/l
LC50	:	= 17
Method	:	
Year	:	1959
GLP	:	
Test substance	:	other TS: p-cresol, no purity reported
Remark	:	results from: Albersmayer & Erichsen: Z. Fisch. 8 (1/3), 29-66 (1959)
Reliability	:	(3) invalid

Study does not follow any guideline. No analytical monitoring, no information about the test substance. Further details are missing

07.05.2004 (90)

Type :
Species : Cyprinus carpio (Fish, fresh water)
Exposure period : 24 hour(s)
Unit : mg/l
LC50 : = 21
Method :
Year : 1959
GLP :
Test substance : other TS: p-cresol, no purity reported

Remark : results from: Albersmayer & Erichsen: Z. Fisch. 8 (1/3), 29-66 (1959)
Test condition : Temperature: 18°C
O2 Content in water: 8 mg/l
Number of animals per test vessel: 10
Effect concentrations for each replicate (LC50) were derived in a coordinate system and finally a mean value was calculated
Reliability : (3) invalid
Study does not follow any guideline. No analytical monitoring, no information about the test substance. Further details are missing

07.05.2004 (90)

Type :
Species : Tinca tinca (Fish, fresh water)
Exposure period : 24 hour(s)
Unit : mg/l
LC50 : = 16
Method :
Year : 1959
GLP :
Test substance : other TS: p-cresol, no purity reported

Remark : results from: Albersmayer & Erichsen: Z. Fisch. 8 (1/3), 29-66 (1959)
Reliability : (3) invalid
Study does not follow any guideline. No analytical monitoring, no information about the test substance. Further details are missing

07.05.2004 (90)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
LC50 : = 4
Limit test :
Analytical monitoring : no
Method : other: Mann, H., Fischtest mit Goldorfen zur vergleichenden Pruefung der akuten Toxizitaet von Wasserinhaltsstoffen und Abwaessern, Praktische Erfahrungen aus 3 Ringtesten, Z. f. Wasser- u. Abwasser-Forschung 9, 103-109 (1976)
Year : 1978
GLP : no
Test substance : other TS: p-cresol, no purity reported

Reliability : (4) not assignable
Secondary Literature

12.05.2004 (19)

Type	:	
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	8.6
Limit test	:	
Analytical monitoring	:	no data
Method	:	
Year	:	1977
GLP	:	no
Test substance	:	other TS: p-cresol, no data on purity available
Remark	:	Personal communication
Reliability	:	(4) not assignable Literature not available

07.05.2004 (91)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	flow through
Species	:	Daphnia pulicaria (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	= 22.7
Analytical monitoring	:	yes
Method	:	EPA OPP 72-2
Year	:	1974
GLP	:	no data
Test substance	:	other TS: p-cresol, purity not noted
Test condition	:	DILUTION AND TEST WATER - Source: well water - Hardness: 707.3 mg CaCO3/l - pH: 8.1 - Oxygen content: 6.5 mg/l (84.5% of saturation) - Conductance: 1212.3 µhos/cm at 25 degrees C - Number of replicates, individuals per replicate: 10 - Test temperature: 14 +- 1 degrees C - Photoperiod: 16 h light, 8 h dark
Reliability	:	(1) valid without restriction Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

22.10.2001 (79)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	= 2.5
EC50	:	= 4.9
Analytical monitoring	:	no
Method	:	other: DIN 38412 part 11
Year	:	1988
GLP	:	no
Test substance	:	other TS: p-cresol, no purity reported
Remark	:	nominal values

Test condition	:	TEST ORGANISMS - Strain: IRCHA strain - Age: 24 h DILUTION WATER - Source: synthetic fresh water - Hardness: 2.5 mmol/l Ca + Mg - Na/K ratio: 10:1 - pH: 8.0 +- 0.2 TEST SYSTEM - Number of replicates: 4 - individuals per replicate: 20 - Test temperature: 25 +- 1 degrees C
Reliability	:	(2) valid with restrictions Test procedure according to national guideline
Flag	:	Critical study for SIDS endpoint
07.05.2004		(92) (93)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC0	:	= 3.1
EC50	:	= 7.7
EC100	:	= 12.5
Analytical monitoring	:	no
Method	:	other: DIN 38412, part 11
Year	:	1989
GLP	:	no
Test substance	:	other TS: p-cresol, no purity reported

Result	:	EC0 (24 h) = 6.3 mg/l EC50 (24 h) = 14 mg/l EC100 (24 h) = 50 mg/l all values are nominal
Reliability	:	(2) valid with restrictions Test procedure according to national guideline
07.05.2004		(94)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	= 12.4
Analytical monitoring	:	no
Method	:	other: AFNOR (1974)
Year	:	1987
GLP	:	no data
Test substance	:	other TS: p-cresol, purity > 95 %

Remark	:	Effect: immobilisation
Result	:	Result is reported as 24-h IC50 "0.115 mmol/l" (which equals 12.4 mg/l)
Test condition	:	Reconstituted hard water, 200 mg/l CaCO3, pH 7.8-8.2 dissolved oxigen >25% of saturation
Reliability	:	(2) valid with restrictions Study in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004		(95) (96)

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)

Unit	:	mg/l
LC50	:	= 1.4
Analytical monitoring	:	no data
Method	:	other: according to the method described by Parkhurst et al. 1977
Year	:	1979
GLP	:	no
Test substance	:	other TS: p-cresol, no purity reported
Method	:	Parkhurst BR, Gehrs CW, Rubin IB (1977): Proceedings of ASTM 2nd Annual Symposium on Aquatic Toxicology, 122-130
Test condition	:	Daphnia magna used in the test were adults. 100-ml test beakers were filled with 80 ml test solution and 4 daphnia. All the tests were run in triplicate. Temperature during the test: 25 +/- 0.5°C 12h light/dark cycle Test solution was prepared with filtered spring water (pH 7.8 alkalinity mg/l, hardness 140 mg/l) Control beakers were used 48h-EC50 values were obtained by PROBIT
Test substance	:	The test substance was obtained from an effluent
Reliability	:	(3) invalid Methodological deficiencies (method description is in the other reference from the same author). Age of daphnias used in the test is not clearly specified: test daphnias were "adults" (in the OECD guideline a 24h-old daphnia is suggested); temperature during the test was 25°C (in the guideline is suggested: 18-22°C); 12 daphnia were used for each test concentration (in the guideline 40 daphnias are suggested)

07.05.2004 (97)

Type	:	static
Species	:	Daphnia sp. (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
TT	:	= 12
Analytical monitoring	:	no
Method	:	
Year	:	1959
GLP	:	no
Test substance	:	other TS: p-cresol, no purity reported
Method	:	test organisms were reared from daphnids collected in surface water
Test condition	:	river water, pH 7.5
Reliability	:	(3) invalid Experimental details missing. Study does not follow any guideline, concentrations tested were not reported, no information about the application method of the test substance is given. Neither O2/pH monitoring nor analytical monitoring were applied

07.05.2004 (98)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	other: biomass and growth
Exposure period	:	48 hour(s)
Unit	:	mg/l
Limit test	:	
Analytical monitoring	:	no
Method	:	other: DIN 38412, part 9
Year	:	1990

GLP : no
Test substance : other TS: p-cresol, no purity reported

Result : EbC10 = 2.3 mg/l
ErC10 = 4.6 mg/l
EbC50 = 7.8 mg/l
ErC50 = 21 mg/l
Test condition : 24 +- 1 degrees C; TS concentration 0.8 - 100 mg/l, dilution series 1:2
preliminary culture 10E5 cells/,l
irradiance 17.0 W/m2
Reliability : (2) valid with restrictions
Test procedure according to national guideline
Flag : Critical study for SIDS endpoint
07.05.2004 (99)

Species : Chlorella pyrenoidosa (Algae)
Endpoint : other: chlorophyll content
Exposure period : 72 hour(s)
Unit : mg/l
EC0 : < 50
EC50 : 116
EC100 : 250
Limit test : no
Analytical monitoring : no
Method :
Year : 1968
GLP : no
Test substance : other TS: p-cresol, no purity reported

Result : Complete destruction of chlorophyll at 1000 mg/l after 1 day.
EC50 was not reported in the study, but it can be taken from the graph
Test condition : TEST ORGANISMS
- Strain: Emerson strain
- Test temperature: 25 +- 1 degrees C
- pH: 7.0
- Photoperiod: continuous illumination
TEST PARAMETER: chlorophyll
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail
12.05.2004 (100)

Species : other aquatic plant: Potamogeton coloratus
Endpoint : other: photosynthesis
Exposure period : 21 day(s)
Unit : mg/l
NOEC : < .22
LOEC : = .22
EC50 : > 1.08
Limit test :
Analytical monitoring : no
Method :
Year : 1983
GLP : no
Test substance : other TS: p-cresol, no purity reported

Method : simulation of running water under summer climate conditions
Test condition : water hardness: 9° dH; conductivity: 300 µS; pH 7.8
Reliability : (3) invalid
Methodological deficiencies. Most test conditions not indicated. No

information about application mode, number of plants, controls, test concentrations, statistics, analytics.

07.05.2004 (101)

Species	:	other aquatic plant: Potamogeton crispus
Endpoint	:	other: photosynthesis
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	= 1.08
LOEC	:	> 1.08
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1983
GLP	:	no
Test substance	:	other TS: p-cresol, no purity reported
Method	:	simulation of running water under summer climate conditions
Test condition	:	water hardness: 9° dH; conductivity: 300 µS; pH 7.8
Reliability	:	(3) invalid Methodological deficiencies. Most test conditions not indicated. No information about application mode, number of plants, controls, test concentrations, statistics, analytics.

07.05.2004 (101)

Species	:	other aquatic plant: Potamogeton lucens
Endpoint	:	other: photosynthesis
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	< .22
LOEC	:	= .22
EC50	:	= .65
EC100	:	> 1.08
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1983
GLP	:	no
Test substance	:	other TS: p-cresol, no purity reported
Method	:	simulation of running water under summer climate conditions
Test condition	:	water hardness: 9° dH; conductivity: 300 µS; pH 7.8
Reliability	:	(3) invalid Methodological deficiencies. Most test conditions not indicated. No information about application mode, number of plants, controls, test concentrations, statistics, analytics.

07.05.2004 (101)

Species	:	Agmenellum quadruplicatum (Algae)
Endpoint	:	other: algal lawn assay (growth inhibition)
Exposure period	:	7 day(s)
Unit	:	
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1978
GLP	:	no
Test substance	:	other TS: p-cresol; purity not noted
Method	:	Algal lawns were initially seeded with 1.0 x 10e+5 cells/ml in 1% agarized (Difco 0140) medium. The test chemical was

absorbed onto antibiotic sensitivity disks (12.7 mm; Schleicher and Schuell, No. 740-E) which were placed directly onto the agar surface. The petri dish cultures were sealed with Scotch Tape and incubated in light from a tungsten lamp for 3-7 days at 28-30 degree C. Zone of inhibition was measured from the edge of the disk in mm. The radius of growth inhibition around the disk was judged visually and microscopically.

Result : Concentration (ug/disk) zone of inhibition (mm)

0	0
500	0
1000	8

0 indicates no inhibition,
36 indicates complete inhibition.
No inhibittion was noted with ethanol controls.

LC50 >1000 ug/disk

Reliability : (3) invalid
Unsuitable test system

24.10.2001 (102)

Species : Ankistrodesmus falcatus (Algae)
Endpoint : biomass
Exposure period : 10 day(s)
Unit : mg/l
MTL : = 100
Limit test :
Analytical monitoring : no
Method :
Year : 1976
GLP : no
Test substance : other TS: p-cresol, no purity reported

Method : described in: Denson & Bold, The University of Texas, Publication No. 6022, 72 (1960)
Remark : MTL = median tolerance limit
Result : sublethal concentration 100 mg/l
lethal concentration 500 mg/l
Reliability : (3) invalid
Experimental details missing

07.05.2004 (103)

Species : Scenedesmus quadricauda (Algae)
Endpoint : biomass
Exposure period : 96 hour(s)
Unit : mg/l
TT : = 6
Limit test :
Analytical monitoring : no
Method : other: Cell multiplication inhibition test
Year : 1959
GLP : no
Test substance : other TS: p-cresol, no purity reported

Remark : TT = toxicity treshold
Reliability : (3) invalid
Experimental details missing

07.05.2004 (98)

Species : other algae: Spirogyra sp.

Endpoint	:	other: Photosynthesis and Respiration
Exposure period	:	
Unit	:	
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1983
GLP	:	no
Test substance	:	other TS: p-cresol, purity at least 99 %
Method	:	Algae exposed in a open channel experimental stream set.
Result	:	The net oxygen production decreased from 0.084 (control) to 0.022 mg O2/mg DW with 8 mg/l TS. Respiration in the dark increased from -0.064 (control) to -0.182 O2/mg DW.
Reliability	:	(3) invalid Unsuitable test system

07.05.2004 (104)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	activated sludge of a predominantly domestic sewage
Exposure period	:	2 hour(s)
Unit	:	mg/l
IC50	:	= 439.5 calculated
Analytical monitoring	:	no
Method	:	other: similar to OECD Guideline 209
Year	:	1999
GLP	:	no
Test substance	:	other TS: p-cresol, analytical grade
Method	:	O2 measured with an optical scanning respirometer; endpoint: inhibition of respiration rate
Test condition	:	pH 7.0; temp. 20 degrees C
Reliability	:	(2) valid with restrictions Study in accordance with generally accepted scientific standards and described in sufficient detail
Flag	:	Critical study for SIDS endpoint

07.05.2004 (105)

Type	:	aquatic
Species	:	activated sludge of a predominantly domestic sewage
Exposure period	:	
Unit	:	mg/l
EC75	:	= 16.5
Analytical monitoring	:	no
Method	:	other: inhibition of nitrification process
Year	:	1966
GLP	:	no
Test substance	:	other TS: p-cresol, no purity reported
Method	:	Quantitative determination of the nitrification rate (1st step, NH4 to NO2) colorimetric measurement of the NO2/NO3 concentration; static test system pre-cleaned activated sludge in particle-free communal waste water (BOD5: 250 mg/l; NH4-N/l: 50-80 mg)
Remark	:	effect: inhibition of ammonia oxidation
Test condition	:	Exposure period: 2-4h; 25 degree C; pH 7.6-7.8
Reliability	:	(2) valid with restrictions

Study in accordance with generally accepted scientific standards and described in sufficient detail

Flag : Critical study for SIDS endpoint

07.05.2004 (106)

Type : Aquatic
Species : Nitrosomonas sp. (Bacteria)
Exposure period : 24 hour(s)
Unit : mg/l
IC50 : = 27
Analytical monitoring : No
Method : other: Inhibition of nitrification, comparable to ISO/DIS 9509
Year : 1991
GLP : No
Test substance : other TS: p-cresol, no purity reported

Method : culture obtained from mixed liquor of a treatment plant
Remark : Effect: inhibition of N-oxidation
Test condition : 25 degrees C
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (107)

Type : Aquatic
Species : Tetrahymena pyriformis (Protozoa)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 157
Analytical monitoring : No
Method : other: growth inhibition test
Year : 1996
GLP : No
Test substance : other TS: p-cresol, purity at least 95 %

Test condition : 27 +- 1 degrees C; pH 7.35
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (108)

Type : Aquatic
Species : Tetrahymena pyriformis (Protozoa)
Exposure period : 24 hour(s)
Unit : mg/l
LC100 : = 400
Analytical monitoring : No
Method :
Year : 1978
GLP : No
Test substance : other TS: p-cresol, no purity reported

Test condition : 28 degrees C
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (109)

Type : Aquatic
Species : Tetrahymena pyriformis (Protozoa)
Exposure period : 24 hour(s)

Unit : mg/l
EC50 : = 160
Analytical monitoring : No
Method :
Year : 1985
GLP : no data
Test substance : other TS: p-cresol; purity analytical grade

Method : The test was carried out under sterile conditions. T. pyriformis was pre-cultured at 30 degree C for 24 hours. The stock solution of chemical was added to the sterile medium to provide a constant ratio of 1.8 in 10 ml of 2% protose peptone. The solutions were then inoculated with 0.2 ml T. pyriformis and cultivated for 24 hours at 30 degree C without agitation. The number of cells were counted manually under a microscope (repeated 3 times) and with a Coulter Counter, Model Zb (repeated twice). Mean values were recorded with each method. Correlation coefficient between manual and Couter Counter was 0.998.
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

24.10.2001 (110)

Type : Aquatic
Species : other bacteria: Aerobic heterotrophs
Exposure period : 49 hour(s)
Unit : mg/l
IC50 : = 260
Analytical monitoring : No
Method :
Year : 1991
GLP : No
Test substance : other TS: p-cresol, no purity reported

Method : culture obtained from mixed liquor of a treatment plant
Remark : Effect: inhibition of respiration; prolonged incubation compared with ISO 8192
Test condition : 25 and 35 degrees C
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (107)

Type : Aquatic
Species : other bacteria: Methanogenic bacteria
Exposure period : 96 hour(s)
Unit : mg/l
IC50 : = 91
Analytical monitoring : No
Method : other: Owen, W.F.: Bioassay for Monitoring Biochemical Methane Potential and Anaerobic Toxicity. Water Res. 13, 485 (1979)
Year : 1991
GLP : No
Test substance : other TS: p-cresol, no purity reported

Remark : Effect: Inhibition of gas production (CH_4 + CO_2)
Test condition : 35 degrees C
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific

standards and described in sufficient detail
07.05.2004 (107)

Type : Aquatic
Species : Escherichia coli (Bacteria)
Exposure period :
Unit : mg/l
TT : > 1000
Analytical monitoring : No
Method :
Year : 1960
GLP : No
Test substance : other TS: p-cresol, no purity reported

Method : test organisms isolated from river water
endpoint: inhibition of glucose metabolism
Remark : TT = toxicity treshold; determined at 5% effect compared to control
Reliability : (3) invalid
Experimental details missing
07.05.2004 (111)

Type : Aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 15 minute(s)
Unit : mg/l
EC50 : = 1.6
Analytical monitoring : No
Method : other: Microtox assay
Year : 1987
GLP : No
Test substance : other TS: p-cresol, analytical grade (either from Merck or EGA Chemie)

Remark : Not enough information supplied for assessment of the test used (Test done according to Beckman manual). Although it is suggested that Microtox may lack reproducibility due to variations in bacterial cell suspensions [Bitton G (1983) Bacterial and Biochemical Tests for Assessing Chemical Toxicity in the Aquatic Environment: A Review. Crit Rev Environ Control 13: 51 -67], no information is supplied on the maintenance of the lyophilized bacteria, their age, duration of reconstitution and other important parameters.
Reliability : (3) invalid
Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.
07.05.2004 (112)

Type : Aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 30 minute(s)
Unit : mg/l
EC50 : = 1.5
Analytical monitoring : No
Method : other: Microtox assay
Year : 1981
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Remark : Inhibition of bioluminescence
Secondary literature; not enough information for assessment of cited result
Test condition : 20 degrees C
Reliability : (4) not assignable

Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

07.05.2004 (113)

Type	:	Aquatic
Species	:	other bacteria: gentechnologically constructed luminescent bacteria originating from wastewater treatment plant
Exposure period	:	30 minute(s)
Unit	:	mg/l
EC50	:	21 measured/nominal
Analytical monitoring	:	No
Method	:	other: Microtox assay
Year	:	1986
GLP	:	no data
Test substance	:	other TS: p-cresol, no purity reported
Remark	:	Inhibition of bioluminescence Modified microorganisms used which represent the metabolic potentials present in a wastewater treatment plant and some properties of a marine organism, but which are not identical to any known species in natural environments
Test condition	:	- Wastewater bacteria (Eschericia coli) which were obtained from a wastewater treatment plant - Bacteria obtained the luciferase operon of Vibrio fischeri by transfer from luminescent E. coli - Incubation at 20 °C - Result calculated from the difference of the luminescence between controls and test substance taking into account the light emissions at 0 and 20 °C
Reliability	:	(3) invalid Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

07.05.2004 (113)

Type	:	Aquatic
Species	:	Pseudomonas fluorescens (Bacteria)
Exposure period	:	
Unit	:	mg/l
TT	:	= 30
Analytical monitoring	:	No
Method	:	
Year	:	1960
GLP	:	No
Test substance	:	other TS: p-cresol, no purity reported
Remark	:	TT = toxicity treshold; determined at 5% effect compared to control endpoint: inhibition of glucose metabolism
Reliability	:	(3) invalid Experimental details missing

07.05.2004 (111)

Type	:	Aquatic
Species	:	other bacteria: Photobacterium (Vibrio) fischeri (marine)
Exposure period	:	5 minute(s)
Unit	:	mg/l
EC10	:	= 1.3
Analytical monitoring	:	No
Method	:	other: Microtox assay
Year	:	1981
GLP	:	No

Test substance : other TS: p-cresol, no purity reported

Remark : Although it is suggested that Microtox may lack reproducibility due to variations in bacterial cell suspensions [Bitton G (1983) Bacterial and Biochemical Tests for Assessing Chemical Toxicity in the Aquatic Environment: A Review. Crit Rev Environ Control 13: 51 -67], no information is supplied on the source of the lyophilized bacteria, their age, duration of reconstitution and other important parameters
Test condition : 15 degrees C
Reliability : (3) invalid
Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals

07.05.2004 (114)

Type : Aquatic
Species : other bacteria: Rhizobium melioti
Exposure period : 30 minute(s)
Unit : mg/l
IC50 : = 7.1 calculated
Analytical monitoring : No
Method :
Year : 1997
GLP : No
Test substance : other TS: p-cresol, no purity reported

Remark : endpoint: inhibition of reduction reaction of a dye (3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide; MTT)
Reliability : (3) invalid
unusual endpoint

07.05.2004 (115)

Type : Aquatic
Species : other bacteria: Pseudomonas Stamm Berlin 33/2
Exposure period :
Unit : mg/l
EC0 : = 80
Analytical monitoring : No
Method :
Year : 1982
GLP : No
Test substance : other TS: p-cresol, no purity reported

Remark : Effect endpoint: inhibition of cell multiplication
Reliability : (4) not assignable
Experimental details missing

12.05.2004 (87)

4.5.1 CHRONIC TOXICITY TO FISH

Species : Pimephales promelas (Fish, fresh water)
Endpoint : other: growth
Exposure period : 32 day(s)
Unit : mg/l
NOEC : 1.35
LOEC : 2.57
Analytical monitoring : no data
Method : other: Early life stage test
Year : 1984
GLP : No

Test substance	:	other TS: p-cresol, no purity reported
Test condition	:	- Delivery system: Flow-through test. - Dilution water: soft water from lake Superior. - Fluorescent lights provided 16h light per day. - Water chemistry data was recorded at the Environmental Research Laboratory, Duluth, MN. Recorded data can be required. - The test was begann with the egg-stage. - Fish were fed newly hatched brine shrimp ad libitum twice per day so that moderate accumulation occured. - Statistical analysis: effect on growth was examined by log-linear dose-response analysis; there was a control and five treatments with two replicates.The lowest effect concentration was determined by Dunnetts multiple range test. Regression analysis was performed. - Endpoint: effect on larval growth by measuring lenght or weight
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; water chemistry data not reported
Flag	:	Critical study for SIDS endpoint

07.05.2004 (82)

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species	:	Daphnia magna (Crustacea)
Endpoint	:	Mortality
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	1
Analytical monitoring	:	Yes
Method	:	other: preliminary guideline proposal of the German Umweltbundesamt, state 1984-01-01
Year	:	1988
GLP	:	no data
Test substance	:	other TS: p-cresol, no purity reported
Method	:	Determination of NOEC for reproduction rate, mortality and the time of the first appearance of offspring; 21d
Remark	:	- Only the ominal value for the most sensitive parameter is given. However no losses were reported to be greater than 20%. - Tested concentration range: 0.003-10 mg/l. - Most sensitive parameter was mortality: NOEC-nominal value = 1 mg/l
Test condition	:	TEST ORGANISMS - Strain: IRCHA strain - Age: 24 h DILUTION WATER - Source: synthetic fresh water - Hardness: 2.5 mmol/l Ca + Mg - Na/K ratio: 10:1 - pH: 8.0 +- 0.2 TEST SYSTEM - semistatic system - Number of replicates: 4 - individuals per replicate: 20 - Test temperature: 25 +- 1 degrees C H-values and oxygen-concentration were measured during the test in two tests-vessels per concentration level.The detected variation of these parameters had no negative influence on the organism.

Reliability : (2) valid with restrictions
Study comparable to national guideline
Flag : Critical study for SIDS endpoint
07.05.2004 (92) (93)

Species : other aquatic worm: Dugesia tigrina
Endpoint : other: mortality, reporduction and
Exposure period : 80 day(s)
Unit : mg/l
NOEC : 1
Analytical monitoring : No
Method : other: see test conditions
Year : 1987
GLP : No
Test substance : other TS: p-cresol, no purity reported

Method : Worms 18-24 days old, length 11-12 mm;
In each flask 10 test organisms (5 each cut into two parts); regeneration of the lacking parts occurred within 10 days; the worms were fed in the next 10 days and reached their original length 20 days after cutting; then animals cut again, altogether 4 times
Result : LC50 = 11.08 mg/l after 10 days
LC10 = 2.0 mg/l after 80 days (4 generations)
LC20 = 4.0 mg/l after 80 days (4 generations)
Test condition : 20 degrees C; medium according ISO/TC 147/SC 5/GT 3 N. 38
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
07.05.2004 (116)

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Species : Raphanus sativus (Dicotyledon)
Endpoint : other: germination and growth rate
Exposure period : 4 day(s)
Unit : g/l
Method :
Year : 1989
GLP : No
Test substance : other TS: p-cresol, special grade purity (obtained from Wako Pure Chemicals Industries, Ltd.)

Method : Seeds exposed to test compounds dissolved in distilled water; 3 replicated of 20 seeds
Result : Concentr. Germination rate% Growth rate%

g/l	1 day	4 days	Radicle	Hypocotyl
10	0	0		
1	0	0		
0.1	70	88.5	65.1	75.6

Test condition : 24 degrees C; 10 h light, 14 h dark
Reliability : (3) invalid
Experimental details missing. No control values for germination reported; effect values cannot be related to environmentally relevant conditions

07.05.2004 (117)

Species : Brassica rapa (Dicotyledon)
Endpoint : other: germination and growth rate
Exposure period : 4 day(s)
Unit : g/l
Method :
Year : 1989
GLP : No
Test substance : other TS: p-cresol, special grade purity (obtained from Wako Pure Chemicals Industries, Ltd.)

Method : seeds exposed to test compounds dissolved in distilled water; 3 replicated of 20 seeds
Result : Concentr. Germination rate% Growth rate%
g/l 1 day 4 days Radicle Hypocotyl

10 0 0
1 0 0
0.1 105.3 100.0 50.9 79.2
Test condition : 24 degrees C; 10 h light, 14 h dark
Reliability : (3) invalid
Experimental details missing. No control values for germination reported; effect values cannot be related to environmentally relevant conditions

07.05.2004 (117)

Species : Brassica campestris var. chinensis (Dicotyledon)
Endpoint : other: germination and growth rate
Exposure period : 4 day(s)
Unit : g/l
Method :
Year : 1989
GLP : No
Test substance : other TS: p-cresol, special grade purity (obtained from Wako Pure Chemicals Industries, Ltd.)

