FOREWORD INTRODUCTION

p-CHLOROTOLUENE

CAS N°: 106-43-4

SIDS Initial Assessment Report

For

SIAM 20

Paris, France, 19 – 22 April 2005

1.	**Chemical Name:**	**p-Chlorotoluene**
2.	**CAS Number:**	**106-43-4**
3.	**Sponsor country:**	Germany Contact Point: BMU (Bundesministerium fuer Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn
4.	**Shared Partnership with:**	EniChem Synthesis S.p.A., Italy; Hoechst AG, Germany.
5.	**Roles/Responsibilities of the Partners:**	-
•	Name of industry Sponsor /consortium	Bayer AG, Germany Contact person: Dr. Burkhardt Stock D-51368 Leverkusen Building 9115
•	Process used	see next page
6.	**Sponsorship History**	
•	How was the chemical or category brought into the OECD HPV Chemicals Programme?	by ICCA-Initiative
7.	**Review Process Prior to the SIAM:**	last literature search (update): 8 October 2004 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 11 November 2004 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search terms OECD/ICCA
8.	**Quality check process:**	IUCLID was used as a basis for the SIDS dossier. All data were checked and validated by BUA. A final evaluation of the human health part has been performed by the Federal Institute for Risk Assessment (BfR) and of the ecotoxicological part by the Federal Environment Agency (UBA).
9.	**Date of Submission:**	Deadline for circulation: 21 January 2005

10. Date of last Update: Last literature search: IUCLID Chapters 1-4: 2003-08-29
Chapter 5: 2002-05-16

11. Comments: The recommendation does not cover the isomeric mixture, as we have not reviewed the uses of the mixture.

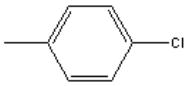
OECD/ICCA - The BUA* Peer Review Process

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 o f 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.	106-43-4
Chemical Name	p-Chlorotoluene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Since there is no developmental toxicity study with p-chlorotoluene, the data from o-chlorotoluene are taken into account to fill the data gap. The comparison of the two isomers showed a rather high degree of qualitative similarity with respect to available data on absorption, excretion and metabolism, toxicity after acute and repeated exposure, Overall o-chlorotoluene and p-chlorotoluene have a similar toxicity profile. o-Chlorotoluene (CAS No 95-49-8) was already discussed and concluded at SIAM 11, 2001; and the initial assessment was published by UNEP in 2004.

Specific toxicokinetic studies with p-chlorotoluene are not available. The available information indicates that absorption of p-chlorotoluene is rapid via gastrointestinal tract or respiratory tract but is limited via dermal contact. Excretion occurs mainly via urine as p-chlorobenzoic acid derivatives by rabbits or as the corresponding hippuric acid by dogs. Exact data on tissue distribution are not available. Thus, p-chlorotoluene as well as o-chlorotoluene are absorbed via the gastrointestinal tract, the lungs and to a lesser extent via skin. For both isomers excretion takes place principally via urine, and in small amounts with faeces and exhaled air. In the metabolism o- and p-chlorotoluene are oxidized at the methyl group leading to chlorobenzyl alcohol glucuronide, chlorobenzoic acid and mercapturic acid.

The LC_{50} of p-chlorotoluene was not determined but an Inhalation Hazard test showed that exposure of rats against 4183 ppm (approximately 22 mg/m³) for 4 hours was not lethal, but signs of intoxication were observed. Exposure for 8 hours resulted in the death of all exposed rats within the 14-day observation period. The dermal LD_{50} (rabbit) is > 2000 mg/kg bw and LD_{50} (rat) is > 5000 mg/kg bw. Following oral application to rats the LD_{50} values ranged between 2100 mg/kg bw and 2389 mg/kg bw. The predominant symptoms were body tremor, accelerated breathing rate, cyanosis, decreased motor activity and palmospasms. With regard to o-chlorotoluene the acute oral toxicity is LD_{50} (rat, male): 3227 mg/kg bw; the acute inhalation toxicity is LC_{50} (rat): 37,517 mg/m³ (4 hrs) and the acute dermal toxicity LD_{50} (rat) is > 1083 mg/kg bw and LD_{50} (rabbit): > 2165 mg/kg bw. Based on the available data of o- and p-chlorotoluene it can be concluded that the acute toxicity of monochlorotoluene in general is low.

p-Chlorotoluene is slightly irritating to the skin when 0.5 ml undiluted substance is applied to intact and abraded skin of rabbits under occlusive conditions for 24 hours. p-Chlorotoluene is slightly irritating to eyes of rabbits when 0.1 ml undiluted substance was applied into the conjunctival sac. o-Chlorotoluene, tested according to OECD TG 404, is slightly irritating to the skin. However, when tested under occlusive conditions, the substance is corrosive. o-Chlorotoluene, tested according to OECD TG 405, was irritating to the eye in 1 out of 3 animals. Based on the available data it can be concluded that monochlorotoluene in general is slightly irritating the skin and eyes of rabbits. However, o-chlorotoluene seems to be a stronger skin irritant under occlusive conditions.

p-Chlorotoluene is a skin sensitizer when tested in the guinea pig maximization test according to OECD TG 406. o-Chlorotoluene, tested according to OECD TG 406, is not sensitizing to the skin of guinea pigs. However the higher sensitizing potential for para-substituted substances is a known effect.

Repeated dose toxicity of p-chlorotoluene was examined in sub-acute (29 days) and sub-chronic (90 days) gavage

studies with rats using dosages of 50, 200 and 800 mg/kg bw/day. The liver and the kidney are the main target organs. Based on liver impairment in the sub-acute as well as in the sub-chronic study, which also revealed an increase in chronic progressive nephropathy at the highest dose level of 800 mg/kg bw/day, the NOAEL for both studies was determined to be 200 mg/kg bw/day.

With respect to o-chlorotoluene the NOEL for repeated dosing (3 months) by gavage in rats is 20 mg/kg bw/day. In higher dosages (80 or 320 mg/kg bw/day) unspecific signs of toxicity were observed, e.g. reduced body weight gain in male animals as well as elevated BUN, elevated WBC count, reduced prothrombine time in both sexes.

The NOEL for repeated dosing via capsule (3 months) in dogs is 20 mg/kg bw/day. In higher dosage (80 mg/kg bw/day) one animal showed vomiting, and red blood was detected in faeces which might be due to the slightly irritating property of o-chlorotoluene.

In range finding study tests, the LOAECs after inhalation were 4 mg/l (4000 mg/m³, 14 d) in rats and 8 mg/l (8000 mg/m³, 23 d) in rabbits. There is no NOEC from these data.

Based on the test conditions in the repeated dose toxicity studies which were taken into account for comparison, o-chlorotoluene is at least as toxic as p-chlorotoluene after repeated dosing.

p-Chlorotoluene was not mutagenic in the *Salmonella typhimurium* TA97, TA98, TA100, TA1535, TA1537, TA102, and TA104 and in *Escherichia coli* WP2uvrA, *Escherichia coli* WP2uvrA/pKM101 with and without a metabolic activation system nor did it induce micronuclei in mice after a single intraperitoneal injection in a study according to OECD TG 474. o-Chlorotoluene showed no mutagenic activity in bacterial and in mammalian cell test systems *in vitro*. o-Chlorotoluene showed no clastogenic activity (chromosome aberration) *in vitro* and *in vivo*. Based on the available data on o- and p-chlorotoluene it can be concluded that both monochlorotoluenes do not reveal mutagenic activity, neither *in vitro* nor *in vivo*.

There are no studies on the possible carcinogenicity available.

There are no specific studies on reproductive toxicity. However, in the repeated dose-toxicity studies which were taken into account for comparison, o-chlorotoluene is at least as toxic as p-chlorotoluene. Furthermore, in the metabolism o- and p-chlorotoluene are oxidized at the methyl group leading to chlorobenzyl alcohol glucuronide, chlorobenzoic acid and mercapturic acid. Thus, the use of o-chlorotoluene to fill data gaps is justified.

There are no specific studies on reproductive toxicity (fertility assessment) available with p-chlorotoluene or with o-chlorotoluene. Evaluation of the reproductive organs in the available repeated dose toxicity studies with p-chlorotoluene or with o-chlorotoluene give no indication of possible impairment of these organs.

With regard to developmental toxicity conclusion should be drawn from developmental toxicity studies in rats and rabbits with o-chlorotoluene as there is no specific study with p-chlorotoluene available. Developmental toxic effects in rats and rabbits occur mostly in the presence of maternal toxicity and without a clear dose-response relationship, however, as a specific malformation, brachydactyly. Thus, for o-chlorotoluene, the NOAEL (rat) is 1.1 mg/l (1100 mg/m³, maternal toxicity), but no NOAEL for developmental toxicity could be derived, the LOAEL (developmental toxicity, rat) is 1.1 mg/l (1100 mg/m³) In rabbits, the NOAEL (maternal toxicity) is 1.5 mg/l (1500 mg/m³) and the NOAEL (developmental toxicity) is 4 mg/l (4000 mg/m³).

The results of the developmental studies with o-chlorotoluene (brachydactyly mostly in maternal toxic doses and without clear dose-response relationship: 1 rabbit fetus at the highest dose; 1 rat fetus at the lowest dose and 6 rat fetuses at the highest dose) lead to the assumption that monochlorotoluene in general might cause malformations in offspring by high dose treatment (i.e. at 1.1 mg/l = lowest dose tested, and 9.0 mg/l).

Environment

p-Chlorotoluene is a clear colorless liquid with a melting point of 7.5 °C, and a boiling point of 162 °C. The density of the liquid is 1.0697 g/cm^3. The vapor pressure is in the range of 310 to 379 Pa at 20 /25 °C. The measured log K_{OW} is 3.33. The solubility in water is 40 mg/l at 20 °C. The flash point is 51.9 °C, the auto-ignition temperature 595 °C.

With regard to the chemical structure, p-chlorotoluene is not expected to hydrolyze under environmental conditions.

According to the Mackay fugacity model level I calculation, the favourite target compartment of p-chlorotoluene is air with 99.67 %, followed by water with 0.25 %. A Henry's law constant of 446.8 Pa x m³/mol at 25 °C calculated according to the Bond method indicates that the compound has a high potential for volatilization from surface waters. The calculated half-life of p-chlorotoluene in air due to indirect photodegradation is $t_{1/2}$ = 8.8 days. Due to the low absorption in the UV-B range, no direct photodegradation is expected.

p-Chlorotoluene is not readily biodegradable, but can be eliminated in industrial wastewater treatment plants. In a modified Zahn-Wellens-test, comparable to the OECD TG 302 B, elimination of p-chlorotoluene of 86 % after 28 days occurred, 68 % of which occurred in the first three hours and is attributed to physical-chemical effects (adsorption, stripping). A manometric respirometry test (in accordance with OECD TG 301 F) was performed with a concentration of p-chlorotoluene of 100 mg/l. After 28 days 1 % of the test substance had been degraded. Aerobic ready tests were performed according to the national Japanese MITI test, comparable to the OECD TG 301 C. After a period of 14 days, the %-age biodegradation from the oxygen consumption was zero or did not exceed 30 % after 2 weeks from the beginning of the test, respectively. At a concentration of 200 mg/l p-chlorotoluene was metabolized in 3 days by a blend of microorganisms able to degrade a range of halogen substituted aromatic compounds.

The bioconcentration factor BCF = 73.13 for p-chlorotoluene, calculated from the octanol-water partition coefficient, indicates a moderate potential for bioaccumulation of p-chlorotoluene in fish. The available experimental data concerning bioaccumulation of p-chlorotoluene in *Cyprinus carpio,* confirm potential for bioaccumulation in fish. The BCF values obtained for concentrations of 0.3 and 0.03 mg/l were in the range of 14 - 101.6 and 21.9 - 76.5, respectively.

Experimentally obtained adsorption coefficients (K_{OC}) revealed a mid sorption potential of p-chlorotoluene. The experimentally achieved K_{oc} values following the OECD TG 106 were in the range of 327 to 512 depending on soil properties. In addition, a K_{OC} value of 434 was calculated with PCKOCWIN v. 1.66 .

Concerning the toxicity of p-chlorotoluene to aquatic species reliable acute and chronic experimental results of tests with fish, *Daphnia*, and algae are available. The tests were performed according to standard procedures or similar methods. The lowest effect values from short-term tests, as well as from chronic toxicity test are (n = nominal concentration; m = measured concentration; m* = geometric mean of analytical values ; s = static test type; ss = semistatic test type):

Danio rerio:	28 d-$NOEC_{growth}$	= 1.9 mg/l (m, ss)
Poecilia reticulata:	14 d-LC_{50}	= 5.92 mg/l (n, ss)
Oryzias latipes :	48 h-LC_{50}	= 5.2 mg/l (n, s or ss)
Daphnia magna:	16 d-$NOEC_{reproduction}$	= 0.32 mg/l (n, ss)
Ceriodaphnia dubia:	48 h-EC_{50}	= 1.7 mg/l (n, s)
Desmodesmus subspicatus:	72 h-$EC_{50growth\ rate}$	= > 0.96 mg/l (m*, s)
Desmodesmus subspicatus:	72 h-$NOEC_{growth\ rate}$	= 0.43 mg/l (m*, s)
Desmodesmus subspicatus:	72 h-$EC_{50biomass}$	= > 0.96 mg/l (m*, s)
Desmodesmus subspicatus:	72 h-$NOEC_{biomass}$	= > 0.96 mg/l (m*, s)

Based on the lowest effect concentration observed for *Daphnia* in a semistatic test the Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 10. Using the effective 16 d-$NOEC_{reproduction}$ of 0.32 mg/l found for the invertebrate *Daphnia magna* a $PNEC_{aqua}$ = 32 µg/l was determined.

Exposure

p-Chlorotoluene is produced by catalytic conversion of toluene with chlorine under moderate temperature and normal pressure. The composition of the crude product, a chlorotoluenes isomers mixture, depends on temperature and the catalyst. The chlorotoluene isomers are separated by fractional distillation.

For 2002, the global monochlorotoluenes output by about a dozen producers is estimated to be approximately 75 000 tonnes (including unseparated isomers). The global p-chlorotoluene production volume in 2002 (tonnes/a) is estimated by region as follows: Western Europe 13 500, Ukraine 1000, Japan 4500, and China 5000 (total 24 000). In the Sponsor country there is one company with a manufacturing volume of 10 000 to 50 000 tonnes/a. Three quarters of the global manufacturing volume stems from OECD member countries.

Pure p-chlorotoluene is solely used as an industrial intermediate for the synthesis of organic chemicals. The

main derivatives are intermediates, e.g. in the production of pesticides, pharmaceuticals, and pigments, like 4-chlorobenzotrichloride (ca. 45 %), 4-chlorobenzyl chloride (ca. 21 %), 4-chlorobenzaldehyde (ca. 18 %), 2,4-dichlorotoluene (ca. 6 %), 4-chlorobenzonitrile (ca. 8 %), and 4-chlorobenzoic (ca. 2 %).

Chlorotoluene isomer mixtures, especially those containing a relatively high amount of o-chlorotoluene, are used as solvents in industry. In the USA p-chlorotoluene is listed as "other" (inert) ingredient in pesticide formulations, however, production of chlorotoluene was ceased in 2001. In the Sponsor country, p-chlorotoluene is not used in any pesticide formulation.

For the Sponsor country, use as a solvent is not known. Also, no direct consumer use is known for p-chlorotoluene in the Sponsor country. No products containing p-chlorotoluene are listed in the Danish, Finnish, Norwegian, Swedish, and Swiss Product Registers.

From the manufacturing site of the Sponsor company virtually no p-chlorotoluene (< 25 kg) was emitted into the environment in 2003. In the Sponsor country for occupational settings no workplace limit concentration is laid down. Workplace air sampling shows that the exposure is below 1 mg/m³ at the Sponsor company. Except from the Sponsor company, no exposure data is available.

p-Chlorotoluene was detected in construction and demolition waste in waste recycling facilities in Florida. p-Chloro-toluene occurs in volcanic gases and is formed in the atmosphere. In most recent studies on its occurrence in the environment, p-chlorotoluene was not detectable in environmental media.

p-Chlorotoluene is exclusively used as an intermediate in chemical processes. No consumer use is known for p-chlorotoluene. In products made from p-chlorotoluene by the Sponsor company, no p-chlorotoluene could be detected. Exposure of consumers to p-chlorotoluene via the environment is low.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard (skin sensitization, indications for reproductive toxicity) to human health. Based on data presented by the Sponsor country, exposure of workers in manufacturing in the only producer in the Sponsor country and of consumers is anticipated to be low. As no worker exposure data except from the producer in the Sponsor country is available, it is recommended to conduct an exposure and if indicated a risk assessment at the workplace apart from the production site. The chemical is a candidate for further work.

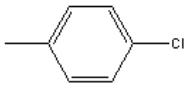
Environment: The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by one producer which accounts for approx. 44 - 56 % of global production and relating to the use in several OECD countries), exposure is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 106-43-4
IUPAC Name: p-Chlorotoluene
Molecular Formula: C_7H_7Cl
Structural Formula:



Molecular Weight: 126.59 g/mol
Synonyms: 1-Chloro-4-methyl-benzene
4-Chlorotoluene
Benzene, 1-chloro-4-methyl-
p-Chlorotoluene
p-Tolyl chloride
Toluene, p-chloro

1.2 Purity/Impurities/Additives

Purity of the technical product: p-Chlortoluene >= 98 % (Rossberg et al., 2000).

Impurities: m-Chlorotoluene (<= 1 % w/w) (Rossberg et al., 2000)

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference	IUCLID
Substance type	Organic, aromatic, chlorinated compound		1.1.1
Physical state	Liquid	Merck Index, 2001	1.1.1
Melting point	7.5 °C	Merck Index, 2001	2.1
Boiling point	162 °C*	NIOSH, 2001	2.2
Density at 20 °C	1.0697 g/cm^3	Merck Index, 2001	2.3
Vapour pressure at 20 °C	3.1 hPa	Bayer AG, 1987	2.4
Vapour pressure at 25 °C	3.79 hPa	Yaws, 1994	2.4
Octanol/water partition coefficient (log K_{ow}) at 25 °C	3.33	Hansch, Leo, and Hoekman, 1995	2.5
Water solubility at 20 °C (modified plunger method)	40 mg/l	Bayer AG, 1987	2.6.1
Flash point (Open cup)	51.9 °C	Daubert et al., 1992	2.7
Auto flammability (ignition temperature)	595 °C	NIOSH, 2001	2.8
Conversion factor at 1013 hPa and 20 °C	1 ml/m^3 (1 ppm) = 5.26 mg/m^3	BIA, 2004	2.14

*) Pressure at boiling point not reported but assumed to be 1013 hPa

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

2.1.1 Production

p-Chlorotoluene is produced by converting toluene with chlorine under moderate temperature and normal pressure in the presence of a catalyst. This gives a crude product with the isomeric ratio of chlorotoluenes depending on temperature and the catalyst (Rossberg et al., 2000).

$C_6H_5\text{-}CH_3 + Cl_2 \rightarrow Cl\text{-}C_6H_4\text{-}CH_3 + HCl$.

As a catalyst, iron chloride, titanium chloride or antimony chloride are used. At a temperature of 50 °C at ambient pressure, with iron chloride as the catalyst, a mixture of approximately 28 % p-chlorotoluene, 2 % m-chlorotoluene, 52 % o-chlorotoluene, 11 % dichlorotoluenes and 7 % unconverted toluene is obtained. The process used by Bayer Chemicals results in a mixture of approximately 47 % p-chlorotoluene, 0.3 % m-chlorotoluene, 51 % o-chlorotoluene, and 1.7 %

dichlorotoluenes. The pure chlorotoluene isomers are separated by fractional distillation (BUA, 1989).

For 2002, the global monochlorotoluene output by about a dozen producers is estimated to be approximately 75 000 tonnes (including unseparated isomers). The global p-chlorotoluene production can be estimated by region as follows (Table 2). Three quarters of the manufacturing volume stems from OECD member countries (Srour, 2003).

Table 2 Estimated p-chlorotoluene production volumes by region in 2002 (Srour, 2003)

Region	Estimated production volume (tonnes/a)
Western Europe	13 500
Ukraine	1000
Japan	4500
China	5000
Total	24 000

Bayer Chemicals AG is the biggest producer of p-chlorotoluene in the EU, and the only producer in the Sponsor country. 10 000 to 50 000 tonnes/a chlorotoluenes isomer mixture are produced by Bayer (Bayer Chemicals, 2004).

2.1.2 Processing and Use

p-Chlorotoluene is exclusively used as an intermediate in the chemical industry (Rossberg et al., 2000; Srour, 2003). More than 50 % of the produced isomer mixture is processed on-site to cresols (Bayer Chemicals, 2004).

Cresols are further used for the production of flame retardants, plasticizers, agrochemicals, material preservatives, thermal oils, fragrances, condenser fluids, and anti-ageing agents (Bayer Chemicals, 2004).

About 5000 tonnes/a p-chlorotoluene are separated from the isomer mixture at Bayer AG for serving as a basic chemical in the chemical industry for producing intermediates (Bayer Chemicals, 2004).

Pure p-chlorotoluene is solely used as an industrial intermediate for the synthesis of organic chemicals (Bayer Chemicals, 2004). The main derivatives are (Srour, 2003):

- 4-chlorobenzotrichloride: intermediate in the production of pesticides and pharmaceuticals (ca. 47 %)
- 4-chlorobenzyl chloride intermediate in the production of pesticides (ca. 20 %)
- 4-chlorobenzaldehyde: intermediate in the production of pesticides and pharmaceuticals (ca. 17 %)
- 2,4-dichlorotoluene: intermediate in the production of pesticides (ca. 6 %)

- 4-chlorobenzonitrile: intermediate in the production of pigments (ca. 7 %)
- 4-chlorobenzoic acid: intermediate in the production of pigments and pharmaceuticals (ca. 3 %).