Method : seeds exposed to test compounds dissolved in distilled water; 3 replicated of 20 seeds
Result : Concentr. Germination rate% Growth rate%
g/l 1 day 4 days Radicle Hypocotyl

10 0 0
1 0 0
0.1 71.9 103.9 79.4 72.0
Test condition : 24 degrees C; 10 h light, 14 h dark
Reliability : (3) invalid
Experimental details missing. No control values for germination reported; effect values cannot be related to environmentally relevant conditions

07.05.2004 (117)

Species : Lactuca sativa (Dicotyledon)
Endpoint : emergence
Exposure period : 3 day(s)
Unit : mg/l
EC50 : 122
Method : other: Seed germination test
Year : 1978
GLP : No
Test substance : other TS: p-cresol, no purity reported

Method : As described by Reynolds 1975 (Characterization of osmotic restraints on

lettuce fruit germination. Ann. Bot. 39, 791-796) and 1977 (Comparative effects of aliphatic compounds on inhibition of lettuce fruit germination. Ann. Bot. 41, 637-648)
- Lettuce cultivar Great Lakes
- Germination temperature 30 °C

Result : Result was reported as "1.13 mmol/l" which equals 122 mg/l
Reliability : (2) valid with restrictions
Basic data given

07.05.2004 (118)

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

Species : other avian: Agelaius phoeniceus (red-winged blackbird)
Endpoint : mortality
Exposure period :
Unit : mg/kg bw
LD50oral : = 96
Method :
Year : 1983
GLP : no data
Test substance : other TS: p-cresol, no purity reported

Test condition : birds pre-conditioned to captivity for 2 to 6 weeks
dosed by gavage with solution in propylene glycol or by pellets resp. gelatine capsules
Reliability : (2) valid with restrictions
Unsuitable test system

07.05.2004 (119)

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

Memo : Sea urchin test

Remark : Strongylocentrotus droebachiensis (sea urchin):
static test, 5 degrees C
Determined effect endpoints: death, pathology, inhibition of cleavage and differentiation, pigment defects
EC50 (96 h): 5 mg/l
Test substance : other TS: p-cresol, purity > 98 % as determined by GC (obtained from Merck)
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

07.05.2004 (84)

Memo : Tree neoplasms

Remark	:	p-cresol (1.5% v/v) showed a toxicity rating from 3-4 (0 = no injury, 5 = complete kill within 14d) in tomato crown gall tumors incited by Agrobacterium tumefaciens
Test substance	:	other TS: p-cresol, no purity reported
Reliability	:	(3) invalid unusual endpoint

07.05.2004 (120)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo : In vitro
Type : Absorption
Species : other: human skin
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle : Water
Route of administration : dermal
Exposure time : 250 minute(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other: see freetext ME
Year : 1977
GLP : no data
Test substance : other TS: p-cresol, purity: reagent grade

Method : The permeability of p-Cresol was measured across 2.5 cm2 epidermal membranes from human abdominal skin. The membranes were supported in a glass cell and the amount of p-Cresol passing to the receptor vessel measured spectrophotometrically. Each test was conducted at least in duplicate and at 25 Degree Celsius
Result : The permeability coefficient of p-Cresol was 2.92 x10 (exp)-4 cm/min and the lag time for a 0.4%w/v solution was 16 min. The threshold concentration for damage i.e. the aqueous concentration at which the permeability coefficient began to increase was 8.85 %w/v.
Reliability : (2) valid with restrictions
in vitro investigation
Flag : Critical study for SIDS endpoint
06.02.2004 (121)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : Rabbit
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle : other: sodium hydroxycarbonate
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:

Toxic behaviour :
Deg. product :
Method : other: see freetext ME
Year : 1949
GLP : No
Test substance : other TS: p-cresol, not specified further

Method : 100-200 mg/kg bw was administered to rabbits (number and sex not mentioned) as single dose as solutions in bicarbonateby gavage. Urine was collected over a period of 24 -48 hours and the levels of free and conjugated cresol was estimated by the method of Folin O. and Ciocalteu V., J. biol. Chem. 73, 627 (1927). Metabolites were identified with the method described in Bray et al., Biochem J. 41, 212 (1947) and 43, 561 (1948)
Result : absorption and excretion:
Within 24 hours 65 % of the p-Cresol dose was excreted in the urine indicating that at least this amount was absorbed through the gastrointestinal tract and urinary excretion was the main route of elimination.
metabolism:
The principal metabolic pathway was conjugation with glucuronic and sulphuric acids: 15% of the dose were discovered as ethereal sulphate and 61% of the dose as ethereal glucuronide and 2% of the dose as free cresol. About 7 % of the dose was free hydroxybenzoic acid, about 3 % of the dose was conjugated hydroxybenzoic acid; conjugated dihydroxytoluene was only discovered in traces as 3,4-dihydroxytoluene.
Reliability : (2) valid with restrictions
no information on sex and number of rabbits used, no information on distribution in the tissue
Flag : Critical study for SIDS endpoint
06.02.2004 (122) (123)

In Vitro/in vivo : In vivo
Type : Distribution
Species : Dog
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : oral unspecified
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other: no data
Year : 1971
GLP : No
Test substance : other TS: p-cresol, not specified further

Result : Following oral exposure cresols in the body concentrate in the blood, liver, and brain initially, but soon become more widespread and appear in the lungs, kidneys and other unspecified organs (no further details given)
Reliability : (4) not assignable

secondary literature
Flag : Critical study for SIDS endpoint
06.02.2004 (124)

In Vitro/in vivo : In vivo
Type : Absorption
Species : Rat
Number of animals
Males :
Females :
Doses
Males :
Females : 10 mg/m3
Vehicle : other: air
Route of administration : inhalation
Exposure time : 4 hour(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other: female rats,concentr.: 10 mg/m3, 4 hrs daily for 100 d up to 4 months
Year : 1975
GLP : no data
Test substance : other TS: p-cresol, not specified further

Remark : female rats were exposed to 10 mg/m3 p-cresol 4 hours per day, daily for 100 d up to 4 months. p-Cresol reached a concentration of 20.7ug/g lung tissue; the neutral red sorption on day 3 resp d 39 was 150 % resp. 212 % of the control value as a marker for cytotoxicity. Full recovery did not occur.
Reliability : (2) valid with restrictions
information on absorption via lung, but study description suffer from deficiencies
Flag : Critical study for SIDS endpoint
06.02.2004 (125) (126)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : other: dogs and rabbits
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : oral unspecified
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :

Deg. product :

Remark : p- Cresol undergoes enterohepatic circulation when administered orally to dogs and rabbits.
Reliability : (2) valid with restrictions
16.01.2003 (127) (128)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : other
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :

Result : At physiological pH, the conjugated metabolites of phenolic compounds are ionized to a greatedr extent than the parent compound, which reduces the renal reabsorption and increases the elemination with the urine.
In addition to urinary excretion, cresols are excreted in the bile, but the most part undergoes enterohepatic circulation. There are known species differences in the specific conjugation reactions of cresol isomers. The relative amounts of glucuronide and sulfate conjugates therefore differ between species and also vary with the dose.
Reliability : (2) valid with restrictions
basic information
Flag : Critical study for SIDS endpoint
09.01.2003 (127) (129) (130) (131)

In Vitro/in vivo : In vivo
Type : Excretion
Species : human
Number of animals
Males : 22
Females : 10
Doses
Males :
Females :
Vehicle :
Method :
Year :
GLP :
Test substance : other TS: p-cresol, not specified further

Result : Daily excretion of p-Cresol was measured in the 24-hrs urine samples from ten healthy females and 22 healthy males. Mean urinary p-Cresol levels were 58.9 +/- 43.7 mg/d for males and 45.7+/-23.5 mg/d for females
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
06.02.2004 (132)

In Vitro/in vivo : In vivo
Type : Excretion
Species : human
Number of animals
Males : 6
Females : 4
Doses
Males :

Females :
Vehicle :
Method :
Year :
GLP :
Test substance : other TS: p-cresol, not specified further

Result : Daily excretion rates of p-cresol were measured on 24-hr urine collections from 4 healthy weman and 6 healthy men ages 21 to 46: women: 59.0 (35.0-75.0) mg/day; men: 46.8 (36.7-56.8) mg/day
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
06.02.2004 (133)

In Vitro/in vivo : In vitro
Type : Metabolism
Species : other: male rat liver slices
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle : other: DMSO
Method :
Year :
GLP :
Test substance : other TS: p-cresol, not specified further

Method : Precision-cut liver slices were prepared from male Sprague-Dawley rats and incubated in Krebs-Hepes buffer for up to 6 hours. Metabolism studies were carried out using 1mM concentration of p-cresol for a period of 1 hour and 1 mM glutathione was added. Supernatants from each slice were analyzed for glutathione conjugates directly by HPLC.
Result : In slices, p-cresol formed a glutathione conjugate at a rate of 2.31 nmol/h/slice which support evidence of formation of quinone methide as intermediate.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
06.02.2004 (134)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : human
Number of animals
Males : 5
Females : 5
Doses
Males :
Females :
Vehicle :

Remark : Urine was collected from 5 women and 5 men during a period of 24 hours who were eating self-selected diets. The 24 hours excretions of p-cresol were 59.7 mg/24 h and 73.9 mg/24 h for males and females, respectively.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
16.01.2003 (135)

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 1800 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	5
Vehicle	:	other: olive oil
Doses	:	1300 - 2700 mg/kg bw
Method	:	other: 5 rats/sex/dose, administration as a 10% solution in olive oil to non-fasted Wistar rats by gavage to give doses of 1000-2700 mg/kg bw, observation time was not reported, section was not performed
Year	:	1944
GLP	:	no data
Test substance	:	other TS: p-cresol, purity = 96-98%
Remark	:	Signs and symptoms of poisoning were similar to those caused by phenol which included muscle twitching, temperature and pulse and respiratory rate fluctuations, salivation and uncoordinated leg movements. There was 100% mortality at 2700 mg/kg bw; time of death not mentioned
Result	:	Dose (mg/kg) Mortality (%) 1300 20 1500 40 1800 30 2000 50 2200 70 2400 90 2700 100
Reliability	:	(2) valid with restrictions no guideline study: substance given as 10 % solution , description sufferes from deficiencies (e.g.: observation time not reported)
Flag	:	Critical study for SIDS endpoint

06.02.2004 (136)

Type	:	LD50
Value	:	775 - 1000 mg/kg bw
Species	:	mouse
Strain	:	ICR
Sex	:	male
Number of animals	:	5
Vehicle	:	other: corn oil
Doses	:	100 - 1000 mg/kg bw
Method	:	other: see freetext ME
Year	:	1989
GLP	:	no data
Test substance	:	other TS: p-cresol, purity: 99.8%
Method	:	The test article was administered by oral gavage at a volume of 5ml/kg. Pre-dosing weight of the animals was 28.0-34.8 grams. Dosing solutions were prepared just prior to dosing. All animals were examined after dosing and periodically throughout the seven day study for toxic effects and/or mortalities.
Remark	:	Quality Assurance statement signed; Range-finding study for mouse dominant lethal assay.
Result	:	5 minutes of dosing, one animal at 775 mg/kg and one at 1000 mg/kg were exhibiting clonic convulsions and labored breathing. All other animals were languid within 5 minutes

of dosing but resumed normal activity within 10 minutes. All surviving animals appeared normal and helthy on the eventh day after dosing.
Summary of Mortalities:

Treatment	Observation
100 mg/kg	0/5
325 mg/kg	0/5
550 mg/kg	0/5
775 mg/kg	1/5
1000 mg/kg	3/5

Reliability : (2) valid with restrictions
dose range finding study
Flag : Critical study for SIDS endpoint
06.02.2004 (137)

Type : LD50
Value : = 1460 mg/kg bw
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Method : other
Year :
GLP : no data
Test substance : other TS: purity not noted

Remark : p-Cresol was administered as a 10% solution in oil. The original data are in Russian and no further experimental details are available from the citing review (IPCS, 1993).
Reliability : (4) not assignable
seondary literature
06.09.2002 (129) (138)

Type : LD50
Value : = 344 mg/kg bw
Species : mouse
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Method : other
Year : 1976
GLP : no data
Test substance : other TS: purity not noted

Remark : p-Cresol was administered as a 10% solution in oil. The original data are in Russian and no further experimental details are available from the citing review (IPCS, 1993).
Reliability : (4) not assignable
secondary literature
06.01.2003 (129) (138)

Type : LD0
Value : = 420 mg/kg bw
Species : rabbit
Strain :
Sex :
Number of animals :

Vehicle	:	
Doses	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	other TS: 96-98% pure
Remark	:	p-Cresol was administered as a 20% aqueous emulsion to non-fasted albino rabbits by stomach tube to give doses of 280-1400 mg/kg bw and the time until death was monitored. According to the methods section, equal numbers of males and females were employed and, in the results section, one animal/dose was tested. Presumably this is one rabbit/sex/dose but this is unclear in the report. The total observation period was not reported. Signs and symptoms of poisoning were similar to those caused by phenol which included muscle twitching, temperature and pulse and respiratory rate fluctuations, salivation, convulsions, lethargy and coma. Animals survived doses of up to 420 mg/kg bw and the times until death at doses of 620, 940 and 1400 mg/kg bw were 4, 12 and 2hr respectively.
Reliability	:	(4) not assignable documentation insufficient for assessment

06.01.2003 (136)

Type	:	LD50
Value	:	= 207 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	male
Number of animals	:	5
Vehicle	:	other: none
Doses	:	100, 147, 215, 316 mg/kg bw
Method	:	other: 5 rats/dose group, 4 doses, undiluted liquid, time of recovery: up to 14 d
Year	:	1969
GLP	:	no data
Test substance	:	other TS: p-cresol, M.P.: 36 C; B.P.: 202 C
Remark	:	Doses and mortality: 100 mg/kg bw: 0/5; 147 mg/kg bw: 0/5; 215 mg/kg bw: 3/5; 316 mg/kg bw: 5/5 Signs of intoxication: hypoactivity, tremors, lacrimation, dyspnea, hemorrhagic rhinitis, convulsions, prostration, death Necropsy of the rats that died revealed gastrointestinal inflammation and haemorrhage and hyperaemia of the lungs, liver and kidney. Survivors showed only gastrointestinal tract inflammation.
Reliability	:	(2) valid with restrictions No information about strain used, GLP
Flag	:	Critical study for SIDS endpoint

06.02.2004 (139)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	> .71 mg/l
Species	:	rat

Strain	:	no data
Sex	:	male
Number of animals	:	6
Vehicle	:	other: air
Doses	:	
Exposure time	:	1 hour(s)
Method	:	other: 6 rats exposed to 0.71 mg/l for 1 hr, room temperature, up to 14 d post exposure observation, gross necropsy
Year	:	1969
GLP	:	no
Test substance	:	other TS: p-cresol, purity not noted, M.P.:36 C, B.P.: 202 C
Result	:	Mortality: 0/6; signs of intoxication: none; gross autopsy: no significant findings
Reliability	:	(2) valid with restrictions no guideline study: 1 hr exposure time
Flag	:	Critical study for SIDS endpoint

06.02.2004 (139)

Type	:	other
Value	:	= .029 mg/l
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	other: aerosol exdosure; no further data
Year	:	
GLP	:	no data
Test substance	:	other TS: p-cresol, purity not noted
Remark	:	The mean lethal concentration of p-cresol in rats was measured. The original data are unpublished and no further experimental details are available from the citing review (IPCS, 1993).
Result	:	Clinical signs of toxicity included irritation of mucous membranes, neuromuscular excitiation and convulsions; hematuria at very high concentrations (no further information)
Reliability	:	(2) valid with restrictions Secondary citation from peer-reviewed data source
Flag	:	Critical study for SIDS endpoint

04.02.2004 (125)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	= 300 mg/kg bw
Species	:	rabbit
Strain	:	
Sex	:	female
Number of animals	:	3
Vehicle	:	other: undiluted
Doses	:	130 - 910 mg/kg bw
Method	:	other: see freetext ME
Year	:	1977
GLP	:	no data
Test substance	:	other TS: p-cresol, not specified further

Method	:	The method used was essentially that of Smyth et al. 1962 (Am. Ind. Hyg. Ass. J. 23, 95-107) except three females/dose were tested 24 hr occlusive exposure to the neat material was followed by a 14-day observation period. the most probable LD50 value was determined by the method of Thompson 1947 (Bact. Rev.11, 115-145)of moving averages. Clinical signs and purity of the Ts are not reported.
Reliability	:	(2) valid with restrictions no guideline study: clinical signs and purity of Ts are not reported
Flag	:	Critical study for SIDS endpoint
06.02.2004		(140)

Type	:	LD50
Value	:	= 750 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	other TS: p-cresol, purity not noted
Remark	:	The dermal LD50 value was measured in rats. No further experimental details are available from the citing reference (IPCS, 1995).
Reliability	:	(4) not assignable secondary citation
13.12.2002		(129) (138) (141)

Type	:	LD50
Value	:	ca. 300 mg/kg bw
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	5
Vehicle	:	other: none
Doses	:	
Method	:	other: 5 rabbits/dose, 4 doses, exposure time not mentioned, up to 14 d observation time, gross autopsy
Year	:	1969
GLP	:	no
Test substance	:	other TS: p-cresol, purity not noted; M.P.: 36 C; B.P.: 202 C
Remark	:	doses and mortality: 215mg/kg bw: 1/5; 316 mg/kg bw: 3/5; 464 mg/Kg bw: 4/5; 681 mg/kg bw: 5/5 signs of intoxication from 4-12 hrs post appl.: tremor, salivation sedation, death dermal irritation: severe subdermal hemorrhaging, severe erythema gross autopsy: survivors: no significant findings; decedents: inflammation of kidneys
Reliability	:	(2) valid with restrictions no information about strain used and no information on GLP
Flag	:	Critical study for SIDS endpoint
06.02.2004		(139)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	other
Value	:	= 110 mg/kg bw
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	no data
Remark	:	p-Cresol, dissolved in 0.9% saline, was administered to anaesthetized albino Sheffield mice by intraperitoneal injection. The dose inducing convulsions in 50% of the mice (CD50) was measured; the endpoint being taken as myoclonic jerks of limbs and tails. The intraperitoneal dose inducing convulsions in 50% of a group of six male mice (CD50) was 1.02 (95% CI 0.68-1.54) mM/kg bw (110 (95% CI 74-167) mg/kg bw).

22.03.2001 (142)

Type	:	LC50
Value	:	= 150 mg/kg bw
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	s.c.
Exposure time	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	no data
Remark	:	Mice received a single subcutaneous injection of p-cresol. No further experimental details are available in the citing reference (Sternitzke et al. 1992).

22.03.2001 (143) (144)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	
PDII	:	
Result	:	corrosive
Classification	:	
Method	:	other: see freetext ME

Year : 1977
GLP : no data
Test substance : other TS: p-cresol, not specified further

Method : TS applied to the clipped backs or flanks of the rabbits (no data whether the test substance was moistened). The material was covered by a surgical gauze two layers thick, gauze patches were held in place with strips of Elastoplast tape for 4 hours. After 4 hrs the patches were carefully removed and the test areas were evaluated for visible tissue destruction.
evaluation criterias:
When visible tissue destruction occurred in at least 2/6 rabbits, the test materials were classified as corrosive (no further details given).
Reliability : (2) valid with restrictions
description of the method suffers from deficiencies
Flag : Critical study for SIDS endpoint
06.02.2004 (140)

Species : rabbit
Concentration : undiluted
Exposure : no data
Exposure time : no data
Number of animals : 6
Vehicle :
PDII :
Result : highly irritating
Classification :
Method : other: 0.5 ml undiluted TS was applied to the intact and abraded skin, time of observation: 24 and 72 hrs.
Year : 1969
GLP : no data
Test substance : other TS: p-cresol, M.P.: 36 C; B.P.: 202 C

Result : intact skin: erythema: 24 hr: Score 4 in 6/6
72 hr: Score 4 in 6/6
edema: 24 hr: Score 4 in 6/6
72 hr: Score 4 in 6/6
abraded skin: erythema: 24 hr: Score 4 in 6/6
72 hr: Score 4 in 6/6
edema: 24 hr: Score 4 in 6/6
72 hr: Score 4 in 6/6
no tissue destruction and /or necrosis reported

Summary: irritation score: 8.00/8.00
Reliability : (2) valid with restrictions
limited documentation; no information on exposure time
Flag : Critical study for SIDS endpoint
06.02.2004 (139)

5.2.2 EYE IRRITATION

Species :
Concentration :
Dose :
Exposure time :
Comment :
Number of animals :
Vehicle :
Result : highly irritating
Classification :
Method : other

Year	:	
GLP	:	no data
Test substance	:	no data
Remark	:	The individual cresol isomers cause severe irritation when applied directly to the cornea. Mice exposed to high atmospheric concentrations of "cresylic acid vapours" suffered eye irritation. The original data for the former effect are unpublished and available from the US EPA Freedom of Information Office. No further details are available in the citing reviews. The latter findings were reported in a 1941 study using Shell cresylic acids; apparently not cresols themselves (Campbell, 1941).
Reliability	:	(4) not assignable Review

13.12.2002 (145) (146) (147) (129)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	unspecified
Comment	:	
Number of animals	:	6
Vehicle	:	
Result	:	highly irritating
Classification	:	
Method	:	other: 0.1 ml undiluted TS, time of reading: 24, 48, 72 hrs
Year	:	1969
GLP	:	no data
Test substance	:	other TS: p-cresol, M.P.: 36 C, B.P.: 202 C
Remark	:	24 hours: cornea, iris, conjunctivae: 84.7/110 (mean score) mean score for cornea: 60; mean score for iris: 10; mean score for conjunctivae: 14.7) 48 hours: cornea, iris, conjunctivae: 89.7/110 (mean score) mean score for cornea: 63.3, mean score for iris: 10, mean score for conjunctivae: 16.3) 72 hours: cornea, iris, conjunctivae: 93.0/110 (mean score) mean score for cornea: 66.6, mean score for iris: 10; mean score for conjunctivae: 16.3) summary: irritation score: 93.0/110
Reliability	:	(2) valid with restrictions no information on GLP, strain used
Flag	:	Critical study for SIDS endpoint

06.02.2004 (139)

5.3 SENSITIZATION

Type	:	other: maximization test
Species	:	human
Number of animals	:	
Vehicle	:	petrolatum
Result	:	not sensitizing
Classification	:	
Method	:	other: see freetext ME
Year	:	1966
GLP	:	no data
Test substance	:	other TS: p-cresol, purity not noted
Method	:	A maximization test was conducted on 25 volunteers using a

4% concentration of p-cresol in petrolatum. The maximization test involves an induction phase of five consecutive 48-hr covered patch tests, sometimes separated by 24-hr periods of treatment with a mild irritant, followed 10-14 days later by a 48-hr challenge patch using the same concentration (see: Kligman AM (1966) The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers, J. invest. Derm. 47, 393)

Result : There were no sensitization reactions in any of the volunteers.
Reliability : (2) valid with restrictions
cited in monograph of a peer-reviewed international journal;
Flag : Critical study for SIDS endpoint
08.01.2003 (148)

Type : other: modified Draize test
Species : guinea pig
Concentration : 1st: Induction .1 % intracutaneous
2nd: Challenge 10 % intracutaneous
3rd: Challenge 10 % other: topical application
Number of animals : 10
Vehicle : no data
Result : not sensitizing
Classification :
Method : other: see freetext ME
Year : 1978
GLP : no data
Test substance : other TS: p-cresol, not specified further

Method : 10 guinea pigs (4 males and 6 females or vice versa). Both flanks of each guinea pig were shaved, intradermal injections or topical applications were performed without occlusion.
Primary irritation tests were performed to determine the suitable concentrations.
METHOD:
Each animal was injected intradermally with 0.1 ml of TS at 2.5 times the determined injection challenge concentration (ICC) of 0.1 % at 4 sites which overlie the 2 auxilliary and the 2 inguinal lymph nodes. 14 days later each animal was challenged intradermally in one flank and topically in the other with 0.1 ml aliquots of TS at the respective ICC and application challenge concentration (ACC; 10%). 24 hours later the reactions were scored. To confirm the result, the procedure was repeated including a confirmatory challenge with controls.
Reliability : (2) valid with restrictions
small number of animals tested; reactions should have been scored additionally at 48 hours
Flag : Critical study for SIDS endpoint
06.02.2004 (149)

5.4 REPEATED DOSE TOXICITY

Type : Sub-acute
Species : rat
Sex : male/female
Strain : other: Fischer 344/N
Route of admin. : oral feed
Exposure period : 28 days
Frequency of treatm. : continuously in diet
Post exposure period : none
Doses : 0, 300, 1000, 3000, 10000, 30000 ppm (see freetext RM)
Control group : yes, concurrent no treatment

NOAEL : 1000 ppm
Method : other: see freetext ME
Year : 1991
GLP : yes
Test substance : other TS: p-cresol, purity > 98%

Method : SIZE OF STUDY GROUP:
5 male and 5 female rat per group
TIME HELD BEFORE STUDY: 13-15 days
METHOD OF ANIMAL DISTRIBUTION:
randomized for each sex on the basis of body weight into groups per sex
DIET: NIH-07 rat ration
ANIMAL ROOM ENVIRONMENT:
temperature: 72° +/-3° F, humidity: 50 % +/-15 %, Fluorescent light: 12 hrs/day, room air changes : 10-12 changes/hr
TYPE AND FREQUENCY OF OBSERVATION:
observed twice daily, body weight taken initially, weekly, and at termination, feed consumption by cage recorded twice weekly
NECROPSY AND HISTOLOGIC EXAMINATION:
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 aninmals 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, oesophagus, heart, kidney, large intestines (caecum, colon, rectum), liver, lungs, lymph nodes (mesenteric), mammary glands, nasal cavity and turbinates, oral cavity, ovaries, pancreas, parathyroids, pharynx, pituirary, preputial gland, prostate, salivary glands, scrotal sac, seminal vesicles, skin, small intestine (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: nasal epithelium, bone marrow, uterus, liver, kidney. Organ weights recorded for brain, liver, right kidney, thymus, heart, and lungs of all animals, and the right testis of all males.
STATISTICAL METHODS:
nonparametric multiple comparison test of Dunn and Shirley, Jonckheere's test

Remark :
mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	25	25
1000 ppm	87	83
3000 ppm	256	242
10000 ppm	835	769
30000 ppm	2180	2060

Result : There were no deaths.
30000 ppm: Decreased mean final body weights, body weight gains and feed consumption occurred in both the
top-dose males and females. These animals also showed
clinical signs of toxicity, including hunched posture and
rough hair coat (individual animal data not given).
At study termination, weights (w) were sign. increased:
liver (male, rel. w from 10000 ppm, p</=0.01; female: rel w from 3000 ppm, p</=0.05); kidney (male, rel. w from 10000 ppm, p</=0.05; female, rel. w. at 30000 ppm p</=0.01); brain (male, rel. and abs. w at 30000 ppm

p</=0.05; female, rel. w at 30000 ppm, p</=0.05); male right testis (rel. w at 30000 ppm, p</=0.05) (individual animal data not given)

No gross lesions were noted at necropsy. No microscopic changes were reported from brain, liver and kidneys.

Histopathological evaluation, characterized by avarage severity score based on a scale of 1 to 4 (1=minimal, 2=mild, 3=moderate, 4=marked), revealed effects:
female uterus (moderate atrophy at 30000 ppm: 3/5); in the nasal cavity, nose: atrophy of olfactory epithelium, at 30000 ppm, male: 5/5, female: 4/5, mild; respiratory epithelium hyperplasia, , from 3000 ppm, male: 1/5, 4/5,5/5, female: 1/5, 3/5, 3/5, minimal to moderate; respiratory epithelium squamous metaplasia, male: 2/5, at 30000 ppm, mild, female: 1/5 at 10000 ppm, mild), bone marrow (hypocellularity: male, from 3000 ppm: 1/5, 1/5, 5/5, mild to moderate; female, from 10000 ppm: 1/5, 3/5 mild to moderate)

local toxicity:
NOAEL(male, female): 1000 ppm

systemic toxicity: NOAEL(male, female): 1000 ppm

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
06.02.2004 (150)

Type : Sub-acute
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 28 days
Frequency of treatm. : continuously in diet
Post exposure period : none
Doses : 0, 300, 1000, 3000, 10000, 30000 ppm (see freetext RM)
Control group : yes, concurrent no treatment
NOAEL : 1000 ppm
Method : other: see freetext ME
Year : 1991
GLP : yes
Test substance : other TS: p-cresol, purity > 98%

Method : SIZE OF STUDY GROUP:
5 male and 5 female mice per group
TIME HELD BEFORE STUDY: 13-15 days
METHOD OF ANIMAL DISTRIBUTION:
randomized for each sex on the basis of body weight into groups per sex
DIET: NIH-07 mouse ration
ANIMAL ROOM ENVIRONMENT:
temperature: 72° +/-3° F, humidity: 50 % +/-15 %, Fluorescent light: 12 hrs/day, room air changes : 10-12 changes/hr
TYPE AND FREQUENCY OF OBSERVATION:
observed twice daily, body weight taken initially, weekly, and at termination, feed consumption by cage recorded twice weekly
NECROPSY AND HISTOLOGIC EXAMINATION:
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 aninmals 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, oesophagus, gallbladder, heart, kidney, large intestines (caecum, colon, rectum), liver, lungs, lymph nodes (mesenteric), mammary glands, nasal cavity and turbinates, oral cavity, ovaries, pancreas, parathyroids, pharynx, pituirary, preputial gland, prostate, salivary glands, scrotal sac, seminal vesicles, skin, small intestine (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: nasal epithelium, bone marrow, liver, kidney and lymphoid organs. Organ weights recorded for brain, liver, right kidney, thymus, heart, and lungs of all animals, and the right testis of all males.
STATISTICAL METHODS:
nonparametric multiple comparison test of Dunn and Shirley, Jonckheere's test

Remark :

mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	50	60
1000 ppm	163	207
3000 ppm	469	564
10000 ppm	1410	1590

Consumption data for the top dose were not calculated due to 100% mortality at this level.

Result : 30000 ppm: all mice died: 5 male and 5 female mice
10000 ppm: 1/5 male died, mean final body weights and mean body weight gains for surviving males were significantly
lower than in the control groups; male and female: feed consumption was depressed at the beginning of the study (individual animal data not given)
Clinical signs of toxicity
included hunched posture, rough hair coat, lethargy, and hypothermia in the top-dose females that died and, together with laboured breathing and paleness, in the males fed >/= 10000 ppm (individual animal data not given)
At study termination weights (w) were sign. increased:
heart (male, rel. w at 10000 ppm, p</=0.01), right kidney (male, rel. w from 3000 ppm, p</=0.05), liver (male, rel. w at 10000 ppm, p</=0.01; female, rel. w from 3000 ppm, p</=0.05 and abs. w at 10000 ppm, p</=0.01)(individual animal data not given)
No gross lesions were noted at necropsy.
Histopathological evaluation, characterized by average severity score based on a scale of 1 to 4 (1=minimal, 2=mild, 3=moderate, 4=marked), revealed effects:
bone marrow hypocellularity (at 30000 ppm, 5/5 male, 4/5 female, mild), renal tubule necrosis (at 30000 ppm: 4/5 male, 3/5 female, mild), liver: centrilobular atrophy: at 30000 ppm, male 1/5, moderate; centrilobular necrosis, at 30000 ppm, 1/5 male, 1/5 female, mild; necrosis,at 30000 ppm, 2/5 male, moderate), nose: olfactorium epithelium (o.e.) atrophy, 1/5 male at 30000 ppm; mild hyperplasia, from 1000 ppm, male 1/5, 1/5, minimal to mild; o.e. necrosis, at 30000 ppm, 2/5 male, 3/5 female, mild; o.e. squamous metaplasia, from 10000 pp, 1/5, 1/5 male, mild to moderate; respiratory epithelium (r.e.) hyperplasia, from 1000 ppm, male, 3/5, 5/5, 5/5, 1/5, minimal to mild, female, from 300 ppm, 1/5, 2/5, 4/5, 5/5, 1/5, minimal (minimal effect without dose response relationship, only in females); r.e. atrophy at 30000 ppm, male,1/5, mild; r.e. squamous metaplasia, 2/5 male, at 10000 ppm, mild)

local toxicity: NOAEL(male): 300 ppm
NOAEL(female): < 300 ppm

systemic toxicity: NOAEL(male, female): 1000 ppm

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
06.02.2004 (150)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 13 weeks
Frequency of treatm. : 7 days/week
Post exposure period : no
Doses : 0, 50, 175, 600 mg/kg bw/day dissolved in corn oil
Control group : yes, concurrent vehicle
NOAEL : 50 mg/kg bw
Method : other: see freetext ME
Year : 1986
GLP : yes
Test substance : other TS: p-cresol, purity: 99.9 %

Method : 30 rats/sex/dose,
additional 10 rats/sex/dose for baseline clinical pathology
interim kill at week 7
bws were recorded on test day1 and weekly thereafter; individual food consumption data were collected weekly;
moribund/mortality check twice daily (moribund rats were killed and necropsied); physical examination weekly; ophthalmologic examination during quarantine period and in test week 13
HAEMATOLOGY
haemoglobin, haematocrit, prothrombine time (PT), erythrocyte count, reticulocyte count, total and differential leucocyte count, activated partial thromboplastin time (APTT)
CLINICAL CHEMISTRY
sodium, chloride, potassium. direct and total bilirubin, alkaline phosphatase, total cholesterol, albumin, CO2, SGPT, SGOT, glucose, BUN, globulin (calculated), total protein, creatinine, Albumin/Globulin ratio (calculated
URINALYSIS
appearance, volume, colour, specific gravity, pH, protein, glucose, ketone, bilirubin, urobilinogen, haemoglobin, microscopic examination
PATHOLOGY
determination of weights of:
heart, liver, spleen, brain, kidneys, gonads, adrenals, thyroid/parathyroid
examination of all control rats and high dose rats at study termination as well as those that died during the study:
all gross lesions,
brain (3 levels), spleen, bone (with marrow), skeletal muscles, salivary gland. mammary gland, thymus, thyroid (with parathyroid), lungs (with mainstem bronchi), trachea, liver, urinary bladder, testes, prostate, ovaries, corpus and cervix uteri, eye, pituitary gland, lymph node, spinal cord, heart, aorta, siatic nerve, pancreas, oesophagus, kidneys, small and large intestine, adrenals, stomach
STATISTICAL ANALYSIS
One-way Analysis of Variance tests with Dunnett's t-test

Result : 600 mg/kg: 3 females died within the first 3 days of dosing. Overt signs of toxicity at this dose included lethargy, tremors, convulsions and coma.
BODY WEIGHT was sign. reduced (p</=0.05):
50 mg/kg bw: female, at week 1, 2, 3, 4, 5, and 7
175 mg/kg bw: male, at week 2, 3, and 4
600 mg/kg bw: male, except week 1 in all weeks; female, week 2, 3, 4, 5, 6,

7, 8, 9, and 14
BODY WEIGHT GAIN was sign. reduced (p</=0.05):
50 mg/kg bw: female, week 2, and 3
175 mg/kg bw: male, week 1, 2, and 3; female, week 1 and 2
600 mg/kg bw: male, all weeks; female, week 1, 2, 3, 4, 5, 6, 7, 10, 13
FOOD CONSUMPTION data was sign. reduced (p</=0.05):
50 mg/kg bw: male, week 5, 9; female, week 1 and 2
175 mg/kg bw: male, week 1, and 5
600 mg/kg bw: male, week 1, 2, 3, 4, 5, 6, 7, and 9; female, week1, 2, and 5
CLINICAL PATHOLOGY, only sign. changes (p</=0.05):
Male:
APTT, 600 mg/kg bw, increased; total protein from 175 mg/kg bw increased; Ca, at 175 mg/kg bw increased; phosphate, 600 mg/kg bw, increased
Female:
RBC, HGB, HCT, from 175 mg/kg bw, decreased; CO2, at 175 mg/kg bw, decreased; SGPT, SGOT, Cholesterin, at 600 mg/kg bw increased;
OPHTHALMOLOGY:
Treatment related changes were not seen.
ORGAN WEIGHTS (rel. and abs., only sign. changes, p</=0.05):
Male:
Heart, rel., at 600 mg/kg bw increased; liver, 600 mg/kg bw, abs. decrease, rel. increase; spleen, 600 mg/kg bw, absol. decreases; right and left kidney, from 175 mg/kg bw, rel. increased; right and left testis, at 600 mg/kg bw, rel. increased; brain, at 600 mg/kg bw, abs. decreased, rel. increased;
Female:
spleen, at 50 mg/kg bw, rel. increased (no histopathologic correlate); right kidney, at 600 mg/kg bw, rel. increased; right ovary, at 600 mg/kg bw, ovary and brain, abs. decreased
PATHOLOGY:
Gross necropsy examinations did not detect treatment- related changes.
Histological examination:
male:
chronic nephropathy in all rats including controls:
a slight increased incidence in all dosed males when compared to the controls. The increased incidence was significantly greater (p</=0.05) at the low and the high dose but not at the middle dose. The proportion of rats with minimal and mild nephropathy was generally similar for all male rats including controls:
controls: 4/20 = 20%, severity(s): minimal 3/4, mild 1/4;
50 mg-gr.: 11/20 = 55%, s: minimal: 3/11, mild: 2/11
175 mg-gr.: 7/20 = 35%, s: minimal: 7/7, mild:0/7
600 mg-gr.: 12/20 = 60%, s: minimal: 9/12, mild: 3/12
(no dose-response relationship, controls also affected, no increase in percentage of severity in dosed rats when compared to the controls)
male, female:
epithelial metaplasia of the trachea:
sign, at 600 mg/kg bw (p</=0.05), 10/20 males, 9/19 females
The incidence of this lesions was similiar for low dose, mid dose and control

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
06.02.2004 (151)

Type :
Species : rat
Sex : female
Strain : no data
Route of admin. : inhalation
Exposure period : 4 months

Frequency of treatm. : daily
Post exposure period : 2 months
Doses : 0.01 mg/l
Control group : no data specified
LOAEL : = .01 mg/l
Method : other
Year :
GLP : no data
Test substance : other TS: p-cresol, purity not noted

Remark : Females were exposed to p-cresol aerosols. The original data are unpublished and no further experimental details are available from the citing review (IPCS, 1993).
Result : Clinical signs of toxicity included loss of appetite, marked emaciation and decreased locomotor activity. Irritative effects, which persisted throughout recovery, were seen on the nose, eye and skin. Decreased body weight gain and lung weight, increased liver weight, oliguria and dystrophic changes in the lung and liver occurred. Throughout recovery the body weights remained depressed and urinary excretion remained low.
Reliability : (4) not assignable
secondary literature: experimental details are missing, only one dose used

15.10.2002 (125)

Type :
Species : mouse
Sex : female
Strain : CBA
Route of admin. : dermal
Exposure period : 6 weeks
Frequency of treatm. : 3x/week
Post exposure period : 6 months
Doses : 0 or 0.5 % in acetone
Control group : yes, concurrent vehicle
NOAEL : < .5 %
LOAEL : <= .5 %
Method : other: see freetext RM
Year : 1974
GLP : no data
Test substance : other TS: p-cresol, purity not noted

Remark : p-Cresol was applied to the skin of five female Agouti mice. Hair colour was observed weekly for the subsequent 6 months. Microscopic examinations of post-treatment hairs and skin biopsies of areas of non-pigmented and normally pigmented hair were made. Control groups of animals received acetone.
Result : Topical application caused hair depigmentation. No microscopic changes were noted.
Reliability : (3) invalid
special study and only one dose used, no dose-response relationship can be derived and thus no NOAEL or LOAEL can be deduced.

15.10.2002 (152)

Type :
Species : mouse
Sex : male
Strain : C57BL
Route of admin. : dermal
Exposure period : 6 weeks
Frequency of treatm. : 3x/week

Post exposure period	:	6 months
Doses	:	0.5 % in acetone
Control group	:	no data specified
NOAEL	:	< .5 %
LOAEL	:	<= .5 %
Method	:	other: see freetext RM
Year	:	1974
GLP	:	no data
Test substance	:	other TS: p-cresol, purity not noted
Remark	:	p-Cresol was applied to the skin of 30 males. Hair colour was observed weekly for the subsequent 6 months. Microscopic examinations of post-treatment hairs and skin biopsies of areas of non-pigmented and normally pigmented hair were made. Control groups of animals received acetone.
Result	:	Topical application caused depigmentation of the hair and pigmented epidermis, especially of the tail. Large amounts of p-cresol were lethal and had a local caustic, erosive effect.
Reliability	:	(3) invalid special study and only one dose used, no dose-response relationship can be derived and thus no NOAEL or LOAEL can be deduced.

15.10.2002 (152)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, TA100, TA1535, TA1537.
Test concentration	:	0.0, 3.3, 10.0, 33.0, 100.0, 333.0 ug/plate in water as solvent
Cycotoxic concentr.	:	to select dose range the chemical was checked for toxicity to S. typh. TA100
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: preincubation methodology according to Ames, Mutat. Res. 31, 347 (1975) and Yahagi, Cancer Lett. 1, 91 (1975);
Year	:	1983
GLP	:	no data
Test substance	:	other TS: p-cresol, purity >97%
Method	:	S-9 FRACTION: liver fractions were prepared from male Sprague-Dawley rats and male Syrian hamsters that were injected with Arcolor 1254; POSITIVE CONTROLS: 2-aminoanthracene, 4-nitro-o-phenylenediamine, sodium acide 9-aminoacridine; SOLVENT: water, POSITIVE RESPONSE: was indicated by a reproducable, dose-related increase wether it be two-fold over background or not STATISTICAL METHODS: analysis based on the models presented by Margolin
Result	:	Positive controls were functional
Reliability	:	(2) valid with restrictions only 4 strains of Salmonella typhimurium were used
Flag	:	Critical study for SIDS endpoint

06.02.2004 (153)

Type	:	Cytogenetic assay
System of testing	:	Chinese hamster ovary cells

Test concentration	:	treatment time: 20 hrs: -S9-mix, 100, 150, 200, 301 ug/ml performed twice; +S9-mix: 301, 601, 902 ug/ml; treatment time: 10 hrs: +S9-mix: 150, 225, 300 ug/ml performed twice
Cycotoxic concentr.	:	Preliminary range-finding assays were performed (3.01-3010 µg/ml) to determine cytotoxicity: -S9-mix: >=301 µg/ml; +S9-mix: >=100µg/ml
Metabolic activation	:	with and without
Result	:	positive
Method	:	OECD Guide-line 473
Year	:	1987
GLP	:	yes
Test substance	:	other TS: p-cresol, 99.8% pure
Method	:	Duplicate CHO cultures were incubated for 20 hrs with 100-301 ug/ml of the test substance in the nonactivation aberrations assay. The metabolic activation cultures were treated with 100-300 ug/ml of the test substance in a 10 hour assay and with 301-902 ug/ml in a 20 hour assay. Solvent: DMSO positive control: Mitomycin C, cyclophosphamide statistical evaluation: Fisher's Exact Test with an adjustment for multiple comparisons
Result	:	nonactivation assay and incubation for 20 hrs: Increases in chromosomally aberrant cells ranging between 6.5 % and 11 % cells with aberrations (versus 1.0% of solvent control) or between 4% and 14 %.cells with aberrations (versus 2.0 % of solvent control), respectively. Positive control was functional in each trial Incubation for 20 hours with metabolic activation: Increases in the chromosomally aberrant cells ranging between 18 % and 40.5 % cells with aberrations(902 µg/ml was toxic, versus 1.5% of solvent control) and between 17 % and 43 % cells with aberrations (902 µg/ml was toxic, versus 3.0 % of solvent control), respectivly. Posivive control was functional in each trial . Incubation for 10 hours in the presence of S9-mix:no significant difference to the solvent controls; positive controls were functional
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

06.02.2004 (154)

Type	:	Mouse lymphoma assay
System of testing	:	L5178Y TK+/- mouse lymphoma cells
Test concentration	:	with activation: 0.256 ug/ml, 0.511 ug/ml, 0.767 ug/ml, 1.02 ug/ml, 1.53 ug/ml, and 3.07 ug/ml. without activation: 51.1 ug/ml, 102 ug/ml, 153 ug/ml, 204 ug/ml, 307 ug/l, and 409 ug/ml.
Cycotoxic concentr.	:	with activation: 7.98 ug/ml. without activation: 511 ug/ml.
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: similar to OECD Guide-line 476, No differentiation between large and small colony mutants see also freetext ME
Year	:	1988
GLP	:	yes
Test substance	:	other TS: p-cresol, 99.8% pure
Method	:	S9-MIX: of rat liver was used as metabolic activation system SOLVENT: DMSO, POSITIVE CONTROLS: ethylmethane sulfonate, 3-methylcholantrene, POSITIVE RESPONSE was indicated by a >= two-fold increase over the concurrent background frequency

Result	:	The positive controls were functional. p-Cresol was evaluated as non-mutagenic in the mouse lymphoma cell system
Reliability	:	(2) valid with restrictions No differentiation between large and small colony mutants; statistical evaluation not mentioned
Flag	:	Critical study for SIDS endpoint

06.02.2004 (155)

Type	:	DNA damage and repair assay
System of testing	:	human lymphocytes
Test concentration	:	5 - 25 uM
Cycotoxic concentr.	:	no data
Metabolic activation	:	without
Result	:	positive
Method	:	other: see freetext ME
Year	:	1986
GLP	:	no data
Test substance	:	other TS: p-cresol, not specified further
Method	:	p-Cresol was tested for its ability to inhibit semiconservative DNA synthesis. Initially, DNA repair was induced by irradiation and, in these cells, semiconservative DNA synthesis was blocked by treatment with hydroxyurea. In both studies, cells were treated with radiolabelled thymidine for 2 hours and incorporation of thymidine into the cells was measured. no solvent mentioned, no negative or positive control, no statistical evaluation reported
Result	:	p-Cresol inhibited both UV-induced DNA repair synthesis and semiconservative DNA synthesis as seen by a reduction in radiolabelled thymidine incorporation. It was unclear from the report if this inhibition was seen at all concentrations tested but at the top dose, 21% inhibition of DNA repair synthesis and 25% inhibition of semiconservative DNA synthesis was found.
Reliability	:	(2) valid with restrictions no solvent mentioned, no negative or positive control, no information on cytotoxicity, no statistical evaluation reported
Flag	:	Critical study for SIDS endpoint

06.02.2004 (156)

Type	:	Sister chromatid exchange assay
System of testing	:	human lymohocytes
Test concentration	:	0 - 0.5 mM
Cycotoxic concentr.	:	no data
Metabolic activation	:	no data
Result	:	negative
Method	:	other: see freetext ME
Year	:	1986
GLP	:	no data
Test substance	:	other TS: p-cresol, 99.9% purity
Method	:	Lymphocyte fraction from healthy donors were grown in Medium 199 with Earles salts. After 24 hrs of cultur p-Cresol diluted in DMSO was added for 88-90 hrs. positive control: Styrene-7,8-oxide. statistical method: Linear regression analysis
Remark	:	Results of the positive control or solvent control in comparison to p-cresol are not given
Reliability	:	(2) valid with restrictions

Study description suffers from deficiencies: no information about cytotoxicity and whether a metabolic activation system was used or not, only summary results given

Flag : Critical study for SIDS endpoint
06.02.2004 (157)

Type : Ames test
System of testing : Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538
Test concentration : 0, 0.5, 5, 50, 500, 5000 ug/plate dissolved in DMSO, highest dose cytotoxic
Cycotoxic concentr. : 5000 ug/plate
Metabolic activation : with and without
Result : negative
Method : other: see freetext ME
Year : 1975
GLP : no data
Test substance : other TS: p-cresol, purity : 98 %

Method : plate incorporation. method according to Ames, Mutat. Res. 31, 347 (1975), solv.: DMSO, S9-MIX: of Aroclor-pretreated rat liver as metabolic activation. system
CONTROLS: as positive control:sodium azide,2-nitrofluorene, 9-aminoacridine,2-aminoanthracene,
as solvent control: DMSO
DATA EVALUATION: Significance level for positive dose-response effects were obtained with the Joncheere test
STATISTICAL ANALYSIS: Joncheere test
Remark : Positive controls were functional
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
06.02.2004 (158)

Type : Sister chromatid exchange assay
System of testing : cultured male human fibroblasts
Test concentration : 0, 0.008, 0.8, 4, 8 mM diluted in 95 % EtOH, 10, 30 mM diluted in MEM
Cycotoxic concentr. : from 10 mM onwards
Metabolic activation : without
Result : negative
Method : other: see freetext ME
Year : 1984
GLP : no data
Test substance : other TS: p-cresol, > 99% pure

Method : p-Cresol was added to the cells and incubated, in triplicate, at 37 C for 2 hours. Following exposure, the cells were washed, reincubated in the absence of the test chemical for 48 hours, harvested and SCE frequency and cell-cycle kinetics analysed.
SOLVENT: p-Cresol was dissolved in 95% ethanol at concentrations up to and including 8 mM and in Eagle's minimum essential medium (MEM) at concentrations above this.
CONTROLS: 95% Ethanol and mitomycin C were used as negative and positive controls respectively.
EVALUATION CRITERIA: positive if a dose-dependant significant incrase in SCE frequencies compared to control is observed
STATISTICAL ANALYSIS: Dunnett's test
Remark : p-Cresol did not induce significant increases over the control SCE frequencies. The positive control was functional.
p-Cresol caused a small but statistically significant decrease in cell-cycle progression at 8 mM (864 mg/l) and above, indicative of a small cytotoxic response.
Reliability : (2) valid with restrictions
only tested in the absence of metabolic activation and no information on

GLP
Flag : Critical study for SIDS endpoint
06.02.2004 (159)

Type : Ames test
System of testing : Salmonella typhimurium TA98, TA100, TA1535, TA1537
Test concentration : no data
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other: according to Ames, Mutation Res. 31, 347 (1975)
Year : 1980
GLP : no data
Test substance : other TS: p-cresol, not specified further

Reliability : (4) not assignable
documentation insufficient for assessment
06.02.2004 (160)

Type : Unscheduled DNA synthesis
System of testing : other: human lung fibroblast
Test concentration : no data
Cycotoxic concentr. : no data
Metabolic activation : with
Result : positive
Method : other: no data reported
Year : 1978
GLP : no data
Test substance : other TS: p-cresol, not specified further

Reliability : (4) not assignable
secondary literature: description of the test suffers from deficiencies
Flag : Critical study for SIDS endpoint
06.02.2004 (161)

Type : other: DNA adduct formation
System of testing : calf thymus DNA
Test concentration : 100 uM
Cycotoxic concentr. : no data
Metabolic activation : with
Result : positive
Method : other: see freetext ME
Year : 2001
GLP : no
Test substance : other TS: p-cresol, highest analytical grade available

Method : p-Cresol was activated with (1) PB-induced rat liver microsomal protein, (2) horseradish peroxidase and then incubated with calf-thymus DNA overnight at 37 degree Celcius and adducts were measured by P-postlabeling analysis .

p-Cresol was oxidized with MnO2 to form a quinone methide and then incubated with calf-thymus DNA as described above and adducts were measured
Result : In vitro activation of p-Cresol with

(1) horseradish peroxidase produced six DNA adducts with a relative adduct level of 8.03 x 10(exp)-7 which were inhibited 65 and 95 % by addition of either 250 or 500 uM ascorbic acid to the incubation.

(2) PB-induced rat liver microsomes resulted in the formation of a single

adduct with a relative adduct level of 0.28 x 10(exp)-7.

Oxidized p-Cresol to a quinone methide and than incubated with calf-thymus DNA resulted in 5 major adducts and a relative adduct level of 20.38 x 10(exp)-7.

The DNA adducts formed by activation of p-cresol with either horseradish peroxidase or microsomes were the same as that produced by the quinone methide of p-cresol.

Reliability : (2) valid with restrictions
no validated test method

Flag : Critical study for SIDS endpoint

06.02.2004 (162)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Dominant lethal assay
Species	:	mouse
Sex	:	male
Strain	:	ICR
Route of admin.	:	gavage
Exposure period	:	Single dose
Doses	:	0, 100, 275, 550 (650) mg/kg bw diluted in corn oil
Result	:	negative
Method	:	other: EPA OTS 798.5450
Year	:	1989
GLP	:	yes
Test substance	:	other TS: p-cresol, 99.8% pure

Method : Dose selection based upon the results of a dose range-finding assay
Number of animals:
25 males/group 50 females/group,
vehicle control: corn oil,
positive control: Triethylenemelamine (TEM)

Due to high mortality and toxicity in the 650 mg/kg bw-group during the first week mice were removed from the study. Two weeks after the initiation of the assay another group of males dosed with 550 mg/kg bw was assigned as the new high dose to be evaluated.

Mating scheme:
1 male was mated with 2 virgin females for a period of up to 5 days. Then females were removed and housed in groups for subsequent necropsy 14 days after the midweek of mating for evidence of pregnancy; the males were rested for 2 days and then mated with 2 new females. This mating sequence was followed for 6 consecutive weeks.