The number of manufacturers is small and most of the production is utilized captively. Chlorotoluene isomer mixtures (which are not in the focus of this SIDS), especially those containing a relatively high amount of o-chlorotoluene, are used as solvents in industry (Kirk-Othmer, 1993).

p-Chlorotoluene is listed as "other" (inert) ingredient in pesticide formulations (EPA, 2003). During catalytic monochlorination of toluene, a mixture of o-, m- and p-chlorotoluene is formed. In general, the price of p-chlorotoluene is higher than that of the other monochlorotoluenes. Thus, it is likely that not p-chlorotoluene but o-chlorotoluene or a mixture of chlorotoluenes is (was) used as an inert ingredient for pesticide formulations. In 1984, an important US herbicide manufacturer ceased using monochlorotoluenes in pesticide formulations (Rossberg et al., 2000). The only US producer of p-chlorotoluene who offered a mixture of chlorotoluenes as solvent for pesticides (Occidental Chem Corp, 1992) ceased production and sale in 2001 (Occidental Chem Corp, 2001). In the Sponsor country, p-chlorotoluene is not used in any pesticide formulation (BVL, 2004).

For the Sponsor country, use as a solvent is not known (Bayer Chemicals, 2004). Also, no consumer use is known for p-chlorotoluene in the Sponsor country (Bayer Chemicals, 2004). No products containing p-chlorotoluene are listed in the Danish, Finnish, Norwegian, Swedish, and Swiss Product Registers (SPIN, 2004, Swiss Product Register, 2004).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Releases of p-chlorotoluene may occur during manufacturing and processing. Information on environmental exposure from manufacturing and processing of p-chlorotoluene is available for the Bayer Chemicals plants in the Sponsor country (Bayer Chemicals, 2004).

The air and water emissions of the Bayer production and processing sites are monitored by an Environmental Surveillance Group which operates independently of any manufacturing unit. This group is equipped with mobile detectors and sampling devices for various potential emissions. It also operates stations with measuring and sampling devices for environmental media (Bayer Chemicals, 2004).

At the Bayer Chemicals sites in the Sponsor country, p-chlorotoluene is manufactured and processed in closed systems (Bayer Chemicals, 2004).

The exhausts from chlorination, distillation, and processing are connected to thermal exhaust purification plants and air washing units. According to the current Official Emission Declaration of 2000, 157 kg/a of chlorotoluenes (sum of isomers) were emitted into the atmosphere at the production and processing sites. p-Chlorotoluene was not separately listed. In 2003 no emissions (chlorotoluenes and p-chlorotoluene) were reportable (< 25 kg) (Bayer Chemicals, 2004).

Waste from manufacturing and processing is incinerated in incinerators for hazardous wastes (BUA, 1989).

There is no wastewater from chlorination (BUA, 1989). Cleaning water and wastewater from air washers is led to Bayer wastewater treatment plants (Bayer Chemicals, 2004).

Within the daily monitoring program p-chlorotoluene was not detected in the effluent of any wastewater treatment plant at the production and processing sites with a detection limit of 2 µg/l and 1 µg/l, respectively (Bayer Chemicals, 2004).

The effluents of the Bayer wastewater treatment plants pass into the river Rhine (10 percentile of the river flow: 1050 m^3/s). At the production and processing site, for the receiving water, a local

Predicted Environmental Concentration (PEC_{local}) of < 0.003 µg/l

is calculated taking into account the dilution factor (700), and the detection limit (2 µg/l) of that site. At the second (only processing) site, a local

Predicted Environmental Concentration (PEC_{local}) of < 0.001 µg/l

is calculated taking into account the dilution factor (1000 [default value, since dilution factor is larger than 1000]), and the detection limit (1 µg/l) (Bayer Chemicals, 2004).

All chlorotoluenes, including p-chlorotoluene, occur in volcanic gases (Jordan et al., 2000; Jordan, 2003) (*cf* Chapter 2.2.8).

Since chlorine is formed in the atmosphere during photooxidation (Roempp 1998; Kahlil, 1999), in principle, p-chlorotoluene could be formed in the atmosphere by reaction of toluene with molecular chlorine in the presence of metals, e.g., on particulate matter surfaces. However, due to the high potential for other reactions, the atmospheric formation rate of p-chlorotoluene is thought to be low (expert judgement).

2.2.2 Photodegradation

p-Chlorotoluene entering in the atmosphere is expected to be degraded by OH-radicals. The calculated half-life of p-chlorotoluene in air (calculation program: AOPWIN v. 1.91 2000) due to indirect photodegradation is $t_{1/2air}$ = 8.8 days, considering a daily mean OH-radicals concentration of 500 000 radicals per cm^3 (Bayer Industry Services, 2004).

Direct photolysis rate constant for p-chlorotoluene could not be estimated because of insufficient spectral and quantum yield data. The rate constant can be considered as zero as no light absorption occurs above the solar cut-off (300 nm). Therefore, direct photolysis is suspected to be not environmentally relevant (Jaber et al., 1984).

In a laboratory study of limited environmental relevance, direct UV-irradiation of p-chlorotoluene in deaerated methanol at 300 nm for 48 hours resulted in a substrate conversion of 2.9 %. When also irradiated in deaerated methanol using acetone as a sensitizer for 9 hours, 54.5 % of p-chlorotoluene disappeared, whereby 52 % was converted into toluene (Choudhry, Webster, and Hutzinger, 1986).

The photodegradation data are compiled in Table 3.

Table 3 Photodegradation of p-chlorotoluene (IUCLID 3.1.1)

Parameter	Method	Result	Reference
Indirect photodegradation in air	Calculation with AOPWIN, v. 1.91 for 24 h-day, 500 000 OH/cm^3	$t_{1/2}$ = 8.8 d	Bayer Industry Services, 2004
Direct photodegradation in a deaerated methanol solution	UV-irradiation at 300 nm for 48 h UV-irradiation at 300 nm for 9 h in presence of acetone	2.9 % degradation 54.5 %	Choudhry, Webster, and Hutzinger, 1986

2.2.3 Stability in Water

p-Chlorotoluene is not expected to undergo hydrolysis in the environment due to the lack of hydrolysable functional groups (Harris, 1990). The chlorotoluenes are neutral and stable compounds (Rossberg et al., 2000). Therefore, hydrolysis is not expected to be an important process in determining the environmental fate of p-chlorotoluene (Jaber et. al., 1984; US EPA/NITS, 1989).

2.2.4 Transport between Environmental Compartments

The distribution of p-chlorotoluene between environmental compartments was calculated according to the Mackay Fugacity Model Level I (v. 2.11). The main target compartment for p-chlorotoluene is air with 99.67 %. Results and input parameters are presented on Table 4, (Bayer Industry Services, 2004).

Table 4 Input parameters and results of the Mackay Fugacity Model Level I

Input Parameters	**Value**
Temperature	25 °C
Vapour Pressure	379 Pa
Water Solubility	0.04 g/l
Log K_{ow}	3.33
Melting Point	7.5 °C

Results pro Compartment	**Calculated distribution**
Air	99.67 %
Water	0.24 %
Sediment	0.041 %
Soil	0.041 %
Suspended Sediment	< 0.01 %
Fish	< 0.01 %
Aerosol	< 0.01 %

The distribution coefficient of p-chlorotoluene between aqueous solutions and air was calculated using the Bond-method. The Henry's law constant (HLC) was 446.8 Pa x m^3/mol (Bayer Industry Services, 2004). The group method leads to a Henry's law constant of 494.5 Pa x m^3/mol (Bayer Industry Services, 2004).

These data indicate that p-chlorotoluene is highly volatile from aqueous solutions according to the scheme of Thomas (1990).

Table 5 Distribution in the environment (IUCLID 3.3.2)

Parameter	Method	Result	Source
Fugacity Water - air Henry's law constant	Bond-method (calculated at 25 °C)	446.8 Pa x m^3/mol	Bayer Industry Services, 2004
Fugacity Water - air Henry's law constant	Group-method (calculated at 25 °C)	494.5 Pa x m^3/mol	Bayer Industry Services, 2004

2.2.5 Biodegradation

According to the available biodegradation results p-chlorotoluene is not readily biodegradable, but it can be eliminated in industrial wastewater treatment plants.

A test designed to evaluate the inherent biodegradability of organic substances, was conducted with predominantly domestic activated sludge following a modified Zahn-Wellens-test, comparable to the OECD TG 302 B. The initial test substance concentration was 22 mg/l DOC. The elimination of approx. 68 % of the test substance after 3 h indicates that elimination occurred due to physical mechanisms (adsorption, stripping). The following degradation is sluggish in comparison to the elimination in the first three hours. Plateau phase was reached at day 7 resulting in a total elimination of 86 % (Bayer AG, 1991a). Due to the significant elimination within 3 h the study does not supply evidence that p-chlorotoluene is inherently biodegradable, but it suggests that p-chlorotoluene can be eliminated by physical mechanisms in wastewater treatment plants.

A test designed to evaluate the ready biodegradability of organic substances, was conducted with the adapted activated sludge obtained from the above mentioned Zahn-Wellens-test following a manometric respirometry test, in accordance with the OECD TG 301 F. The initial test substance concentration was 100 mg/l test substance (Bayer AG, 1991b). After a 28 days incubation period elimination rate was 1 %, indicating that under this test conditions no biodegradation occurred.

Aerobic ready tests were performed according to the national Japanese MITI test, comparable to the OECD TG 301 C guideline. After a period of 14 days, p-chlorotoluene was judged to be not or almost not biodegradable, respectively. The %-age biodegradation from the oxygen consumption was zero or did not exceed 30 % after 2 weeks from the beginning of the test, respectively (MITI, 1992; Sasaki, 1978).

In an experiment a blend of organisms was tested for its ability to degrade a range of halogen substituted aromatic compounds, including p-chlorotoluene. A microbial blend which consisted of five *Pseudomonas*, one *Klebsiella*, four *Rhodococci* and two fungal strains was used. At a concentration of 200 mg/l p-chlorotoluene was completely metabolized in 3 days (Goulding, Gillen and Bolton, 1988). This suggests that p-chlorotoluene can be metabolized in industrial wastewater treatment plants with adapted microorganisms.

The key data of the biodegradation studies are listed in Table 6.

Table 6 Tests on biodegradation of p-chlorotoluene (IUCLID 3.5)

Inoculum	Procedure	Result	Reference
activated sludge, predominantly domestic	OECD TG 302 B Inherent biodegradability	68 % after 3 hours 86 % after 28 days	Bayer AG, 1991a
activated sludge, domestic, adapted	OECD TG 301 F	1 % after 28 days	Bayer AG, 1991b
Activated sludge	MITI-test (comparable to OECD TG 301 C)	0 % after 14 days	MITI, 1992
Activated sludge	MITI (comparable to OECD TG 301 C)	< 30 % after 14 d	Sasaki, 1978
Microbial blend	Microbial degradation	100 % after 3 d	Goulding, Gillen and Bolton, 1988

2.2.6 Bioaccumulation

The proposed moderate bioaccumulation potential of p-chlorotoluene is based on experimental and calculated BCF values:

Taking into account the octanol-water partition coefficient, a bioconcentration factor (BCF) can be calculated with the BCFWIN Program (v. 2.15). Using log K_{OW} = 3.33, the calculated BCF was 73.13 (Bayer Industry Services, 2004). The US EPA (1989) published a further calculated BCF value of 230. However, no details of the calculation method were reported. Experimental investigations confirm the accumulation potential of p-chlorotoluene. Bioconcentration factors were determined according to the Japanese MITI test at 0.03 and 0.3 mg/l in the carp *Cyprinus carpio* after a 56-days exposure period. BCF values obtained for the two concentrations were in the range of 14 - 101.6 and 21.9 - 76.5, respectively (MITI, 1992).

Table 7 Bioaccumulative properties of p-chlorotoluene (IUCLID 3.7)

Parameter	**Method**	**Result**	**Source**
Bioconcentration factor	Calculated by BCFWIN Program (v. 2.15)	BCF = 73.13	Bayer Industry Service, 2004
Bioconcentration factor	MITI-Test corresponding to OECD TGD 305C, for 56 d at 0.03 mg/l	BCF = 14 - 101.6	MITI, 1992
Bioconcentration factor	MITI-Test corresponding to OECD TGD 305C, for 56 d at 0.3 mg/l	BCF = 21.9 - 76.5	MITI, 1992

2.2.7 Geoaccumulation

The distribution of p-chlorotoluene between the organic phase of soil or sediments and the porewater was calculated using QSAR. A K_{OC} of 434 was calculated with PCKOCWIN v. 1.66 (Bayer AG, 2004).

Experimental Koc values were obtained according to the OECD TG106 in three soil types treated with p-chlorotoluene solutions (Research Consulting Company, 1992). The soils used for testing were sand, loamy sand and sandy loam. Adsorption of p-chlorotoluene reached a constant value after 10 min of equilibration time for sandy loam, 30 min for loamy sand and 60 min for sand. Three achieved K_{oc} values were in the range of 327 - 512 (average K_{OC} = 391.6) indicating that p-chlorotoluene is a substance with mid geoaccumulation potential according to Litz (1990).

Table 8 Geoaccumulative properties of p-chlorotoluene (IUCLID 3.3.1)

Parameter	Method	Result	Reference
Soil organic carbon-water distribution coefficient	OECD TG 106	**Soil: Koc** sand: 512 sandy loam: 327 loamy sand: 336	Research Consulting Company, 1992
Soil organic carbon-water distribution coefficient	Calculated with PCKOCWIN, V1.66	K_{OC} = 434	Bayer Industry Service, 2004

2.2.8 Environmental Monitoring

Soil

No (historic) data are available on the occurrence of p-chlorotoluene in the geosphere (BUA, 1989).

Water

The GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA) compiled historical data on the environmental occurrence of chlorotoluenes. Oldest data cover 1975 and 1976, when 0.4 µg/l p-chlorotoluene were detected in the German part of the Rhine. In 1979, 0.03 µg/l p-chlorotoluene are reported for the Rhine at Lobith, and 0.03 µg/l and 2.4 µg/l for the Dutch part of the Rhine. In 1983, at the confluent of the river Main with the Rhine, the average p-chlorotoluene concentration was 0.73 µg/l (about 48 samples), yielding a p-chlorotoluene load of 5.4 tonnes for the Main. Steeply decreasing concentrations of the chlorotoluenes were demonstrated by several measurements of the waterworks associations in the Rhine catchment area, and in 1987 chlorotoluenes were not detectable with a detection limit of 0.02 µg/l (BUA, 1989).

In 1992 - 1993, in a 2 years study on ground and drinking water in an contaminated area (industrial site for about one century, contaminated with several organic halogenes) in the Turin province of Northern Italy, p-chlorotoluene was not detectable with a detection limit in the range of 0.1 - 0.01 µg/l (Passarino et al., 1995).

In 1998, p-chlorotoluene was not detectable in treated wastewater from semiconductor industry and in groundwater from monitoring wells of an aquifer which was recharged with reclaimed wastewater in the desert south of Phoenix (detection limit 0.002 mg/l) (Freeman and Harvey, 1999).

In the United States, water departments of several cities and other organisations monitor drinking water and rivers used for water supply also for substances not regulated by the US EPA. As one

member of these unregulated volatile organic substances, p-chlorotoluene has not been detected recently with a typical limit of detection of 0.5 µg/l, e.g. in the New River (California Regional Water Quality Control Board, 2003), the Trinity River Basin (Land et al., 1998), the Duck River (Duck River Utility Commission, 2003), or in the drinking water of Ocean City MD (Ocean City, 2002), Phoenix AZ (City of Phoenix, 2000), Anderson SC (City of Anderson, 2004), and Elizabethtown NC (Town of Elizabethtown, 2004). p-Chlorotoluene was not detected in a springwater from Kentucky (Rockcastle Springs, 2002).

Air

In their compilation on volatile organics in the air of the United States, Shah and Singh (1988) report that the average daily concentration of p-chlorotoluene was 0.204 ppb v/v, with the median of 310 data points at 0.09 ppb v/v. These authors stated that the data base contained data from sources in all forms, and "inconsistencies, duplications, unsupported validation procedures, un-published methods, and often, numerical errors" were detected.

In a study from April to December 1997, p-chlorotoluene was not detectable in atmospheric air with a detection limit of 0.02 ppb v/v in 50 samples taken from three sites with low, moderate and high level of traffic and urbanisation in New Jersey, USA (Pankow et al., 1998).

2.3 Human Exposure

2.3.1 Occupational Exposure

Occupational exposure to p-chlorotoluene is most likely to occur through inhalation and dermal contact.

Workplaces

At the Bayer manufacturing sites, workplaces where p-chlorotoluene is manufactured or processed (Bayer Chemicals, 2004), include

- Manufacturing processes: Chlorination of toluene to chlorotoluenes mixture, distillation (*cf* Chapter 2.1)
- Processing: Use in chemical synthesis, e.g. production of chemical intermediates.

At the Bayer sites, p-chlorotoluene is manufactured continuously in closed systems (*cf* Chapter 2.2.1). It is transported on site in pipelines, and off site in rail and road tankers and rolling channel drums (Bayer Chemicals, 2004).

In the fine fraction of waste generated from construction and demolition, p-chlorotoluene (up to 35 µg/kg) was detected in 4 out of 43 samples taken from old waste stock piles and newly generated piles of 14 waste recycling facilities in Florida (Jang and Townsend, 2002).

p-Chlorotoluene is listed as "other" (inert) ingredient in pesticide formulations in the USA (*cf.* Chapter 2.1.2). However, the only US producer of p-chlorotoluene who offered a mixture of chloro-toluenes as solvent for pesticides (Occidental Chem Corp, 1992) ceased production and sale in 2001 (Occidental Chem Corp, 2001). In the Sponsor country, p-chlorotoluene is not used in any pesticide formulation (BVL, 2004).

Precautionary measures at the workplace

In accordance with the principles of Responsible Care and Sustainable Development, at Bayer Chemicals the exposure of workers is reduced to the lowest technically practicable level (Bayer Chemicals, 2004).

Surveys of the Bayer workplaces are performed according to German Technical Guidances TRGS 402 and TRGS 901. This includes regular surveys in the working area for any possible exposure to p-chlorotoluene and other substances under all relevant work situations, and appropriate control measures (Bayer Chemicals, 2004).

To protect workers from exposure, several precautionary and protective measures are taken. The filling and drumming takes place in a closed system with special suction devices. Repair and maintenance work is only carried out on parts of the manufacturing or processing systems which have been emptied and cleaned. Special written permits are required which include a detailed description of the protective measures depending on the work to be done (e.g. full protective clothing and gas filter masks (classification ABEK)) (Bayer Chemicals, 2004).

Down stream users of p-chlorotoluene are informed by way of a material safety data sheet on the recommended safety measures (see above) (Bayer Chemicals, 2004).

Potential exposure at the workplace

In Germany for occupational settings no workplace limit concentration (MAK) is laid down (TRGS 900, 2004). The Finnish workplace limit concentration is set at 260 mg/m³.

During recent years, measurements within the scope of the monitoring duty according to the Gefahrstoff-Verordnung (German Dangerous Substances Regulations) were below 1 mg/m³ at the Sponsor company (Bayer Chemicals, 2004). Except from the Sponsor company, no exposure data is available.

2.3.2 Consumer Exposure

p-Chlorotoluene is exclusively used as an intermediate in chemical processes (Srour, 2003). No consumer use is known for p-chlorotoluene (Bayer Chemicals, 2004).

Since there are virtually no emissions of p-chlorotoluene from manufacturing and processing from the Sponsor company, consumers exposure via the environment is negligible in the Sponsor country.

End-products made from p-chlorotoluene are not expected to contain significant p-chlorotoluene levels, because p-chlorotoluene - as can be seen from the variety of products synthesized from p-chlorotoluene - is used as a basic intermediate in chemical synthesis (*cf.* Chapter 2.1.2). Consistently, in an end-product made from p-chlorotoluene by the Sponsor company, p-chlorotoluene was not detectable with a detection limit of 0.02 % w/w. Also in an intermediate made from p-chlorotoluene, no chlorotoluene could be detected with a detection limit of approximately 0.001 % w/w (Bayer Chemicals, 2004).

In the Sponsor country, p-chlorotoluene is not permitted to be used in pesticide formulations (BVL, 2004).

Thus, consumers are not exposed to p-chlorotoluene via consumer products in the Sponsor country.

3 Human Health Hazards

3.1 Effects on Human Health

Since there is no developmental toxicity study with p-chlorotoluene, the data from o-chlorotoluene are taken into account to fill the data gap. The comparison of the two isomers showed a rather high degree of qualitative similarity with respect to available data on absorption, excretion and metabolism, toxicity after acute and repeated exposure. Overall, o-chlorotoluene and p-chlorotoluene have a similar toxicity profile. o-Chlorotoluene was already discussed and concluded in SIAM 11, 2001; the data are published by UNEP in 2004.

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

In vivo Studies

Specific toxicokinetic studies with p-chlorotoluene are not available. The respective acute toxicity studies indicate absorption via oral and inhalation exposure, whereas absorption after dermal contact seems to be limited (Bayer AG, 1977a, b; Occidental Chem Corp, 1980a, b; Hoechst AG, 1975a, b, c). Following single oral administration of 300 mg/kg bw p-chlorotoluene to rabbits 64 - 83 % of the dose was excreted with the urine as ether-soluble p-chlorobenzoic acid derivatives and 1 % of the dose was found in the urine as ester glucuronides (Bray et al., 1955). In a further oral study with rabbits, benzoic acid was also detected as urinary metabolite. The corresponding hippuric acid was detected in the urine when 5000 mg p-chlorotoluene was given via capsule to a dog (Hildebrandt, 1903).

Following intraperitoneal injection of 1000 mg p-chlorotoluene/kg bw to rats, concentration in blood and lung peaked at 4 hours post injection. The concentration in the liver reached the maximum at 1 hour post application and started to decline at 4 hour. Lowest tissue level was observed at 12 hours post dosing, indicating effectively total clearance by this time point (Zewdie, Silverman, and Schatz, 1997).

Conclusion

Specific toxicokinetic studies with p-chlorotoluene are not available. The available information indicates that absorption of p-chlorotoluene is rapid via gastrointestinal tract or respiratory tract but is limited via dermal contact. Excretion occurs mainly via urine as p-chlorobenzoic acid derivatives by rabbits or as the corresponding hippuric acid by dogs. Exact data on tissue distribution are not available.

o-Chlortoluene (SIAM11):

Following oral administration o-chlorotoluene is quickly absorbed from the gastrointestinal tract. 85 - 92 % of o-chlorotoluene given to rats, was eliminated in urine, 5 - 8 % was excreted in feces and 1 - 4 % of the applied dose was exhaled as volatile ^{14}C. The major urinary and fecal metabolites were 2-chlorohippurate, a beta-glucuronide of 2-chlorobenzyl alcohol and mercapturic acid. Analysis of the ^{14}C residues in plasma showed that the two major radioactive components were mercapturic acid and the beta-glucuronide of 2-chlorobenzyl alcohol (38 and 25 % of plasma ^{14}C, respectively), while trace levels of 2-chlorotoluene, 2-chlorobenzoic acid, 2-chlorobenzyl alcohol and 2-chlorohippurate were detectable also. Virtually all of the administered o-chlorotoluene was eliminated within 4 d with < 1 % remaining in the carcass.

Overall conclusion

Both, o-chlorotoluene and p-chlorotoluene, are absorbed via the gastrointestinal tract, the lungs and to a lesser extent via skin. For both isomers, excretion takes place principally via urine, and in small amounts with faeces and exhaled air. In the metabolism o- and p-Chlorotoluene are oxidized at the methyl group leading to chlorobenzyl alcohol glucuronide, chlorobenzoic acid and mercapturic acid.

3.1.2 Acute Toxicity

Studies in Animals

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

Inhalation

Male Wistar rats were exposed (whole body exposure) to p-chlorotoluene-saturated vapour atmosphere for 4, 5, 6 and 8 hours (Inhalation Hazard test), respectively, and then observed for 14 days (Hoechst AG, 1975a). Each exposure period group consisted of 6 rats. The vapour atmosphere was generated at room temperature and the concentrations were determined to be 4180 ppm (approximately 22,04 mg/m³), 4100 ppm (approximately 21,63 mg/m³), 3950 ppm (20,82 mg/m³) and 4300 ppm (approximately 22,68 mg/m³) during the 4, 5, 6 or 8 hour exposure period, respectively. As signs of intoxication during and following of the exposure all animals showed slightly closed eyelids, disturbed balance, lowered reflex response to acoustic stimuli, tremor, tachypnea, hypopnea and anesthesia. The 4 h-exposure period was survived by 6/6 rats and rats recovered within 24 hours post exposure. In the 5-hour exposure group 3/6 rats died during the first night following exposure; 3/6 rats survived and recovered 24 hours post exposure. In the 6-hour exposure group 3/6 rats died within 5 hours during exposure; 2/6 rats died within the first night post exposure; 1/6 rats died 24 hours later. In the 8 hour-exposure group death of 6/6 rats occurred within the first night post exposure. Red colored lungs were found at the gross pathologic examination of the dead animals, survivors showed no gross pathological findings.

Dermal

2000 mg/kg bw undiluted p-chlorotoluene was applied to the back of each of two rabbits per sex and covered under occlusive conditions for 24 hours. Afterwards the animals were observed for 14 days (Occidental Chem Corp, 1980a). Animals revealed marked irritational effects but no animal died. At necropsy no remarkable findings were detected in males whereas females had dark red mottled lungs. In other studies with 5 male and 5 female or with 6 female rats, 5000 mg/kg bw undiluted p-chlorotoluene was applied on the back under occlusive conditions for 24 hours. No animal died during exposure or during the 14-day-post-exposure observation time. Detailed symptoms were not mentioned. Pathological examination revealed no findings (Bayer AG, 1977a; Hoechst AG, 1975b).

Oral

Groups of 10 male Wistar rats were given single oral doses of 1 - 3.1 ml undiluted p-chlorotoluene/kg bw (approximately 1070 - 3320 mg/kg bw) and observed for 14 days. The animals revealed palmospasm, sedation and at high doses flaccid paralysis of the extremities. Death occurred from the second day after treatment. The LD_{50} was calculated 2.1 ml/kg bw (approximately 2273 mg/kg bw; Bayer AG, 1977a, b). In other acute toxicity studies 5 with male and 5

female Sprague-Dawley or 10 female Wistar rats per dose group, the resulting LD_{50} values were 2100 mg/kg bw (Occidental Chem Corp, 1980b) and 2389 mg/kg bw (Hoechst AG, 1975c), respectively. As signs of intoxication salivation, body tremor, accelerated breathing rate, cyanosis, decreased motor activity, and palmospasms were reported. Histopathologic evaluation (Occidental Chem Corp, 1980b) showed irritational effects in the gastrointestinal tract and lungs increasing in severity with increasing dose.

Studies in Humans

Inhalation

Goldblatt (1955) reported in a survey article that concentrations of 400 ppm (approx. 2108 mg/m³) mono-chlorotoluene (2- and 4-chlorotoluene, composition not specified) in the atmosphere for more than 60 minutes cause severe toxic effects in workers, 200 ppm (approx. 1054 mg/m³) lead to symptoms of illness if the exposure continues for more than a short time and 75 ppm (approx. 395 mg/m³) indicate unsatisfactory conditions (no further details included). In the recent open literature no cases of acute poisoning are reported.

Conclusion

The LC_{50} of p-chlorotoluene was not determined but an Inhalation Hazard test showed that exposure of rats against 4183 ppm (approximately 22 mg/m^3) for 4 hours was not lethal, but signs of intoxication were observed; Exposure for 8 hours resulted in the death of all exposed rats within 24 hours. Red colored lungs were found at the gross pathologic examination of the dead animals. The dermal LD_{50} is > 2000 mg/kg bw for rabbits and > 5000 mg/kg bw for rats. Following oral application to rats the LD_{50} values ranged between 2100 mg/kg bw and 2389 mg/kg bw. The predominant symptoms of intoxication were body tremor, accelerated breathing rate, cyanosis, decreased motor activity, and palmospasms. Irritational effects in the gastrointestinal tract and lungs increased in severity with increasing doses.

o-Chlorotoluene (SIAM 11):

The acute oral toxicity :	LD_{50} (rat, male):	3227 mg/kg bw;
	LD_{50} (rat, female):	3860 mg/kg bw
The acute inhalation toxicity:	LC_{50} (rat):	37 517 mg/m³(4 hrs);
The acute dermal toxicity	LD_{50} (rat):	> 1083 mg/kg bw,
	LD_{50} (rabbit):	> 2165 mg/kg bw

Overall conclusion
Based on the available data of o- and p-chlorotoluene it can be concluded that the acute toxicity of both monochlorotoluenes in general is low.

3.1.3 Irritation

Skin Irritation

Studies in Animals

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

Intact and abraded skin of rabbits was tested with 0.5 ml undiluted p-chlorotoluene and with a 10 % solution of p-chlorotoluene in sesame oil under occlusive conditions for 24 hours (Hoechst AG 1975d). Only slight edema (score 1 of maximum 3) was observed in some animals (intact and

abraded skin) for at least 48 hours, which has disappeared after 72 hours yielding irritation indices (24 and 72 hours) of 0.21 (0.5 ml undiluted p-chlorotoluene) and 0.04 (10 % solution) of max. 8.0. In another study under nearly the same conditions (undiluted substance, observation period: 72 h; Occidental Chem Corp, 1980c) only slight erythema (score 1 of maximum 4, intact and abraded skin) was observed in 6/6 animals for 24 hours and in 4/6 animals at the 72-hour reading resulting in a total irritation index (24 and 72 hours) of 0.85 of max 8.0.

Eye Irritation

Studies in Animals

0.1 ml undiluted p-chlorotoluene was applied into the conjunctival sac of one eye of each of 6 rabbits. 24 hours after application the eyes were rinsed (Hoechst AG, 1975d). Slight conjunctival redness (score 1 of maximum 3: n = 6/6 at 1 h-reading up to n = 3/6 at 72 h-reading) and slight conjunctival swelling (score 1 of maximum 4: n = 4/6 at 1 h-reading up to n = 3/6 at 72 h-reading) were the only signs of irritation observed. At the end of the observation period (day 14) the eyes had returned to normal. Average score was not calculated. In another study under nearly the same conditions the eyes of 6 rabbits were not rinsed (Occidental Chem Corp, 1980d). Signs of irritation were conjunctival redness from day 1 - 7 (max score 2 of 3) in 6/6 rabbits, chemosis from day 1 - 3 (max. score 2 of 4) in 6/6 rabbits and discharge from d1-d2 or d7 (max score 1 of 3) in 2/6 rabbits. The maximum average score (day 1) was 5.7 of 110. At the end of the observation time (day 14) appearance of the eyes had returned to normal.

Conclusion

p-Chlorotoluene is slightly irritating to the skin when 0.5 ml undiluted substance is applied to intact and abraded skin of rabbits under occlusive conditions for 24 hours. p-Chlorotoluene is slightly irritating to eyes of rabbits when 0.1 ml undiluted substance was applied into the conjunctival sac.

o-Chlortoluene (SIAM 11):

o-Chlorotoluene, tested according to OECD TG 404, is slightly irritating to the skin. However, when tested under occlusive conditions, the substance is corrosive.

o-Chlorotoluene, tested according to OECD TG 405, was irritating to the eye in 1 out of 3 animals.

Overall conclusion:
Based on the available data it can be concluded that monochlorotoluene in general is slightly irritating to the skin and eyes of rabbits. However, o-chlorotoluene seems to be a stronger skin irritant under occlusive conditions.

3.1.4 Sensitisation

Studies in Animal

Skin

A maximization test performed with 20 guinea pigs according to OECD TG 406 (intradermal induction concentration: 5 %; induction concentration by topical application: 100 %). revealed a positive response in 14/20 animals 48 hours and in 7/20 animals 72 hours after challenge with a 25 % solution. A 12 % solution of p-chlorotoluene caused a positive response in 3/20 at the 48 hour- and in 1/20 animals at the 72 hour-reading. As negative control substance Cremophor E1 in physiological saline was used, 0/10 guinea pigs showed a reaction. (Bayer AG, 1992a).

Conclusion

p-Chlorotoluene is a skin sensitizer when tested in the guinea pig maximization test according to OECD TG 406.

o-Chlorotoluene (SIAM 11):

o-Chlorotoluene is not sensitising when tested in the guinea pig maximization test according to OECD TG 406.

Overall conclusion
Based on the available data o-chlorotoluene is not sensitizing to the skin whereas p-chlorotoluene has shown a skin sensitizing potential. However, the higher sensitising potential for para-substituted isomers is a known effect.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Oral

The repeated dose toxicity of p-chlorotoluene was examined in 5 male and 5 female Wistar rats per group for a period of 29 days according to OECD TG 407 (Bayer AG, 1993). The substance was given via gavage seven days per week in doses of 0, 50, 200 or 800 mg/kg bw/day dissolved in polyethylene glycol 400. To investigate the effects of p-chlorotoluene on reproductive organs additional examinations were carried out (Bayer AG, 2004); the results are reported in Section 3.1.8.

1/5 Male in the 200 mg-group, and 1/5 male and 1/5 female in the 800 mg-group suffered from difficulties in breathing, reduced condition, and rough fur. Animals of the 800 mg-group had additionally distended abdomen and transient increased salivation. 1/5 control male and 2/5 males and 1/5 female in the 800 mg-group died or had to be sacrificed before scheduled term.

Animals dosed with 50 mg/kg bw/day tolerated the treatment without impairment with respect to mortality, body weight development, food and water intake, clinical laboratory examinations (haematology, clinical chemistry, urinalysis) and gross- and histopathology. Only the mean value for calcium in males was significantly reduced when compared to concurrent control males: 2.49 mmol/l versus 2.57 mmol/l. As the value is in the range of the historical control values of 2.43 - 2.68 mmol/l, this finding is regarded to be of no toxicological relevance.

In the 200 mg-group, the changes compared to the respective controls included reduced body weight in 1/5 male, significantly lowered mean thrombocyte count in males (837 [exp. 9]/l versus 1119 [exp. 9]/l, historical control range: 774 - 1295 [exp. 9]/l) and mean MCH value in females (17.7 pg versus 18.3 pg, historical control range: 15.9 - 20 pg), significantly increased mean protein value of females (63.9 g/l versus 60.9 g/l, historical control range: 53.1 - 77.9 g/l) and the significantly lowered urinary protein excretion rate of males (4.4 mg versus 8.4 mg, historical control range: 3 - 23 mg) and total protein excretion rate of females (0.16 g/l versus 0.34 g/l, historical control range: 0.05 - 0.45 g/l), but are all within the historical control range and therefore of no toxicological relevance.

In the 800 mg-group male rats showed in general lowered body weight development than the control males. At necropsy mean values of relative and absolute liver weights were increased in both, males and females, when compared to controls (males absolute/relative: 12 619 mg/5052 mg versus 11 351 mg/4282 mg and females, absolute/relative: 7710 mg/4702 mg versus 7125 mg/ 4192 mg). Only 1/5 female in this dose-group showed histopathologically liver changes including

moderate inflammatory-cellular focal infiltrates in the liver and vacuoles in the hepatocytes. All other investigated parameters were without pathological findings.

In summary, the reported isolated statistically significant changes up to and including 200 mg/kg bw/day were evaluated to be of no toxicological or biological relevance, because the differences to the respective control values were low, there is no dose-response relationship and no histo-pathological correlate. The only findings which might be substance related are the lowered body weight development and the liver changes in the 800 mg/kg bw/day-group. Thus, the NOAEL (general toxicity) is determined as 200 mg/kg bw/day.

In a further study 10 Sprague-Dawley rats/sex/group received 0, 50, 200 and 800 mg/kg bw/day dissolved in corn oil per gavage seven days per week over a period of 90 days (Terrill et al., 1990). Dosage was chosen on the basis of a dose-finding study. Results from evaluation of the reproductive organs are also described in Section 3.1.8.

Up to and including 200 mg/kg bw/day treatment with p-chlorotoluene was tolerated without significant pathological findings: No signs of intoxication were reported and mortality did not occur. Only, in both groups, urinalysis yielded decreased pH-values when compared to the respective controls: 50 mg-gr. (f = 6.85) and 200 mg-gr. (m/f = 6.80/6.35) versus controls (m/f = 7.50/7.25). Ophthalmoscopy, hematology and clinical chemistry showed no differences to the respective controls. At necropsy, organ weights and gross examination were without pathological findings except in females of the 50 mg-group that had significantly decreased mean absolute lung weights: 1.28 g versus 1.41 g. Histopathologically, in 1/10 female in each of the 200 mg- and 50 mg-group, dark areas and minimal mucosal erosion in the glandular portion of the stomach were observed which were considered to be stress induced.

In the 800 mg-group the animals displayed languid behaviour, prostration, sensitivity to touch, tremor, epistaxis, wheezing, dyspnea and/or polypnea resulting in death of 4/10 males and 2/10 females. In treated males mean body weight gain (only shown as figure) and mean terminal body weight was decreased (489 g versus 571 g of controls). In females, body weight gain was comparable to control females but mean terminal body weight differed between treated and control females (282 g versus 321 g of controls). Ophthalmoscopy and hematology yielded no pathological findings. In clinical chemistry, male values of bilirubin (0.23 mg/dl versus 0.16 mg/dl), ALP (136 IU/l versus 87 IU/l), BUN (blood urea nitrogen) (33 mg/dl versus 11 mg/dl), creatinine (1.0 mg/dl versus 0.5 mg/dl), were significantly increased and sodium was decreased: 139 mEq/l versus 143 mEq/l. Female data were comparable to the respective control data. As in the 50 and 200 mg-groups urinary pH-values were significantly decreased (m/f: 6.42/6.50 versus 7.50/7.25). At necropsy, relative organ weights were significantly increased including brain (m/f: 0.456/ 0.742 % bw versus m/f: 0.386/0.643 % bw), liver (m/f: 3.134/3.481 % bw versus m/f: 2.616/ 2.748 % bw), kidneys (m/f: 0.878/0.835 % bw versus m/f: 0.628/0.694 % bw). In addition, male mean absolute and relative adrenal weights (0.0164 g/1.54 % bw versus 0.0104 g/1.63 % bw) and female relative heart weight (0.370 % bw versus 0.377 % bw) and absolute lung weight (1.24 g versus 1.41 g) differed significantly. Reproductive organs were not affected. Histopathological changes were detected in males and females. In the liver there was centrilobular hypertrophy of hepatocytes. Kidneys in 10/10 males and 9/10 females but also in 2/10 control males but not in control females suffer from chronic progressive nephropathy to be seen by degeneration and regeneration of tubular epithelial cells, interstitial fibrosis and mononuclear cell infiltrates. These morphological findings were consistent with the data from clinical chemistry and urinary analysis and therefore regarded as compound-related. Changes in the adrenal gland included hyperplasia of the zona fasciculate together with mucosal erosions in the glandular stomach, the findings in adrenals and stomach were considered to be induced by stress.

Thus, the NOAEL is 200 mg/kg bw/day based on liver and kidney toxicity at the highest dose of 800 mg/kg bw/day.

Studies in Humans

There are no data available.

Conclusion

Repeated dose toxicity of p-chlorotoluene was examined in sub-acute (29 days) and sub-chronic (90 days) gavage studies with rats using dosages of 50, 200 and 800 mg/kg bw/day. The liver and the kidney are the main target organs of toxicity. Based on liver impairment in the sub-acute as well as the liver and kidney impairment in the sub-chronic study at the highest dose level of 800 mg/kg bw/day, the NOAEL for both studies was determined to be 200 mg/kg bw/day.

o-Chlorotoluene (SIAM 11):

The NOEL for repeated dosing (3 months) by gavage in rats is 20 mg/kg bw/day. In higher dosages (80 or 320 mg/kg bw/day) unspecific signs of toxicity were observed, e.g. reduced body weight gain in male animals as well as elevated BUN, elevated WBC count, reduced prothrombine time in both sexes.

The NOEL for repeated dosing via capsule (3 months) in dogs is 20 mg/kg bw/day. In higher dosage (80 mg/kg bw/day) one animal showed vomiting, and red blood was detected in faeces, which might be due to the slightly irritating property of o-chlorotoluene.

In range finding study tests, the LOAECs after inhalation were 4 mg/l (4000 mg/m³, 14 d) in rats and 8 mg/l (8000 mg/m³, 23 d) in rabbits. There is no NOEC from these data.

Overall conclusion:
Based on the test conditions in the repeated dose toxicity studies with rats which were taken into account for comparison, o-chlorotoluene is at least as toxic as p-chlorotoluene after repeated dosing.

3.1.6 Mutagenicity

Studies in Animals

In vitro Studies

In tests performed according to the current standards (preincubation methodology), p-chlorotoluene was not mutagenic in *Salmonella typhimurium* TA97, TA98, TA100, TA 1535, TA 1537, TA 102 and TA 104 and in *Escherichia coli* WP2uvrA, *Escherichia coli* WP2uvrA/pKM101/ (dose-range, with and without metabolic activation: 0.0763 - 5000 µg/plate (JETOC, 1996); 3.3 - 1000.0 µg/plate (Zeiger et al., 1992)) The studies gave no indication of gene mutation with and without metabolic activation and including cytotoxic concentrations. The positive controls were functional. In-vitro tests for chromosome aberrations with mammalian cell systems are not available.

In vivo Studies

One study is available regarding chromosomal damage in-vivo. The in-vivo micronucleus assay was conducted according to OECD TG 474 in male and female NMRI mice dosed with 1000 mg/kg bw by single intraperitoneal injection. After administration the animals showed the following symptoms until sacrifice: apathy, roughened fur, staggering gait, spasm, twitching shivering and difficulty in breathing. p-Chlorotoluene treated groups were sacrificed at 16 hours, 24 hours or 48 hours after treatment. There was no altered ratio between polychromatic and normochromatic

erythrocytes. There was no indication of a clastogenic activity. In none of the p-chlorotoluene treated groups were micronuclei induced. The positive control was functional (Bayer AG, 1992b).

Conclusion

p-Chlorotoluene was not mutagenic in *Salmonella typhimurium* TA97, TA98, TA100, TA1535, TA1537, TA102 and TA104 and in *Escherichia coli* WP2uvrA, *Escherichia coli* WP2uvrA/ pKM101 with and without a metabolic activation system and including cytotoxic concentrations nor did it induce micronuclei in mice after a single intraperitoneal injection in a study according to OECD TG 474.

o-Chlorotoluene (SIAM 11):

o-Chlorotoluene showed no mutagenic activity in bacterial and in mammalian cell test systems in vitro. o-Chlorotoluene showed no clastogenic activity (chromosome aberration) in vitro and in vivo.

overall conclusion
Based on the available data on o- and p-chlorotoluene it can be concluded that both monochlorotoluenes do not reveal mutagenic activity, neither in vitro nor in vivo.

3.1.7 Carcinogenicity

There are no studies available.

3.1.8. Toxicity for Reproduction

There are no specific studies on reproductive toxicity. However, in the repeated dose-toxicity studies which were taken into account for comparison, o-chlorotoluene is at least as toxic as p-chlorotoluene. Furthermore, in the metabolism o- and p-chlorotoluene are oxidized at the methyl group leading to chlorobenzyl alcohol glucuronide, chlorobenzoic acid and mercapturic acid. Thus, the use of o-chlorotoluene to fill data gaps is justified.