Observation of all animals for toxic effects and/or mortality, at termination record of male body weight, determination of fertility index, total number of implantations. dead implantations, proportion of females with 2 or more dead implants, dead implants/total implants

Statistical methods:
Chi-square test, analysis of variance (ANOVA), Dunnett's one-tailed t test

Result : Mortality:
650 mg/kg bw: 10/25 males within the first week;
as signs of toxicity mice exhibited rapid breathing, several became languid with mild clonic convulsions and squinted eyes and were prostrate and had scruffy coats
550 mg/kg bw: 6/25 males died during the test

body weight:
No significant reduction in body weight were observed in any of the males in any of the dose groups.
The statistical evaluation of the parameters indicated that no significant effects of p-cresol were induced at any dose levels.
The treatment had no adverse effects with respect to number of early and late resorptions, and live implants, indicating that the test compound did not induce dominant lethal mutations in male germ cells of mice under the conditions of this assay.
The concurrent positive control substance TEM induced a significant increase in :
the number of dead implantations, in the portion of females with either one or more dead implantations, the frequency of dead implants relative to the total number of implants in each female during mating weeks 1 through 3
TEM induced a significant reduction in total implants relative to the vehicle control group.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
06.02.2004 (163)

Type : Drosophila SLRL test
Species : Drosophila melanogaster
Sex : male
Strain : other: Oregon-R
Route of admin. : oral feed
Exposure period : 3 days
Doses : 0, 60, 300 and 600 ug/ml 5 % sucrose
Result : negative
Method : OECD Guide-line 477 "Genetic Toxicology: Sex-linked Recessive Lethal Test in Drosophila melanogaster"
Year : 1989
GLP : yes
Test substance : other TS: p-cresol, 99.8% purity

Result : negative; the treatment did not increase the frequency of sex-linked recessive lethal mutations, indicating that the test substance was not mutagenic in Drosophila under the conditions of this assay.
The positive control substance ethylmethansulfonate (EMS) was functional
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
06.02.2004 (164)

Type : Sister chromatid exchange assay
Species : mouse
Sex : male
Strain : DBA
Route of admin. : i.p.
Exposure period : single dose
Doses : 0, 75 mg/kg bw in sunflower oil
Result : negative
Method : other: see freetext ME
Year : 1984
GLP : no data
Test substance : other TS: p-cresol, purity >99%

Method : p-Cresol was administered to 2 or 3 intact or hepatectomized male mice by single intraperitoneal injection. After 30 min, DNA labelling was initiated using BrdU. After a further 21 hr the animals were killed, cells isolated and harvested and sister chromatid exchange (SCE) frequency in bone marrow cells, alveolar macrophages and regenerating liver cells analysed. Some of the mice were partially hepatectomized to induce liver cell regeneration

NEGATIVE CONTROL: 0.35 ml sunflower oil (4 intact and 5 hepatectomized male mice, bone marrow cells, alveolar macrophages, liver cells)
POSITIVE CONTROL: 5 mg cyclophosphamide/kg bw (2 intact male mice, bone marrow cells, alveolar macrophages).
STATISTICAL ANALYSIS: One way analysis of variance; Dunnett's test for comparison

Result : p-Cresol did not induce significant increases in SCE frequencies in any of the cell types examined: bone marrow cells, alveolar macrophages, liver cells.
The dose tested was overtly toxic to the mice, causing lethargy, piloerection and lacrimation.
The positive control was functional.

Reliability : (2) valid with restrictions
only one dose tested, no information on GLP

Flag : Critical study for SIDS endpoint

06.02.2004 (159)

5.7 CARCINOGENICITY

Species : mouse
Sex : female
Strain : other: Sutter
Route of admin. : dermal
Exposure period : 12 weeks (I) or 20 weeks (II)
Frequency of treatm. : twice weekly
Post exposure period : no
Doses : 20 (I) or 5.7 % (II) solutions in benzene
Result :
Control group : yes, concurrent vehicle
Method : other: tumor promotion test (see freetext RM)
Year : 1959
GLP : no
Test substance : other TS: p-cresol, not specified further

Remark : Groups of 20-29 Sutter strain mice:
I. method: initiator: single dermal appl. of 0.3 % 9,10-dimethyl-1,2-benzanthracene (DMBA) in acetone; p-cresol (in benzene) was applied as promotor to the back of each mouse
I. result: 20/28 mice (12/12 benzene control animals); survived and in 35 % (0 % in control animals); skin papillomas were found; no carcinomas were detected
II. method: initiator: single dermal appl. of 0.3 % DMBA in benzene; promotor: p-cresol was applied to the back of each mouse
II.result: 14/20 mice (18/20 benzene control animals) survived and in 29 % (0 % in control animals) skin papillomas were found; no carcinomas were detected

Result : p-Cresol was evaluated as promotor

Reliability : (2) valid with restrictions
no data on the purity, benzene a known carcinogen as solvent, high mortality rate; no information on skin irritation effects

Flag : Critical study for SIDS endpoint

06.02.2004 (165)

Species : hamster
Sex : male
Strain : other: Syrian Golden
Route of admin. : oral feed
Exposure period : 20 weeks

Frequency of treatm.	:	daily
Post exposure period	:	no
Doses	:	0 or 1.5 % in diet (corresponding to about 1100 mg/kg bw/d)
Result	:	
Control group	:	yes, concurrent no treatment
Method	:	other: 15 males/group,
Year	:	1986
GLP	:	no data
Test substance	:	other TS: >98% pure.
Result	:	An increased incidence of mild to moderate forestomach hyperplasia occurred (10 animals: moderate; 5 animals: mild) when compared with the controls. Marked hyperplasia or papillomatous lesions were not observed.
Reliability	:	(2) valid with restrictions limited documentation; small number of animals; limited scope of examinations; short exposure

16.12.2002 (166)

Species	:	other: in vitro cell transformation assay
Sex	:	
Strain	:	other: mouse BALB/c-3T3 cells
Route of admin.	:	
Exposure period	:	
Frequency of treatm.	:	
Post exposure period	:	
Doses	:	0.81, 3.25, 5, 10, 15 nl/ml culture medium
Result	:	positive
Control group	:	other: yes, neg control: culture medium with 10 %FCS; pos. control: 3-methylcholanthrene
Method	:	other: 40CFR 795.285 (modified); preliminary cytotoxicity test, performance of the test according Kakunaga, Int. J.Cancer 12,463,1973, without metabolic activation
Year	:	1988
GLP	:	yes
Test substance	:	other TS: p-cresol, purity: 99.8 %
Result	:	p-cresol produced a dose-related increase in the number of foci/plate over the entire concentration range. The test material induced cell transformation that was significantly elevated when compared to the controls. Test material toxicity was determined in priliminary assays
Reliability	:	(2) valid with restrictions non-validated test system
Flag	:	Critical study for SIDS endpoint

06.02.2004 (167)

5.8.1 TOXICITY TO FERTILITY

Type	:	Two generation study
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	see remarks
Frequency of treatm.	:	5 days per week
Premating exposure period		
Male	:	10 weeks
Female	:	10 weeks
Duration of test	:	see remarks

No. of generation studies	:	2
Doses	:	0, 30, 175, 450 mg/kg bw
Control group	:	yes, concurrent vehicle
NOAEL parental	:	ca. 30 mg/kg bw
other: NOAEL (fertility)	:	ca. 450 mg/kg bw
Result	:	see freetext RS
Method	:	EPA OPP 83-4
Year	:	1989
GLP	:	yes
Test substance	:	other TS: p-cresol, 98.93% pure

Remark : 25 rats/sex/dose (F0) were administered p-cresol in corn oil. Exposure began 10 weeks prior to breeding and continued in the females throughout mating, gestation and lactation.
25 randomly selected F1 pups/sex/dose were gavaged with the appropriate concentration of p-cresol for 11 weeks and then bred to produce F2 litters (dosing was continued throughout mating, gestation and lactation).
The F2 offspring were sacrificed at weaning.

Reproductive Indices: mating indices for males and females, fertility indices for male and females, gestational index, live birth index, 4-day survival index, 7-day survival index, 14-day survival index, 21-day survival index, lactation index

Necropsy and pathology:
all F0 and F1 parental rats in all groups were subjected to a complete necropsy ; 25 male and 25 female adults from the controls and from the high dose groups were subjected to histopathology examination: pituitary, vagina, uterus, ovaries. testes, epididymides, seminal vesicles, prostate and other tissues with gross lesions identified as potentially treatment related; any of thze above organs or tissues showing gross alterations were also evaluated microscopically in other dose groups
A complete gross necropsy and histopathologic examination were conducted for any parental rat dying on test
Gross necropsy included examination of the external surfaces, all orificwes, cranila cavity, carcass, external and cut surfaces of the brain and spinal cord, the thoracic,abdominal and pelvic cavities and their viscera, cervical tissues and organs
a gross internal examination on any F1 and F2 pup appearing abnormal or dying on test

Statistical methods:
Levene's test for equal variances,
analysis of variance (ANOVA),
t-test,
Kruskal-Wallis test,
Mann-Whitney U test
Fisher's exact test

Result : Mortality: 8/28 males and 5/25 females at 450 mg/kg bw; 1/25 females at 30 mg/kg bw
Clinical signs of toxicity
occurred in F0 and F1 males and females at 450 mg/kg bw/day and included hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration, perinasal encrustation (not in F0 males), and perioral wetness occurred at >= 175 mg/kg bw.
body weight:
F0 adult males, sign reduced ($p<0.01$) week1 to week 13 in the 450 mg/kg bw group;
F0 adult females:
sign. reduced week 1 ($p<0.05$) in the 450 mg/kg bw-group,

gestational weight gain not significantly different from control group, lactational body weight sign. reduced ($p<0.05$) at d4 at 450 mg/kg bw group

F1 or F2: No reproductive parameters were affected in either of the two generations (mating index of male and females, fertility index of males and females, gestational index.

Still births in the F1 and F2 generations:
in F1 pups increased at 175 mg/kg/day, but not at 450 mg/kg bw) and
in F2 pups increased at 30 and 450 mg/kg bw, but not at 175 mg/kg/bw
There was some variability in the number of stillborn in control groups in F1 and F2 generation (2 versus 0). There was no clear dose-dependent effect in both generations (control/low/mid/high dose: F1 pups: 2/4/13/6; F2 pups: 0/7/4/9).

F1,F2: Pup survival indices in both generations were not affected by treatment (4-day survival index, 7-day survival index, 14-day surval index 21-day survival index and lactation index), except live birth indices in F2 (but not F1) which were reduced at 30 and 450 mg/kg bw, but not at 175 mg/kg/day. Without any other effects especially in the 30 mg/kg bw-group it is unclear whether the effects on live birth indices were substance related.
ross lesions of parental males and females which died prior to scheduled sacrifice included diffuse, focal or multifocal color changes in the lung and stained skin for males and lung congestion and congestion in the nasal turbinates and erythrocytes on the skin surface for females.
There were no treatment related histologic lesions observed in the examination of organs from parental F0 and F1 adults which survived to scheduled sacrifice.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
06.02.2004 (168)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	days 6 - 15
Frequency of treatm.	:	daily
Duration of test	:	until gd 21
Doses	:	0, 30, 175, 450 mg/kg bw in corn oil
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 175 mg/kg bw
NOAEL teratogen.	:	= 175 mg/kg bw
Method	:	other: following the TSCA Health Effects Test guidelines for Specific Organ/Tissue Toxicity - Developmental Toxicity (EPA, 1984,1987)
Year	:	1988
GLP	:	yes
Test substance	:	other TS: p-cresol, purity = 98.93%

Method : Dose selection was based on the results of a range-finding study.
25 mated females/group, 50 control females, all females were weighed on gd 0, 6, 11, 15, and 21, food consumption was measured throughout gestation, all females were examined daily for clinical signs, for mortality and morbidity
sacrifice on gd 21:
does were evaluated for body weight, liver and gravid uterine weight,

number of corpora lutea and number and status of implantation sites (i.e. resorptions, dead fetuses, live fetuses)
live fetuses were dissected from uterus, counted and weighed, examined for external malformations and variations, and for visceral malformaltions and variations, and for soft tissue craniofacial malformations
statistical analysis:
Levene's test, ANOVA, pooled t-test, Kruskal-Wallis test, Mann-Whitney U-test, Fisher's exact test

Result : Maternal toxicity:
mortality: 3/25 females at 450 mg/kg bw/day
No abortions or early deliveries (1 litter at 30 mg/kg bw was fully resorbed)
450 mg/kg bw:
decreased food consumption
stat. sign. reduction in periodic maternal body weight and weight gain during dosing, maternal gestational weight gain reduced when corrected for the weight of the gravid uterus and reduced maternal terminal bw, relative but not absolute liver weight was increased
clin. signs of toxicity: hypoactivity, ataxia and tremors, prone position audible respiration and perioral wetness

gestational parameters were unaffected by treatment except fetal body weight per litter were reduced at 450 mg/kg bw.

fetal evaluations:
No significant changes in the incidence of any individual malformation, malformation by category (external, visceral including craniofacial or skeletal) or total malformations for any dose group.
450 mg/kg bw:
7 skeletal variations exhibited sign. different incidences relative to those in the control groups:
incidence of cervical centrum 6 bilobed, reduced number of ossified caudal segments, unossified sternebrae, reduced incidence of unossified cervical centrum no. 7, poorly ossified parietal skull bone (30 mg/kg bw), reduced incidence of some (1-4) proximal phalanges of the hind limb unossified

p-Cresol caused mild fetotoxicity at the 450 mg/kg, as seen by reduced ossification in three skeletal districts. In addition, fetal body weight was reduced at the 450 mg/kg dose level. There was no treatment-related increased incidence of malformations at any dosage.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
06.02.2004 (169)

Species : rabbit
Sex : female
Strain : New Zealand white
Route of admin. : gavage
Exposure period : days 6 - 18 of gestation
Frequency of treatm. : daily
Duration of test : until gd 29
Doses : 0, 5, 50, 100 mg/kg bw in corn oil
Control group : yes, concurrent vehicle
NOAEL maternal tox. : = 5 mg/kg bw
NOAEL teratogen. : = 100 mg/kg bw
Result : see freetext ME
Method : other: following the TSCA Health Effects Test guidelines for Specific Organ/Tissue Toxicity - Developmental Toxicity (EPA, 1984,1987)
Year : 1988
GLP : yes
Test substance : other TS: p-cresol, purity = 98.93%

Remark	:	Dose selection was based on the results of a range-finding study. 14 mated females/group, 28 control females, all females were weighed on gd 0, 6, 12, 18, 24 and 29, food consumption was measured throughout gestation, all females were examined daily for clinical signs, for mortality and morbidity sacrifice on gd 29: does were evaluated for body weight, liver and gravid uterine weight, number of corpora lutea and number and status of implantation sites (i.e. resorptions, dead fetuses, live fetuses) live fetuses were dissected from uterus, counted and weighed, examined for external malformations and variations, and for visceral malformaltions and variations, and for soft tissue craniofacial malformations statistical analysis: Levene's test, ANOVA, pooled t-test, Kruskal-Wallis test, Mann-Whitney U-test, Fisher's exact test
Result	:	mortality: 100 mg/kg bw: 5/14; 50 mg/kg bw: 2/14; all were pregnant 1 control female aborted and one each at 5.0 and 50 mg/kg bw was removed due to dosing error gestational weights and weight changes were not stat. significant different among groups for periodic body weights or weight changes. 50, 100 mg/kg bw: clinical signs included hypoactivity, gasping, cyanosis, laboured rapid and audible respiration and ocular discharge food consumption: no significant differences among groups for any time period measured; no treatment related gross lesions at necropsy of does maternal organ weights: no significant difference among the groups: terminal bw., gravid uterine weight, corrected bw. or weight change, absolute and relative liver weight gestational parameters: no significant difference for number of ovarian corpora lutea, number of implantations sites including total, nonviable (early or late resorptions or dead fetuses) or viable percent live fetuses per litter or fetal body weight per litter; sex ratio was significantly increased (more males) at 50 mg/kg bw but not at 100 mg/kg bw (considered due to biological variabilty) fetal evaluation: No significant differences among groups for any individual malformations, malformations by category or total malformations; no treatment-related significant differences for any individual external variations, variations by category or total variations.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

06.02.2004 (170)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type	:	other
In vitro/in vivo	:	In vivo
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	28 d
Frequency of treatm.	:	continuously in diet
Duration of test	:	28 d
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
Result	:	See freetxt RS
Method	:	other: the reproductive organs were examined as part of the 28-day study, see chapter 5.4

Year	:	1991
GLP	:	yes
Test substance	:	other TS: p-cresol, Purity > 98 %
Result	:	Histopathological examination revealed no effects on the reproductive organs.
Reliability	:	(1) valid without restriction

06.02.2004 (150)

Type	:	other
In vitro/in vivo	:	In vivo
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	134 weeks
Frequency of treatm.	:	daily
Duration of test	:	14 weeks
Doses	:	0, 50,175, 600 mg/kg bw dissolved in corn oil
Control group	:	yes, concurrent vehicle
Result	:	600 mg-gr.: death of 3 females, decreased ovary weights; males: increased testes weight
Method	:	other: the reproductive organs were examined as part of the 13 week toxicity study, see chapter 5.4
Year	:	1986
GLP	:	yes
Test substance	:	other TS: p-cresol, purity 99.9 %
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

06.02.2004 (151)

5.9 SPECIFIC INVESTIGATIONS

Endpoint	:	Neurotoxicity
Study descr. in chapter	:	5.9 Specific Investigations
Reference	:	
Type	:	other: subchronic
Species	:	rat
Sex	:	male/female
Strain	:	other: CD
Route of admin.	:	gavage
No. of animals	:	20
Vehicle	:	other: corn oil
Exposure period	:	90 day(s)
Frequency of treatm.	:	once daily
Doses	:	0, 50, 175, 600 mg/kg bw
Control group	:	yes, concurrent vehicle
Observation period	:	13 weeks during dosing
Result	:	see freetext RS
Method	:	other: see freetext ME
Year	:	1986
GLP	:	no data
Test substance	:	other TS: purity: no data
Method	:	10 male and 10 female CD rats/treatment group received corn oil solutions of 50, 175 or 600 mg/kg bw /day by gavage once daily for 13 weeks. 20 male and 20 female CD rats received corn oil alond to serve as control.Rats were observed for body weight gain, food consumption, clinical signs.

Signs of neurobehavioral toxicity were documented during pretreatment, 1 and 6 hours after dosing on study day 1 and prior dosing on study days 2, 7, 14, 30, 60 and 90 including salivation, urination, tremors, piloerection, diarrhea, pupil size, pupil response, lacrimation, hypothermia, vocalization, exophthalmus, palpebral closure, convulsions (type and severity), respiration (rate and type), impaired gait, positional passivity, locomotor activity, stereotypy, startle response, righting reflex, performance on a wire maneuver, forelimb grip strength, positive geotropism, extensor thrust, limb rotation, tail pinch reflex, toe pinch reflex, hind limb splay.
gross and histopathologic examination

Result : Mortality: control: 1 female(2.5 %), 600 mg-gr: 4 males and 4 females (40 %), gross and histopathologic examination: aspiration or inhalation of the TS, pulmonary edema
body weight gain: 600 mg-gr., males less than control during week 1
mean food consumption, 600 mg-gr., males and females: significantly less than control
clinical signs: dose related in incidence: salivation, myotonus, tremors, urine wet abdomen, hypoactivity, rapid respiration
neurobehavioral toxicity:
600 mg-group, males and females: initial part of the study: incidence of palpebral closure, rales, laboured respiration; locomotor activity less than concurrent controls; at study termination: a trend towards increased urination.
Other differences from controls with regard to behavioral tests were evaluated as sporadic in nature by the authors (no further details given).
necropsy:
brain weights of treated animals comparable to controls; gross and microscopic examination of tissues revealed no lesions which were attributable to treatment

Reliability : (2) valid with restrictions
limited documentation (only study summary available)

Flag : Critical study for SIDS endpoint

04.02.2004 (145) (129) (171)

5.10 EXPOSURE EXPERIENCE

Remark : In vitro production of p-cresol from tyrosine by bacteria isolated from normal human gut was examined. Strictly anaerobic and facultatively anaerobic bacteria were grown at 37oC in the presence of 0.01% tyrosine for 72 and 48 hr respectively. The growth atmospheres for the bacteria were nitrogen, hydrogen and carbon dioxide and air respectively. p-Cresol production from tyrosine was seen with the strictly anaerobic gut bacteria but not the facultatively anaerobic bacteria. p-Cresol is, therefore, produced endogenously from tyrosine, an amino acid present in most proteins, by strictly anaerobic bacteria in the intestine.
According to the results of studies in cancer patients, endogenous p-Cresol does not contribute significantly to the development of large bowl caner (18 patients versus 10 normal healthy persons.

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

15.01.2003 (133)

Remark : The probable oral lethal dose for humans is 50-500 mg/kg bw.

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

10.01.2003 (172)

Remark : Case reports: intentional or accidental oral intake of cresols (all isomers): irritation of mouth and throat, abdominal pain, vomiting, hemolytic anemia, increased heart ratem liver and kidney damage, headaches, facial paralysis, drowsiness, cramps coma and death
Reliability : (2) valid with restrictions
description suffers from deficiencies as the isomers are not specified
Flag : Critical study for SIDS endpoint
14.01.2003 (173) (174) (175) (176)

Remark : It is reported that certain individuals are hypersensitive to cresol (isomer not specified, no further information)
Reliability : (4) not assignable
Flag : Critical study for SIDS endpoint
15.01.2003 (127)

Remark : Skin depigmentation (chemical leukoderma has been reported after local exposure to cresols (isomer not specified)
Reliability : (4) not assignable
Flag : Critical study for SIDS endpoint
15.01.2003 (150)

Remark : It is reported that skin contact has alo resulted in effects on the nervous system, liver and kidneys and caused human fatalities.
Reliability : (4) not assignable
Flag : Critical study for SIDS endpoint
17.01.2003 (175)

Remark : A cresol solution, unintentionally poured over the trunk, caused gross hematuria, gastrointestinal bleeding, hypertension and septic shock with severe jaundice and renal failure.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
15.01.2003 (177)

Remark : The development of tumours in persons who had been exposed occupationally to cresol (unspecified isomer) has been reported, and two cases of transitional cell bladder carcinoma were described after longterm exposure to cresol. since no information on exposure levels are available and since co-exposure to other ssubstances cannot be excluded a carcinogenic potential of the cresol isomers cannot be deduced fron these cases.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
15.01.2003 (178)

Remark : Case report: a worker in an oil rafinery was exposed to cresol, dichlorooctane and chromic acid for a long period developed a squamous epithelial carcinoma of the vocal cords. Since no information on exposure levels is available and since co-exposure to other substances is included a carcinogenic potential of the cresol isomers cannot be deduced from this case report.
Reliability : (4) not assignable
Flag : Critical study for SIDS endpoint

15.01.2003 (175)

Remark : Anomalous menstrual cycles were found and hormonal disorders were reported from women who were employed in ther production to enamelled wire or of tricresyl phosphate and were exposed to a variety of compounds, including chlorobenzenes and phosphoryl chloride. It was claimed that the incidence of perinatal child death was increased and that developmental disorders were frequent among new-born babies. since no data on exposure levels and duration of exposure are given and data on controls were not provided a relationship between fthe described effects and cresol exposure cannot be deduced.
Reliability : (4) not assignable
Flag : Critical study for SIDS endpoint
15.01.2003 (175)

Remark : According to the results of studies in patients, endogenous p-Cresol does not contribute significantly to the development of human bladder (32 patients vs 32 age/sex-matched controls).
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
15.01.2003 (132)

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I U C L I D

Data Set

Existing Chemical	:	ID: 15831-10-4
CAS No.	:	15831-10-4
EINECS Name	:	m-Cresol, compd. with p-cresol (2:1) (8CI)

Producer related part

Company	:	Bayer AG
Creation date	:	12.01.2001

Substance related part

Company	:	Bayer AG
Creation date	:	12.01.2001
Status	:	
Memo	:	ICCA m/p-Cresol mixture
Printing date	:	24.05.2004
Revision date	:	
Date of last update	:	24.05.2004
Number of pages	:	87
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type : cooperating company
Name : American Chemistry Council, Cresols Panel
Contact person :
Date :
Street : 1300 Wilson Blvd.
Town : 22209 Arlington, VA
Country : United States
Phone : 703-741-5629
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

Type : cooperating company
Name : ADCHEMCO Corporation
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

Type : cooperating company
Name : Bayer Corporation
Contact person :
Date :
Street : 100 Bayer Road
Town : PA 15205-9741 Pittsburgh
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
28.02.2001

Type : cooperating company
Name : Concord Chemical Company
Contact person :
Date :
Street :
Town :

Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
28.02.2001

Type : cooperating company
Name : Dakota Gasification Company
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
28.02.2001

Type : cooperating company
Name : Honshu Chemical Industry Company, Ltd.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

Type : cooperating company
Name : LaPorte (formerly Inspec Fine Chemicals, Inc.)
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
28.02.2001

Type : cooperating company
Name : Merisol (Merichem-Sasol USA LLC)
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
28.02.2001

Type : cooperating company
Name : Mitsui Chemicals, Inc.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

Type : cooperating company
Name : Nippon Steel Chemical Company, Ltd.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

Type : cooperating company
Name : PMC Specialties Group, Inc.
Contact person :
Date :
Street :
Town :
Country : United States
Phone :
Telefax :

Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
28.02.2001

Type : cooperating company
Name : Sumikin Chemical Company, Ltd.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

Type : cooperating company
Name : Sumitomo Chemical Company, Ltd.
Contact person :
Date :
Street :
Town :
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint
31.05.2001

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : organic

Physical status : liquid
Purity :
Colour :
Odour :

Remark : mixture of m-cresol (60-75%) and p-cresol (25-40%)
20.01.2003

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

m-/p-cresol mixture

Flag : Critical study for SIDS endpoint
20.01.2003

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : - tonnes produced in

Remark : 128,000 t in 2001, estimated world capacity
Flag : Critical study for SIDS endpoint
28.05.2002

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits :
Symbols : T, , ,
Nota : , ,
R-Phrases : (24/25) Toxic in contact with skin and if swallowed
(34) Causes burns
S-Phrases : (36/37/39) Wear suitable protective clothing, gloves and eye/face protection
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)

Remark : labelling for m- and p-Cresol
Flag : Critical study for SIDS endpoint
20.01.2003

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC
Class of danger : corrosive

R-Phrases : (34) Causes burns
Specific limits :

Remark : classification for m- and p-Cresol
20.01.2003

Classified : as in Directive 67/548/EEC
Class of danger : toxic
R-Phrases : (24/25) Toxic in contact with skin and if swallowed
Specific limits :

Remark : classification for m- and p-Cresol
20.01.2003

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : industrial
Category : Chemical industry: used in synthesis

29.05.2002

Type of use : use
Category : Intermediates

29.05.2002

Type of use : use
Category : Solvents

29.05.2002

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : TLV (US)
Limit value : 5 other: ppm

Remark : Skin notation. Critical effects: dermatitis, irritation, CNS
Flag : Critical study for SIDS endpoint
20.01.2003 (1)

Type of limit : TLV (US)

Limit value : 22 mg/m3

Remark : Skin notation. Critical effects: dermatitis, irritation, CNS.
Flag : Critical study for SIDS endpoint
21.03.2001 (2)

Type of limit : MAK (DE)
Limit value : 5 other: ppm
Short term exposure limit value
Limit value : 5 other: ppm
Time schedule :
Frequency : times

Remark : Risk of cutaneous absorption
Source : TRGS 900 (DE)
Flag : Critical study for SIDS endpoint
27.05.2002

Type of limit : MAK (DE)
Limit value :

Remark : MAK list Canc. cat 3A
Danger of resorption through the skin.
27.05.2002 (3)

Type of limit : MAC (NL)
Limit value : 22 mg/m3

Remark : Grenswaarde voor blootstelling van korte duur:
a) Numerieke waarde: onbekend
b) Meeteenheid : onbekend
c) Numerieke waarde: onbekend
d) Tijdscheme : onbekend
e) Frequentie : onbekend
Source : B.V. CONSOLCO Amsterdam
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
21.03.2001

Type of limit : MAK (DE)
Limit value : 22 mg/m3

Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
07.06.1994 (4)

Type of limit : MAK (DE)
Limit value : 22 mg/m3
Short term exposure limit value
Limit value : 22 mg/m3
Time schedule :
Frequency : times

Remark : danger of cutaneous absorption
Source : TRGS 900 (DE)
Flag : Critical study for SIDS endpoint
24.05.2002

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : other: Bayer AG
Labelled by :
Class of danger : 2 (water polluting)

27.05.2002

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung (DE)
Substance listed :
No. in Seveso directive :

Remark : Annex I, No. 2
27.05.2002

1.8.5 AIR POLLUTION

Classified by : TA-Luft (DE)
Labelled by :
Number : 3.1.7 (organic substances)
Class of danger : I

27.05.2002

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered :
Date of search :

Remark : Toxicology: November 2002
Environmental aspects and ecotoxicology: January 2002
Search in external and internal databases, e.g. HSDB, Aquire, Biosis, Embase, Toxline, Scisearch.

22.01.2003

1.13 REVIEWS

2.1 MELTING POINT

Value : ca. 10 °C
Sublimation :
Method : other: no information supplied
Year : 2001
GLP : no data
Test substance : other TS: 63-75 % m-cresol + 25-36 % p-cresol (dried)

Flag : Critical study for SIDS endpoint
11.05.2004 (5)

2.2 BOILING POINT

Value : ca. 200 °C at
Decomposition :
Method : other: no information supplied
Year : 2001
GLP : no data
Test substance : other TS: 63-75 % m-cresol + 25-36 % p-cresol

Flag : Critical study for SIDS endpoint
11.05.2004 (5)

2.3 DENSITY

Type : density
Value : ca. 1.035 g/cm³ at 20 °C
Method : other: no information supplied
Year : 2001
GLP : no data
Test substance : other TS: 63-75 % m-cresol + 25-36 % p-cresol

Flag : Critical study for SIDS endpoint
11.05.2004 (5)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : ca. 1 hPa at 20 °C
Decomposition :
Method : other (measured)
Year : 2001
GLP : no data
Test substance : other TS: 63-75 % m-cresol + 25-36 % p-cresol

Remark : static method, the measured value is presumably higher than the vapour pressure for the m- and p-cresol isomers, because of the water content the m/p-mixture which is not separated with the static method

vapour pressure for m- and p-cresol isomers = 0.147 hPa
Result : other results:

ca. 6 hPa at 50 °C
ca. 8 hPa at 55 °C

11.05.2004 (5)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	
Log pow	:	1.94 - 1.96 at °C
pH value	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	other TS: isolated cresol isomers
Remark	:	The log octanol-water partition coefficients of the cresol isomers range from 1.94-1.96
Flag	:	Critical study for SIDS endpoint

11.05.2004 (6)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	24.4 g/l at °C
pH value	:	4.3
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: measured
Year	:	2003
GLP	:	no data
Test substance	:	other TS: 63-75 % m-cresol + 25-36 % p-cresol
Remark	:	measured at room temperature
Flag	:	Critical study for SIDS endpoint

11.05.2004 (7)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	ca. 86 °C
Type	:	
Method	:	other: DIN 51758
Year	:	2001
GLP	:	no data
Test substance	:	other TS: 63-75 % m-cresol + 25-36 % p-cresol

11.05.2004 (5)

2.8 AUTO FLAMMABILITY

Value : >= 500 °C at
Method : other: DIN 51794
Year : 2001
GLP : no data
Test substance : other TS: 63-75 % m-cresol + 25-36 % p-cresol

Remark : Ignition temperature
Test substance : 63-75% m-cresol + 25-36% p-cresol
11.05.2004 (5)

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Result : other: lower limit ca 1.1%, upper limit 7.6% by vol.

Test substance : 63-75% m-cresol + 25-36% p-cresol
22.10.2001 (5)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

Test type : Capillary Method
Test procedure : DIN 53211
Value : ca. 18.6 - mm2/s (static) at °C
Result :
Method : other: DIN 53211
Year : 2001
GLP : no data
Test substance : other TS: 63-75 % m-cresol + 25-36 % p-cresol

11.05.2004 (5)

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (measured)
Year	:	1995
GLP	:	no data
Test substance	:	other TS: m-cresol, purity > 99 %
Method	:	Determination of the temperature-dependency of the OH-radical reaction under simulated tropospheric conditions
Remark	:	With a OH radical concentration of 1 000 000 molec cm-3 and a temperature of 299 K, the half-life is 3.8 h
Result	:	kOH = 5.17 x 10E-12 exp[(686+-231)/T] cm3 molec.-1 s-1 for a temperature range of 299-373 K
Test condition	:	test substance concentration 0.05-5 ppm reference compound (o-cresol) 0.05-2.3 ppm radical source methylnitrite 1.5-11 ppm together with NOx 2-70 ppm
Reliability	:	(1) valid without restriction Test procedure in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

12.05.2004 (8)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (measured): critical review
Year	:	1994
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	With a OH radical concentration of 1 000 000 molec/cm3, the half-life is 3.0 h at room temperature
Result	:	K[OH] = 64 [10E-12 cm3 molecule-1 s-1] K[NO3] = 9.74[10E-12 cm3 molecule-1 s-1] K[O3] = 1.9 [10E-19 cm3 molecule-1 s-1]
Reliability	:	(1) valid without restriction Critical review, evaluation of all available experimental data
Flag	:	Critical study for SIDS endpoint

11.05.2004 (9)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (measured)
Year	:	1990
GLP	:	no data
Test substance	:	other TS: m-cresol, purity > 99 % (obtained from Aldrich Chemical Company)

Method : smog chamber experiment with black light irradiation
dry air pressure 735 Torr
Temp. 296+-2 K
irradiation time 4-20 min
reference substance: propene
OH radical concentration: (1-3) x 10E7 molecule cm-3
Result : k[OH] = 67.8 [10E-12 cm3 molecule-1 s-1]
Reliability : (1) valid without restriction
Test procedure in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions

11.05.2004 (10)

Type : air
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product :
Method :
Year : 1987
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Method : I. Smog chamber experiment
II. Inkrement method
Result : m-cresol:
I. observed: k[OH] = 57 [10E-12 cm3 molecule-1 s-1]
II. calculated: k[OH] = 94 [10E-12 cm3 molecule-1 s-1]
Reliability : (1) valid without restriction
Test procedure in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions

12.05.2004 (11)

Type : air
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product :
Method : other (measured)
Year : 1978
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Method : smog chamber
Temp. 300 +-1 K
reference substances: n-butane, neopentane
initial concentration ca. 0.25 ppm for m-cresol
OH radical concentration: (1-4)x10E6 molecule cm-3
Result : k[OH] = 67 [10E-12 cm3 molecule-1 s-1]
Reliability : (1) valid without restriction
Test procedure in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions

12.05.2004 (12) (13)

Type : air
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight

Deg. product :
Method :
Year : 1989
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Method : No information on the method
Result : K[OH] = 59 [10E-12 cm3 molecule-1 s-1]
t[1/2] = 0.3 d
Reliability : (4) not assignable
secondary literature
11.05.2004 (14)

Deg. product :
Method : other (measured)
Year : 1985
GLP : no data
Test substance : other TS: m-cresol, no purity reported, but in most cases purity exceeded 98 %

Method : substance adsorbed onto silica gel (100 ng/g)
irradiated with UV lamp (290 nm) in a microphotoreactor
Result : degradation 33.3% of applied amount
Test condition : 17 h at 15 degrees C
Reliability : (3) invalid
Unsuitable test system
12.05.2004 (15)

3.1.2 STABILITY IN WATER

Deg. product :
Method :
Year :
GLP :
Test substance : other TS: m-cresol

Remark : Based on the chemical structure of the compound hydrolysis is not expected under temperature and pH values occuring in the environment.
Reliability : (2) valid with restrictions
Expert judgement
Flag : Critical study for SIDS endpoint
11.02.2003

3.1.3 STABILITY IN SOIL

Type : laboratory
Radiolabel :
Concentration :
Soil temperature : °C
Soil humidity :
Soil classification :
Year :
Deg. product :
Method :
Year : 1990
GLP : no
Test substance : other TS: m-cresol

Method	:	Bench-scale experiments with contaminated soil. Determination of passive evaporation and biodegradation of cresols
Result	:	passive evaporation half-life 4.2 - 4.8 weeks biodegradation: after 4 days below detection limit
Test condition	:	Passive evaporation: plastic petri plates (88x18 mm) placed on canopy-covered table. Temp. 10-17 degrees C, humidity 75% Shake-flask biodegradation test: 8-25 g soil mixed with 50 ml buffer solution; shaken for 4 days
Reliability	:	(3) invalid Methodological deficiencies

11.02.2003 (16)

Type	:	laboratory
Radiolabel	:	yes
Concentration	:	
Soil temperature	:	°C
Soil humidity	:	
Soil classification	:	
Year	:	
Deg. product	:	
Method	:	other: see Method below
Year	:	1985
GLP	:	no
Test substance	:	other TS: m-cresol
Method	:	Inocolum: subsurface microbial community of a pristine aquifer (Lula, Okla.) Soil: aquifer solid sample, unconsilated sand, from a depth of 4.5-5.6 m below surface All substances were radiolabeled. Incubation period: 8 months Determination of mineralization via 14CO2 evolution
Remark	:	The highest percent biodegradation achieved for nearly all the substances tested was 35% (e.g. anilin, which is the standard reference substance for all ready tests in OECD 301 achieved after 100 days only 15% biodegradation).
Result	:	- After 160 days and at a concentration of 39 ng/g m-cresol in soil, ca.15% mineralization was observed. - The percent mineralized increased slowly and linearly with time. - For the majority of the test compounds no adaptation period was observed.
Reliability	:	(3) invalid No standard test procedure. Test design can only be used to assess degradation in soil of the pristine aquifer of Lula, Okla.

11.02.2003 (17)

3.2.1 MONITORING DATA

Type of measurement	:	other: contamination at a special working place
Media	:	
Concentration	:	
Method	:	
Remark	:	Combined m-/p-cresol isomers were detected among other chemicals in the indoor air at a shale oil wastewater facility at a concentration of 5.1 ppb.

Reliability : (2) valid with restrictions
Basic data given

20.01.2003 (18)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : volatility
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: measured
Year : 1999

Method : Thermodynamic column method of Brunner et al. 1990 applied [Brunner S, Hornung E, Santl H, Wolff E, Pringer OG, Altschuh J, Brueggemann R (1990) Henry´s law constants for polychlorinated biphenyls: Experimental determination and structure-property relationship. Environ Sci Technol 24, 1751 - 1754]:
- Aqueous solution of the TS produced in a generator column
- Solution is passed through gas liquid desorption column where it contacts a gas stream and the partition equilibrium is reached
- Gas and water are separated: water flows to the receiver dosing funnel, the gas is conducted into an absorption vessel where the TS is absorbed in organic solvent

Result : Henry's law constant (25 degrees C) for m-cresol:
H = 3.5 E-5 calculated to
H = 8.67 E-2 Pa.m3.mol-1

Test condition : - Temperature 25 °C
- Gas phase: Nitrogen
- Liquid phase: Demineralized, distilled water
- Analysis: GC/ECD

Reliability : (2) valid with restrictions
basic data given

Flag : Critical study for SIDS endpoint

12.05.2004 (19)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: batch equilibrium method similar to OECD Guideline 106
Year : 1982

Remark : Koc value was determined for clay loam soil
Result : Koc=34.58 for m-cresol
Test condition : Test substance: m-cresol
Soil: Brookston clay loam soil, collected from top 15 cm, air-dried, 5.10 % organic matter, pH 5.7
soil/solution ratio 1:10
TS concentrations 5, 10, 20, 30, 50 mg/l, deoxygenated by

purging with N2
triplicate samples, temp. 20+-1 degrees C, incubation period 24 h

Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with general accepted scientific standards; sufficient documentation

Flag : Critical study for SIDS endpoint
12.05.2004 (20)

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level I
Year : 2001

Result : Calculation for m-cresol:
Calculated distribution between environmental compartments:
Air: 2.33 %
water: 96.32 %
soil: 0.69 %
bottom sediment: 0.65 %
suspended sediment: 0.001 %
biota: 0.0004 %

Test condition : data used in calculation
temperature (°C): 25
molar mass (g/mol): 108.14
vapor pressure (Pa): 14.7
water solubility (g/l): 22.7
log Kow: 1.96

volumes in unit world (m3)
air: 6 000 000 000
water: 7 000 000
soil: 45 000
sediment: 21 000
susp. sediment: 35
biota (fish): 7

Reliability : (2) valid with restrictions
generally accepted calculation method

Flag : Critical study for SIDS endpoint
11.02.2003 (21)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : predominantly domestic sewage
Concentration : .8 mg/l related to COD (Chemical Oxygen Demand)
related to
Contact time :
Degradation : = 90 (±) % after 28 day(s)
Result : readily biodegradable
Kinetic of testsubst. : 7 day(s) = 45 - 80 %
14 day(s) = 70 - 90 %
21 day(s) = 75 - 70 %
28 day(s) = 90 - 90 %

%
Control substance : other: phenol, 0.8 mg/l
Kinetic : 28 day(s) = 73 %
%
Deg. product :
Method : OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year : 1988
GLP : no
Test substance : other TS: m-cresol pure

Result : 10-day window criteria is met
Test condition : Inoculum
- Type of sludge: activated sludge
- Source: treatment plant, receiving domestic sewage
- Sampling site: Odenthal
Concentration of control substance: 0.8 mg/l
Analytical parameter: Oxygen consumption
Test temperature: 20 degrees C
Test was performed in two paralleles.

Reliability : (2) valid with restrictions
Guideline Study
Flag : Critical study for SIDS endpoint
12.05.2004 (22)

Type : aerobic
Inoculum : predominantly domestic sewage
Concentration : 2.4 mg/l related to COD (Chemical Oxygen Demand)
related to
Contact time :
Degradation : = 65 (±) % after 28 day(s)
Result :
Kinetic of testsubst. : 7 day(s) = 55 - 58 %
14 day(s) = 58 - 66 %
21 day(s) = 61 - 65 %
28 day(s) = 65 - 65 %
%
Control substance : other: phenol, 2.4 mg/l
Kinetic : 28 day(s) = 69 %
%
Deg. product :
Method : OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year : 1988
GLP : no
Test substance : other TS: m-cresol pure

Remark : In two further tested concentrations (8 and 24 mg/l) the dissolved oxygen was completely emaciated within 7 days (concentration of control substance 8 and 24 mg/l for tests with 8 and 24 mg/l of test substance, respectively. Also i n these control experiments, oxygen was emaciated).
Result : Compared to the test with 0.8 mg/l the extent of degradation is lesser at 2.4 mg/l presumably due to the fact that most of the oxygen was used up at the high test substance concentration
Test condition : Inoculum / test organism
- Type of sludge: activated sludge
- Source: treatment plant, receiving domestic sewage
- Sampling site: Odenthal
Concentration of control substance: 2.4 mg/l
Analytical parameter: Oxygen consumption
Test temperature: 20 degrees C

Test was performed in two paralleles.
Reliability : (2) valid with restrictions
Guideline Study
12.05.2004 (22)

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : 100 mg/l related to Test substance
related to
Contact time :
Degradation : 80 - 95 (±) % after 40 day(s)
Result :
Deg. product :
Method : other: comparable to OECD Guide-line 301 C
Year : 1981
GLP : no
Test substance : other TS: m-cresol, purity > 99 %

Method : Initial sludge concentration: 30 mg d.w./l; aniline as reference compound
Remark : Incubation period: 20-40 days; no oxygen uptake curve given; degradation of reference substance aniline >/= 60 % within 28 days
Result : The oxygen uptake curves are not reported. However, the authors state that all test compounds revealed the lag phase, biodegradation phase and the plateau region within a period of 10 days, indicating that the 10-day window criteria is met.
First order biodegradation constant (hr-1): ln k = -5.77
maximum specific substrate uptake rate per unit biomass km = 17.3 / day (Aniline 16.1, Phenol 16.9).
m-Cresol is slightly better biodegradable than phenol and aniline.
Test condition : Inoculum /test organism
- Type of sludge: activated
- Source: municipal treatment plant, receiving predominantly domestic sewage
- Initial cell concentration: 30 mg/l
Test system
- Culturing apparatus: Sapromat
- Closed vessels used: yes
Initial test substance concentration: 100 mg/l
Duration of the test: 20-40 days
Test conditions
- Composition of synthetic medium: OECD
- Test temperature: 25 degrees C
Reference substance: aniline 100 mg/l
Reliability : (2) valid with restrictions
study comparable to OECD Guideline 301 C
Flag : Critical study for SIDS endpoint
12.05.2004 (23)

Type : aerobic
Inoculum : activated sludge, industrial
Contact time :
Degradation : 96 (±) % after 10 day(s)
Result :
Deg. product :
Method : OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year : 1990
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Result	:	90% degradation during the log-phase (8 days)
Test condition	:	Test substance conc. 50-400 mg/l DOC, 200-1000 mg/l COD acclimatization phase 2 days
Reliability	:	(2) valid with restrictions Guideline study; basic data given
Flag	:	Critical study for SIDS endpoint
24.05.2004		(24)

Type	:	aerobic
Inoculum	:	activated sludge, adapted
Concentration	:	200 mg/l related to COD (Chemical Oxygen Demand) related to
Contact time	:	
Degradation	:	95.5 (±) % after 5 day(s)
Result	:	
Deg. product	:	
Method	:	other: batch system (similar to OECD 302B "Zahn-Wellens Test")
Year	:	1976
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	- Test compound was sole source of carbon - Inoculum density: 100 mg dry matter/l; gradual increase of TS concentration during 20 days adaptation period - With volatile substances a test without inocculum was done to differentiate the actual biological degradation from the losses due to mere volatilization
Result	:	Initial degradation rate: 55.0 mg COD/g/h
Test condition	:	20 +- 3 degrees C; pH 7.2; mineral salts medium; dark; continuously stirred
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; basic data given
Flag	:	Critical study for SIDS endpoint
24.05.2004		(25)

Type	:	anaerobic
Inoculum	:	anaerobic sludge
Deg. product	:	yes
Method	:	
Year	:	1981
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Deg. products	:	74-82-8 200-812-7 methane
Method	:	primary anaerobic sludge from 12 treatment plants receiving mainly domestic wastewater were diluted to 10 % in a mineral salts medium, test substance concentration: 30 mg/l; secondary anaerobic sludge from 2 treatment plants diluted to 10 % in a mineral salts medium, test substance: 50 mg/l; incubation for 8 weeks; triplicate samples
Result	:	primary sludges: no degradation was observed in 4 sludges; degradation ranged from 55 to 103 % in 6 sludges (lag times for approx 20 % of theoretical CH4 production: 4-6 weeks); insufficient data for 2 sludges. secondary sludge: degradation was 92% after 4 weeks with the first sludge and

90% after 5 weeks with the second (degradation related to theoretical methane and CO2 production)
Test condition : 35 degrees C, due to storage of sludges before incubation, lag phase of methanogenesis could be increased in some sludges
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag : Critical study for SIDS endpoint
12.05.2004 (26)

Type : anaerobic
Inoculum : anaerobic sludge
Concentration : 50 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time : 56 day(s)
Degradation : (±) % after
Result :
Deg. product : yes
Method :
Year : 1984
GLP : no
Test substance : other TS: m-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Method : primary and secondary anaerobic sewage sludge from 9 treatment plants diluted to 10 % in a mineral salts medium; degradation measured as gas pressure increase
Remark : data have been published by the authors as a NTIS-study (previous data set)
Result : in 2 different secondary sludges >75% degradation
in 9 different primary sludges degradation 0-103%
Test condition : incubation for 8 w at 35 degrees C
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
Flag : Critical study for SIDS endpoint
12.05.2004 (27)

Type : anaerobic
Inoculum : anaerobic sludge
Concentration : 50 mg/l related to DOC (Dissolved Organic Carbon) related to
Deg. product : yes
Method :
Year : 1988
GLP : no
Test substance : other TS: m-cresol, no purity given (obtained from Aldrich Chemicals)
Deg. products : 74-82-8 200-812-7 methane

Method : primary anaerobic digesting sludge receiving a mixture of domestic and industrial wastewater
Result : lag time 40 days, accompanied with inhibition of gas production
net total gas production was 75 % +/- 15 % of the theoretical production (CH4+CO2)
Test condition : - medium 2-3 g dw/l sludge
- incubation for >= 60 d at 35 degrees C
- 3 replicates

- sterile controls for abiotic gas production
- gas production measured with hand-held pressure meter

Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
Flag : Critical study for SIDS endpoint
11.02.2003 (28)

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : .05 mg/l related to Test substance
related to
Contact time :
Degradation : 35.6 (±) % after 5 day(s)
Result :
Deg. product :
Method : other: Activated sludge test
Year : 1985
GLP : no
Test substance : other TS: 14C-labelled m-cresol presumably > 98 % purity; no specific activity given

Remark : The bioaccumulation factor of the substance and its metabolites in activated sludge was 1100
Result : The readily biodegradable compounds methanol and phenol were about equally degraded like m-Cresol (41, 37 and 36 %)
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
24.05.2004 (15)

Type : aerobic
Inoculum : other bacteria: acclimatized mixed culture of pentachlorophenol-degrading bacteria
Concentration : 5 mg/l related to Test substance
related to
Contact time : 29 day(s)
Degradation : (±) % after
Result :
Kinetic of testsubst. : 38 hour(s) 50 %
46 hour(s) 90 %
%
%
%
Deg. product :
Method : other: Die-away Test
Year : 1990
GLP : no
Test substance : other TS: m-cresol, gas chromatographic grade

Result : no lag phase
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
24.05.2004 (29)

Type : aerobic
Inoculum : other: denitrifying cultures from unadapted mixed wastewater

Concentration : .39 mg/l related to Test substance
related to
Contact time :
Degradation : 100 (±) % after 17 day(s)
Result :
Deg. product :
Method : other: measured
Year : 1989
GLP : no
Test substance : other TS: m-cresol, no purity reported

Result : lag phase 3 days, completely degraded in 17 d
Test condition : inoculum prepared by mixing waste water samples from 12 denitrifying treatment plants
incubated at 27 degrees C in the dark
Reliability : (2) valid with restrictions
Study in accordance with generally accepted scientific standards and described in sufficient detail

24.05.2004 (30)

Type : anaerobic
Inoculum : other: municipal sewage sludge from primary anaerobic digesters
Concentration : 50 mg/l related to Test substance
related to
Contact time : 56 day(s)
Degradation : 100 (±) % after 49 day(s)
Result :
Deg. product : yes
Method : other: measured
Year : 1983
GLP : no
Test substance : other TS: m-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Result : substance disappeared completely after 7 weeks
net CH4 production >90% of theoretical value
no transformation products observed
Test condition : mineral salt medium with 10% sludge
Temperature 35 degrees C
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (31)

Type : anaerobic
Inoculum : anaerobic sludge
Deg. product : yes
Method : other: measured
Year : 1983
GLP : no
Test substance : other TS: m-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Remark : sensitivity of acid formers and methanogenic consortia examined
Result : at <= 400 mg/l, m-cresol was not fermented and showed no inhibition of methane formation from degradable substrates as compared to control cultures; 1000 mg/l inhibited the methane production significantly (60 % of control values)

Test condition : screening optimized for mechanistic study
m-cresol concentration: 200, 400 or 1000 mg/l
incubation for 6 w at 37 degrees C
Reliability : (4) not assignable
No standard test procedure, but in accordance with generally accepted scientific standards; not relevant for purpose of HPV program
12.05.2004 (32)

Type : anaerobic
Inoculum : other: anaerobic sludge, adapted
Concentration : 300 mg/l related to Test substance
related to
Deg. product : yes
Method : other: see test condition
Year : 1986
GLP : no
Test substance : other TS: m-cresol, no purity reported (Aldrich chemicals) (methyl 14C-labelled from Pathfinder Lab.)
Deg. products : 74-82-8 200-812-7 methane

Result : Degradation: ca. 100 % after 9 days
Most of the methyl carbon of m-cresol (87 %) was converted to CH4.
Test condition : preincubation for 2-3 months
incubation for 20 d at 37 degrees C
Test substance : 14C-methyl labeled
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
12.05.2004 (33)

Type : anaerobic
Inoculum : anaerobic sludge
Concentration : 50 mg/l related to DOC (Dissolved Organic Carbon)
related to
Deg. product : yes
Method : other: measured
Year : 1982
GLP : no
Test substance : other TS: m-cresol, purity > 95 %
Deg. products : 74-82-8 200-812-7 methane

Method : - Sludge from 2 municipal plants
- Methane production monitored
- HPLC to monitor disappearance of substrate
Result : mineralization (related to theoretical methane and CO2 production) was 92% after 4 weeks with the first sludge and 90% after 5 weeks with the second
Test condition : incubation at 35 degrees C in the dark, 10 % sludge inoculum, duplicate tests
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
12.05.2004 (34)

Type : anaerobic
Inoculum : other: anoxic lake sediment
Concentration : .1 mg/l related to Test substance
.8 mg/l related to Test substance

Deg. product : yes
Method : other: measured
Year : 1982
GLP : no
Test substance : other TS: m-cresol, purity > 95 %
Deg. products : 74-82-8 200-812-7 methane

Result : after 29 weeks no significant CH4 or CO2 formation observed
Test condition : incubation at 20 degrees C in the dark with occasional shaking
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
12.05.2004 (34)

Type : anaerobic
Inoculum : other bacteria: acclimatized mixed culture of pentachlorophenol-degrading bacteria
Concentration : 5 mg/l related to Test substance related to
Contact time : 29 day(s)
Degradation : (±) % after
Result :
Kinetic of testsubst. : 144 hour(s) 10 %
197 hour(s) 50 %
236 hour(s) 90 %
%
%
Deg. product :
Method : other: Die-away Test
Year : 1990
GLP : no
Test substance : other TS: m-cresol, gas chromatographic grade

Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
11.02.2003 (29)

Type : anaerobic
Inoculum : other: phenol-enriched methanogenic culture
Concentration : 100 mg/l related to Test substance related to
Contact time :
Degradation : 100 (±) % after 58 day(s)
Result :
Deg. product : yes
Method : other: measured
Year : 1988
GLP : no
Test substance : other TS: m-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Result : lag time 42 d, complete disappearance after 58 d, the CH4 production was 85 % of the theoretical production
Test condition : nominal test concentrations m-cresol 50, 100, 150, 250, 300, 400, 500, and 700 mg/l + phenol 200 mg/l
incubation at 35 °C with continuous shaking
Reliability : (2) valid with restrictions

No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (35)

Type : anaerobic
Inoculum : other: shallow anaerobic alluvial sand aquifer
Deg. product : yes
Method : other: measured
Year : 1986
GLP : no
Test substance : other TS: m-cresol, no purity reported (obtained from Aldrich Chemical Co.)
Deg. products : 74-82-8 200-812-7 methane

Method : 2 sampling sites: 1 methanogenic, 1 sulfate-reducing
both aquifers receive leachate from a municipal landfill
Result : lag time 43 days under sulfate-reducing and 46-90 days under methanogenic conditions, no data for complete degradation given
Test condition : test medium: 50 g [wet weight] of aquifer solids and 50 ml of groundwater
incubation at room temperature in the dark, quadruplicates
preincubation 5 days, addition of 150 to 200 µM test substance
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (36)