Studies in Animals

Effects on Fertility

There are no specific studies on fertility available according to the current standard. Therefore the evaluation is based on the available sub-acute and sub-chronic studies.

In the sub-acute study, p-chlorotoluene was dosed to 5 male and 5 female Wistar rats per group for a period of 29 days according to OECD TG 407 (Bayer AG, 1993). The substance was administered via gavage seven days per week in doses of 0, 50, 200 or 800 mg/kg bw/day dissolved in polyethylene glycol 400 yielding a NOAEL (general toxicity) of 200 mg/kg bw/day (see Section 3.1.5). To investigate the effect of p-chlorotoluene treatment on reproductive organs of males and females, histopathological examinations were additionally carried out on these organs (Bayer AG, 2004). These histopathological investigations revealed no changes in testes, epididymides, prostate, seminal vesicles, ovaries/oviduct, uterus and vagina, which can be attributed to treatment. Thus the NOAEL (reproductive organs) is 800 mg/kg bw/day.

In a sub-chronic study (90 days), 10 Sprague-Dawley rats/sex/group received 0, 50, 200 and 800 mg/kg bw/day dissolved in corn oil per gavage seven days per week over a period of 90 days (Terrill et al., 1990). The NOAEL (general toxicity) was determined to be 200 mg/kg bw/day for males and females (see Section 3.1.5). Considering the reproductive organs absolute and relative weights of testes and ovaries of the dosed animals showed no differences to the respective controls.

Gross and histopathological changes were not reported. Thus, the NOAEL (reproductive organs) is 800 mg/kg bw/day.

In a study, with insufficient documentation for assessment (e.g. no individual animal data were shown), a single dose of 1100 or 1833 mg/kg bw (= 1/5 or 1/3 LD_{50}); 55 or 550 mg/kg bw (1/100 or 1/10 LD_{50}) for 2 months; 0.01, 0.1 or 1.0 mg/kg bw for 6 months was given orally to rats. The 2-month study showed a statistically significant increase in embryonic mortality in animals in the 550 mg/kg group, caused by preimplantation losses. In addition, 12.7 % of the fetuses in this dose group exhibited liver hypertrophy, while 47 % displayed hypotrophy. p-Chlorotoluene did not show a teratogenic or cytogenetic effect. Only after the single dose of 1833 mg/kg bw was a slight tendency towards chromosome fragmentation observed (Pisko et al., 1981).

Developmental Toxicity

There are no studies on developmental toxicity available according to the current standard.

Conclusion

There are no specific studies on reproductive toxicity available, but data from repeated dose toxicity studies give no suspicion for possible effects of p-chlorotoluene on reproductive organs. There are no data on developmental toxicity available.

o-Chlorotoluene (SIAM 11):

Regarding reproductive toxicity (fertility assessment) there are no specific studies available. Examination of the reproductive organs in 3-months studies on rats and dogs showed no treatment-related effects. But in the SIAR of o-chlorotoluene a structurally related compound (2,4-dichlorotoluene) is reported showing effects on fertility without histopathological findings, however only at parental toxic concentrations.

The developmental toxicity of o-chlorotoluene was examined in rats and rabbits during organogenesis using inhalation exposure over 6 hours per day. Female rats were exposed to 0, 1.1, 3.1 and 9.0 mg/l 6 h/d from days 6 to 19 of gestation. The NOAEL for maternal toxicity is 1.1 mg/l. Animals in the 3.1 mg/l group exhibited slight ataxia during exposure. Animals in the 9.0 mg/l group displayed ataxia, lacrimation and/or salivation, as well as a brownish discoloration of the fur. Beginning at 3.1 mg/l, a dose-dependent reduction in feed intake and body weight gain was observed, as well as a dose-dependent increase in drinking water consumption. At 3.1 mg/l there were no significant deviation from control values in litter parameters and among incidences of malformations, anomalies and skeletal variants of the offspring. At 1.1 mg/l one fetus with a specific malformation (brachydactyly and brachymelia of all four limbs) and at 9.0 mg/l six fetuses from 4 litters showed brachydactyly of a single fore- or hindpaw. In addition, in the highest dose (9.0 mg/l), the mean values for litter and fetal weight are significantly reduced. The fetuses of the 3.1 mg/l exposure group had no notable adverse effects at all. Historical control data for developmental toxicity studies by the same laboratory show that the brachydactyly malformation does occur spontaneously, but with a very low incidence (2189 litters: 12.209 fetuses: 3 with brachydactyly (one of them additional with brachymelia), 3 with oligodactyly (one of them additional with brachymelia), and one only with brachymelia). Therefore, a NOAEL for developmental toxicity cannot be derived, the LOAEL is 1.1 mg/l (UNEP, 2004)

Female rabbits were exposed to 0, 1.5, 4.0 and 10.0 mg/l 6 h/d from days 6 to 28 of gestation. The NOAEL for maternal toxicity is 1.5 mg/l. During the first days of exposure, animals in the 4.0 mg/l group showed partial ptosis, while those in the 10.0 mg/l group exhibited lacrimation, salivation, and ptosis. Immediately after each exposure, animals in both of these dose groups exhibited an increased breathing rate. At 4.0 mg/l and above, a dose-related reduction in feed intake and body

weight gain was determined during the initial experimental period. In all exposure groups no significant effect on litter size, pre- and post implantation loss or litter and mean fetal weight occurred. In 10.0 mg/l dose group a specific fetal malformation (brachydactyly) was observed in one animal. Historical control data for developmental toxicity studies by the same laboratory show that the brachydactyly malformation does occur spontaneously, but with a very low incidence (1058 litters: 8646 fetuses, 2 with brachydactyly and 1 with oligodactyly). Therefore, 4.0 mg/l can be regarded as the NOAEL for developmental toxicity (UNEP, 2004).

In summary, with regard to o-chlorotoluene, developmental toxic effects in rats and rabbits occur mostly in the presence of maternal toxicity and without a clear dose-relationship, however as a specific malformation, brachydactyly. Thus the NOAEL (rat) is 1.1 mg/l (1100 mg/m³, maternal toxicity), but no NOAEL for developmental toxicity could be derived, the LOAEL (developmental toxicity) is 1.1 mg/l (1100 mg/m³). In rabbits, the NOAEL (maternal toxicity) is 1.5 mg/l (1500 mg/m³) and the NOAEL (developmental toxicity) is 4 mg/l (4000 mg/m³).

Overall conclusion

There are no specific studies on reproductive toxicity. However, in the repeated dose-toxicity studies which were taken into account for comparison, o-chlorotoluene is at least as toxic as p-chlorotoluene. Furthermore, in the metabolism o- and p-chlorotoluene are oxidized at the methyl group leading to chlorobenzyl alcohol glucuronide, chlorobenzoic acid and mercapturic acid. Thus, the use of o-chlorotoluene to fill data gaps is justified.

There are no specific studies on fertility available according to the current standard with p- and o-chlorotoluene. Evaluation of the reproductive organs in the repeated dose toxicity studies with p-and o-chlorotoluene give no indication of possible impairments of these organs.

With regard to developmental toxicity conclusion should be drawn from developmental toxicity studies in rats and rabbits with o-chlorotoluene as there is no specific study with p-chlorotoluene available. The results of the developmental studies with o-chlorotoluene (brachydactyly mostly in maternal toxic doses and without clear dose-response relationship: 1 rabbit fetus at the highest dose; 1 rat fetus at the lowest dose and 6 rat fetuses at the highest dose) lead to the assumption that monochlorotoluene in general might cause malformations in offspring by high dose treatment (i.e. at 1.1 mg/l = lowest dose tested, and 9.0 mg/l).

3.2 Initial Assessment for Human Health

Since there is no developmental toxicity study with p-chlorotoluene, the data from o-chlorotoluene are taken into account to fill the data gap. The comparison of the two isomers showed a rather high degree of qualitative similarity with respect to available data on absorption, excretion and metabolism, toxicity after acute and repeated exposure. Overall, o-chlorotoluene and p-chloro-toluene have a similar toxicity profile. o-Chlorotoluene was already discussed and concluded in SIAM 11, 2001; the data are published by UNEP in 2004.

Specific toxicokinetic studies with p-chlorotoluene are not available. The available information indicates that absorption of p-chlorotoluene is rapid via gastrointestinal tract or respiratory tract but is limited via dermal contact. Excretion occurs mainly via urine as p-chlorobenzoic acid derivatives by rabbits or as the corresponding hippuric acid by dogs. Exact data on tissue distribution are not available. Thus, p-chlorotoluene as well as o-chlorotoluene are absorbed via the gastrointestinal tract, the lungs and to a lesser extent via skin. For both isomers excretion takes place principally via urine, and in small amounts with faeces and exhaled air. In the metabolism o- and p-chlorotoluene are oxidized at the methyl group leading to chlorobenzyl alcohol glucuronide, chlorobenzoic acid and mercapturic acid.

The LC_{50} of p-chlorotoluene was not determined but an Inhalation Hazard test showed that exposure of rats against 4183 ppm (approximately 22 mg/m³) for 4 hours was not lethal, but signs of intoxication were observed; Exposure for 8 hours resulted in the death of all exposed rats within the 14-day observation period. The dermal LD_{50} (rabbit) is > 2000 mg/kg bw and LD_{50} (rat) is > 5000 mg/kg bw. Following oral application to rats the LD_{50} values ranged between 2100 mg/kg bw and 2389 mg/kg bw. The predominant symptoms were body tremor, accelerated breathing rate, cyanosis, decreased motor activity, and palmospasms. Irritational effects in the gastrointestinal tract and lungs increased in severity with increasing doses.

With regard to o-chlorotoluene the acute oral toxicity is LD_{50} (rat, male): 3227 mg/kg bw; the acute inhalation toxicity is LC_{50} (rat): 37 517 mg/m³ (4 hrs) and the acute dermal toxicity LD_{50} (rat) is > 1083 mg/kg bw and LD_{50} (rabbit): > 2165 mg/kg bw.

Based on the available data of o- and p-chlorotoluene it can be concluded that the acute toxicity of monochlorotoluene in general is low.

p-Chlorotoluene is slightly irritating to the skin when 0.5 ml undiluted substance is applied to intact and abraded skin of rabbits under occlusive conditions for 24 hours. p-Chlorotoluene is slightly irritating to eyes of rabbits when 0.1 ml undiluted substance was applied into the conjunctival sac. o-Chlorotoluene, tested according to OECD TG 404, is slightly irritating to the skin. However, when tested under occlusive conditions, the substance is corrosive. o-Chlorotoluene, tested according to OECD TG 405, was irritating to the eye in 1 out of 3 animals. Based on the available data it can be concluded that monochlorotoluene in general is slightly irritating the skin and eyes of rabbits. However, o-chlorotoluene seems to be a stronger skin irritant under occlusive conditions.

p-Chlorotoluene is a skin sensitizer when tested in the guinea pig maximization test according to OECD TG 406. o-Chlorotoluene, tested according to OECD TG 406, is not sensitizing to the skin of guinea pigs. However the higher sensitizing potential for para-substituted substances is a known effect.

Repeated dose toxicity of p-chlorotoluene was examined in sub-acute (29 days) and sub-chronic (90 days) gavage studies with rats using dosages of 50, 200 and 800 mg/kg bw/day. The liver and the kidney are the main target organs. Based on liver impairment in the sub-acute as well as in the sub-chronic study, which also revealed an increase in chronic progressive nephropathy at the highest dose level of 800 mg/kg bw/day, the NOAEL for both studies was determined to be 200 mg/kg bw/day.

With respect to o-chlorotoluene the NOEL for repeated dosing (3 months) by gavage in rats is 20 mg/kg bw/day. In higher dosages (80 or 320 mg/kg bw/day) unspecific signs of toxicity were observed, e.g. reduced body weight gain in male animals as well as elevated BUN, elevated WBC count, reduced prothrombine time in both sexes. The NOEL for repeated dosing via capsule (3 months) in dogs is 20 mg/kg bw/day. In higher dosage (80 mg/kg bw/day) one animal showed vomiting, and red blood was detected in faeces which might be due to the slightly irritating property of o-chlorotoluene. In range finding study tests, the LOAECs after inhalation were 4 mg/l (4000 mg/m³, 14 d) in rats and 8 mg/l (8000 mg/m³, 23 d) in rabbits. There is no NOEC from these data.

Based on the test conditions in the repeated dose toxicity studies which were taken into account for comparison, o-chlorotoluene is at least as toxic as p-chlorotoluene after repeated dosing.

p-Chlorotoluene was not mutagenic in the *Salmonella typhimurium* TA97, TA98, TA100, TA1535, TA1537, TA102, and TA104 and in *Escherichia coli* WP2uvrA, *Escherichia coli* WP2uvrA/ pKM101 with and without a metabolic activation system nor did it induce micronuclei in mice after a single intraperitoneal injection in a study according to OECD TG 474.

o-Chlorotoluene showed no mutagenic activity in bacterial and in mammalian cell test systems in vitro. o-Chlorotoluene showed no clastogenic activity (chromosome aberration) in vitro and in vivo.

Based on the available data on o- and p-chlorotoluene it can be concluded that both monochlorotoluenes do not reveal mutagenic activity, neither in vitro nor in vivo.

There are no studies on the possible carcinogenicity available.

There are no specific studies on reproductive toxicity. However, in the repeated dose-toxicity studies which were taken into account for comparison, o-chlorotoluene is at least as toxic as p-chlorotoluene. Furthermore, in the metabolism o- and p-chlorotoluene are oxidized at the methyl group leading to chlorobenzyl alcohol glucuronide, chlorobenzoic acid and mercapturic acid. Thus, the use of o-chlorotoluene to fill data gaps is justified.

There are no specific studies on reproductive toxicity (fertility assessment) available with p-chlorotoluene or with o-chlorotoluene. Evaluation of the reproductive organs in the available repeated dose toxicity studies with p-chlorotoluene or with o-chlorotoluene give no indication of possible impairment of these organs.

With regard to developmental toxicity conclusion should be drawn from developmental toxicity studies in rats and rabbits with o-chlorotoluene as there is no specific study with p-chlorotoluene available. Developmental toxic effects in rats and rabbits occur mostly in the presence of maternal toxicity and without a clear dose-response relationship, however, as a specific malformation, brachydactyly. Thus, for o-chlorotoluene, the NOAEL(rat) is 1.1 mg/l (1100 mg/m³, maternal toxicity), but no NOAEL for developmental toxicity could be derived, the LOAEL (developmental toxicity, rat) is 1.1 mg/l (1100 mg/m³) In rabbits, the NOAEL (maternal toxicity) is 1.5 mg/l (1500 mg/m³) and the NOAEL(developmental toxicity) is 4 mg/l (4000 mg/m³).

The results of the developmental studies with o-chlorotoluene (brachydactyly mostly in maternal toxic doses and without clear dose-response relationship: 1 rabbit fetus at the highest dose; 1 rat fetus at the lowest dose and 6 rat fetuses at the highest dose) lead to the assumption that monochlorotoluene in general might cause malformations in offspring by high dose treatment (i.e. at 1.1 mg/l = lowest dose tested, and 9.0 mg/l).

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Because of the high volatility from aqueous solutions p-chlorotoluene is difficult to test in aquatic systems. Data on aquatic toxicity of p-chlorotoluene are summarised in Table 9.

Acute Toxicity Test Results

With the fish species *Oryzias latipes* a 48 h-LC_{50} of 5.2 mg/l was obtained in an acute toxicity test according to the national Japanese MITI test (MITI, 1992). In a test with p-chlorotoluene performed with *Poecilia reticulata* under semi-static conditions a 14 d-LC_{50} of 5.92 mg/l was obtained (Koenemann, 1981).

With the invertebrate *Ceriodaphnia dubia* a 48 h-EC_{50} value of 1.7 mg/l, based on initial measured concentrations, was obtained in an acute toxicity test according to US EPA standard methods (Rose et al., 1998). Hermens et al. (1984) evaluated the acute toxicity of p-chlorotoluene to the invertebrate *Daphnia magna* according to the Dutch Standardization Organization Method NEN 6501. For a test period of 48 hours an EC_{50} value of 3.57 mg/l was obtained.

Concerning the algal toxicity, a test with *Desmodesmus subspicatus* in the presence of p-chlorotoluene was performed according to the Directive 92/69/EEC, C.3 (Bayer Industry Services, 2004). At the highest test-concentration of 0.96 mg/l (geometric mean of analytical value at start of incubation [nominal 30 mg/l] and half the detection limit [0.05 mg/l]. Because after the incubation, p-chlorotoluene concentration was below the limit of detection,the geometric mean could still overestimate the exposure concentrations) inhibition of growth rate and biomass was 6.1 % and 10.9 %, respectively. Therefore, the EC_{50} is expected to be above the concentrations which could be attained in experiments due to the limited water solubility of 40 mg/l. NOEC for growth rate and biomass was 0.43 mg/l (geom. mean;nominal 7.5 mg/l) and > 0.96 mg/l (geom. mean; nominal > 30 mg/l), respectively.

Chronic Toxicity Test Results

The chronic toxicity of p-chlorotoluene towards *Danio rerio* (former scientific name: *Brachydanio rerio*) was investigated in an early-life stage toxicity test generally performed in accordance with OECD TG 210, 1992 (Van Leeuwen, Adema, and Hermens, 1990). Retardation of growth was shown to be the most sensitive endpoint. In this test, the test solutions were renewed 3 times a week and analyses were performed before and after renewal of the solutions with HPLC. Since the mean concentrations were below the nominal concentrations, the results are based on mean concentrations. The 28-d NOEC for body length was reported as 1.9 mg/l. The no observed lethal concentration (NOLC) was determined to be 3.4 mg/l and the 28-d LC_{50} is given as 4.4 mg/l.

Chronic toxicity tests towards *Daphnia magna* were performed according to the Dutch Standardization Organization Method NEN 6502 (Hermens et al., 1984, 1985). The first test was carried out regarding the endpoints reproduction and mortality (Hermens et al., 1984). During an exposure period of 16 days under semi-static conditions, a LC_{50} of 1.59 mg/l for mortality was observed. The corresponding 16 d-NOEC was 1.0 mg/l. For the endpoint reproduction an EC_{50} of 0.58 mg/l and a corresponding 16 d-NOEC of 0.32 mg/l was obtained. In the second study the toxicity on inhibition of growth for *Daphnia magna* was observed (Hermens et al., 1985). At the start of the experiments and after 16 days of exposure the lengths of the daphnids were measured. Under semi-static conditions an EC_{50} of 1.71 mg/l with a corresponding 16 d-NOEC of 0.32 mg/l was observed. The stability of the test substance was experimentally determined with GC during the exposure period of 16 days. The recovery rates were in the range between 80 % and 110 %. Therefore, the results are based on nominal concentrations.

Table 9 Aquatic toxicity of p-chlorotoluene to fish, *Daphnia*, and algae

Species	Test type	Parameter	Effects	Reference	IUCLID
Oryzias latipes	Static or semi static	48 h-LC_{50}	5.2 mg/l (n)	MITI, 1992	4.1
Poecilia reticulata	Semi static	14 d-LC_{50}	5.92 mg/l (n)	Koenemann, 1981	4.1
Danio rerio	Semi static	28 d-$NOEC_{growth}$	1.9 mg/l (m)	Van Leeuwen, Adema, and Hermens, 1990	4.5.1
Daphnia magna	Static	48 h-EC_{50}	3.57 mg/l (n)	Hermens et al., 1984	4.2
Ceriodaphnia dubia	Static	48 h-EC_{50}	1.7 mg/l (m)	Rose et al., 1998	4.2
Daphnia magna	Semi static	16 d-$NOEC_{reproduction}$ 16 d-$NOEC_{growth}$	0.32 mg/l (n) 0.32 mg/l (n)	Hermens et al., 1984; 1985	4.3
Desmodesmus subspicatus	Static	Growth rate: 72 h-EC_{50} 72 h-NOEC Biomass: 72 h-EC_{50} 72 h-NOEC	 > 0.96 mg/l (m*) 0.43 mg/l (m*) > 0.96 mg/l (m*) > 0.96 mg/l (*)	Bayer Industry Services, 2004	4.3

m: measured concentration

m*: geometric mean of analytical values

n: nominal concentration

Determination of $PNEC_{aqua}$

Since chronic toxicity tests are available for three trophic levels (fish, *Daphnia* and algae), an assessment factor of 10 was applied for the derivation of the $PNEC_{aqua}$ of p-chlorotoluene according to the EU Technical Guidance Document. The lowest of the two available NOEC values was obtained for the species *Daphnia magna*, 16 d-NOEC = 0.32 mg/l, therefore resulting in a

$$PNEC_{aqua} = 32\ \mu g/l.$$

Toxicity to Microorganisms

In a toxicity test of p-chlorotoluene performed with *Spirostomum ambiguum* in which the cell deformation and lethal response were the endpoints, a 48 h-EC_{50} of 95.8 and 110.8 mg/l were obtained, respectively (Nalecz-Jawecki and Sawicki, 2002).

The toxicity to *Pseudomonas putida* was tested in a 18 hours test using the cell multiplication impairment as endpoint. The test was performed according to DIN 38412 part 8 (Trénel and Kuehn, 1982). An EC_{10} of > 25 mg/l was observed. Since the measured concentration in the stock solution was only 15 % of the initial amount weighed in, the estimated EC_{10}-value of > 25 mg/l should be considered rather than the nominal concentration of > 160 mg/l.

Microbial toxicities of p-chlorotoluene are listed in Table 11.

Table 10 Tests on acute toxicity of p-chlorotoluene to microorganisms (IUCLID 4.4)

Species	Endpoint	Parameter	Effects	Reference
Spirostomum ambiguum	Deformation and lethal response (Spirotox test)	48 h-$EC_{50deformation}$ 48 h-$EC_{50lethal\ response}$	95.8 mg/l (n) 110.8 mg/l (n)	Nalecz-Jawecki and Sawicki , 2002
Pseudomonas putida	Cell multiplication	18 h-EC_{10}	> 25 mg/l (m)	Trenel and Kuehn, 1982

(n): nominal concentration
(m): measured concentration

4.2 Terrestrial Effects

No tests to the toxicity of p-chlorotoluene towards terrestrial organisms are available.

4.3 Other Environmental Effects

No data available.

4.4 Initial Assessment for the Environment

p-Chlorotoluene is a clear colourless liquid with a melting point of 7.5 °C, and a boiling point of 162 °C. The density of the liquid is 1.0697 g/cm^3. The vapor pressure is approximately 310 -379 Pa at 20 - 25 °C. The measured log K_{OW} is 3.33. The solubility in water is 40 mg/l at 20 °C. The flash point is 51.9 °C, the auto-ignition temperature 595 °C.

With regard to the chemical structure, p-chlorotoluene is not expected to hydrolyze under environmental conditions.

According to the Mackay fugacity model level I calculation, the favorite target compartment of p-chlorotoluene is air with 99.67 %, followed by water with 0.25 %. A Henry's law constant of 446.8 Pa x m³/mol at 25 °C calculated according to the Bond method indicates that the compound has a high potential for volatilization from surface waters. The calculated half-life of p-chlorotoluene in air due to indirect photodegradation is $t_{1/2}$ = 8.8 days. Due to the low absorption in the UV-B range, no direct photodegradation is expected.

p-Chlorotoluene is not readily biodegradable, butcan be eliminated in industrial wastewater treatment plants. In a modified Zahn-Wellens-test, comparable to the OECD TG 302 B, elimination of p-chlorotoluene of 86 % after 28 days occurred, 68 % of which occurred in the first three hours and is attributed to physical-chemical effects (adsorption, stripping). A manometric respirometry test (in accordance with OECD TG 301 F) was performed with a concentration of p-chlorotoluene of 100 mg/l. After 28 days 1 % of the test substance had been degraded. Aerobic ready tests were performed according to the national Japanese MITI test, comparable to the OECD TG 301 C. After a period of 14 days, the %-age biodegradation from the oxygen consumption was zero or did not exceed 30 % after 2 weeks from the beginning of the test, respectively. At a concentration of 200 mg/l p-chlorotoluene was metabolized in 3 days by a blend of microorganisms able to degrade a range of halogen substituted aromatic compounds.

The bioconcentration factor BCF = 73.13 for p-chlorotoluene, calculated from the octanol-water partition coefficient, indicates a moderate potential for bioaccumulation of p-chlorotoluene in fish. The available experimental data concerning bioaccumulation of p-chlorotoluene in *Cyprinus carpio,*

confirm potential for bioaccumulation in fish. The BCF values obtained for concentrations of 0.3 and 0.03 mg/l were in the range of 14 - 101.6 and 21.9 - 76.5, respectively.

Experimentally obtained adsorption coefficients (K_{OC}) revealed a mid sorption potential of p-chlorotoluene. The experimentally achieved K_{OC} values following the OECD TG 106 were in the range of 327 to 512 depending on soil properties. In addition, the K_{OC} value of 434 was calculated with PCKOCWIN v. 1.66 .

Concerning the toxicity of p-chlorotoluene to aquatic species reliable acute and chronic experimental results of tests with fish, *Daphnia*, and algae are available. The tests were performed according to standard procedures or similar methods. The lowest effect values from short-term tests, as well as from chronic toxicity test are (n = nominal concentration; m = measured concentration; m* = geometric mean of analytical values ; s = static test type; ss = semistatic test type):

Danio rerio:	28 d-$NOEC_{growth}$	=	1.9 mg/l	(m, ss)
Poecilia reticulata:	14 d-LC_{50}	=	5.92 mg/l	(n, ss)
Oryzias latipes:	48 h-LC_{50}	=	5.2 mg/l	(n, s or ss)
Daphnia magna:	16 d-$NOEC_{reproduction}$	=	0.32 mg/l	(n, ss)
Ceriodaphnia dubia:	48 h-EC_{50}	=	1.7 mg/l	(n, s)
Desmodesmus subspicatus:	72 h-$EC_{50growth\ rate}$	=	> 0.96 mg/l	(m*, s)
Desmodesmus subspicatus:	72 h-$NOEC_{growth\ rate}$	=	0.43 mg/l	(m*, s)
Desmodesmus subspicatus:	72 h-$EC_{50biomass}$	=	> 0.96 mg/l	(m*, s)
Desmodesmus subspicatus:	72 h-$NOEC_{biomass}$	=	> 0.96 mg/l	(m*, s)

Based on the lowest effect concentration observed for *Daphnia* in a semistatic test the Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 10. Using the effective 16 d-$NOEC_{reproduction}$ of 0.32 mg/l found for the invertebrate *Daphnia magna* a

$PNEC_{aqua}$ = 32 µg/l

was determined.

5 RECOMMENDATIONS

Human Health:

The chemical possesses properties indicating a hazard (skin sensitization, indications for reproductive toxicity) to human health. Based on data presented by the Sponsor country, exposure of workers in manufacturing in the only producer in the Sponsor country and of consumers is anticipated to be low. As no worker exposure data except from the producer in the Sponsor country is available, it is recommended to conduct an exposure and if indicated a risk assessment at the workplace apart from the production site. The chemical is a candidate for further work.

Environment:

The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by one producer which accounts for approx. 44 - 56 % of global production and relating to the use in several OECD countries), exposure is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

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S I D S

Dossier

Existing Chemical	:	ID: 106-43-4
CAS No.	:	106-43-4
EINECS Name	:	4-chlorotoluene
EC No.	:	203-397-0
TSCA Name	:	Benzene, 1-chloro-4-methyl-
Molecular Formula	:	C7H7Cl

Producer related part

Company	:	Bayer AG
Creation date	:	14.12.1993

Substance related part

Company	:	Bayer AG
Creation date	:	14.12.1993
Status	:	
Memo	:	X Update 1998 AKTUELL EG / ICCA
Printing date	:	05.09.2005
Revision date	:	02.06.1994
Date of last update	:	05.09.2005
Number of pages	:	116
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	:	EniChem Synthesis S.p.A.
Contact person	:	
Date	:	
Street	:	
Town	:	20138 Milano
Country	:	Italy
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

Type	:	cooperating company
Name	:	Hoechst AG
Contact person	:	
Date	:	
Street	:	
Town	:	65903 Frankfurt/Main
Country	:	Germany
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

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

IUPAC Name	:	Benzene, 1-chloro-4-methyl-
Smiles Code	:	c(ccc(c1)Cl)(c1)C
Molecular formula	:	C7H7Cl
Molecular weight	:	126.59 g/mol
Petrol class	:	

Flag : Critical study for SIDS endpoint
22.12.2004 (1)

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : other: technical product
Substance type : organic
Physical status : liquid
Purity : >= 98 % w/w
Colour : colourless
Odour : faint, similar to benzene

Flag : Critical study for SIDS endpoint
27.11.2004 (2)

Purity type : other: purified technical product
Substance type : organic
Physical status : liquid
Purity : > 99.5 % w/w
Colour : colourless
Odour : faint, similar to benzene

27.11.2004 (2)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1-CHLORO-4-METHYLBENZENE

Remark : IUPAC name
Flag : Critical study for SIDS endpoint
27.11.2004 (3) (4) (5)

BENZENE, 1-CHLORO-4-METHYL-

Remark : CAS name
Flag : Critical study for SIDS endpoint
27.11.2004 (3) (4)

P-CHLOROTOLUENE

Remark : Common name
Flag : Critical study for SIDS endpoint
27.11.2004 (3) (4)

4-CHLOROTOLUENE

Flag : Critical study for SIDS endpoint
18.10.2004 (3)

P-TOLYL CHLORIDE

Flag : Critical study for SIDS endpoint

PCT

19.10.2004 (5)

TOLUENE, P-CHLORO-

Flag : Critical study for SIDS endpoint

1.3 IMPURITIES

Purity : other: technical grade
CAS-No : 108-41-8
EC-No : 203-580-5
EINECS-Name : 3-chlorotoluene
Molecular formula : C7H7Cl
Value : < 1 % w/w

Flag : Critical study for SIDS endpoint
18.10.2004 (2)

Purity : other: technical grade
CAS-No : 95-49-8
EC-No : 202-424-3
EINECS-Name : 2-chlorotoluene
Molecular formula : C7H7Cl
Value : < .5 % w/w

18.10.2004 (4) (2)

Purity : other: technical grade
CAS-No :
EC-No :
EINECS-Name : dichlorotoluenes
Molecular formula : C7H6Cl2
Value : < .5 % w/w

18.10.2004 (4) (2)

Purity : other: pure grade
CAS-No :
EC-No :
EINECS-Name :
Molecular formula :
Value :

Result : The following data are reported:
2-chlorotoluene < 0.2 %
3-chlorotoluene < 0.2 %
dichlorotoluenes < 0.1 %
18.10.2004 (4) (2)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : ca. 24000 - tonnes produced in 2002

Result : For 2002, the global monochlorotoluene output by about a dozen

producers is estimated to be approximately 75,000 tonnes (including unseparated isomers). The global 4-chlorotoluene production volume in 2002 (tonnes/a) is estimated by region as follows:
Western Europe 13,500
Ukraine 1,000
Japan 4,500
China 5,000
Total 24,000
Three quarters of the manufacturing volume stems from OECD member countries.

Flag : Critical study for SIDS endpoint
01.12.2004 (6)

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits :
Symbols : Xn, N, ,
Nota : , ,
R-Phrases : (20) Harmful by inhalation
(43) May cause sensitization by skin contact
(51/53) Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S-Phrases : (24/25) Avoid contact with skin and eyes
(61) Avoid release to the environment. Refer to special instructions/Safety data sets

Remark : EG-No. 602-040-00-X
27.11.2004 (7)

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC
Class of danger : dangerous for the environment
R-Phrases : (51/53) Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Specific limits :

27.11.2004 (7)

Classified : as in Directive 67/548/EEC
Class of danger : harmful
R-Phrases : (20) Harmful by inhalation
Specific limits :

27.11.2004 (7)

Classified : other, as in legislation
Class of danger : sensitizing
R-Phrases : (43) May cause sensitization by skin contact
Specific limits :

Remark : additional by manufacturer

27.11.2004 (7)

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Use in closed system

Flag : Critical study for SIDS endpoint
27.11.2004 (2) (6)

Type of use : industrial
Category : Chemical industry: used in synthesis

Result : p-Chlorotoluene is exclusively used as an intermediate in chemical processes.
Flag : Critical study for SIDS endpoint
27.11.2004 (2) (6)

Type of use : use
Category : Intermediates

Result : The main derivatives are:
· 4-chlorobenzotrichloride: intermediate in the production of pesticides and pharmaceuticals
(ca. 47 %)
· 4-chlorobenzyl chloride intermediate in the production of pesticides
(ca. 20 %)
· 4-chlorobenzaldehyde: intermediate in the production of pesticides and pharmaceuticals
(ca. 17 %)
· 2,4-dichlorotoluene: intermediate in the production of pesticides
(ca. 6 %)
· 4-chlorobenzonitrile: intermediate in the production of pigments
(ca. 7 %)
· 4-chlorobenzoic acid : intermediate in the production of pigments and pharmaceuticals
(ca. 3 %).
Flag : Critical study for SIDS endpoint
01.12.2004 (6)

Type of use : use
Category : Intermediates

Remark : Chlorotoluenes are exclusively used in the chemical industry, most of the production volume as intermediates
Flag : Critical study for SIDS endpoint
27.11.2004 (2)

Type of use : use
Category : Intermediates

Remark : Greenpeace (2004) [Appendix 1. www.greenpeace.to/pdfs/gujarat%20pt%20II.PDF] states that noncaptive end-use sales accounted for between 100 to 1000 tonnes/a for o- and p-

chlorotoluenes. As a source Greenpeace cites Kirk-Othmer. In contrast to the Greenpeace statement, Kirk-Othmer does not report these numbers, and there is circumstantial information that data of Kirk-Othmer were misinterpreted by Greenpeace.

Result : The number of manufacturers of p-chlorotoluene is small and much of the production is utilized captively. Many uses of p-chlorotoluene as intermediate in the synthesis of organic chemicals are reported.
It is also reported that "Chlorotoluene isomer mixtures, especially those containing a relatively high amount of o-chlorotoluene, are widely used as solvents in industry for such purposes as metal cleaning formulations, railroad industrial cleaners, diesel fuel additives, carbon removal procedures, paint thinners, and agricultural chemicals."

Flag : Critical study for SIDS endpoint
27.11.2004 (5)

Type of use : use
Category :

Remark : p-Chlorotoluene is not listed in the Nordic Product Registers
Flag : Critical study for SIDS endpoint
27.11.2004 (8)

Type of use : use
Category : other: Inert ingredient in pesticides

Remark : During large-scale catalytic monochlorination of toluene, a mixture of o-, m- and p-chlorotoluene is formed. In general, the price of p-chlorotoluene is higher than that of the other monochlorotoluenes. Thus, it is likely that not p-chlorotoluene but o-chlorotoluene or a mixture of chlorotoluenes is (was) used as an inert ingredient for pesticide formulations.
At the middle of 1984, Monsanto (at Muscatine, Iowa) discontinued the use of monochlorobenzenes as a carrier for the herbicide Lasso (Rossberg et al., 2000).
A US producer of p-chlorotoluene who offered a mixture of chlorotoluenes as solvent for pesticides (Occidental Chemical Corporation, 1992) ceased production and sale in 2001 (Occidental Chemical Corporation, 2001).
For Germany, it was unequivocally shown that p-chlorotoluene is not used in any pesticide (BVL, 2004)

Result : p-Chlorotoluene is listed as "other" (inert) ingredient in pesticide formulations, in the EPA (2003) list 3 (Inerts of unknown toxicity), without specifying any product. It is unlikely that it is used as an ingredient in pesticide formulations in the US. It is unequivocally demonstrated that it is not used for this application in the Sponsor country (BVL, 2004).

Flag : Critical study for SIDS endpoint
01.12.2004 (9) (10) (11) (12) (2)

Remark : Environmental Defense states that p-chlorotoluene is used in consumer products, building materials, or furnishing that contribute to indoor air pollution. This information is specified as "drain pipe solvent".
The information goes back to the EPA "SRD" Databank, which is not currently updated.
The SRD Databank cites Flick, EW. 1989a. Advanced cleaning product formulations. Park Ridge, NJ: Noyes Publications (literature not available).
According to Flick (cited according to EPA), amoung 800 cleaning product formulations there is one which contains 2.5 % of each o-, m- and p-chlorotoluene. No other component is reported for this "drain pipe solvent".
It is highly unlikely that the composition of this "drain pipe solvent" is correctly reported: There is no synthesis for chlorotoluens which leads to equal amounts of the 3 isomers.

On the other hand, a manufacturer (K & K Chemical Co., 2004) has been identified who offers a drain pipe cleaner which contains traces of monochlorotoluenes (CAS 25168-05-2). However, the traces of monochlorotoluene (CAS 25168-05-2) contained in this product are not in the focus of this SIDS.

Result : Monochlorotoluene (CAS 25168-05-2) at concentrations of less than 1 % is contained in a drain pipe cleaner manufactured in the USA

09.12.2004 (13) (14)

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

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)

Remark : Identification no. 237
Class of danger: according to VwVwS Appendix 2

22.12.2004 (7)

1.8.4 MAJOR ACCIDENT HAZARDS

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

Remark : No. 3

27.11.2004 (7)

1.8.5 AIR POLLUTION

Classified by : TA-Luft (DE)
Labelled by : TA-Luft (DE)
Number : other: 5.2.5 organic substances
Class of danger :

27.11.2004 (15)

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 : 1
Date of search : 29.08.2003

18.10.2004

Type of search : Internal and External
Chapters covered : 2
Date of search : 29.08.2003

18.10.2004

Type of search : Internal and External
Chapters covered : 3, 4
Date of search : 29.08.2003

18.10.2004

Type of search : Internal and External
Chapters covered : 5
Date of search : 16.05.2002

18.10.2004

1.13 REVIEWS

Memo : BUA Report 38, Chlorotoluenes (Methylchlorobenzenes)

Flag : Critical study for SIDS endpoint
14.10.2004 (4)

2.1 MELTING POINT

Value : 7.5 °C
Sublimation :
Method :
Year : 2001
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
27.11.2004 (16)

Value : 6.2 - 7.8 °C
Sublimation :
Method :
Year : 2003
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : Beilstein reports several melting points of 4-Chlorotoluene from literature references between 1889 and 1979:

Melting Point(°C)	Reference (year)
6.2	1912
6.85	1913
6.86	1943
7	1933
7.15 - 7.3	1940
7.2	1939
7.4	1977*
7.4	1889
7.5	1963*, 1979*
7.5	1901
7.5	1917
7.8	1922

All data are from handbooks, except data labelled with asterix.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (17)

Value : 7.5 °C
Sublimation :
Method :
Year : 1992
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (18)

Value : 7.5 °C

Sublimation :
Method :
Year : 2001
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (19)

Value : 7 °C
Sublimation :
Method :
Year : 2003
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (20)

Value : ca. 6.5 °C
Sublimation :
Method :
Year : 1993
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (4) not assignable
Data from non-peer reviewed handbook or collection of data
27.11.2004 (21)

Value : 7.6 °C
Sublimation :
Method :
Year : 1988
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (4) not assignable
Data from non-peer reviewed handbook or collection of data
27.11.2004 (22)

2.2 BOILING POINT

Value : 162 °C at
Decomposition :
Method :
Year : 2001
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
27.11.2004 (19)

Value : 162 °C at

Decomposition :
Method :
Year : 2003
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (20)

Value : 162 °C at
Decomposition :
Method :
Year : 1992
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : 44 °C at 13.3 hPa
Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (18)

Value : 162 - 162.4 °C at 1013 hPa
Decomposition :
Method :
Year : 2003
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : Beilstein reports several boiling points (°C) versus pressure (torr) of p-chlorotoluene from literature references between 1889 and 1983. In case of n.d. (no data), atmospheric pressure can be assumed:

Pressure(hPa)	Boiling Point(°C)
n.d.	150 - 155
n.d.	156
n.d.	159 - 161
n.d.	160
n.d.	160 - 161.5
n.d.	160.8 - 161.1
n.d.	161 - 162
n.d.	162
n.d.	162 - 162.2
n.d.	162 - 163
n.d.	162.2
n.d.	162.3
n.d.	170 - 172
1025	161.5
1018.3	163.5
1013	159 - 163
1012.9	161.7 - 162.2
1013	161.98 - 161.99
1013	162.4
1007.7	160
1006.3	162.1
1008.2	162.3
931.7	161.7 - 161.8
93.3	87 - 87.5
38.7	66.5 - 67
36	75 - 75.2

24 58 - 62
18.7 106
13.3 44
average pressure at sea level is 1013.25 hPa)

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (17)

Value : 162.4 °C at
Decomposition :
Method :
Year : 2001
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (16)

Value : 162 - 166 °C at
Decomposition :
Method :
Year : 1993
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (4) not assignable
Data from non-peer reviewed handbook or collection of data
27.11.2004 (21)

Value : 161.5 °C at 1013 hPa
Decomposition :
Method :
Year : 1988
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (4) not assignable
Data from non-peer reviewed handbook or collection of data
27.11.2004 (22)

Value : 162.4 °C at
Decomposition :
Method :
Year : 1979
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (4) not assignable
Secondary literature
27.11.2004 (23)

2.3 DENSITY

Type : relative density
Value : 1.0697 at 20 °C
Method :
Year : 2001

GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : Relative density given as the ratio of the density of the test substance at 20 °C and the density of water at 4 °C.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
27.11.2004 (16)

Type : relative density
Value : 1.0697 at 20 °C
Method :
Year : 1992
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : Relative density given as the ratio of the density of the test substance at 20 °C and the density of water at 4 °C.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (18)

Type : relative density
Value : 1.07 at °C
Method :
Year : 2001
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (19)

Type : relative density
Value : at °C
Method :
Year : 2003
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : Beilstein reports several relative density data versus measured temperature(°C) of p-chlorotoluene from literature references between 1889 and 1995:

Temperature (°C) reference/measurement	Relative Density
4/4	1.0847
5/5	1.0836
10/10	1.0791
-/10-30	1.0792-1.0595*
15/15	1.0749
-/18	1.0705
15/19.5	1.0695
-/20	1.06968*
4/20	1.0723
4/20	1.0692
4/20	1.06974
20/20	1.071
20/20	1.0714

4/20-86.7 1.071-1.0077
4/24.3 1.0651
-/25 1.06514*
25/25 1.0672
4/25-160 1.065-0.928
-/30 1.06052*
4/30 1.0596
4/40 1.0503
4/50 1.0401
4/58 1.031
-/162.3 0.9236*
*Density in g/cm3

Reliability : (2) valid with restrictions
Data from handbook or collection of data
01.12.2004 (17)

Type : relative density
Value : 1.065 - 1.067 at °C
Method :
Year : 1993
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Test condition : Temperature: 25/15°C
Reliability : (4) not assignable
Data from non-peer reviewed handbook or collection of data
27.11.2004 (21)

Type : relative density
Value : 1.0697 at 20 °C
Method :
Year : 1988
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (4) not assignable
Data from non-peer reviewed handbook or collection of data
27.11.2004 (22)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : 3.1 hPa at 20 °C
Decomposition :
Method :
Year : 1987
GLP :
Test substance : other TS: p-Chlorotoluene

Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
01.12.2004 (24)

Value : ca. 3.79 hPa at 25 °C
Decomposition :

Method :
Year : 1994
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Result : A curve is given of the pressure (psia) in relation to the temperature (F). From this curve a pressure of 0.055 psia at a temperature of 77 F (25 °C) can be read. (1 psia=68.95 hPa)
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
27.11.2004 (25)

Value : 3.72 hPa at 20 °C
Decomposition :
Method :
Year : 1991
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
01.12.2004 (26)