Type : anaerobic
Inoculum : other: undefined methanogenic consortia from river sediment
Concentration : 54 mg/l related to Test substance
related to
Deg. product : yes
Method : other: measured
Year : 1989
GLP : no
Test substance : other TS: m-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Method : black anoxic mud collected from a river inoculated in a mineral medium (10% w/v)
Result : non-acclimated consortia: turnover rate 1.10 µmol/day/g sediment dw (lag-phase 16 d)
acclimated consortia: turnover rate 2.37 µmol/day/g sediment dw (lag-phase 0 d, based on a 24-days-incubation period), the CH4 production was 96 % of the theoretically possible yield
Test condition : incubation at 28 degrees C in the dark
cultures were refed with 60 mg/l test substance every 2-4 w for a total of 18 months
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (37)

Type : aerobic
Inoculum :
Concentration : 10 mg/l related to Test substance

related to
Contact time : 3 day(s)
Degradation : 26 - 100 (±) % after 3 day(s)
Result :
Deg. product :
Method : other: cultivation method
Year : 1987
GLP : no data
Test substance : other TS: m-cresol, no purity reported in abstract

Result : biodegradation in river water = 100 %
biodegradation in sea water = 26 %
The authors assume the compound to be moderately to easily biodegradable
Reliability : (4) not assignable
Japanese reference with short abstract in English
12.05.2004 (38)

Type : anaerobic
Inoculum : other: microcosm containing aquifer and ground water
Concentration : 18 mg/l related to Test substance
related to
Deg. product : yes
Method : other: measured
Year : 1989
GLP : no data
Test substance : other TS: m-cresol, no purity reported
Deg. products : 74-82-8 200-812-7 methane

Result : lag time 110 days, disappearance after approx. 225 d (values taken from a graphics)
Test condition : methanogenic conditions in a microcosm
Reliability : (3) invalid
Insufficient documentation
12.05.2004 (39)

Type : anaerobic
Inoculum : other: anoxic aquifer
Concentration : 300 µmol/l related to Test substance
related to
Deg. product :
Method : other: measured
Year : 1990
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Method : anoxic aquifer slurries held under sulfate- and nitrate-reducing conditions
Result : m-cresol was largely degraded in less than 6 d
degradation dependant on sulfate, inhibited by 1.0 mM molybdate, not influenced by bromoethanesulfonic acid
Reliability : (4) not assignable
only abstract available
12.05.2004 (40)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species	:	Leuciscus idus melanotus (Fish, fresh water)
Exposure period	:	3 day(s) at °C
Concentration	:	.05 mg/l
BCF	:	20
Elimination	:	no data
Method	:	other: measured
Year	:	1985
GLP	:	no
Test substance	:	other TS: 14C-labelled m-cresol presumably > 98 % purity; no specific activity given
Remark	:	Determination of radioactivity includes possible metabolized and/or incorporated intermediates The authors report BCF in different tables to be 17 or 20
Test condition	:	5 fish (2-4 g) were exposed to m-cresol in a closed system and concentrations were determined by following radioactivity in fish and water; BCF values related to wet weight; 20-25 degrees C; pH 7; hardness 100 mg CaO/l
Reliability	:	(2) valid with restrictions No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail
Flag	:	Critical study for SIDS endpoint

12.05.2004 (15)

Species	:	other: Chlorella fusca (algae)
Exposure period	:	24 hour(s) at °C
Concentration	:	.05 mg/l
Elimination	:	no data
Method	:	other: measured
Year	:	1985
GLP	:	no
Test substance	:	other TS: 14C-labelled m-cresol presumably > 98 % purity; no specific activity given
Remark	:	In this study BCF-values of 40 and 4,900 for algae are reported without explanation for the difference. It is a common observation that test substance adsorbes at the surface of the algae. Due to the high surface / volume ratio a high BCF could be obtained.
Test condition	:	20-25 degrees C
Reliability	:	(2) valid with restrictions No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (15)

Species	:	other: Activated Sludge
Exposure period	:	5 day(s) at °C
Concentration	:	
BCF	:	1100
Elimination	:	
Method	:	other: measured
Year	:	1985
GLP	:	no
Test substance	:	other TS: 14C-labelled m-cresol presumably > 98 % purity; no specific activity given

Remark : Values of bioaccumulation factors range from 10 up to 42,800.
Esters and higher alcohols are placed in the intermediate range between 3,000 and 5,000. Sodium acetat with an accumulation factor of 29,100 is remarkable. In this ranking m-Cresol belongs to the group of compounds with low accumulation potential.
Correlation between accumulation factors and physico-chemical parameters was not practicable.

Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail.

12.05.2004 (15)

3.8 ADDITIONAL REMARKS

Memo : biodegradation under anaerobic conditions

Method : enrichment cultures prepared by addition of 3 g/l m-cresol once per week
initial concentration 200-300 mg/l test substance
incubation at 37 degrees C in the dark

Result : 1st step: incorporation of CO2 giving 4-hydroxy-2-methylbenzoic acid
2nd step:
2a: dehydroxylation to 2 methylbenzoic acid (not further metabolized) to a minor degree
2b: ring reduction, ring fission and beta-oxidation to acetate. Ring reduction appeared to be the rate-limiting step, because no subsequent intermediates accumulated

Test substance : 1. U-ring-14C m-cresol
2. methyl-14C m-cresol

Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

11.12.2002 (41)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	8.9
Limit test	:	
Analytical monitoring	:	yes
Method	:	other: US EPA, Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians. Nat. Environm. Res. Center, Corvallis (1974)
Year	:	1980
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Method	:	Mean length/mean weight of fish: 7.9 cm/6.0 g
Result	:	sublethal effects: hyperactivity, rapid operculation, sensitive to disturbance and gathering at the surface
Test condition	:	DILUTION WATER - Source: well water - Hardness: 707.3 mg CaCO3/l - Conductance: 1212.3 µmhos/cm at 25 degrees C TEST SYSTEM - Concentrations: 1:2 dilution series - Number of replicates: 2 - fish per replicate: 10 - Test temperature: 14 degrees C - Dissolved oxygen: 6.5 mg/l (84.5% of saturation) - pH: 8.1 - Photoperiod: 16 h light, 8 h dark
Reliability	:	(1) valid without restriction Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

12.05.2004 (42)

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	55.9
Limit test	:	
Analytical monitoring	:	yes
Method	:	other: US EPA, Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians. Nat. Environm. Res. Center, Corvallis (1974)
Year	:	1980
GLP	:	no data
Test substance	:	other TS: m-cresol
Method	:	Mean length/mean weight of fish: 4.9 cm/1.6 g
Result	:	sublethal effects: loss of equilibrium, erratic swiming and twitching at a test substance concentration of 49.8 mg/l
Test condition	:	DILUTION WATER - Source: well water - Hardness: 707.3 mg CaCO3/l - Conductance: 1212.3 µmhos/cm at 25 degrees C

TEST SYSTEM
- Concentrations: 1:2 dilution series
- Number of replicates: 2
- fish per replicate: 10
- Test temperature: 14 degrees C
- Dissolved oxygen: 6.5 mg/l (84.5% of saturation)
- pH: 8.1
- Photoperiod: 16 h light, 8 h dark

Reliability : (1) valid without restriction
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag : Critical study for SIDS endpoint
11.02.2003 (42)

Type : static
Species : Salmo trutta (Fish, fresh water, marine)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 8.4
Limit test :
Analytical monitoring : no
Method :
Year : 1969
GLP : no
Test substance : other TS: m-cresol, reported to be "purified grade"

Method : 10 acclimated fish exposed per concentration, 20 served as controls.
Result : LC50 (6 h) = 11.0 mg/l
LC50 (24 h) = 8.6 mg/l
LC50 (48 h) = 8.4 mg/l
Test condition : 12 degree C, reconstituted water
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
Flag : Critical study for SIDS endpoint
12.05.2004 (43)

Type : static
Species : Salvelinus fontinalis (Fish, estuary, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 7.6
Limit test :
Analytical monitoring : no
Method :
Year : 1969
GLP : no
Test substance : other TS: m-cresol, reported to be "purified grade"

Method : 10 acclimated fish exposed per concentration, 20 served as controls.
Result : LC50 (6 h) = 11.4 mg/l
LC50 (24 h) = 8.2 mg/l
LC50 (48 h) = 7.6 mg/l
at concentrations of 6 to 20 mg/l, the approximate incidences of surfacing were 20 %
Test condition : 12 degree C, reconstituted water
Reliability : (2) valid with restrictions

Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

Flag : Critical study for SIDS endpoint

12.05.2004 (43)

Type : static
Species : Oncorhynchus mykiss (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 8.6
Limit test :
Analytical monitoring : no
Method :
Year : 1969
GLP : no
Test substance : other TS: m-cresol, reported to be "purified grade"

Method : 10 acclimated fish exposed per concentration, 20 served as controls.
Result : LC50 (6 h) = 14.9 mg/l
LC50 (24 h) = 10.4 mg/l
LC50 (48 h) = 10.2 mg/l
In an additional test under flow-through conditions a concentration of 10 mg/l caused total incapacitation in 15 of 20 fish within 11.5 min, after which a recovery to a higher level of activity was observed
Test condition : 12 degree C, reconstituted water
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

12.05.2004 (43)

Type : semistatic
Species : Poecilia reticulata (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 23.12
Limit test :
Analytical monitoring : no
Method :
Year : 1982
GLP : no
Test substance : other TS: m-cresol, purity 99 % (BDH Chemicals)

Method : 80 % of the test solution renewed at 12 h intervals
Test condition : 25-27 degrees Celsius, pH 7
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

12.05.2004 (44)

Type : static
Species : Brachydanio rerio (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC0 : 11
LC50 : 15.9
LC100 : 22

Limit test :
Analytical monitoring : no
Method : other: Pruefrichtlinie UBA (summer 1980)
Year : 1982
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Test condition : pH 7.5 +- 0.3
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
12.05.2004 (45)

Type : static
Species : Gadus morrhua (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : > 30
Limit test :
Analytical monitoring : yes
Method :
Year : 1985
GLP : no
Test substance : other TS: m-cresol, purity > 98 % as determined by GC (obtained from Merck)

Method : effect endpoints: death, pathology, inhibition of cleavage and differentiation, pigment defects
Result : parallel test with larvae (6 days after hatching) showed pigment effects at 10 and 30 mg/l
Test condition : 5 degrees C
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
12.05.2004 (46)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
LC0 : 10
LC50 : 17
LC100 : 22
Limit test :
Analytical monitoring : no
Method : other: Test procedure of the Abwasserabgabengesetzentwurf (Deutscher Bundestag 1974)
Year : 1982
GLP : no
Test substance : other TS: m-cresol, no purity reported

Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
12.05.2004 (47)

Type :
Species : Cyprinus carpio (Fish, fresh water)

Exposure period : 24 hour(s)
Unit : mg/l
LC50 : 25
Method :
Year : 1959
GLP :
Test substance : other TS: m-cresol

Remark : results from: Albersmayer and Erichsen: Z. Fisch. 8 (1/3), 29-66 (1959)
Reliability : (3) invalid
Study does not follow any guideline. No analytical monitoring, no information about the test substance. Further details are missing

11.02.2003 (48)

Type :
Species : Rutilus rutilus (Fish, fresh water)
Exposure period : 24 hour(s)
Unit : mg/l
LC50 : 23
Method :
Year : 1959
GLP :
Test substance : other TS: m-cresol, no purity reported

Remark : results from: Albersmayer and Erichsen: Z. Fisch. 8 (1/3), 29-66 (1959)
Reliability : (3) invalid
Study does not follow any guideline. No analytical monitoring, no information about the test substance. Further details are missing

12.05.2004 (48)

Type :
Species : Tinca tinca (Fish, fresh water)
Exposure period : 24 hour(s)
Unit : mg/l
LC50 : 21
Method :
Year : 1959
GLP :
Test substance : other TS: m-cresol, no purity reported

Remark : results from: Albersmayer and Erichsen: Z. Fisch. 8 (1/3), 29-66 (1959)
Reliability : (3) invalid
Study does not follow any guideline. No analytical monitoring, no information about the test substance. Further details are missing

12.05.2004 (48)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
LC50 : 6
Limit test :
Analytical monitoring : no

Method	:	other: Mann, H., Fischtest mit Goldorfen zur vergleichenden Pruefung der akuten Toxizitaet von Wasserinhaltsstoffen und Abwaessern, Praktische Erfahrungen aus 3 Ringtesten, Z. f. Wasser- u. Abwasser-Forschung 9, 103-109 (1976)
Year	:	1978
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Reliability	:	(4) not assignable Secondary literature not available (Mann 1976)

12.05.2004 (49)

Type	:	static
Species	:	other: Pleuronectes sp. (plaice)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	10 - 33
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1971
GLP	:	no
Test substance	:	other TS: cresol, isomer not specified
Test condition	:	15 degrees C
Test substance	:	cresol (isomer not specified)
Reliability	:	(4) not assignable secondary literature

12.05.2004 (50)

Type	:	
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	10 - 13.6
Method	:	
Year	:	1971
GLP	:	
Test substance	:	other TS: m-cresol, no puritiy reported
Reliability	:	(4) not assignable secondary literature

12.05.2004 (51)

Type	:	
Species	:	Oryzias latipes (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	24
Method	:	
Year	:	1986
GLP	:	
Test substance	:	other TS: m-cresol, no puritiy reported
Reliability	:	(4) not assignable secondary literature, original source unknown

12.05.2004 (52)

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	48 hour(s)

Unit	:	mg/l
LC0	:	10
LC50	:	17 - 19
LC100	:	21 - 26
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische. DEV, L 15 (1976)
Year	:	1978
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Reliability	:	(4) not assignable Insufficient documentation

12.05.2004 (53)

Type	:	
Species	:	other: Agonus cataphractus (poacher)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	10 - 33
Method	:	
Year	:	1960
GLP	:	
Test substance	:	other TS: m-cresol
Reliability	:	(4) not assignable reference not available

11.02.2003 (54)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	13
EC50	:	25
EC100	:	50
Analytical monitoring	:	no
Method	:	other: immobilisation test according to Bringmann & Kühn: Z. Wasser Abwasser Forsch. 10, 162-166 (1977)
Year	:	1982
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	Exposure of 24 h old Daphnia (strain IRCHA); 10 individuals per concentration, duplicate samples
Result	:	effect values refer to nominal test substance concentrations
Test condition	:	20 degrees C; initial pH 8.0 +/-0.2; water saturated with oxygen; hardness: 16° d.h. (corresponding to 286 mg CaCO3/l)
Reliability	:	(1) valid without restriction Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

12.05.2004 (55)

Type	:	flow through
Species	:	Daphnia pulicaria (Crustacea)

Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	> 99.5
Analytical monitoring	:	yes
Method	:	other: US EPA, Methods for acute toxicity test with fish, macroinvertebrates, and amphibians. Nat. Environm. Res. Center, Corvallis (1974)
Year	:	1980
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Test condition	:	DILUTION AND TEST WATER - Source: well water - Hardness: 707.3 mg CaCO3/l - pH: 8.1 - Oxygen content: 6.5 mg/l (84.5% of saturation) - Conductance: 1212.3 µhos/cm at 25 degrees C - Number of replicates, individuals per replicate: 10 - Test temperature: 14 +- 1 degrees C - Photoperiod: 16 h light, 8 h dark
Reliability	:	(1) valid without restriction Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

12.05.2004 (42)

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	1.6
EC50	:	8.9
EC100	:	25
Analytical monitoring	:	no
Method	:	
Year	:	1977
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	Effect endpoint: immobilisation
Test condition	:	Hardness 16 degrees (German), pH 7.6-7.7, 20-22 degrees Celsius
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
Flag	:	Critical study for SIDS endpoint

12.05.2004 (56)

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	19.2
Analytical monitoring	:	no
Method	:	other: AFNOR (1974)
Year	:	1987
GLP	:	no data
Test substance	:	other TS: m-cresol, purity > 95 %

Remark : Effect endpoint: immobilisation
Test condition : Reconstituted hard water 200 mg/l CaCO3
pH 7.8-8.2
dissolved oxigen >25% of saturation
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
12.05.2004 (57) (58)

Type : other: not specified
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
LC50 : 18.8
Limit Test : no
Analytical monitoring : no data
Method : other: according to the method described by Parkhurst et al. 1977
Year : 1979
GLP : no
Test substance : other TS: m-cresol, no purity reported

Method : Parkhurst BR, Gehrs CW, Rubin IB (1977): Proceedings of ASTM 2nd Annual Symposium on Aquatic Toxicology, 122-130
Test condition : Daphnia magna used in the test were adults.
100-ml test beakers were filled with 80 ml test solution and 4 daphnia. All the tests were run in triplicate.
Temperature during the test: 25 +/- 0.5°C
12h light/dark cycle
Test solution was prepared with filtered spring water (pH 7.8 alkalinity mg/l, hardness 140 mg/l)
Control beakers were used
48h-EC50 values were obtained by PROBIT
Test substance : The test substance was obtained from an effluent
Reliability : (2) valid with restrictions
Study well documented (method description in an other reference) with some restriccions. Age of daphnia used in the test is not clear. Daphnias were "adults" and adults can be older than 24h (24h is suggested in the guideline); temperature was 25°C (in guideline is suggested: 18-22°C); 12 daphnia were used for each test concentration (in guideline are suggested: 40)
12.05.2004 (59)

Type : static
Species : Daphnia sp. (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
TT : 28
Analytical monitoring : no
Method :
Year : 1959
GLP : no
Test substance : other TS: m-cresol, no purity reported

Method : test organisms were reared from daphnids collected in surface water
Remark : TT = Toxicity threshold; test organisms were reared from daphnids collected in surface water
Test condition : river water, pH 7.5
Reliability : (3) invalid

Experimental details missing. Study does not follow any guideline, concentrations tested were not reported, no information about the application method of the test substance is given. Neither O2/pH monitoring nor analytical monitoring were applied

12.05.2004 (60)

Type :
Species : other aquatic mollusc: Glossosiphonia complanata
Exposure period :
Unit :
Method :
Year :
GLP :
Test substance : other TS: m-cresol, no purity reported

Result : perturbation level: 1.1 mg/l
Reliability : (4) not assignable
Secondary literature

12.05.2004 (61)

Type :
Species : other aquatic arthropod: Limnoria tripunctata
Exposure period : 100 hour(s)
Unit : mg/l
LC50 : 100
Method :
Year :
GLP :
Test substance : other TS: m-cresol

Reliability : (4) not assignable
Reference not available

11.02.2003 (54)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Scenedesmus quadricauda (Algae)
Endpoint : biomass
Exposure period : 8 day(s)
Unit : mg/l
TT : 15
Limit test :
Analytical monitoring : no
Method : other: Cell multiplication inhibition test
Year : 1977
GLP : no
Test substance : other TS: m-cresol, no purity reported

Method : incubation of 10 ml test solution (algae in defined mineral salts medium)
Remark : TT (toxic threshold concentration) refers to nominal test substance concentration and was determined at 3 % effect compared to the control
Test condition : 27 degrees C; initial pH 7.0
Reliability : (3) invalid
It is unclear whether the algae are within the exponential growth throughout the whole exposure period of 8 days.

12.05.2004 (62)

Species	:	Chlorella pyrenoidosa (Algae)
Endpoint	:	other: chlorophyll content
Exposure period	:	72 hour(s)
Unit	:	mg/l
EC0	:	> 50
EC50	:	127
EC100	:	250
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1968
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Result	:	1000 mg/l: complete destruction of chlorophyll EC50 was not reported in the study, but it can be taken from the graph
Test condition	:	TEST ORGANISMS - Strain: Emerson strain - Test temperature: 25 +- 1 degrees C - pH: 7.0 - Photoperiod: continuous illumination TEST PARAMETER: chlorophyll
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

12.05.2004 (63)

Species	:	Microcystis aeruginosa (Algae, blue, cyanobacteria)
Endpoint	:	other: cell multiplication
Exposure period	:	8 day(s)
Unit	:	mg/l
TGK	:	13
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Modified DEV L9 (cell multiplication inhibition test)
Year	:	1975
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	TGK = Toxicity treshold, determined at 1% effect compared to control
Reliability	:	(3) invalid It is unclear whether the algae are within the exponential growth throughout the whole exposure period of 8 days.

12.05.2004 (64) (65)

Species	:	other aquatic plant: Potamogeton lucens
Endpoint	:	other: photosynthesis
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	.22
LOEC	:	.65
EC50	:	.65
EC100	:	> 1.08
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1983
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported

Method	:	simulation of running water under summer climate conditions
Test condition	:	water hardness: 9° dH; conductivity: 300 uS; pH 7.8
Reliability	:	(3) invalid Methodological deficiencies. Most test conditions not indicated. No information about application mode, number of plants, controls, test concentrations, statistics, analytics.

12.05.2004 (66)

Species	:	other aquatic plant: Potamogeton coloratus
Endpoint	:	other: photosynthesis
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	1.08
LOEC	:	> 1.08
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1983
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported

Method	:	simulation of running water under summer climate conditions
Test condition	:	water hardness: 9° dH; conductivity: 300 uS; pH 7.8
Reliability	:	(3) invalid Methodological deficiencies. Most test conditions not indicated. No information about application mode, number of plants, controls, test concentrations, statistics, analytics.

12.05.2004 (66)

Species	:	other aquatic plant: Potamogeton crispus
Endpoint	:	other: photosynthesis
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	1.08
LOEC	:	> 1.08
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1983
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported

Method	:	simulation of running water under summer climate conditions
Test condition	:	water hardness: 9° dH; conductivity: 300 uS; pH 7.8
Reliability	:	(3) invalid Methodological deficiencies. Most test conditions not indicated. No information about application mode, number of plants, controls, test concentrations, statistics, analytics.

12.05.2004 (66)

Species	:	Agmenellum quadruplicatum (Algae)
Endpoint	:	
Exposure period	:	
Unit	:	
Method	:	
Year	:	1974
GLP	:	no

Test substance	:	other TS: m-cresol, no purity reported
Method	:	algae cells embedded in agar, test substance absorbed on discs (12.7 mm) which are placed directly on the agar surface incubation 5 to 8 days
Result	:	no effect with 0.5 mg test substance on the plate with 1 mg inhibition between 1 to 10 mm from the disc edge, with 10 mg complete killing within a zone of 36 mm
Reliability	:	(3) invalid Unsuitable test system

12.05.2004 (67)

Species	:	other algae: Chlorella autotrophica
Endpoint	:	
Exposure period	:	
Unit	:	
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	algae cells embedded in agar, test substance absorbed on discs (12.7 mm) which are placed directly on the agar surface incubation 5 to 8 days
Result	:	with 1 mg inhibition between 1 to 4 mm from the disc edge, with 2 mg 1nhibition between 3 to 35 mm from the disc edge
Reliability	:	(3) invalid Unsuitable test system

12.05.2004 (67)

Species	:	Scenedesmus quadricauda (Algae)
Endpoint	:	biomass
Exposure period	:	96 hour(s)
Unit	:	mg/l
TT	:	40
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Cell multiplication inhibition test
Year	:	1959
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	TT = toxicity treshold
Reliability	:	(3) invalid Methodological deficiencies

12.05.2004 (60)

Species	:	Ankistrodesmus falcatus (Algae)
Endpoint	:	biomass
Exposure period	:	10 day(s)
Unit	:	mg/l
MTL	:	100
Method	:	
Year	:	1976
GLP	:	
Test substance	:	other TS: m-cresol, no purity reported
Method	:	described in: Denson & Bold, The University of Texas Publication No. 6022, 72 (1960)

Remark : MTL = median tolerance limit
Result : sublethal concentration 100 mg/l
lethal concentration 500 mg/l
Reliability : (4) not assignable
Insufficient documentation
12.05.2004 (68)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species : activated sludge, domestic
Exposure period : 3 hour(s)
Unit : mg/l
EC50 : 461.4
Analytical monitoring : no
Method : OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year : 1985
GLP : no
Test substance : other TS: m-cresol, reagent grade

Remark : synthetic sewage stock solution slightly different from OECD guideline; reference substance 1,5-dichlorophenol
Test condition : 21 degrees C; continuous aeration with 0.5-10 l/min
Reliability : (1) valid without restriction
Guideline study
Flag : Critical study for SIDS endpoint
12.05.2004 (69)

Type : aquatic
Species : activated sludge of a predominantly domestic sewage
Exposure period :
Unit : mg/l
EC75 : 11.4
Analytical monitoring : no
Method : other: inhibition of nitrification process
Year : 1966
GLP : no
Test substance : other TS: m-cresol, no purity reported

Method : Quantitative determination of the nitrification rate (1st step, NH4 to NO2),
colorimetric measurement of the NO2/NO3 concentration;
static test system
Pre-cleaned activated sludge in particle-free communal waste water (BOD5: 250 mg/l; NH4-N/l: 50-80 mg)
Remark : effect: inhibition of ammonia oxidation
Test condition : Exposure period: 2-4 h; 25 degree C; pH 7.6-7.8
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation
Flag : Critical study for SIDS endpoint
12.05.2004 (70)

Type : aquatic
Species : other bacteria
Exposure period :
Unit :
Analytical monitoring : no
Method : other

Year : 1985
GLP : no
Test substance : other TS: m-cresol, purity 99.5 %

Method : 6 different pure bacteria cultures: 3 isolated from a laboratory activated sludge, 2 from activated sludge from a municipal plant receiving some industry wastewater, and 1 from a lake sediment
Effect: 50 % resazurin reduction (determination of dehydrogenase activity)
Result : from laboratory sludges: EC50 = >500, 225, and 410 mg/l
from activated sludges: EC50 = 360 and >500 mg/l
from lake sediment: EC50 = >500 mg/l
Test condition : 21 degrees C; incubation 30-60 min
Test substance : purity 99.5%
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (71)

Type : aquatic
Species : other bacteria: Aerobic heterotrophic
Exposure period : 49 hour(s)
Unit : mg/l
IC 50 : 440
Analytical monitoring : no
Method :
Year : 1991
GLP : no
Test substance : other TS: m-cresol, no purity reported

Method : culture obtained from mixed liquor of a treatment plant
Remark : Effect: inhibition of respiration; prolonged incubation compared with ISO 8192
Test condition : 25 and 35 degrees C
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

12.05.2004 (72)

Type : aquatic
Species : other bacteria: Methanogenic bacteria
Exposure period : 96 hour(s)
Unit : mg/l
IC 50 : 890
Analytical monitoring : no
Method : other: Owen, W.F.: Bioassay for Monitoring Biochemical Methane Potential and Anaerobic Toxicity. Water Res. 13, 485 (1979)
Year : 1991
GLP : no
Test substance : other TS: m-cresol, no purity reported

Remark : Effect: inhibition of gas production
Test condition : 35 degrees C
Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

12.05.2004 (72)

Type	:	aquatic
Species	:	Nitrosomonas sp. (Bacteria)
Exposure period	:	24 hour(s)
Unit	:	mg/l
IC 50	:	.78
Analytical monitoring	:	no
Method	:	other: Inhibition of nitrification, comparable to ISO/DIS 9509
Year	:	1991
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	culture obtained from mixed liquor of a treatment plant
Remark	:	Effect: inhibition of N-oxidation
Test condition	:	25 degrees C
Reliability	:	(3) invalid In principal the test is comparable to standard methods, but the authors state that the compounds with log IC50<1,5 umol/l had questionable accurate results, so that this effect value has to be considered invalid.

12.05.2004 (72)

Type	:	aquatic
Species	:	anaerobic microorganisms
Exposure period	:	
Unit	:	
Analytical monitoring	:	yes
Method	:	
Year	:	1989
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	phenol-enriched methanogenic culture nominal concentrations 50, 100, 150, 250, 300, 400, 500, and 700 mg/l m-cresol + 200 mg/l phenol incubation at 35 degrees C
Result	:	m-cresol concentrations above 150 mg/l inhibited the anaerobic phenol degradation
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

12.05.2004 (35)

Type	:	aquatic
Species	:	Pseudomonas putida (Bacteria)
Exposure period	:	16 hour(s)
Unit	:	mg/l
TT	:	53
Analytical monitoring	:	no
Method	:	other: Cell multiplication inhibition test
Year	:	1977
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	TT = Toxicity threshold; determined at 3 % effect compared to control
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; sufficient documentation

12.05.2004 (65) (62)

Type	:	aquatic
Species	:	other bacteria: Mixed marine bacteria culture
Exposure period	:	16 hour(s)
Unit	:	mg/l
EC10	:	33.4
EC50	:	324 - 326
Analytical monitoring	:	no
Method	:	other: Static bioassay (determination of bacterial growth)
Year	:	1989
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	mixed culture of 13 unidentified bacterial strains isolated from sea water
Test condition	:	Incubation at 25-30 degrees Celsius, artificial saltwater
Reliability	:	(2) valid with restrictions No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (73) (74)

Type	:	aquatic
Species	:	Chilomonas paramaecium (Protozoa)
Exposure period	:	48 hour(s)
Unit	:	mg/l
TT	:	114
Analytical monitoring	:	no
Method	:	other: cell multiplication inhibition test
Year	:	1980
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	TT = Toxicity threshold; determined at 5 % effect compared to control
Test condition	:	20 degrees C; initial pH 6.9
Reliability	:	(2) valid with restrictions No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (75)

Type	:	aquatic
Species	:	Entosiphon sulcatum (Protozoa)
Exposure period	:	72 hour(s)
Unit	:	mg/l
TT	:	31
Analytical monitoring	:	no
Method	:	other: cell multiplication inhibition test
Year	:	1978
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	TT = Toxicity threshold; determined at 5 % effect compared to control
Test condition	:	25 degrees C; initial pH 6.9
Reliability	:	(2) valid with restrictions No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (76)

Type : aquatic
Species : Tetrahymena pyriformis (Protozoa)
Exposure period : 24 hour(s)
Unit : mg/l
LC100 : 375
Analytical monitoring : no
Method :
Year : 1978
GLP : no
Test substance : other TS: m-cresol, no purity reported

Test condition : 28 degrees C
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (77)

Type : aquatic
Species : Uronema parduzci (Protozoa)
Exposure period : 20 hour(s)
Unit : mg/l
TT : 62
Analytical monitoring : no
Method : other: cell multiplication inhibition test
Year : 1980
GLP : no
Test substance : other TS: m-cresol, no purity reported

Remark : TT = Toxicity threshold; determined at 5 % effect compared to control
Test condition : 25 degrees C; initial pH 6.9
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (78)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 5 minute(s)
Unit : mg/l
EC50 : 11
Analytical monitoring : no
Method : other: Microtox assay
Year : 1983
GLP : no data
Test substance : other TS: m-cresol, no purity reported

Remark : effect: reduction of bioluminescence
Secondary literature. Not enough information supplied for assessment. Although the author suggests that Microtox may lack reproductibility due to variations in bacterial cell suspensions, no information is supplied on the maintenance of the lyophilized bacteria, their age, duration of reconstitution and other important parameters.
Reliability : (3) invalid
Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of

chemicals.

12.05.2004 (79)

Type	:	aquatic
Species	:	Photobacterium phosphoreum (Bacteria)
Exposure period	:	15 minute(s)
Unit	:	mg/l
EC50	:	8
Analytical monitoring	:	no
Method	:	other: Microtox assay
Year	:	1987
GLP	:	no
Test substance	:	other TS: m-cresol, analytical grade (either from Merck or EGA Chemie)
Remark	:	Not enough information supplied for assessment of the test used (Test done according to Beckman manual). Although it is suggested that Microtox may lack reproducibility due to variations in bacterial cell suspensions [Bitton G (1983) Bacterial and Biochemical Tests for Assessing Chemical Toxicity in the Aquatic Environment: A Review. Crit Rev Environ Control 13: 51 -67], no information is supplied on the maintenance of the lyophilized bacteria, their age, duration of reconstitution and other important parameters.
Reliability	:	(3) invalid Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

12.05.2004 (80)

Type	:	aquatic
Species	:	other bacteria: Photobacterium (Vibrio) fischeri (marine)
Exposure period	:	5 minute(s)
Unit	:	mg/l
EC50	:	8.2
Analytical monitoring	:	no
Method	:	other: Microtox assay
Year	:	1981
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	Although it is suggested that Microtox may lack reproducibility due to variations in bacterial cell suspensions [Bitton G (1983) Bacterial and Biochemical Tests for Assessing Chemical Toxicity in the Aquatic Environment: A Review. Crit Rev Environ Control 13: 51 -67], no information is supplied on the maintenance of the lyophilized bacteria, their age, duration of reconstitution and other important parameters. In contrast to Bulich [Bulich AA (1977), Aquatic Toxicology: Second conference ASTM STP 667, American Society for Testing of Materials, Philadelphia, pp 98 - 106], pH not buffered.
Test condition	:	15 degrees C
Reliability	:	(3) invalid Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

12.05.2004 (81)

Type	:	aquatic
Species	:	Escherichia coli (Bacteria)
Exposure period	:	19 day(s)

Unit :
Analytical monitoring : no
Method :
Year : 1983
GLP : no
Test substance : other TS: m-cresol, no purity reported

Method : Incubation in microcosms containing sterile sea water
Result : Number of viable cells remained constant
Number of culturable cells decreased, no plasmids were detected. Changes in membrane protein composition observed. After transfer into rich medium without test substance, growth resumed and plasmids were again detectable.
Test condition : Test concentration 1 µg/l, 18 degrees C
Reliability : (3) invalid
Tested organism not relevant for environment

12.05.2004 (82) (83)

Type : aquatic
Species : Pseudomonas putida (Bacteria)
Exposure period : 48 hour(s)
Unit :
Analytical monitoring : no
Method :
Year : 1989
GLP : no
Test substance : other TS: m-cresol, no purity reported

Method : in the culture medium absorbance at 660 nm was measured
Result : absorbance 0.46 with 0.5 g/l and 0.22 with 1 g/l
Test condition : 30 degrees C
Reliability : (3) invalid
Experimental details missing

12.05.2004 (84)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 30 minute(s)
Unit : mg/l
EC50 : 11.8
Analytical monitoring : no
Method : other: Microtox
Year : 1981
GLP :
Test substance : other TS: m-cresol, no purity reported

Remark : Inhibition of bioluminescence
Secondary literature; not enough information for assessment of cited result
Test condition : 20 degrees C
Reliability : (3) invalid
Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals

12.05.2004 (85)

Type : aquatic
Species : other bacteria: gentechnologically constructed luminescent bacteria originating from wastewater treatment plant
Exposure period : 30 minute(s)
Unit : mg/l

EC50	:	68 measured/nominal
Analytical monitoring	:	no
Method	:	other: Microtox assay
Year	:	1986
GLP	:	no data
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	Inhibition of bioluminescence Modified microorganisms used which represent the metabolic potentials present in a wastewater treatment plant and some properties of a marine organism, but which are not identical to any known species in natural environments
Test condition	:	- Wastewater bacteria (Eschericia coli) which were obtained from a wastewater treatment plant - Bacteria obtained the luciferase operon of Vibrio fischeri by transfer from luminescent E. coli - Incubation at 20 °C - Result calculated from the difference of the luminescence between controls and test substance taking into account the light emissions at 0 and 20 °C
Reliability	:	(3) invalid Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

12.05.2004 (85)

Type	:	aquatic
Species	:	Escherichia coli (Bacteria)
Exposure period	:	2 hour(s)
Unit	:	mg/l
EC50	:	1000
Method	:	
Year	:	1954
GLP	:	
Test substance	:	other TS: m-cresol, no purity reported
Result	:	endpoint related to growth inhibition no effect on cell size
Test condition	:	37 degrees C
Reliability	:	(3) invalid Methodological deficiencies

12.05.2004 (86)

Type	:	aquatic
Species	:	Escherichia coli (Bacteria)
Exposure period	:	
Unit	:	mg/l
TT	:	600
Analytical monitoring	:	no
Method	:	
Year	:	1959
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Method	:	test organisms isolated from river water endpoint: inhibition of glucose metabolism
Remark	:	TT = toxicity treshold; determined at 5 % effect compared to control
Reliability	:	(3) invalid Methodological deficiencies

12.05.2004 (60) (87)

Type	:	aquatic
Species	:	Pseudomonas fluorescens (Bacteria)
Exposure period	:	
Unit	:	mg/l
TT	:	40
Analytical monitoring	:	no
Method	:	
Year	:	1960
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	TT = toxicity treshold; determined at 5 % effect compared to control endpoint: inhibition of glucose metabolism
Reliability	:	(3) invalid Methodological deficiencies

12.05.2004 (60)

Type	:	aquatic
Species	:	other bacteria: Pseudomonas Stamm Berlin 33/2
Exposure period	:	
Unit	:	mg/l
EC0	:	180
Analytical monitoring	:	no
Method	:	other
Year	:	1982
GLP	:	no
Test substance	:	other TS: m-cresol, no purity reported
Remark	:	Effect endpoint: cell multiplication inhibition
Reliability	:	(4) not assignable Insufficient documentation

12.05.2004 (47)

Type	:	aquatic
Species	:	Paramaecium caudatum (Protozoa)
Exposure period	:	
Unit	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: m-cresol, no purity reported
Result	:	pertubation level 0.9 mg/l
Reliability	:	(4) not assignable secondary literature

12.05.2004 (61)

Type	:	aquatic
Species	:	other protozoa: Vorticella campanula
Exposure period	:	
Unit	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: m-cresol, no purity reported
Result	:	pertubation level 0.5 mg/l
Reliability	:	(4) not assignable secondary literature

12.05.2004 (61)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Species	:	other terrestrial plant: Lactuca sativa Ravel R2
Endpoint	:	growth
Exposure period	:	14 day(s)
Unit	:	mg/kg soil dw
EC50	:	96
Method	:	OECD Guide-line 208 "Terrestrial Plants, Growth Test"
Year	:	1993
GLP	:	no data
Test substance	:	other TS: m-cresol, purity >= 95 %
Method	:	analytical monitoring at start and end of test
Result	:	EC50 based on nominal concentration; for most of the examined phenols (including m-cresol) applied concentrations dropped to < 20% of the nominal values
Reliability	:	(2) valid with restrictions Guideline study; applied test concentrations not stable during the test period
Flag	:	Critical study for SIDS endpoint

12.05.2004 (88)

Species	:	other terrestrial plant: Lactuca sativa Ravel R2
Endpoint	:	growth
Exposure period	:	16 day(s)
Unit	:	mg/l
EC50	:	50
Method	:	
Year	:	1993
GLP	:	no data
Test substance	:	other TS: m-cresol, purity >= 95 %
Method	:	semistatic test in nutrient solution, renewed 3 times/week nutrient solution as described in Steiner, A.A.: Soilless culture. Proceedings, Sixth Colloqium of the International Potash Institute, Florence, Italy, 324-341 (1968); analytical monitoring of TS at start and end of exposure and before renewal of test solution
Result	:	EC50 based on nominal concentration; TS concentration before renewal of test solution > 50% of initial concentration
Reliability	:	(3) invalid unsuitable test system

11.02.2003 (88)

Species	:	Raphanus sativus (Dicotyledon)
Endpoint	:	other: germination and growth rate

Exposure period : 4 day(s)
Unit : g/l
Method :
Year : 1989
GLP : no
Test substance : other TS: m-cresol, special grade purity (obtained from Wako Pure Chemicals Industries, Ltd.)

Method : seeds exposed to test compounds dissolved in distilled water
24 degrees C, 10h light, 14 h dark
3 replicates of 20 seeds

Result : Concentr. Germination rate% Growth rate %

g/l	1 day	4 days	Radicle	Hypocotyl
10	0	0	-	-
1	0	5.3	2.0	-
0.1	82.6	95.0	80.8	104.7

Reliability : (3) invalid
Methodological deficiencies

12.05.2004 (89)

Species : Brassica rapa (Dicotyledon)
Endpoint : other: germination and growth rate
Exposure period : 4 day(s)
Unit : g/l
Method :
Year : 1989
GLP : no
Test substance : other TS: m-cresol, special grade purity (obtained from Wako Pure Chemicals Industries, Ltd.)

Method : seeds exposed to test compounds dissolved in distilled water
24 degrees C, 10h light, 14 h dark
3 replicates of 20 seeds

Result : Concentr. Germination rate% Growth rate %

g/l	1 day	4 days	Radicle	Hypocotyl
10	0	0	-	-
1	0	0	-	-
0.1	85.8	91.5	54.9	72.8

Reliability : (3) invalid
Methodological deficiencies

12.05.2004 (89)

Species : Brassica campestris var. chinensis (Dicotyledon)
Endpoint : other: germination and growth rate
Exposure period : 4 day(s)
Unit : g/l
Method :
Year : 1989
GLP : no
Test substance : other TS: m-cresol, special grade purity (obtained from Wako Pure Chemicals Industries, Ltd.)

Method : seeds exposed to test compounds dissolved in distilled water
24 degrees C, 10h light, 14 h dark
3 replicates of 20 seeds

Result : Concentr. Germination rate% Growth rate %

g/l	1 day	4 days	Radicle	Hypocotyl
10	0	0	-	-

1	0	0	-	-	
0.1	100	100	86.5	77.1	

Reliability : (3) invalid
Methodological deficiencies

12.05.2004 (89)

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

Species : other avian: Agelaius phoeniceus (red-winged blackbird)
Endpoint : mortality
Exposure period :
Unit : mg/kg bw
LD50 oral : 113
Method :
Year : 1983
GLP : no data
Test substance : other TS: m-cresol

Test condition : birds pre-conditioned to captivity for 2 to 6 weeks
dosed by gavage with solution in propylene glycol or by pellets resp. gelatin capsules
Reliability : (2) valid with restrictions
Unsuitable test system

11.02.2003 (90)

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

Remark : In aquarium water of 12 species of freshwater fish 48 h after exposure to 3-15 mg/l m-cresol, cresyl sulphate (55-64% of 14C recovered) or m-hydroxybenzoic acid (0-39 %) were found
In bile of 11 species, cresyl glucuronide (63-74 %), cresyl sulphate (8-20 %) and m-hydrobenzoic acid (5-12 %) were found
Unchanged m-cresol detected in both aquarium water and bile
Test substance : m-[U-14C]cresol
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

17.10.2001 (91)

4.9 ADDITIONAL REMARKS

Memo : Sea urchin test

Remark : Strongylocentrotus droebachiensis (sea urchin):
static test, 5 degrees C
Determined effect endpoints: death, pathology, inhibition of

cleavage and differentiation, pigment defects
EC50 (96 h): ca. 30 mg/l

Test substance : other TS: m-cresol, purity > 98 % as determined by GC (obtained from Merck)

Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards and described in sufficient detail

12.05.2004 (46)

Memo : Tree neoplasms

Remark : m-cresol (1.5 % v/v) showed a toxicity rating from 3-4 (0 = no injury, 5 = complete kill within 14 d) in tomato crown gall tumors incited by Agrobacterium tumefaciens.

Test substance : other TS: m-cresol, no purity reported

Reliability : (3) invalid
Unsuitable test system

12.05.2004 (92)

Memo : Hela cell screening

Remark : In a rapid-cell culture assay with HeLa cells, m-cresol (4x10-5 to 4x10-3 M, 4 h incubation) showed a concentration-dependent inhibition of 3H labeled thymidine incorporation into DNA incubation 4 h

Test substance : other TS: m-cresol, no purity reported

Reliability : (3) invalid
Unsuitable test system

12.05.2004 (93) (94)

Memo : Mollusc

Remark : Teredo diegensis (Mollusca):
LC50 (72 h): 100 mg/l

Test substance : other TS: m-cresol, no purity reported

Reliability : (4) not assignable
Reference not available

12.05.2004 (54)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo	:	In vivo
Type	:	Toxicokinetics
Species	:	other
Number of animals		
Males	:	
Females	:	
Doses		
Males	:	
Females	:	
Vehicle	:	
Result	:	At physiological pH, the conjugated metabolite of phenolic compounds are ionized to a greater extent than the parent compound, which reduces renal reabsorption and increases elimination with the urine. In addition to urinary excretion, cresols are excreted in the bile, butr the most part undergoes enterohepatic circulation. there are known species differences in the specific conjugation reactions of cresol isomers. The relative amounts of gluucuronide and sulfate conjugates therefore differ between species and also vary with dose.
Reliability	:	(2) valid with restrictions basic information

09.01.2003 (95) (96) (97) (98)

5.1.1 ACUTE ORAL TOXICITY

5.1.2 ACUTE INHALATION TOXICITY

17.06.2002

5.1.3 ACUTE DERMAL TOXICITY

17.06.2002

5.1.4 ACUTE TOXICITY, OTHER ROUTES

17.06.2002

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)

Number of animals	:	3
Vehicle	:	other: none
PDII	:	
Result	:	corrosive
Classification	:	
Method	:	other: in accordance with classification of corrosive hazards, Fed. Reg. Vol. 37, No.57, §173.240 - D.O.T., see freetext ME
Year	:	1972
GLP	:	no
Test substance	:	other TS: no data on purity and composition of mixture
Method	:	0.5 ml of undiluted sample was applied to the clipped, intact skin of 3 New Zealand white male and female rabbits under 1 inch square patch, 2 single layers thick. The patches were held in place with adhesive tape in such a manner that evaporation was retarded, but not prevented, for the 4 hour exposure period. The data were scored according to the method of Draize, Woodward and Calvery (J. of Pharm. Exp. therapeutics Vol. 82, December, 1944)
Result	:	4-Hours: necrosis, severe edema 24 hours: eschar formation (corrosive) Scab sloughed off in 14 - 17 days showing injury in depth
Reliability	:	(2) valid with restrictions only a summary description: individual animal data not given, no purity of the TS given
Flag	:	Critical study for SIDS endpoint

16.12.2002 (99)

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

Type	:	other
Species	:	guinea pig
Number of animals	:	
Vehicle	:	other: acetone
Result	:	not sensitizing
Classification	:	
Method	:	other: a 7,5 % solution of a mixture of m- and p-cresol in acetone was repeatedly supplied to the skin of guinea pig
Year	:	1998
GLP	:	no data
Test substance	:	other TS: mixture of m- and p-cresol, not specified further
Reliability	:	(2) valid with restrictions limited documentation
Flag	:	Critical study for SIDS endpoint

05.02.2004 (100)

04.12.2002

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rat

Sex	:	male/female
Strain	:	other: F334/N
Route of admin.	:	oral feed
Exposure period	:	13 w
Frequency of treatm.	:	continuously in feed
Post exposure period	:	no
Doses	:	0, 1880, 3750, 7500, 15000, 30000 ppm (see RM)
Control group	:	yes, concurrent no treatment
NOAEL	:	3750 ppm
Method	:	other: see freetext ME
Year	:	1991
GLP	:	yes
Test substance	:	other TS: m-/p-cresol (60%:40% mixture)

Method :

SIZE OF STUDY GROUP:
20 male and 20 female rats (10 of each group designated for clinical pathology studies)
TIME HELD BEFORE STUDY: 12-13 days
METHOD OF ANIMAL DISTRIBUTION:
randomized for each sex on the basis of body weight into groups per sex
DIET: NIH-07 rat ration
ANIMAL ROOM ENVIRONMENT:
temperature: 72° +/-3° F, humidity: 50 % +/-15 %,
Fluorescent light: 12 hrs/day, room air changes: 10-12 changes/hr
TYPE AND FREQUENCY OF OBSERVATION:
observed twice daily, body weight taken initially, weekly, and at termination, feed consumption by cage recorded twice weekly
NECROPSY AND HISTOLOGIC EXAMINATION:
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 aninmals 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, oesophagus, heart, kidney, large intestines (caecum, 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 intestine (duodenum, ileum, jejunum), spleen, stomach, testes, thymus, thyroid, tongue, trachea, tunica vaginalis, urinary bladder, uterus and Zymbal's glands. For lower level dose groups, all gross lesions and the following target organs were examined histopathologically: bone marrow, nasal mucosa, thyroid gland, uterus. Organ weights recorded for brain, liver, right kidney, thymus, heart, and lungs of all animals, and the right testis of all males.
HAEMATOLOGIC, CLINICAL CHEMISTRY, and URINALYSIS determinations included.
haematocrit, haemoglobin, red blood cell count, mean cell volume (only females), meam cell haemoglobin, mean cell haemoglobin concentration (only females), platelets, reticulocytes, white blood cell count, lymphocytes,

monocytes, eosinophila, urea nitrogen, alanine aminotransferase, alkaline phosphatase, 5'-nucleotidase, sorbitoldehydrogenase, bile acids, urine aspartate aminotransferase, urine n-acetyl-ß-glucose amidase, urine volume, specific gravity
reproductive toxicity evaluation as described in chapter 5.8.3.
STATISTICAL METHODS:
nonparametric multiple comparison test of Dunn and Shirley, Jonckheere's test,
arcine transformation,
multivariate analysis of variance

Remark : mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
1880 ppm	123	131
3750 ppm	241	254
7500 ppm	486	509
15000 ppm	991	1024
30000 ppm	2014	2050

Result : All rats lived to the end of the study;
clinical signs of toxicity: 30000 ppm: males, females, rough hair coat, urine-stained fur; females, thin appearance; 15000-3750 ppm: females, urine stained fur
15000, 30000 ppm: males, females, final body weight reduced; females, reduced weight gain; 30000 ppm: males, weight gain reduced; males, females, reduced feed consumption during the first week
At study termination weights (w) were sign. increased (mainly p </= 0.05):
Brain (males, rel. w. at 30000 ppm ; females, rel. w. from 15000 ppm), heart (males, abs. w. from 15000 ppm; females, abs. w. at 30000 ppm), lungs (males, females, abs. w. from 15000 ppm; males, rel. w. at 30000 ppm), thymus (males and females abs. w. at 30000 ppm), right kidney (male,rel. w. from 7500 ppm, abs w from 15000 ppm; females: rel. w. at 30000 ppm), liver (males, abs. w. from 3750 ppm, rel. w. from 7500 ppm; females, rel. and abs. w from 7500 ppm) and in males relative weights of right testes from 15000 ppm.

Microscopically, the following changes were reported (contr. low to high dose, average severity score based on a scale of 1 to 4 given[1 = minimal, 2 = mild, 3 = moderate, 4 = marked]):
Nose (respiratory epithelium hyperplasia, male: 0/10, 3/10[1.0], 8/10[1.1], 10/10[1.4], 8/10[2.2],10/10[3.8]; female: 3/10[1.0],1/10[1.0], 5/10[1.2], 9/10[1.7], 8/10[2.0], 10/10[2.8] and glandular hyperplasia, male: 0/10, 3/10[1.0], 8/10[1.5], 10/10[1.6], 9/10[2.6], 9/10[3.8]; female: 0/10, 2/10[1.0], 6/10[1.3], 10/10[2.1], 8/10[2.5], 6/10[2.8], no evidence of other inflammatory or degenerative changes),
thyroid gland (increased colloid in follicles: males: 0/10, 0/10, 0/10, 0/10, 7/10[1.1], 9/10[1.6]; females: 0/10, 0/10, 0/10, 0/10, 6/10[1.0]),
the biological significance is uncertain (the effect was not noted in studies with the individual isomers, nor was it associated with overt follicular cell hypertrophy and/or hyperplasia)
bone marrow (hypocellularity: males: 0/10, 0/10, 0/10, 0/10, 1/10[1.0], 8/10[1.0]; females: 0/10, 0/10, 0/10, 0/10, 0/10,

6/10[1.0]) and
uterus atrophy in females: 0/10, 0/10, 0/10, 0/10, 3/10[1.0], 7/10[1.7].

Evaluation of other reproductive organs (see also chapter 5.8.3) revealed no significant findings in males but lengthened oestrus cycle in females significant from 7500 ppm

Haematology, clinical chemistry, urinalysis data (only sign. changes, incidences not given):
haematocrit (male, female, increase, 30000 ppm, d5; female, decrease, d43 from 15000 ppm), haemoglobin (increase, male, female, d5, 30000 ppm), red blood cell count (increase, male, female, d5, d21, 30000 ppm), mean cell volume (decrease, female, 30000 ppm at d5, from 15000 ppm d21 to d90), mean cell haemoglobin (decrease, female, 30000 ppm, d21, d90), mean cell haemoglobin concentration (increase, female, from 15000 ppm d5, d43), platelet count (increase, male, 15000 ppm, d21; 30000 ppm, d21, d43; female, d21 from 7500 ppm, d43 at 15000 ppm), reticulocytes (decrease, female, from 15000 ppm d5), white blood cell count (increase, male, d21, 15000 ppm), lymphocytes (male, increase, d21, 15000 ppm), monocytes (male, increased from 1880 ppm at d5; female, decrease d90 at 30000 ppm), urea nitrogen (male, increase, from 15000 ppm at d5, decrease from 1880 ppm at d43 and from 15000 ppm at d90; female, increase at d 5 from 3750 ppm, decrease at d43 from 3750 ppm),
alanine aminotransferase (increase, d5: male, 30000 ppm, female from 15000 ppm), alkaline phosphatase (male, decrease, d21 from 15000 ppm, d43, 7500 ppm, 30000 ppm), 5'-nucleotidase (decrease, male, d5 30000 ppm, d21 from 3750 ppm, d43 from 7500 ppm, d90 30000 ppm: female, d5 from 15000 ppm, d21, d43 from 7500 ppm, d90 from 3750 ppm), sorbitol dehydrogenase (male, increase d5 from 7500 ppm), bile acids (increase, male, d5 from 15000 ppm and at 30000 ppm, d21, d43, and d90 at 3750 ppm and 30000 ppm; female, d21 from 1880 ppm, d43 from 15000 ppm, d90 30000 ppm),
urine aspartate aminotransferase (male, increase, d43, d90, from 7500 ppm; female, decrease, d41, from 3750 ppm), urine N-acetyl-ß-glucose aminidase (increase, male, d41, from 7500 ppm, d90 from 15000 ppm; female, d90 30000 ppm), urine volume (decrease, male, d41 30000 ppm, d90 from 7500 ppm), specific gravity (increase, male, d41,d90, from 7500 ppm)

local toxicity: NOAEL(male, female): < 1880 ppm
systemic toxicty: NOAEL(male, female): 3750 ppm

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.12.2002 (101)

Type : Sub-chronic
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 13 w
Frequency of treatm. : continuously in feed
Post exposure period : no
Doses : 0, 625, 1250, 2500, 5000, 10000 ppm (see RM)

Control group : yes, concurrent no treatment
NOAEL : 2500 ppm
Method : other: see freetext ME
Year : 1991
GLP : yes
Test substance : other TS: m-/p-cresol (60%:40% mixture)

Method : SIZE OF STUDY GROUP:
10 male and 10 female mice per group
TIME HELD BEFORE STUDY: 12-13 days
METHOD OF ANIMAL DISTRIBUTION:
randomized for each sex on the basis of body weight into groups per sex
DIET: NIH-07 mouse ration
ANIMAL ROOM ENVIRONMENT:
temperature: 72° +/-3° F, humidity: 50 % +/-15 %, Fluorescent light: 12 hrs/day, room air changes : 10-12 changes/hr
TYPE AND FREQUENCY OF OBSERVATION:
observed twice daily, body weight taken initially, weekly, and at termination, feed consumption by cage recorded twice weekly
NECROPSY AND HISTOLOGIC EXAMINATION:
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 aninmals in higher dose groups inclusive of early deaths. The following organs an/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, oesophagus, gallbladder, heart, kidney, large intestines (caecum, 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 intestine (duodenum, ileum, jejunum), spleen, stomach, testes, thymus, thyroid, tongue, trachea, tunica vaginalis, urinary bladder, uterus and Zymbal's glands. For lower level dose groups, all gross lesions and the following target organs were examined histopathologically: nasal mucosa. Organ weights recorded for brain, liver, right kidney, thymus, heart, and lungs of all animals, and the right testis of all males.
Haematologic, clinical chemistry, and urinalysis determinations performed at necropsy. Sperm morphology and vaginal cytology< examinations were performed.
HAEMATOLOGY and CLINICAL CHEMISTRY DATA:
haematocrit, haemoglobin, red blood cell count, mean cell volume (only male), mean cell haemoglobin, mean cell haemoglobin concentration, platelets, reticulocytes, white blood cell count, urea nitrogen, creatinine, alanine aminotransferase,alkaline phosphatase, 5'-nucleotidase, sorbitol dehydrogenase (only male)
STATISTICAL METHODS:
nonparametric multiple comparisontest of Dunn and Shirley, Jonckheere's test,
arcsine transformation,
multivariate analysis of variance

Remark : mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
625 ppm	96	116
1250 ppm	194	239
2500 ppm	402	472
5000 ppm	776	923
10000 ppm	1513	1693

Result : All mice lived to the end of the study;
as clinical signs of toxicity rough fur in females of the 10000 ppm-group.
10000 ppm: male, female reduced final body weight, slightly decreased feed consumption, males: reduced body weight gain

At study termination significantly increased abs. and rel. liver weight were noted from males at 5000 ppm (abs: p</=0.05; rel: p</=0.01) and 10000 ppm (p</=0.01) and relative liver weights in females at 10000 ppm (p</=0.01).

Microscopical examination:
liver: no changes were observed (both sexes);
nose (contr. low to high dose, average severity score based on a scale of 1 to 4 given[1 = minimal, 2 = mild, 3 = moderate, 4 = marked]):
respiratory epithelium hyperplasia: male, 1/10[1.0], 0/10, 0/10, 0/10, 4/10[1.0], 8/10[1.0]; female, 2/10[1.5], 0/10, 0/10, 3/10[1.0], 2/10[1.0], 5/10[1.0]
respiratory glandular hyperplasia: male, 1/10[1.0], 0/10, 0/10, 0/10, 0/10, 2/10[1.0]; female, 1/10[1.0], 0/10,0/10, 0/10, 07/10, 2/10[1.5]

Evaluation of reproductive organs revealed no biologically sign. findings in males and females (see also chapter 5.8.3 for further information)
Hematology, clinical chemistry and urinalysis data (sign. changes):
In males at 30000 ppm, d90.haemoglobin as significantly reduced and Sorbitol dehydrogenase was significantly increased. In Females hemoglobin was reduced on d90 at 30000 ppm and 5'-Nucleotidase was significantly increased on d 90 from 5000 ppm.

local toxicity: NOAEL(male, female): 2500 ppm
systemic toxicity:
NOAEL(male): 2500 ppm; NOAEL(female): 5000 ppm

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
04.05.2004 (101)

Type : Sub-acute
Species : rat
Sex : male/female
Strain : other: F344/N
Route of admin. : oral feed
Exposure period : 28 d
Frequency of treatm. : continuously in feed
Post exposure period : no
Doses : 0, 300, 1000, 3000, 10000, 30000 ppm (see RM)
Control group : yes, concurrent no treatment
NOAEL : 1000 ppm
Method : other: see freetext ME

Year : 1991
GLP : yes
Test substance : other TS: m-/p-cresol (60%:40% mixture)

Method : SIZE OF STUDY GROUP:
5 male and 5 female rats per group
TIME HELD BEFORE STUDY: 13-15 days
METHOD OF ANIMAL DISTRIBUTION:
randomized for each sex on the basis of body weight into groups per sex
DIET: NIH-07 rat ration
ANIMAL ROOM ENVIRONMENT:
temperature: 72° +/-3° F, humidity: 50 % +/-15 %, Fluorescent light: 12 hrs/day, room air changes : 10-12 changes/hr
TYPE AND FREQUENCY OF OBSERVATION:
observed twice daily, body weight taken initially, weekly, and at termination, feed consumption by cage recorded twice weekly
NECROPSY AND HISTOLOGIC EXAMINATION:
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 aninmals 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, oesophagus, heart, kidney, large intestines (caecum, colon, rectum), liver, lungs, lymph nodes (mesenteric), mammary glands, nasal cavity and turbinates, oral cavity, ovaries, pancreas, parathyroids, pharynx, pituirary, preputial gland, prostate, salivary glands, scrotal sac, seminal vesicles, skin, small intestine (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 lowere doses until a no-observed chemical effect was determined. Target organs included the following: nasal epithelium, bone marrow, forestomach, oesophagus, thyroid and uterus. Organ weights recorded for brain, liver, right kidney, thymus, heart, and lungs of all animals, and the right testis of all males.
STATISTICAL METHODS:
nonparametric multiple comparison test of Dunn and Shirley, Jonckheere's test

Remark : mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	26	27
1000 ppm	90	95
3000 ppm	261	268
10000 ppm	877	886
30000 ppm	2600	2570

Result : All rats survived.
30000 ppm: Body weight gain was significantly reduced in males and females, feed consumption was depressed during the first week, all rats had thin appearance by day 6 not beyond d 7.

At study termination, weights (w) were sign. increased: brain (males: rel. w. at 30000 ppm, p</=0.01)), right kidney (males: rel. w. from 10000 ppm, p</=0.05); females: abs. and rel. from 10000 ppm, p</=0.05), liver (males: rel. from 3000 ppm, p</=0.05 and absol. at 10000 ppm, p</=0.05; females: rel and absol. w. from 1000 ppm, p</=0.05), and rel right testes weight in males at 30000 ppm (p</=0.01).
No gross lesions were noted at necropsy.
Microscopically no changes were reported from brain, liver and kidney.
Microscopically changes: (avarage severity score based on a scale of 1 to 4 (1=minimal. 2=mild, 3=moderate, 4=marked), contr., low to high dose):
respiratory epithelium in the nasal cavity (hyperplasia: males, 0/5, 0/5, 0/5, 5/5[2.0], 5/5[2.4], 5/5[3.2]; female, 0/5, 0/5, 3/4[1.0], 5/5[1.6], 5/5[1.6], 5/5[2.8]),
thyroid gland (increased colloid in the follicles: males, 0/5, low dose: not performed, 0/5, 3/5[1.0], 5/5[1.0], 5/5[1.8]; female,1/5[1.0], low dose not performed, 0/5[1.0], 4/5[1.0], 5/5[1.8], 4/5[3.2], the biological significance is uncertain (not noted with the individual isomers,nor associated with overt follicular cell hypertrophy and/or hyperplasia),
oesophagus (hyperplasia and hyperkeratosis of the epithelium: males, females, minimal from 3000 ppm),
forestomach (hyperplasia of the epithelium: males, females, minimal from 10000 ppm; females, minimal hyperkeratosis from 10000 ppm)
and bone marrow (hypocellularity: males, minimal from 30000 ppm; females, minimal from 10000 ppm)

local toxicity: NOAEL(male, female): 300 ppm
systemic toxicty: NOAEL(male, female): 1000 ppm

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
02.05.2003 (101)

Type : Sub-acute
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 28 d
Frequency of treatm. : continuously in feed
Post exposure period : no
Doses : 0, 300, 1000, 3000, 10000, 30000 ppm (see RM)
Control group : yes, concurrent no treatment
NOAEL : 300 ppm
Method : other: EPA OTS 7952600
Year : 1991
GLP : yes
Test substance : other TS: m-/p-cresol (60%:40% mixture)

Method : SIZE OF STUDY GROUP:
5 male and 5 female mice per group
TIME HELD BEFORE STUDY: 13-15 days
METHOD OF ANIMAL DISTRIBUTION:
randomized for each sex on the basis of body weight into groups per sex
DIET: NIH-07 mouse ration
ANIMAL ROOM ENVIRONMENT:

temperature: 72° +/-3° F, humidity: 50 % +/-15 %,
Fluorescent light: 12 hrs/day, room air changes : 10-12 changes/hr
TYPE AND FREQUENCY OF OBSERVATION:
observed twice daily, body weight taken initially, weekly, and at termination, feed consumption by cage recorded twice weekly
NECROPSY AND HISTOLOGIC EXAMINATION:
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 aninmals 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, oesophagus, gallbladder, heart, kidney, large intestines (caecum, 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 intestine (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: nasal epithelium, bone marrow, forestomach, oesophagus, lung and uterus and ovaries. Organ weights recorded for brain, liver, right kidney, thymus, heart, and lungs of all animals, and the right testis of all males.
STATISTICAL METHODS:
nonparametric multiple comparison test of Dunn and Shirley, Jonckheere's test

Remark : mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	50	65
1000 ppm	161	200
3000 ppm	471	604
10000 ppm	1490	1880
30000 ppm	4530	4730

Result : No effect on survival;
clinical signs of toxicity in males and females: alopecia, dehydration, hunched posture, hypothermia, lethargy, rough hair coat, thin appearance.
30000 ppm, males, females: weight loss; decreased feed consumption during the first week and during the third week (females only);
30000 and 10000 ppm: sign. decreased weight gain,
At study termination weights (w) were sign. increased: brain (male, female: abs. and rel. w at 30000 ppm, p</=0.01), right kidney (male: abs. w at 30000 ppm, p</=0.01; female: rel. w at 30000 ppm, p</=0.05), liver (male: rel. w from 1000 ppm, p</=0.05; female: rel. and abs. w from 3000 ppm, p</=0.05) and right testes in males at 30000 ppm (p</=0.01)
No gross lesions were observed at necropsy.
Microscopically no changes were reported from brain, kidney

and liver.
Microscopic changes which were characterized by average severity score based on scale of 1 to 4 (1=minimal, 2=mild, 3=moderate, 4=marked) were reported from
nose (contr., low dose to high dose, respiratory epithelium hyperplasia: male, 0/5, 300 and 1000 ppm: not performed, 0/5, 1/5[1.0], 5/5[1.6]; female, 2/5[1.5], low dose: not performed, 0/5, 3/5[1.0], 3/5[1.7], 4/5[1.5]; olfactorium epithelium: at 30000 ppm, male, atrophy 2/5[1.0] and respiratory metaplasia 3/5 [1.3]; female, olfactory epithelium respiratory metaplasia at 30000 ppm, 2/5[1.0]),
lung (bronchiolar hyperplasia, minimal in males and females at 30000 ppm),
oesophagus (males, minimum hyperplasia and hyperkeratosis at 30000 ppm),
forestomach (males, at 30000 ppm, minimal hyperplasia of the squamous epithelium),
bone marrow (minimal hypocellularity at 30000 ppm),
atrophy of the ovary (mild) and uterus (moderate) at 30000 ppm

local toxicity:
NOAEL(male): 3000 ppm; NOAEL(female): 1000 ppm systemic toxicity:
NOAEL(male): 300 ppm; NOAEL(female): 1000 ppm

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
05.02.2004 (101)

Type : Sub-acute
Species : mouse
Sex : male/female
Strain : CD-1
Route of admin. : oral feed
Exposure period : 14 d
Frequency of treatm. : daily
Post exposure period : no
Doses : 0, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0 % (target dose: 0, 375, 750, 1500, 2250, 3000, 4500 mg/kg bw)
Control group : yes, concurrent no treatment
Method : other: NTP continuous breeding protocol, task 1 see freetext ME
Year : 1990
GLP : yes
Test substance : other TS: m-/p-cresol (60%/40%)

Method : 48 male and 48 female mice: 8 per sex per dose, data collected included clinical signs, individual body weights, feed and water consumption, mortality data
Result : mortality:
3.0 %-gr.: 1/8 (12.5 %) males, 1/8 (12.5 %) females (due to indeterminant causes)
Clinical signs:
all mice in 3.0 %-, and some in 2.0 %- and 1.0 %-group: lethargy, hunched back, squinted eyes, rough coat
dose related reduced feed consumption, water consumption and reduced body weight gain
3 %-group: sign. terminal weight loss of males and females
Reliability : (2) valid with restrictions
preliminary dose range finding study for the two generation reproductive study: see also chapter 5.8.1
04.09.2002 (102)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 97, TA98, TA100, TA 1535
Test concentration	:	0, 10, 33, 100 333, 1000, 3333 , 6666 ug/plate dissolved in DMSO
Cycotoxic concentr.	:	High dose was limited by toxicity or solubility
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: EPA OTS 798.5265, see also fretext ME
Year	:	1990
GLP	:	yes
Test substance	:	other TS: m/p-cresol (60/40),
Method	:	detailed protocol in Zeiger 1988 Environ. Molec. Mutagen. 11 (Suppl.12), 1-158: The metabolic activation system was prepared from Aroclor 1254-induced male Sprague-Dawley rat and male Syrian hamster livers, and used as 10% or 30% concentrations SOLVENT: DMSO CONTROL. DMSO and 2-aminoanthracene, 4-nitro-o-phenylenediamine, sodium azide, 9-aminoacridine served as negative and positive controls, respectively.
Remark	:	The positive control was functional.
Reliability	:	(2) valid with restrictions only 4 strains were used
Flag	:	Critical study for SIDS endpoint

05.02.2004 (101)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	13 weeks
Doses	:	0, 625, 1250, 2500, 5000, 10000 ppm (approx. m: 0,96, 194, 402, 776, 1513mg/kg bw; f: 116, 239, 472, 923, 1693 mg/kg bw)
Result	:	negative
Method	:	other: see ME
Year	:	1990
GLP	:	yes
Test substance	:	other TS: m/p-Cresol: 60:40
Method	:	10 mice/sex/dose treated for 13 weeks (see also Chapter 5.4) at termination smears were prepared from blood sampled by cardiac puncture from control and dosed mice: 10000 normochromatic erythrocytes from each mice scored for micronuclei
Remark	:	for signs of toxicity see chapter 5.4
Result	:	No significant elevation in the frequency of micronucleated erythrocytes was observed in either male or female mice
Reliability	:	(2) valid with restrictions not fully in accordance with the guideline, e.g. no positive control
Flag	:	Critical study for SIDS endpoint

16.12.2002 (101)

Type	:	other
Species	:	Drosophila melanogaster
Sex	:	no data
Strain	:	other: Berlin - Wild Type eggs
Route of admin.	:	other: see method
Exposure period	:	other: see method
Doses	:	other: see method
Result	:	negative
Method	:	other: Isolated ovaries of Berlin wild Typ Drosophila melanogaster were treated with cresol (1:10^3) for 15 min and then implanted into a host. The chromosomes of the descendants were examined.
Year	:	1949
GLP	:	no
Test substance	:	other TS: no data
Result	:	no mutations were found.
Reliability	:	(4) not assignable unusual test method

23.10.2002 (103)

5.7 CARCINOGENICITY

17.06.2002

17.06.2002

5.8.1 TOXICITY TO FERTILITY

Type	:	other: Reproductive Assessment by Continuous breeding (RACB)
Species	:	mouse
Sex	:	male/female
Strain	:	CD-1
Route of admin.	:	oral feed
Exposure period	:	14 w
Frequency of treatm.	:	continuously in diet
Premating exposure period		
Male	:	7 d
Female	:	7 d
Duration of test	:	41 w
No. of generation studies	:	2
Doses	:	0, 0.25, 1.0, 1.5 % (target dosage: 0, 375, 1500, 2250 mg/kg bw/day)
Control group	:	yes, concurrent no treatment
NOAEL parental	:	.25 %
other: NOAEL (Fertility F0, F1)	:	1 %
Method	:	other: NTP 2 generation continuous breeding protocol, see freetext ME
Year	:	1990
GLP	:	yes
Test substance	:	other TS: m-/p-cresol (60%:40% mixture)
Method	:	NTP continuous breeding protocol: Task 1: dose-finding, see Chapter 5.4 Task 2: reproduction and fertility study: 20 ps/group, 40 ps

(contr.); exposure period, F0: 7d prior to cohousing, 98 d (14 w) of continuous breeding, then pairs were seperated and any litters born after the final litter were reared by the dams until weaning, at the end of week 15: evaluation of clinical signs, parenteral bw, fertility (number producing a litter/number of breeding pairs), litters per pair, live pups per litter, proportion of pups born alive, sex of live pups, pup body weights within 24 hrs of birth, feed and water consumption.
Task 3:
determination of the affected sex only when pos. effects on reproductive function during task 2:
one week crossover mating trial with parental mice from control and high dose groups, vaginal cytology evaluation for 12 d prior to sacrifice; low dose and mid dose mice were hold for necropsy together with task 3 mice: body and organ weight determination and sperm evaluation of all males.
Task 4:
offspring assessment: mice born after week 15 were kept until maturity and cohabited for 7 d and housed singly until delivery, collection of vaginal smears, body and selcted organ weights, epididymal and testicular spermatozoa evaluation, mating index, pregnancy index, fertility index, live F2 pups per litter, proportion of F2 pups born alive, sex ratio, live F2 pup weight, adjusted live F2 pup weight, average dam weight, average number of days to litter
Statistical methods:
Test for linear trend: ANOVA
Turkey's test for pairwise compairison to controls
nonparametric multiple comparison procedures of Dunn and Shirley as modified by Williams
Jonckheere's test
Cochran-Annitage test
Chi-square test
parametric analysis of covariance
F-test,
Dunn's test

Result **:** F0:
mortality:
7 mice died: 2 in the controlgr., 2 in the 1.5 % dose-gr., 1 in the 1.0 %-dose-gr., 2 in the 0.25 %-dose-gr.
1.0 and 1.5 %-group:
reduced body weight gain and feed consumption after 16 w, especially in delivering and lactating dams
1.5 %-group:
decreased bw, increased liver and kidney weight
all mice:
reproductive competence was not affected, including inital fertility, the proportion of pups born alive or the sex of the pups born alive,
1.5 % -group:
adjusted live pup weight and the number of pups per litter (both sexes) were decreased by 5% and 20%, respectively; cumulative days to fifth litter were increased by almost 3 d compared to control
1.5 %-group, males:
decreased epididymal and seminal vesicle weights by 10 and 21 %, respectively, but no change in testis weight, sperm parameters or testicular and epididymal histology

Cross over mating did not clearly reveal the affected sex,

as the only parameter affected (adjusted live pup weight) was decreased if either sex was dosed.

F1-pups: 1.5 %-group:
birth weights decreased by 5 %, decreased preweaning growth by 26 % and postweaning survival decreased by 39 %
clinical signs: reduced size, dehydratation, lethargy, rough coat
F1-adults:
no effect on reproductive performance:
1.0 and 1.5%-group, male:
decreased bw, decreased reproductive organ weights (prostate, seminal vesicles, testes), but no effects on sperm parameters or histology, increased relative liver and kidney weights
1 and 1.5 %-group, female:
terminal bw reduced
0.25-, 1.0-, and 1.5 %-group, female:
ovarian weight reduced, kidney- and liver-weights increased
no effect of treatment on oestrous cyclicity and ovarian or liver and kidney histology

NOAEL(F0, F1, general toxicity): 0.25 %, based on differences in bw and organ weights to the concurrent controls.
Reproductive competence of F0, F1-generation was not affected by treatment.
NOAEL(fertility, F0, F1): 1 %
F0-generation 1.5 % - group: decreased adjusted live pups weights, decreased number of live pups per litter and increase of the cumulative days to the fifth litter
F1 generation 1.5 % -group: live pup weights and adjusted live pup weights reduced.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
05.02.2004 (102)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

19.06.2002

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type : other:
In vitro/in vivo : In vivo
Species : rat
Sex : male/female
Strain : other: F344/N
Route of admin. : oral feed
Exposure period : 13 w
Frequency of treatm. : daily
Duration of test : 13 w
Doses : 0, 1880, 7500, 30000 ppm
Control group : yes, concurrent no treatment
Result : See freetext RS

Method	:	other: determination of sperm motility and concentration in males and length of oestrus cycle and vaginal cytology following repeated dose according EPA OPP 82-1
Year	:	1991
GLP	:	yes
Test substance	:	other TS: m-/p-cresol (60%:40% mixture)
Remark	:	see also chapter 5.4.
Result	:	males: no difference to the respective controls in weights of right testicle, right epididymis, right epididymal tail, no difference in the concentration of viable sperm, only slight but sign. reduced sperm motility at 30000 ppm females: increased oestrus cycle length from 7500 ppm
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

16.12.2002 (101)

Type	:	other
In vitro/in vivo	:	In vivo
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	13 w
Frequency of treatm.	:	daily
Duration of test	:	13 w
Doses	:	0, 625, 2500, 10000 ppm
Control group	:	yes, concurrent no treatment
Result	:	No findings
Method	:	other: determination of sperm motility and concentration in males and length of oestrus cycle and vaginal cytology following repeated dose according EPA OPP 82-1
Year	:	1991
GLP	:	yes
Test substance	:	other TS: m-/p-cresol (60%:40% mixture)
Remark	:	see also chapter 5.4.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

18.06.2002 (101)

Type	:	other
In vitro/in vivo	:	In vivo
Species	:	rat
Sex	:	male/female
Strain	:	other: F344/N
Route of admin.	:	oral feed
Exposure period	:	28 d
Frequency of treatm.	:	continuously in feed
Duration of test	:	28 d
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm (m: 0, 26, 90, 261, 877, 2600 mg/kg bw; f: 0, 27, 95, 268, 886, 2570 mg/kg bw)
Control group	:	yes, concurrent no treatment
Result	:	male, 30000 ppm: increased right testes weight without histopathologic correlate
Method	:	other: description in chapter 5.4
Year	:	1991
GLP	:	yes
Test substance	:	other TS: m/p-cresol (60%:40% mixture)

Reliability : (1) valid without restriction
12.11.2002 (101)

Type : other
In vitro/in vivo : In vivo
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 28 d
Frequency of treatm. : continuously in feed
Duration of test : 28 d
Doses : 0, 300, 1000, 3000, 10000, 30000 ppm (m: 0, 50, 161, 471, 1490, 4530 mg/kg bw; f: 0, 65, 200, 604, 1880, 4730 mg/kg bw)
Control group : yes, concurrent no treatment
Result : m, 30000 ppm: increased testes weight without histopathologic correlate; f, 30000 ppm: atrophy of ovaries and uterus
Method : other: see chapter 5.4.
Year : 1991
GLP : yes
Test substance : other TS: m/p-cresol (60%:40% mixture)

Reliability : (1) valid without restriction
05.09.2002 (101)

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Remark : Case Report: Muenchhausen's Syndrome with multiple skin ulcers caused by cresol is the diagnosis resulting from the findings of a 25 years old female nursing student.
Reliability : (4) not assignable
16.01.2003 (104)

Remark : It is reported that mortality from bladder cancer was increased among molders in the foundry industry. The author suggest that cresols might act as tumour promotor.
Reliability : (4) not assignable
16.01.2003 (105)

Remark : It is reported that 2 patients with chronic exposure to cresol or creosote developed multifocal transitional carcinoma of the bladder with muscle invasion.
Reliability : (2) valid with restrictions
16.01.2003 (106)

Remark : Case Report: A 52 year old man attempted to commit suicide by ingesting approximately 100 ml of penetrating oil, a petroleum distillate containing 85% kerosine, 12% mixed cresols, 2% surfactant and 1% artificial colour. He revealed a massive intravascular Heinz-body hemolytic anemia associated with the presence of bizarre-looking erythrocytes. He was treated successfully.

Reliability : (2) valid with restrictions
16.01.2003 (107)

Remark : Case Report: A 74 old widow died after ingestion of an overdose of lysol. Post morten findings: lower third of the oesophagus and the whole of the stomach lining were bleached white, areas of mucosal desquamation, pylorus and duodenum showed a marked degree of congestion; 30.4 mg/100 ml mixed cresols in the urine, 48.0 mg/100 g mixed cresols in the liver; 19.0 mg/100 ml mixed cresols in the blood.
Reliability : (2) valid with restrictions
16.01.2003 (108)

Remark : A 76 year old unmarried woman swallowed an unknown quantity of lysol. She was found shortly afterwards unconscious, and despite resuscitative measures, she died within 2 hours; post mortem findings: oesophagus, denuded of mucosa, was deep purple; stomach dilated, containing 500 ml chocolate - coloured fluid, mucosa: dark brown, necrotic; small perforations on the anterior gastric wall; trachea and bronchi with mucosal oedema, lungs congested; 90 mg mixed cresols/100 g liver; 39.6 mg mixed cresols/100 g kidney ; 7.1 mg mixed cresols/100 ml blood.
Reliability : (2) valid with restrictions
16.01.2003 (108)

Remark : Case report: A 46 year old labourer, working in a chemical factory, had a cresol solution poured over his upper trunk when he was transporting a tub containing hot cresol. The lesion consisted of a light brown eschar with well-defined margine, minimal oedema. He developed gross haemeturia, oliguria and finally anuria within 24 h, upper gastrointestinal bleeding within 2 days, on day 4 progressive dyspnoe and tachypnoe, hypertension with blood pressure arround 200/100 mmHg during the first 10 days. On day 15 he developed a septic shock with severe jaundice and renal failure. He was treated successfully and discharged on day 38 after injury.
Reliability : (2) valid with restrictions
16.01.2003 (109)

Remark : Case Report: A man (50 years old) has drunk cresol solution to commit suicide. 2 hours later he was found to be unconscious, cyanotic with methemoglobinemia, blood pressure 90-136 mm Hg; pulse 101/min; light reflex: slow; urine colour: black brown. Methb increased in the patients blood drastically within 15 hours. He was treated successfully.
Reliability : (2) valid with restrictions
16.01.2003 (110)

Remark : Workers exposed to organic solvents (i.e. cresol) showed increased levels of cresol, hippuric acid and phenols in urine and decreased levels of albumiun and delta-globulin in the serum.
Reliability : (4) not assignable
16.01.2003 (111)

Remark : There are several human case studies reporting the use of Lysol, a cresol-containing solution, as an abortificant. In addition, intravaginal application of Lysol produces extensive hemolysis, erosion of blood vessels, kidney tubular damage, liver necrosis and death.
Reliability : (4) not assignable
16.01.2003 (112) (113)

Remark : The probable oral lethal dose for humans is 50-500 mg/kg bw
Reliability : (2) valid with restrictions
16.01.2003 (114)

5.11 ADDITIONAL REMARKS

Type : other

Remark : 0.2% Formocresol, containing 35% cresol and 19% formaldehyde, causes the cell death of 50% of the treated Hela cells within 4 hours.
Reliability : (4) not assignable
16.01.2003 (115)

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