Value : 3.5 hPa at 20 °C
Decomposition :
Method :
Year : 2001
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (19)

Value : 3.6 hPa at 20 °C
Decomposition :
Method :
Year : 1988
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : 6.5 hPa at 30 °C, 19 hPa at 50 °C
Reliability : (4) not assignable
Data from non-peer reviewed handbook or collection of data
27.11.2004 (22)

Value : 4.72 hPa at 25 °C
Decomposition :
Method :
Year : 1973
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (4) not assignable
Secondary literature
27.11.2004 (27)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : 3.33 at °C
pH value :
Method : other (measured)
Year : 1995
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
27.11.2004 (28)

Partition coefficient : octanol-water
Log pow : 3.33 at °C
pH value :
Method : other (measured)
Year : 1989
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : Three coefficients are mentioned in regard to p-chlorotoluene:
Log Kow = 3.33
Log Kow = 3.30
Log Kow = 3.42, whereas the log Kow value of 3.33 was recommended.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (29)

Partition coefficient : octanol-water
Log pow : 3.18 at °C
pH value :
Method : other (calculated): with KOWWIN v1.67
Year : 2000
GLP :
Test substance : other TS: p-chlorotoluene

Reliability : (2) valid with restrictions
Accepted calculation method
27.11.2004 (30)

Partition coefficient : octanol-water
Log pow : 3.33 at °C
pH value :
Method :
Year : 2001
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (19)

Partition coefficient : octanol-water
Log pow : 3.35 at °C
pH value :

Method : other (calculated)
Year : 1998
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : Log Kow was calculated from the MEDCHEM (CLOGP v. 3.55) software.
Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
27.11.2004 (31)

Partition coefficient : octanol-water
Log pow : 3.51 at °C
pH value :
Method : other (calculated)
Year : 1984
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (32)

Partition coefficient : octanol-water
Log pow : 3.27 at °C
pH value :
Method : other (calculated)
Year : 1994
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Method : A linear solvation energy equation was used to calculate log Kow values. Experimental values were used for modelling. A log Kow (experimental) of 3.33 was reported with regard to p-chlorotoluene.
Remark : QSAR model not peer-reviewed; experimental value is sec. quotation
Reliability : (4) not assignable
Documentation insufficient for assessment
27.11.2004 (33)

Partition coefficient : octanol-water
Log pow : 3.31 at °C
pH value :
Method : other (calculated):
Year : 1993
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (4) not assignable
Secondary literature
27.11.2004 (34) (35)

Partition coefficient : octanol-water
Log pow : 3.29 at °C
pH value :
Method : other (calculated)
Year : 1997
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark	:	QSAR model not peer-reviewed; experimental value is secondary quotation The partition coefficient Kow was predicted by two linear regression models based on various topological indices. Further, a backpropagation neural network model implemented in AUTOLOG (v. 4.0) was developed. This model is based on molecular descriptors by means of autocorrelation method (nonlinear analysis using a learning process). A) Observed value: log Kow = 3.33 B) Calculation 1 and 2 based on linear regression resulted in log Kow of 2.79 and 2.83, respectively. C) Calculation based on neural network revealed a log Kow of 3.29.
Reliability	:	(4) not assignable Documentation insufficient for assessment
27.11.2004		(36)

Partition coefficient	:	octanol-water
Log pow	:	3.5 at °C
pH value	:	
Method	:	other (calculated): ClogP version 3.4
Year	:	1996
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene
Reliability	:	(4) not assignable Secondary literature
27.11.2004		(37)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	.04 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: modified plunger method
Year	:	1987
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity 99.9%
Method	:	Tests were done using a simplified version of the so called "plunger method"; stirring times 3 to 4 days at 20°C (water: aqua bidest.). Measurements of water phase were done by HPLC. Result is average of 4 repetitive tests; the purity of the test substance was evaluated by GC.
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles
Flag	:	Critical study for SIDS endpoint
27.11.2004		(38)

Deg. product	:	
Method	:	
Year	:	2003
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity is not specified

Remark : Beilstein reports several data of solubility(g/l) in water versus temperature of 4-Chlorotoluene:

Temperature(°C)	Solubility(g/l)
5	0.099
15	0.103
25	0.123
35	0.136
45	0.153

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (17)

Solubility in : Water
Value : .1 g/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 2001
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
01.12.2004 (19)

Solubility in : Water
Value : .106 g/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 1992
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (4) not assignable
Original reference not available
27.11.2004 (39)

Solubility in : Water
Value : ca. .0917 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: calculated
Year	:	1997
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity is not specified

Remark : Calculation method not peer reviewed
The prediction of the aqueous solubility of a diverse set of environmentally relevant chemicals was based on the mobile order thermodynamics. One of the main characteristics of all these chemicals ranging from low to very hydrophobic was their poor aqueous solubility.
The reported prediction value at 25° with regard to p-chlorotoluene in mol was log -3.14 (which corresponds to 91.7 mg/l).
An experimentally determined value was reported as well,
namely S(exp.) = log -3.08 mol (corresponding to 105.3 mg/l)

Reliability : (4) not assignable
Documentation insufficient for assessment

27.11.2004 (40)

Solubility in	:	Water
Value	:	.2 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: calculated
Year	:	1995
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity is not specified

Remark : Calculation method not peer reviewed
Group contribution method was studied on the basis of a test set of 694 organic nonelectrolytes for estimating water solubility by means of stepwise multilinear regression.
The experimental and calculated values of the water solubility at 25°C reported for p-chlorotoluene in mol/l were:
log Sw = -3.08 and -2.80, respectively (corresponding to 105.3 and 200.6 mg/l).

Reliability : (4) not assignable
Documentation insufficient for assessment

27.11.2004 (41)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	51.9 °C
Type	:	open cup
Method	:	
Year	:	1992
GLP	:	no data

Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
27.11.2004 (26)

Value : 49 °C
Type :
Method :
Year : 2001
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (19)

Value : 51 °C
Type :
Method : other: DIN 51755
Year : 2003
GLP : no data
Test substance : other TS: p-chlorotoluene, pure

Reliability : (4) not assignable
Manufacturer data without proof
27.11.2004 (7)

2.8 AUTO FLAMMABILITY

Value : 595 °C at
Method :
Year : 2001
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
27.11.2004 (19)

Value : >= 595 °C at
Method : other: DIN 51794
Year : 2003
GLP : no data
Test substance : other TS: p-chlorotoluene, pure

Reliability : (4) not assignable
Manufacturer data without proof
27.11.2004 (7)

2.9 FLAMMABILITY

Result : flammable
Method :

Year : 2001
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
27.11.2004 (19)

2.10 EXPLOSIVE PROPERTIES

Method :
Year : 2001
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : Explosive limits in air:
lower: 0.7 % by vol.
upper: 12.2 % by vol.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
27.11.2004 (19)

Method :
Year : 1988
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : Explosive limits: lower: 0.7 % by vol.
upper: 12.2 % by vol.

Explosive limits at 20°C at 1013 bar in (g/m³):
lower: 37
upper: 642
Reliability : (4) not assignable
Data from non-peer reviewed handbook or collection of data
27.11.2004 (22)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Conversion factor

Result : Conversion factor at 1013 hPa and 20 °C:
1 ml/m3 (1 ppm) = 5.26 mg/m3
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data

Flag : Critical study for SIDS endpoint
18.10.2004 (42)

Memo : Conversion factor

Result : Conversion factor at 1013 hPa and 20 °C:
1 ml/m3 (1 ppm) = 5.27 mg/m3
1 mg/m3 = 0.19 ppm

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
18.10.2004 (4)

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	:	.0000000000018174 cm³/(molecule*sec)
Degradation	:	50 % after 8.8 day(s)
Deg. product	:	
Method	:	other (calculated): AOPWIN v1.91, 2000
Year	:	2004
GLP	:	
Test substance	:	other TS: p-chlorotoluene
Remark	:	In deviation from the U.S. EPA AOPWIN (calculation program) the calculated half-life is based on a mean OH radical concentration of 5E+05 OH radicals/cm3 as a 24 h average.
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

01.12.2004 (30) (1)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	
Year	:	1984
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity is not specified
Remark	:	Direct photolysis rate constant could not be estimated because of insufficient spectral and quantum yield data. However, the rate constant could be considered as zero as no light absorption occurs above the solar cutoff (300 nm). Photolysis for p-chlorotoluene is suspected to be not environmentally relevant.
Reliability	:	(2) valid with restrictions Data from handbook or collection of data
Flag	:	Critical study for SIDS endpoint

27.11.2004 (32)

Type	:	other: deaerated methanol solution
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	
Year	:	1986
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity is not specified
Remark	:	Direct UV-irradiation of p-chlorotoluene in deaerated methanol at

wavelengths around 300 nm for 48 hours resulted in a substrate conversion of 2.9 %. No photoproduct was observed by gas chromatography.
p-Chlorotoluene was also irradiated in deaerated methanol using acetone as sensitizer for 9 hours, 54.5 % of the test substance disappeared, whereby 52 % of the photoproducts formed as a result of reductive dechlorination of p-chlorotoluene was toluene

Result : p-Chlorotoluene is formed by direct irradiation of p-chloro-alpha-chlorotoluene in waterfree, deaerated methanol.
Since p-chlorobenzyl radicals react with molecular oxygen, and the precursor p-chloro-alpha-chlorotoluene occurs only in minute concentrations in the environment, the formation of p-chlorotoluene by direct irradiation of p-chloro-alpha-chlorotoluene is apparently of minor importance in the environment

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

27.11.2004 (43)

Type : other
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
INDIRECT PHOTOLYSIS
Sensitizer : other: tert.-butylperoxy radicals
Conc. of sensitizer :
Rate constant : $cm^3/(molecule*sec)$
Degradation : % after
Deg. product :
Method :
Year : 1973
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Result : The absolute rate constant for the reaction of p-chlorotoluene with tert-butylperoxy radicals at 30°C was reported as 0.030 l · mol-1 · s-1

Reliability : (4) not assignable
Documentation insufficient for assessment

27.11.2004 (44)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method :
Year : 1989
GLP :
Test substance : other TS: p-chlorotoluene

Remark : As chlorine is a ring substituent, hydrolysis is not expected to be an important process in determining the environmental fate of p-chlorotoluene.

Reliability : (2) valid with restrictions
Reliable source

Flag : Critical study for SIDS endpoint
27.11.2004 (32) (45)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method :
Year : 2000
GLP : no data
Test substance :

Remark : The chlorotoluenes are neutral and stable compounds
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
27.11.2004 (2)

Type : biotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method : other
Year : 1980
GLP : no
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : Sampling of river Rhine water was performed in July 1979 along the length of the river. Quantification of the chemicals was carried out via GC-MS analyses. As no important discharge of chemicals was expected half-lives of chemicals presented at concentrations in the range of 0.01-1 ug/l were estimated under field conditions (Number of observations: n=1). Assuming that the reduction of the chemical concentration is a first order process, the corresponding reaction constant and half-lives were estimated from the observed drop in concentration during the known retention period. The surface water considered has a depth of ca. 4-5 m. The estimated half-life for p-chlorotoluene in river surface water is 1.2 days.
Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
27.11.2004 (46)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

Type of measurement : concentration at contaminated site
Media : other: treated wastewater and recharged groundwater
Concentration : < .002 mg/l
Method :

Remark : Documentation insufficient for assessment
Result : In 1998, p-chlorotoluene was not detectable in treated wastewater from semiconductor industry and in groundwater from monitoring wells of an aquifer which was recharged with reclaimed wastewater in the desert south

of Phoenix (detection limit 0.002 mg/l)
Reliability : (4) not assignable
Flag : Critical study for SIDS endpoint
01.12.2004 (47)

Type of measurement : concentration at contaminated site
Media : other: ground and drinking water
Concentration :
Method : GC

Remark : Study published in Italian
Result : p-Chlorotoluene was not detectable with a detection limit in the range of 0.1-0.01 µg/l in ground and drinking water of a contaminated area. However, the groundwater contained several pollutants at concentrations from "not detectable" to up to 152 µg/l, e.g. bromodichloromethane, chloromethane, dibromochloromethane, 1,1-dichloroethane, 1,2-dichloroethane, 1,1,1-trichloroethane and trichloromethane.
Test condition : - 2 years study performed in 1992-1993
- Ground and drinking water of a contaminated area in the Turin province of Northern Italy examined
- The area was used as an industrial site for about one century
- Detection limit in the range of 0.1-0.01 µg/l (not explictedly stated for p-chlorotoluene)
- Analysis by GC with electron capture detector. Some samples were analyzed by purge and trap extractive technique with gas chromatographic separation and photoionization and electrolytic detectors as well
Reliability : (4) not assignable
Documentation insufficient for assessment
Flag : Critical study for SIDS endpoint
27.11.2004 (48)

Type of measurement : background concentration
Media : drinking water
Concentration :
Method :

Remark : In the United States, water departments of several cities and other organisations monitor drinking water and rivers used for water supply also for substances not regulated by the US EPA. As one member of these unregulated volatile organic substances, p-chlorotoluene has not been detected recently with a typical limit of detection of 0.5 µg/l, e.g. in the New River (California Regional Water Quality Control Board, 2003), the Trinity River Basin (Land et al., 1998), the Duck River (Duck River Utility Commission, 2003), or in the drinking water of Ocean City MD (Ocean City, 2002) and Phoenix AZ (City of Phoenix, 2000)
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
23.11.2004 (49) (50) (51) (52) (53)

Type of measurement : background concentration
Media : drinking water
Concentration :
Method :

Result : Concentration below limit of detection
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
23.11.2004 (54) (55)

Type of measurement : background concentration
Media : other: spring water
Concentration :
Method :

Result : p-Chlorotoluene p-Chlorotoluene was not detected in Rockcastle springs (Kentucky) water
Test condition : - 3 samplings, 2 of them by Suntory/CE Consultants, one of them by owner of the springs
- Huge variety of potential contaminants tested, mostly limit of detection reported but not for p-chlorotoluene
- Vicinity of the spring was at least 3 times surveyed for potential sources of contamination but was thought to be free of any potential source
Reliability : (4) not assignable
Documentation insufficient for assessment
Flag : Critical study for SIDS endpoint
20.10.2004 (56)

Type of measurement : other: concentrations of background and contaminated sites
Media : air
Concentration :
Method : GC/MS

Result : p-Chlorotoluene was not detectable (limit of detection <0.02 ppb v/v) in atmospheric air from sites with low, moderate and high level of traffic and urbanisation in New Jersey, USA
Test condition : - Air sampling from April to December 1997
- 16-18 samples taken from each one site with low, moderate, and high level of traffic and urbanisation in New Jersey, USA (total number of samples: 50)
- Sampling by adsorption/thermal desorption technique on Carbotrap B/Carboxen 1000
- Analysis by GC/MS
- Method detection limit of 0.02 ppb v/v
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
27.11.2004 (57)

Type of measurement : other: not specified
Media : air
Concentration :
Method : not specified

Method : Literature study
- Compilation on volatile organics in the air of the United States
- Data base contains data from sources in all forms
- "inconsistencies, duplications, unsupported validation procedures, unpublished methods, and often, numerical errors" were detected. No method reported to detect and eliminate false data
Remark : The data base contains data from sources in all forms, and "inconsistencies, duplications, unsupported validation procedures, unpublished methods, and often, numerical errors" were detected. However, the authors did not report how they distinguished between relaible and unreliable data and what criteria were used to remove inconsistant data from the data base
Result : In the outdoor air of the United States, the average daily concentration of p-chlorotoluene was 0.204 ppb v/v, with the median of 310 data points at 0.09 ppb v/v, the 25-percentile at 0.020 ppb v/v and the 75-percentile at 0.290 ppb v/v.

Reliability : (4) not assignable
Documentation insufficient for assessment
Flag : Critical study for SIDS endpoint
27.11.2004 (58)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

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 : OECD Guide-line 106
Year : 1992

Method : Adsorption/desorption was determined on three different soils, namely sand, loamy sand, and a sandy loam.

sand: 0.7% OC, pH 6.1
loamy sand: 2.29% OC, pH 6.2
sandy loam: 1.34% OC, pH 6.9
OC = organic carbon

The study was conducted in sealed flasks by shaking the samples with aqueous CaCl2-solutions on a laboratory shaker at 20°C. After sedimentation the aqueous phase was filtered followed by extraction with dichlormethane. The organic phase was dried over NaSO4. Before evaporation n-hexane was added. The quantification was performed by measuring the flame ionisation detector-signal (FID) of the test article after High-resolution gas chromatography (HRGC) separation of the sample.

Result : Adsorption of p-chlorotoluene reached a constant value after 60 min. of equilibration time for sand, 30 min. for loamy sand and a constant value for sandy loam after 10 min. Adsorption showed an approximate linear behavior for higher concentrations used. The Freundlich adsorption constants as well as their corresponding Koc values calculated by K = [x/m]/ Ce are:

sand: K = 3.59; Koc = 512.2
loamy sand: K = 7.49; Koc = 327.1
sandy loam: K = 4.5; Koc = 335.9

Test substance : p-chlorotoluene, purity: 99%
Reliability : (1) valid without restriction
GLP guideline study
Flag : Critical study for SIDS endpoint
23.11.2004 (59)

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: QSAR Estimation Method: PCKOCWIN v1.66
Year : 2004

Result : Koc = 434
Test substance : p-chlorotoluene
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
10.08.2004 (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: Estimation method
Year : 2000

Remark : The correlation between octanol-water partitioning coefficient (Kow), water solubility and a normalized soil/sediment partitioning coefficient (Koc) was investigated by examining 148 chemicals. Linear models were developed to correlate the Kow in each category.
Values reported concerning p-chlorotoluene were as follows:
Kow = 2000 (log Kow = 3.3)
Koc = 1200 (ml/g)
water solubility 44 mg/l
Origin of the values was not specified
Test substance : 4-chlorotoluene, purity is not specified
Reliability : (4) not assignable
Secondary literature
01.12.2004 (60)

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: QSAR Estimation Method: HENRYWIN v3.10
Year : 2004

Result : Henry's Law Constant calculated for 4-chlorotoluene:
-Bond method: 446.8 Pa*m³/mol
-Group method: 494.5 Pa*m³/mol
All results at 25 °C.
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
10.08.2004 (30)

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: calculated
Year : 1989

Remark : The Henry's Law Constant calculated with no further specification for 4-chlorotoluene is 0.043 atm m³/mol (corresponding to 4357 Pa m³/mol).
Reliability : (4) not assignable
Documentation insufficient for assessment

13.08.2004 (45)

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: calculated
Year : 2001

Remark : Henry's Law Constant for 4-chlorotoluene: 1084 Pa m³/mol (calculated with no further specification)
Reliability : (4) not assignable
Documentation insufficient for assessment

10.08.2004 (61)

3.3.2 DISTRIBUTION

Media : other: air - biota - sediment(s) - soil - water - aerosol
Method : Calculation according Mackay, Level I
Year : 2004

Method : Data used in the calculation:
Temperature (°C) = 25
Molar mass (g/mol) = 126.59
Vapour pressure (Pa) = 379 Pa
Water solubility (g/l) = 0.040 g/l
log Kow = 3.33
Melting point = 7.5°C

Phase properties and composition of the compartments (OC = organic carbon):

	Volume (m3)	Density (kg/m3)	Composition
Air:	6.0 E+09	1.185	
Water:	7.0 E+06	1000	
Soil:	4.5 E+04	1500	2 % (OC)
Sediment:	2.1 E+04	1300	5 % (OC)
Susp. Sed.:	3.5 E+01	1500	16.7 % (OC)
Aerosol:	1.2 E-01	1500	
Aquatic Biota:	7.0 E+00	1000	5% (lipid)

Calculation was performed according to the model described in the first publication of Mackay (1991). Phase properties

and composition of the compartments were modified as suggested by the Federal Environmental Agency (UBA, Germany).

Result : Based on the model calculations (Mackay level I, v.2.11), the target compartment for the environmental distribution of p-chlorotoluene is the air.
Water: 0.24 %
Air: 99.67 %
Soil: 0.041 %
Sediment: 0.041 %
Susp. Sediment: 2.64E-04 %
Biota (fish): 2.57E-05 %
Aerosol: 3.16E-05 %

Reliability : (2) valid with restrictions
Accepted calculation method

Flag : Critical study for SIDS endpoint

27.11.2004 (30)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : predominantly domestic sewage, adapted
Concentration : 22 mg/l related to DOC (Dissolved Organic Carbon)
related to
Contact time :
Degradation : 86 (±) % after 28 day(s)
Result : other: Due to the significant elimination within 3 h there is no evidence that p-chlorotoluene is inherently biodegradable
Kinetic of testsubst. : 3 hour(s) 68 %
1 day(s) 73 %
7 day(s) 86 %
28 day(s) 86 %
%
Control substance : Aniline
Kinetic : 1 day(s) 20 %
28 day(s) 99 %
Deg. product :
Method : other: DIN 38 412, 25 comparable to OECD TG 302 B
Year : 1991
GLP : yes
Test substance : other TS: p-chlorotoluene, purity: 99.8 %

Remark : - Concentration of inoculum (dry matter): 1 g/l
- Due to the low solubility of the test substance, the stock solution had a p-chlorotoluene concentration of 0.1 g/l (recommended: 50-400 mg/l)
- Kinetic of aniline degradation:
1 d: 20 %
7 d: 99 %
14 d: 99 %
21 d: 99 %
28 d: 99 %

Result : Within the first three hours 68% of p-chlorotoluene was removed from water indicating physical-chemical mechanisms (adsorption and stripping) responsible for the elimination.

Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions

Flag : Critical study for SIDS endpoint
02.09.2005 (62)

Type : aerobic
Inoculum : predominantly domestic sewage, adapted
Concentration : 100 mg/l related to Test substance
related to
Contact time :
Degradation : 1 (±) % after 28 day(s)
Result : under test conditions no biodegradation observed
Kinetic of testsubst. : 12 day(s) 0 %
18 day(s) 1 %
28 day(s) 1 %
%
%
Control substance : Aniline
Kinetic : 28 day(s) 68 %
%
Deg. product : not measured
Method : other: EEC Directive 79/831 (Painter) comparable to OECD TG 301 F
Year : 1991
GLP : yes
Test substance : other TS: p-chlorotoluene, purity: 99.8 %

Remark : Concentration of inoculum (dry matter): 30 mg/l.
The inoculum used in this study was obtained from the Zahn-Wellens test performed under study No. 185 A/90.
Reliability : (1) valid without restriction
GLP guideline study
Flag : Critical study for SIDS endpoint
01.12.2004 (63)

Type : aerobic
Inoculum : activated sludge
Concentration : 100 mg/l related to Test substance
related to
Contact time :
Degradation : 0 (±) % after 14 day(s)
Result : under test conditions no biodegradation observed
Deg. product :
Method : other: Japanese Guideline by MITI (1974). Comparable to OECD TG 301 C, Modified MITI Test I
Year : 1992
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Method : The test was conducted in accordance with 'Biodegradation test of chemical substance by microorganisms etc.' stipulated in the Order Prescribing the Items of the Test Relating to the New Chemical Substance (1974, Order of the Prime Minister, the Minister of Health and Welfare, the Minister of International Trade and Industry No.1). This guideline corresponds to '301C, Ready Biodegradability: Modified MITI Test I' stipulated in the OECD Guidelines for Testing of Chemicals (1981)
Test condition : Sludge concentration: 30 mg/l
Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions
Flag : Critical study for SIDS endpoint
27.11.2004 (64) (65) (66)

Type : aerobic
Inoculum : activated sludge
Concentration : 100 mg/l related to Test substance
related to
Deg. product :
Method : other: Japanese Guideline by MITI (1974). Comparable to OECD TG 301 C, Modified MITI Test I
Year : 1978
GLP : no
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : Criteria for judging biodegradability:
If %-age biodegradation from the oxygen consumption exceeds 30% after 2 weeks from the beginning of the test and the result of a direct analysis is at least this value, the test substance is judged as well-biodegradable.
Result : p-Chlorotoluene was classified as a substance almost not biodegradable.
Test condition : - sludge concentration: 30 ppm (to 100 ppm test substance)
- temperature: 25 +/- 2 °C
- pH of supernatant of active sludge: 7.0 +/- 1
- test period: 14 days
- reference substance: aniline
Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions
Flag : Critical study for SIDS endpoint
02.09.2005 (67)

Type : aerobic
Inoculum : other: selected microbial blend
Concentration : 200 mg/l related to Test substance
related to
Contact time :
Degradation : 100 (±) % after 3 day(s)
Result :
Deg. product :
Method : other: see method
Year : 1988
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Method : The microbial blend consisted of 5 pseudomonads, one Klebsiella, four rhodococci and two fungal strains. 200 mg/l chlorotoluene was incubated in 100 ml medium inoculated with the bacterial blend (72 h at 30°C on orbital shaker at 150 rev/min.). Extracted samples were removed at 24 h intervals and analysed for substrate concentration on HPLC using an UV detector. Percentage removal was corrected for volatilization using an uninoculated control. The elimination rate was calculated over the initial 48 h period.
Remark : Test system reveals the capability of the bacterial blend to metabolize the offered test substances rather than a complete biodegradation.
Result : Elimination rate: 2.6 mg/l/h
Test substance : All substituted benzenes tested were provided in ethanol solution (0.1-1%).
Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
Flag : Critical study for SIDS endpoint
02.09.2005 (68)

Type : aerobic
Inoculum : predominantly domestic sewage, adapted
Concentration : 8 mg/l related to
related to
Contact time :
Degradation : 0 (±) % after 20 day(s)
Result : under test conditions no biodegradation observed
Kinetic of testsubst. : 5 day(s) 0 %
10 day(s) 0 %
20 day(s) 0 %
%
%
Deg. product :
Method : other: Closed Bottle Test, comparable to OECD TG 301 D
Year : 1979
GLP : no
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : -related to BOD
-pH 6.4
Reliability : (2) valid with restrictions
Guideline study without detailed documentation

01.12.2004 (69)

Type : aerobic
Inoculum : Pseudomonas putida (Bacteria)
Deg. product :
Method : other: enzyme activity
Year : 1992
GLP :
Test substance : other TS: p-chlorotoluene, purity: highest analytical grade available

Remark : The capability of the xylene degradation sequence of Pseudomonas putida strain PaW1 to convert chlorinated substrates and the enzymes ability to convert substituted substrate analogs (e.g. p-chlorotoluene) was demonstrated.
Hybrid strains WR1441 and WR233 were shown to grow on 4-chlorotoluene. Besides the temporary accumulation of 4-chlorobenzoate observed in both strains 5-chlorohydroxy muconic semialdehyde, the meta-cleavage product from 4-chlorocatechol, was formed in strain WR233.
Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

01.12.2004 (70)

Type : aerobic
Inoculum : Pseudomonas putida (Bacteria)
Deg. product : yes
Method : other: metabolism
Year : 1968
GLP : no
Test substance : other TS: p-chlorotoluene, purity: distillation was performed prior to use
Deg. products : (+)-cis-4-chloro-2,3-dihydroxy-1-methylcyclohexa-4,6-diene
4-chloro-2,3-dihydroxy-1-methylbenzene

Remark : A 25 l culture of P. putida was incubated with p-chlorotoluene for 10 h. Ethyl acetate extraction was performed. Column chromatography was used to separate catechols, glycols, and phenols. Analyses were performed by spectrophotometer (UV, NMR); catechols were determined colorimetrically.

Two compounds isolated in sufficient amounts were identified: It was suggested that the diol formed from p-chlorotoluene was (+)-cis-4-chloro-2,3-dihydroxy-1-methyl-cyclohexa-4,6-diene. Further, 4-chloro-2,3-dihydroxy-1-methylbenzene was identified as metabolite of p-chlorotoluene. p-Chlorotoluene was converted through cis-dihydrodiols to their respective catechols which are resistant to further degradation.

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

01.12.2004 (71) (72)

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	60 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	
Degradation	:	< 10 (±) % after 20 day(s)
Result	:	
Deg. product	:	
Method	:	other: Respiration test
Year	:	1982
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity is not specified

Reliability : (4) not assignable
Original reference not available

27.11.2004 (73) (74)

Type	:	aerobic
Inoculum	:	other: river water or seawater
Contact time	:	
Degradation	:	44 - 64 (±) % after 3 day(s)
Result	:	
Deg. product	:	not measured
Method	:	other: cultivation method
Year	:	1988
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity is not specified

Remark : Biodegradation in river and sea water was tested according to a simple and rapid cultivation method. p-Chlorotoluene (20 ppm) was judged to be moderately/easily biodegradable based on the results obtained after a 3-d exposure period for river water and seawater inoculum, respectively (44% and 64% biodegradation).

Reliability : (4) not assignable
Original reference in Japanese. Only abstract in English available.

01.12.2004 (75)

Type	:	anaerobic
Inoculum	:	other: soil slurry microorganisms
Deg. product	:	yes
Method	:	other: see method
Year	:	1993
GLP	:	
Test substance	:	other TS: 2,4-Dichlorotoluene (DCT) or 3,4-DCT, purity is not specified
Deg. products	:	106-43-4 203-397-0 4-chlorotoluene 108-88-3 203-625-9 toluene

Method	:	Soil samples were obtained from a site located in Niagara Falls, New York. The subsurface clay loam soil samples had nitrogen and phosphorus contents of 37.0 and 16.5 ppm, respectively; pH 7.2; organic matter content: 5.38%. Soil was air dried, passed through a 3.25 mm sieve and transferred to anaerobic glove box before use. Defined mineral salts medium was prepared; 65 ml serum bottles containing 30 ml sterile medium were inoculated with 10% slurry inoculum (v/v) that had been actively metabolizing chlorotoluenes (CTs) and amended with 0.1 to 0.6 mM 2,4-Dichlorotoluene (DCT) or 3,4-DCT. One bottle amended with $NaNO_3$ was used as poisoned control. At intervals, the contents of the duplicates bottles were extracted with pentane and analyzed for parent substance and its metabolites by GC.
Result	:	Biotransformation of 2,4-Dichlorotoluene (2,4-DCT) and 3,4-DCT resulted predominantly in the formation of 4-chlorotoluene (the metabolites 2-CT and 3-CT, respectively, occurred at minor concentrations). Further dechlorination of 4-CT was evident from toluene formation.
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles

01.12.2004 (76)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species	:	Cyprinus carpio (Fish, fresh water)
Exposure period	:	56 day(s) at 25 °C
Concentration	:	.03 mg/l
BCF	:	14 - 101.6
Elimination	:	
Method	:	other: MITI bioaccumulation test of chemical substance in fish and shellfish
Year	:	1992
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity is not specified
Remark	:	The test was conducted in accordance with "Bioaccumulation test of chemical substance in fish and shellfish" stipulated in the Order Prescribing the Items of the Test Relating to the New Chemical Substance (1974, Order of the Prime Minister, the Minister of Health and Welfare, the Minister of International Trade and Industry No. 1). This guideline corresponds to "305C, Bioaccumulation: Degree of Bioconcentration in Fish" stipulated in the OECD Guidelines for Testing of Chemicals (1981)
Result	:	With a concentration of 0.3 mg/l, a BCF of 21.9 - 76.5 was obtained.
Test condition	:	- Fish were supplied by Sugishama fish farm - After external desinfection under static conditions with 50 mg/l Terramycin and 7 g/l sodium chloride, the fish were reared in a flow through system for about 28 d - Fish were reared in an acclimatization tank (flow through system) for another 28 d at 25 +/- 2 °C - Fish feeding with pelleted food (Japan Haigo Shiryo K.K.), about 1 % of body weight twice per day

- Fish at start of incubation: ca. 30 g, ca. 10 cm, lipid content 5.2 %
- Water was groundwater from the Kurume Research Laboratories
- Water temperature, pH, dissolved oxygen were continuously measured
- Total hardness, COD, chloride, and other parameters were measured every 6 months
- Incubation of each 15-20 fish per level in glass tank containing 100 l of liquid each
- 6-8 mg/l dissolved oxygen
- Incubation temperature 25 +/- 2 °C

Reliability : (2) valid with restrictions
Test procedure according to national standards, comparable with guideline
Flag : Critical study for SIDS endpoint
02.09.2005 (66)

BCF : 73.13
Elimination :
Method : other: calculated with BCFWIN v2.15, 2000
Year : 2004
GLP :
Test substance : other TS: p-chlorotoluene

Remark : A log Kow of 3.33 was used for calculation.
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
02.09.2005 (30)

BCF : 230
Elimination :
Method : other: calculated
Year : 1989
GLP :
Test substance : other TS: p-chlorotoluene

Remark : calculated for aquatic organisms with no further specification
Reliability : (4) not assignable
Documentation insufficient for assessment
27.11.2004 (45)

3.8 ADDITIONAL REMARKS

Memo : Formation by Biotransformations

Method : Biodegradation of dichlorotoluenes by soil slurry microorganisms examined under anaerobic conditions:
- Soil samples were obtained from a site located in Niagara Falls, New York
- The subsurface clay loam soil samples had nitrogen and phosphorus contents of 37.0 and 16.5 ppm, respectively; organic matter content: 5.38%, pH 7.2.
- Soil was air dried, passed through a 3.25 mm sieve and transferred to anaerobic glove box before use.
other:
- Incubation: Defined mineral salts medium was prepared; 65 ml serum bottles containing 30 ml sterile medium were inoculated with 10 % slurry inoculum (v/v) that had been actively metabolizing chlorotoluenes (CTs) and amended with 0.1 to 0.6 mM 2,4-Dichlorotoluene (DCT) or 3,4-DCT. One bottle amended with NaNO3 was used as poisoned control.

- Analysis: At intervals, the contents of the duplicates bottles were extracted with pentane and analyzed for parent substance and its metabolites by GC.

Result : Biotransformation of 2,4-Dichlorotoluene (2,4-DCT) and 3,4-DCT resulted predominantly in the formation of 4-chlorotoluene (the metabolites 2-CT and 3-CT, respectively, occurred at minor concentrations).
Further dechlorination of 4-CT was evident from toluene formation.
identifiied degradation products (intermediates)
106-43-4 203-397-0 4-chlorotoluene
108-88-3 203-625-9 toluene

Test substance : other TS: 2,4-Dichlorotoluene (DCT) or 3,4-DCT, purity not specified

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

Flag : Critical study for SIDS endpoint
01.12.2004 (76)

Memo : Occurence in waste

Method : Recovered soil fines from construction and demolition waste recycling facilities were characterized for organic pollutants (waste generated from construction, demolition or renovation of buildings and other such structures). Over a period of 18 months, samples from old stock piles and newly generated piles were taken from 14 waste recycling facilities in Florida.
Analysis by GC/MS

Result : 4 out of 43 samples contained 4-chlorotoluene in the range of 20-35 µg/kg.

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

Flag : Critical study for SIDS endpoint
01.12.2004 (77)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	other: static or semistatic
Species	:	Oryzias latipes (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	5.2
Limit test	:	no
Analytical monitoring	:	no
Method	:	other: Japanese Industrial Standard (JIS K 0102-1986-71) "Testing methods for industrial waste water"
Year	:	1992
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity not specified
Result	:	The 48 hours LC50 value was estimated by Doudoroff method or Probit method.
Test condition	:	- Fish were supplied by Nakashima fish farm - After external desinfection under static conditions with 50 mg/l Terramycin and 7 g/l sodium chloride, the fish were reared in a flow through system for about 28 d - Fish were reared in an acclimatization tank (flow through system) for another 28 d at 25 +/- 2 °C - Water was groundwater from the Kurume Research Laboratories - Water temperature, pH, dissolved oxygen were continuously measured - Total hardness, COD, chloride, and other parameters were measured every 6 months - Incubation of each 10 fish per level in round glass vessel containing 4 l of liquid each - Incubation temperature 25 +/- 2 °C - Static or semi static system (renewal of test water at every 8-16 hours)
Reliability	:	(2) valid with restrictions Test procedure according to national standards
Flag	:	Critical study for SIDS endpoint

02.09.2005 (66)

Type	:	semistatic
Species	:	Poecilia reticulata (Fish, fresh water)
Exposure period	:	14 day(s)
Unit	:	mg/l
LC50	:	5.92
Limit test	:	no
Analytical monitoring	:	no
Method	:	other: see test conditions
Year	:	1981
GLP	:	no
Test substance	:	other TS: p-chlorotoluene, purity not specified
Result	:	LC50 values were calculated according to Litchfield and Wilcoxon (1949. A simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther. 96, 99-113) or in case of a steep concentration-effect relationship by estimating using a log/probit plot. Experimentally determined log LC50 value (14d): 1.67 µmol/l (corresponding to LC50 (14d): 5.92 mg/l)
Test condition	:	- 2-3 months-old guppies were exposed to several concentrations of the solute in 1.5 l vessels - Acetone or propanol-2 stock solutions were used to prepare the desired concentrations of the solute (100 µl of the stock solution was added to each

litre of standard water)
- The concentrations increased in geometrical progression with a ratio of 1.8 or 3.2
- Each vessel was filled with 1 l standard water (hardness 25 mg/l as CaCO3) and covered with glass
- 8 fish per concentration were tested
- Test solution was renewed daily
- Guppies were fed 0.5 h before the test with a commercial fish food
- Oxygen content remained above 5 mg/l
- Temperature was 22 +/- 1°C. LC50 values were calculated according to Litchfield and Wilcoxon or in case of a steep concentration-effect relationship by estimating using a log/probit plot.

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
Flag : Critical study for SIDS endpoint
02.09.2005 (78) (79)

Type : other: static, open
Species : Brachydanio rerio (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC0 : 15
LC50 : 24
LC100 : 50
Limit test :
Analytical monitoring : no
Method : other: Letale Wirkung beim Zebrabärbling Brachydanio rerio (LC0; LC50, LC100; 48-96 Stunden) des Umweltbundesamtes, 1982
Year : 1979
GLP : no
Test substance : other TS: p-chlorotoluene, purity not specified

Remark : Period of investigation: May 1979 - November 1983
Test condition : -3.5 l test medium, ventilated
-10 fish (30 +/-5 mm) each were exposed to 15, 20, 30, 40, and 50 mg p-chlorotoluene/l
-Preparing the stock solution 1g of the test substance and 1 g ethanol were dissolved followed by sonification
followed by sonification
-temperature: 23+/-2 °C
-Ca:Mg ratio: 4:1
-water hardness: 15° dH (German water hardness)
-pH 7.0 +/-2°C
-LD50 (96 h) was determined by Probit analysis

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
02.09.2005 (80)

Type :
Species : Leuciscus idus (Fish, fresh water)
Exposure period :
Unit : mg/l
LC50 : > 10
Method :
Year : 1984
GLP :
Test substance : other TS: p-chlorotoluene, purity not specified

Remark : Data compilation; no further information on the tests available.

Reliability : (4) not assignable
Documentation insufficient for assessment
02.09.2005 (81)

Type :
Species : Poecilia reticulata (Fish, fresh water)
Exposure period :
Unit : mg/l
LC50 : 5.4 - 14.54
Limit test :
Analytical monitoring : no data
Method : other: calculated with QSAR
Year : 2001
GLP : no
Test substance : other TS: p-chlorotoluene

Result : QSAR models were developed using molecular structure descriptors (constitutional, topological, geometrical, electrostatic, and quantum-chemical). The best multilinear regression was used to determine the best two-parameter-model (a); the best multiparameter regression was determined by using a forward stepwise regression procedure (b).
Experimental result obtained from Ramos et al., J. Chem. Inf. Comput. Sci. 38, 845-852 (1998) in µmol/l:
Measured log LC50 = 1.67 (corresponding to LC50 = 5.9 mg/l)
Calculated values in µmol/l:
a) log LC50 = 2.06 (corresponding to LC50 = 14.54 mg/l)
b) log LC50 = 1.63 (corresponding to LC50 = 5.4 mg/l)
Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method
02.09.2005 (82)

Type :
Species : Poecilia reticulata (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 11.55
Method : other: calculated with QSAR
Year : 1998
GLP :
Test substance : other TS: p-chlorotoluene

Remark : Units for the experimental and calculated value are not given, but are supposed to be mol/l
Result : QSAR models were developed using log Kow and hydrogen bonding capacity descriptors to predict the acute toxicity of narcotic nonpolar and polar pollutants to the water flea, guppy and the pond snail. The models were constructed by using partial least squares (PLS) regression. Leave one out cross validation was used to determine the optimum number of latent variables.
Experimental values were obtained from literature summarized by Verhaar et al. (1995) for two fish species with comparable sensitivity (Poecilia reticulata and Pimephales promelas). However, originally reported experimental value was obtained from Koenemann (1979), who performed the test on Poecilia reticulata (EC50, 7-d).
Experimental value:
log LC50 = -4.33 (corresponding to LC50 = 5.92 mg/l)
Calculated value:

log LC50 = -4.04 (corresponding to LC50 = 11.55 mg/l)

Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (83) (84) (85)

Type :
Species : Poecilia reticulata (Fish, fresh water)
Exposure period :
Unit : mg/l
LC50 : 17.47
Method : other: calculated with QSAR
Year : 2003
GLP :
Test substance : other TS: p-chlorotoluene

Remark : QSAR models were developed to predict the toxicity of chemicals on Poecilia reticulata by using topological structure methods.
Experimental value obtained from literature (Koenemann, (1979), who performed the test on Poecilia reticulata (EC50, 7-d).) concerning p-chlorotoluene:
pLC50 = 4.33 (corresponding to LC50 = 5.92 mg/l)
calculated pLC50 = 3.86 (corresponding to LC50 = 17.47 mg/l)

Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (86)

Type :
Species : Poecilia reticulata (Fish, fresh water)
Exposure period :
Unit : mg/l
LC50 : 5.48 - 6.21
Method : other: calculated with QSAR
Year : 1992
GLP :
Test substance : other TS: p-chlorotoluene

Remark : The experimentally determined toxicity data given in this study are based on a data collection for the guppy. This data set which is comprised of 7 to 14-days LC50 data was published by Verhaar HJM et al (1992). QSAR models used for prediction the LC50 values were based on quantum-chemical descriptors (originally reported experimental value was obtained from Koenemann (1979), who performed the test on Poecilia reticulata (EC50, 7-d).

Result : 1) log 1/LC50 = 4.330 mol/l (observed value) corresponding to LC50 = 5.92 mg/l
2) log 1/LC50 = 4.364 mol/l (calculated value) corresponding to LC50 = 5.48 mg/l
3) log 1/LC50 = 4.309 mol/l (calculated value) corresponding to LC50 = 6.21 mg/l

Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (37) (87)

Type :
Species : Poecilia reticulata (Fish, fresh water)

Exposure period :
Unit :
Method : other: calculated with QSAR
Year : 1999
GLP :
Test substance : other TS: p-chlorotoluene

Remark : Molecular toxicity was characterized by the quantum expectation value of electron-electron repulsion energy calculations in relation to toxicity data of Poecilia reticulata. A good correlation of the aquatic toxicities of benzene derivatives was shown (r^2 = 0.889) as well as a good predictive capacity of the model (q^2 = 0.877). Predicted values are presented as graph (cross validation) without chemical identification.

The reported EC50 values for P. reticulata are expressed as log EC50 = 4.33 (unit not given, probably: mol/l, which corresponds to 5.92 mg/l).
Originally reported experimental value was obtained from literature (Koenemann, 1979), who performed the test on Poecilia reticulata (EC50, 7-d).

Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (88)

Type :
Species : Pimephales promelas (Fish, fresh water)
Exposure period :
Unit : mg/l
LC50 : 10.8
Method : other: calculated with QSAR
Year : 1984
GLP :
Test substance : other TS: p-chlorotoluene

Method : Structure-activity relationship analysis (description of the substituent is defined to its presence or absence on the benzene ring) were performed to predict LC50 values via regression analysis.
Remark : Originally reported experimental value was obtained from literature (Koenemann, 1979), who performed the test on Poecilia reticulata (7-d).
Result : Reported calculated value in mol/l:
-log LC50 = 4.07 (corresponding to LC50 = 10.8 mg/l)
Reported experimental value in mol/l:
-log LC50 = 4.33 (corresponding to LC50 = 5.92 mg/l)
Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (89) (90)

Type :
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 7.1
Method : other: calculated with QSAR
Year : 1996
GLP :
Test substance : other TS: p-chlorotoluene

Remark	:	QSAR studies were performed based on the target theory (toxicity occurs as a result of the toxicants binding to the specific receptor sites -target molecules in a target cell) examining the correlations between the acute toxicity and the physicochemical properties for fathead minnow. The experimental data used by Feng et al. were obtained from Hall et al. (1989) Environ. Toxicol. Chem. 8, 431-436. However, originally reported experimental value was obtained from literature (Koenemann, 1979), who performed the test on Poecilia reticulata (7-d). Experimental value reported in mol/l: log 1/LC50 = 4.33 (corresponding to LC50 = 5.92 mg/l) Calculated value reported in mol/l: log 1/LC50 = 4.25 (corresponding to LC50 = 7.10 mg/l)
Reliability	:	(4) not assignable Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (91)

Type	:	
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	9.8 - 22
Method	:	other: calculated with QSAR
Year	:	2000
GLP	:	
Test substance	:	other TS: p-chlorotoluene
Remark	:	A novel QSAR study of benzamidines complement-inhibitory activity and benzene derivatives acute toxicity was developed and compared to each other. Further, the use of statistical and neural net approaches in predicting toxicity of chemicals was investigated. However, originally reported experimental value was obtained from literature (Koenemann, 1979), who performed the test on Poecilia reticulata (7-d).
Result	:	Reported calculated values are in the range from 3.76 to 4.13 (unit not reported, probably given as mol/l, which corresponds from 9.8 to 22 mg/l). Observed LC50 value expressed as -log LC50 = 4.33 (unit not reported, probably given as mol/l, which corresponds to 5.92 mg/l). Data were obtained from Hall et al. (1984). Environ. Toxicol. Chem. 3, 355-365.
Reliability	:	(4) not assignable Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (92) (93)

Type	:	
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96
Unit	:	mg/l
LC50	:	13
Method	:	other: calculated with QSAR
Year	:	2001
GLP	:	
Test substance	:	other TS: p-chlorotoluene
Remark	:	The acute toxicity LC50 (96-h) to Pimephales promelas were correlated by developing a group contribution method.

Multilinear regression and computational neural networks were used for modelling. Both models revealed good correlation ($r^2 > 0.9$).

Experimental value concerning p-chlorotoluene was obtained from literature in mol/l:
-log LC50 = 4.33 (corresponding to LC50 = 5.92 mg/l)
However, originally reported experimental value was obtained from literature (Koenemann, 1979), who performed the test on Poecilia reticulata (7-d).

Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (94)

Type :
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 13.3
Method : other: calculated with QSAR
Year : 1999
GLP :
Test substance : other TS: p-chlorotoluene

Result : A QSAR study was performed using only calculated structural features as independent variables. Multiple linear regression and computational neural networks were used for model building.
The experimental data used were obtained from the COMPUTOX (1995) toxicity database of the Canadian National Water Research Institute. For p-chlorotoluene the following experimental 96h-LC50 value was reported in mmol/l: -log 96h-LC50 = 1.33 (corresponding to an 96h-LC50 value of 5.92 mg/l)

Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (95)

Type :
Species : Pimephales promelas (Fish, fresh water)
Exposure period :
Unit : mg/l
LC50 : 8.6 - 9.6
Method : other: calculated with QSAR
Year : 1995
GLP :
Test substance : other TS: p-chlorotoluene

Remark : Originally reported experimental value was obtained from literature (Koenemann, 1979), who performed the test on Poecilia reticulata (7-d).

Result : Reported experimental value in mol/l:
Log l/LC50 = 4.33 (corresponding to LC50 = 5.92 mg/l)

Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (96) (97) (34)

Type :

Species	:	other: fish (species not specified)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	6
Method	:	other: calculated with QSAR
Year	:	2001
GLP	:	
Test substance	:	other TS: p-chlorotoluene
Remark	:	A set of 125 chemicals (derived from the first European priority list in compliance with Directive 76/464/EEC) for which toxicological data on Daphnia, algae and fish were available, were taken to develop QSAR-classification models, based on traditional and non-traditional molecular descriptors. The classification results were good in agreement with the "a priori" classification as well as with the original water quality objectives classification (it is unclear whether the data concerning p-chlorotoluene are experimentally determined values or predicted ones by using QSAR's).
Reliability	:	(4) not assignable Secondary literature

27.11.2004 (98)

Type	:	
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	7
Method	:	other: calculated with QSAR
Year	:	1996
GLP	:	
Test substance	:	other TS: p-chlorotoluene
Remark	:	LC50 value was obtained from literature.
Result	:	Experimental value reported in mol/l: log 1/LC50 = 4.33 (corresponding to LC50 = 5.92 mg/l)
Reliability	:	(4) not assignable Development of QSAR correlation. Currently, not commonly used calculation method

27.11.2004 (99)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	other aquatic crustacea: Ceriodaphnia dubia
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	1.7
Limit Test	:	no
Method	:	other: according to US EPA/600/4-90/027F, 1993
Year	:	1998
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity > 97%
Method	:	Test procedure was according to US EPA/600/4-90/027F (1993) Methods for measuring the acute toxicity of effluents and receiving water to freshwater and marine organisms.
Result	:	Test substance recovery was at least >80%.

Experimentally determined toxicity concerning
p-chlorotoluene was:
EC50 (immobilization) = 13.00 umol/l (8.0-23.0 µmol/l)
(corresponding to EC50 = 1.7 mg/l; 1.0-2.9 mg/l)

Test condition : - Sealed 214 ml bottles were used as test vessels rather than 250 ml beaker.
- Stock solutions were made using nanograde acetone.
- Mean water quality parameters used in the study were: pH 7.7; free and total chlorine 0.01 and 0.03 mg/l; ammonia 0.01 mg/l; hardness 65.2 mg/l as CaCO3, and conductivity 500 µS/cm.
- The concentrations of the test chemicals were determined at the beginning and at the end of the test using capillary column gas chromatography.
- EC50 values and the 95% confidence limits were determined using the trimmed Spearman-Karber method. Values are based on measured initial concentrations.

Reliability : (2) valid with restrictions
Guideline study without detailed documentation

Flag : Critical study for SIDS endpoint

02.09.2005 (100) (101)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : 3.57
Limit Test : no
Analytical monitoring : no data
Method : other: Concept NEN 6501 (1980). Determination of the acute toxicity with Daphnia magna. Dutch Standard Organization, Delft
Year : 1984
GLP : no data
Test substance : other TS: p-chlorotoluene, purity is not specified

Method : -Daphnids used in the tests were <2 days-old
-25 daphnids per test group
-test volume per group: 1 l
-temperature: 22+/-1°C
-test medium: Dutch standard water
-ratio of concentrations: 1.8 (nominal concentrations not specified)
-all tests were carried out in duplicate

Result : Results are based on nominal concentrations.
Endpoint: immobilisation

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

Flag : Critical study for SIDS endpoint

05.09.2005 (102)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 24 hour(s)
Unit : mg/l
EC50 : 2.53
Method : other: see method
Year : 1998
GLP : no data
Test substance : other TS: p-chlorotoluene, purity > 95%

Method : -Daphnia magna were cultured at 22+/-2°C with a photoperiod

of 14 h light/10 h darkness
-Daphnids were fed with green algae
-6-24 h old daphnids were used for toxicity tests:
-10 daphnids in 25 ml test water (closed vessels)
-each test with 60 daphnids
-daphnids were not feed during the test
-number of immobilized daphnids were recorded regularly

Result : Results were regarded as valid if dissolved oxygen measured at the end of the test was at least equal to 65% saturation and if the percentage of immobilization in control was zero.
EC50 (24 h)expressed as log 1/EC50= 4.70 mol/l
(corresponding to EC50 (24 h) = 2.53 mg/l)
Results are based on nominal concentrations.

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

27.11.2004 (31)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 24 hour(s)
Unit : mg/l
EC50 : 9
Limit Test : no
Analytical monitoring : yes
Method : other: see method
Year : 1982
GLP : no
Test substance : other TS: p-chlorotoluene, purity is not specified

Method : 50 ml test vessels filled with 20 ml test solution (10 daphnids/vessel, daphnids <24 h old); distinct test substance concentrations diluted in water were tested in duplicate; reconstituted water; test vessels were covered with filter paper; vessels were kept at 20°C; pH at test initiation and at test term was determined as well as O2 content.
EC50 values were determined graphically (Probability network: logarithmic test concentration versus %-age of immobilized daphnids).

Remark : Measured concentration of the stock solution was 15% of originally weighed in substance.

Result : Since the measured concentration in the stock solution was only 15% of the initial amount weighed in, the estimated EC50-value of 9 mg/l should be considered rather than the EC50-value of 61 mg/l related to the nominal concentration.

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

27.11.2004 (103)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period :
Unit :
Method : other: see method
Year : 1985
GLP : no
Test substance : other TS: p-chlorotoluene, purity is not specified

Method : Young daphnids (<12 hours old) were exposed to a range of contaminated sediment pore water dilutions collected from the Grand Calumet River,

Indiana.
Organic chemical analyses were conducted at test initiation. Identification and quantification of chemical analytes were performed with GC/MS.
Mortality (lack of movement or respiration) was recorded after 48 h. Results were reported as the percentage of pore water causing 50 % mortality.

Remark : The given EC values were not based on test substance concentrations. The effects cannot be attributed to p-chlorotoluene

Result : 48h-EC50 values from 5.5 to >100 % were reported.
Analytically determined p-Chlorotoluene concentrations in sediment pore water: 5.4 - 54.6 µg/l.

Test substance : Blend of organic chemicals including p-chlorotoluene in sediment pore waters from the Grand Calumet River, Indiana Harbor

Reliability : (3) invalid
Unsuitable test system

02.09.2005 (104)

Type : static
Species : other aquatic crustacea: Ceriodaphnia dubia
Exposure period :
Unit :
Method : other: see method
Year : 1985
GLP : no
Test substance : other TS: p-chlorotoluene, purity is not specified

Method : Young daphnids (<12 hours old) were exposed to a range of contaminated sediment pore water dilutions collected from the Grand Calumet River, Indiana.
Organic chemical analyses were conducted at test initiation. Identification and quantification of chemical analytes were performed with GC/MS.
Mortality (lake of movement or respiration) was recorded after 48 h.
Results were reported as the percentage pore water causing 50 % mortality.

Remark : The given EC values were not based on test substance concentrations. The effects cannot be attributed to p-chlorotoluene

Result : 48h-EC50 values from 3.2 to >100 % were reported.
Analytically determined p-Chlorotoluene concentrations in sediment pore water: 5.4 - 54.6 µg/l.

Test substance : blend of organic chemicals including p-chlorotoluene in sediment pore waters from the Grand Calumet River, Indiana Harbor

Reliability : (3) invalid
Unsuitable test system

02.09.2005 (104)

Type : static
Species : other: Chironomus tentans (Chironomidae)
Exposure period :
Unit :
Method : other: see method
Year : 1988
GLP : no
Test substance : other TS: p-chlorotoluene, purity is not specified

Method : Second instar individuals (12 days post-hatching) were exposed to different sediments collected from the Grand Calumet River, Indiana.
Tests were conducted for 10-d at 22 +/- 1°C with a 16L:8D photoperiod. At test termination surviving larvae
were recovered, dried and weighed.
Results are reported as mean percentage inhibition in dry wt gain at each station relative to a control sediment.

Organic chemical analyses were conducted at test initiation. Identification and quantification of chemical analytes were performed with GC/MS.

Remark : The given EC values were not based on test substance concentrations. The effects cannot be attributed to p-chlorotoluene

Result : Values from 37.0 to 100% inhibition are reported.
Analytically determined p-chlorotoluene concentrations in bulk or whole sediments: 1.74 - 21.43 µg/l.

Test substance : blend of organic chemicals including p-chlorotoluene in sediment pore waters from the Grand Calumet River, Indiana Harbor

Reliability : (3) invalid
Unsuitable test system

02.09.2005 (104)

Type :
Species : other aquatic crustacea: Nitocra spinipes (copepod)
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : 10 - 20
Method :
Year : 1983
GLP :
Test substance : other TS: p-chlorotoluene, purity is not specified

Remark : Reported EC50 values are given without specification of the unit in the original report. Aquire-database (EPA) reported this value in mg/l.

Result : Due to evaporation a poor correlation between dose and response was achieved. The subsequent probit analysis did not result in acceptable LC50 values (too high Chi square values). But based on repeated tests the possible range was estimated.
An 96h-EC50 from 10 to 20 is reported.

Reliability : (4) not assignable
Documentation insufficient for assessment

02.09.2005 (105)

Type :
Species : Daphnia magna (Crustacea)
Exposure period : 24 hour(s)
Unit : mg/l
EC50 : 4.7
Method : other: calculated with QSAR
Year : 1998
GLP :
Test substance : other TS: p-chlorotoluene

Remark : QSAR models were developed using log Kow and hydrogen bonding capacity descriptors to predict the acute toxicity of narcotic nonpolar and polar pollutants to the water flea, guppy and the pond snail. The models were constructed by using partial least squares (PLS) regression. Leave one out cross validation was used to determine the optimum number of latent variables.
Experimental values were obtained from literature summarized by Verhaar et al. (1995) for Daphnia magna.

Reported experimental value obtained from literature:
log LC50 = -4.00 (corresponding to LC50 = 12.66 mg/l)
Calculated value:
log LC50 = -4.43 (corresponding to LC50 = 4.7 mg/l)

(Units are not given, but are supposed to be mol/l)

Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (83) (84) (85)

Type :
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : 2.29
Method : other: calculated with QSAR
Year : 2001
GLP :
Test substance : other TS: p-chlorotoluene

Remark : A set of 125 chemicals (derived from the European priority list in compliance with Directive 76/464/EEC) for which toxicological data on Daphnia, algae and fish were available, were taken to develop QSAR-classification models, based on traditional and non-traditional molecular descriptors.
The classification results were good in agreement with the "a priori" classification as well as with the original water quality objectives classification (it is unclear whether the data concerning p-chlorotoluene are experimentally determined values or predicted ones by using QSAR's).

Reliability : (4) not assignable
Secondary literature

27.11.2004 (98)

Type :
Species : Daphnia magna (Crustacea)
Exposure period : 24 hour(s)
Unit : mg/l
EC0 : ca. 3
EC50 : 6 - 12
Analytical monitoring : no
Method : other: DIN 38412, part 11
Year : 1982
GLP : no
Test substance : other TS: p-chlorotoluene, purity is not specified

Reliability : (4) not assignable
Original reference not available

27.11.2004 (73) (74)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Scenedesmus subspicatus (Algae)
Endpoint : growth rate
Exposure period : 72 hour(s)
Unit : mg/l
NOEC : .43
EC50 : .96
Limit test : no
Analytical monitoring : yes
Method : Directive 92/69/EEC, C.3
Year : 2004
GLP : yes

Test substance : other TS: p-clorotoluene, purity 99.9 %

Method : Method is in most parts equivalent to the OECD TG 201 Alga, Growth inhibition test.

Remark : - Accepted new scientific name for Scenedesmus subspicatus: Desmodesmus subspicatus.
- The pH shows a variation of 2.3 units (pH 8.0 - 10.3) during the tests whereas a variation not higher than 1.5 is recommended in the OECD guideline for the control medium.
- The p-chlorotoluene concentrations decreased during the incubations below the limit of detection. An estimate of exposure concentrations has been performed using the geometric mean of measured concentrations at the start of incubation (nominal concentration and half the detection limit (0.05 mg/l). Because after the incubation, p-chlorotoluene concentration was below the limit of detection, this geometric mean could still overestimate the real exposure concentrations during the test.

Result : Recovery rates of the test substance ranged from 39.5 - 67.3% of nominal values at 0 hours. At 72 hours the values of all concentrations are below the quantification limit of 0.1 mg/l. Values below the quantification limit are regarded as 0.05 mg/l, i.e. half of the quantification limit. Geometric means of analytical values were calculated. Analytical results are listed in the table:

nominal (mg/l)	T0 measured	T72 measured	Geom.mean (mg/l)		
30	18.32	<0.1	0.96		
15	9.3	<0.1	0.68	7.5	3.69	<0.1	0.43
3.75	1.96	<0.1	0.31		
1.9	0.75	<0.1	0.19		

At the highest test concentration of 0.96 mg/l (nominal 30 mg/l) inhibition of growth rate and biomass was 6.1 % and 10.9 %, respectively. Therefore, the EC50 is expected to be above the concentrations which could be attained in experiments due to the limited water solubility of 40 mg/l. The no effect concentration (NOEC) for growth rate and biomass was 0.43 mg/l (geom. mean; nominal 7.5 mg/l) and >0.96 mg/l (geo. mean; >30 mg/l), respectively.

Test condition : - To prepare the stock solution (125.1 mg/l) an amount of the test substance was weighed into water, treated for 60 seconds at 8000 rpm with an ultra-turrax, afterwards stirred for 24 hours on a magnetic stirrer and finally filtered.
- Static conditions.
- Algal inoculum about 10E+04 cells/ml initial cell density.
- 300 ml Erlenmeyer flasks with stoppers as test vessels.
- Temperature during the test: 21-25 °C.
- Lighting 60-120 µE m-2 s-1.
- pH is measured at the beginning of the test and at 72 h.
- pH was in the range of 8.0 - 10.3
- Experimental design: 5 test concentrations plus control, 3 replicates per concentration, 6 replicates per control, highest test concentration without algae.
- Nominal test concentrations: 1.9, 3.75, 7.5, 15, 30 mg/l
- Cell densities measured at 24 h intervals using a microcell counter.
- Inhibition of algal population measured as reduction on biomass growth (index b) and population density growth rate (index r), relative to control cultures under identical conditions.
- Test substance concentrations were analysed with GC/MS at 0 and 72 hours

Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions
Flag	:	Critical study for SIDS endpoint
05.09.2005		(106)
Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	biomass
Exposure period	:	7 day(s)
Unit	:	mg/l
EC3	:	> 24
Limit test	:	no
Analytical monitoring	:	yes
Method	:	other: see method
Year	:	1982
GLP	:	no
Test substance	:	other TS: p-chlorotoluene, purity is not specified
Method	:	300 ml test vessels filled with 50 ml test solution (algal suspension; distinct test substance concentrations; algal medium); cell density was determined and adjusted by measuring the extinction/turbidity of the algal stock solution (monochromatic light Hg at 580 nm; 10 mm light path); test vessels were loosely closed with metal caps; tests were performed in duplicate; test cultures were kept at 27°C with continuous illumination; once a day algal cultures were shaken. Data assessment was performed by regression analysis. A 3% deviation in extinction of the treated algae to the control algae was defined as toxicological threshold (TT) which is equivalent to the EC3 value.
Remark	:	Accepted new scientific name for Scenedesmus subspicatus: Desmodesmus subspicatus. Measured concentration of the stock solution was 15% of originally weighed in substance.
Result	:	Since the measured concentration in the stock solution was only 15% of the initial amount weighed in, the estimated EC3-value of > 24 mg/l should be considered rather than the EC10-value of > 160 mg/l related to the nominal concentration.
Reliability	:	(3) invalid - It is not clear whether the algae were within the exponential growth throughout the whole exposure period of 7 days. - Exposure concentrations could not be maintained during 7 days under static conditions considering the volatilisation potential of the substance.
02.09.2005		(103)
Species	:	Chlorella vulgaris (Algae)
Endpoint	:	growth rate
Exposure period	:	6 hour(s)
Unit	:	mg/l
EC50	:	38.2
Limit test	:	no
Analytical monitoring	:	
Method	:	other: see method
Year	:	1986
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity is not specified
Method	:	- Static test in merry-go-round incubator - Initial cell density of synchronous culture: 7.5 x 10E6/ml - Light intensity: 28 W/m²

- Temperature: 36.5 °C
- Aeration with air enriched in carbon dioxide (2 %) (no gas flow rate reported)
- Growth rate was measured as optical density at 680 and 750 nm after 6 hours
- EC50 value (growth inhibition) was determined graphically by interpolation of results from (typically) 4-6 measured concentrations

Remark : - Documentation insufficient for assessment (further information has been published in University publication which was not available)
- High initial cell density
- Extent of evaporative losses cannot be elucidated
- Short incubation period

Result : Result is reported as log EC50 = 3.52 mol/l (corresponding to 38.2 mg/l).
Reliability : (3) invalid
Significant methodological deficiences

02.09.2005 (107) (108) (109)

Species : other algae: Scenedesmus obliquus
Endpoint : growth rate
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : 21.5
Limit test : no
Analytical monitoring : no
Method : other: see method
Year : 1994
GLP : no
Test substance : other TS: p-chlorotoluene, purity: analytical grade

Method : - Algae were cultured in medium at pH 7.5 +/-0.2 at 24.1 +/-1°C
- Cool white light: 4000 Lux +/-10%; 12:12 h light:dark cycle
- Initial algal density: 10E4 cells/ml
- 5 concentrations in triplicate and controls were used
- Cell density was measured after 0, 24, 48, 72, and 96h - 96h-EC50 for growth inhibition was graphically determined by extrapolation

Further data on method is published in Chinese only

Remark : Unsuitable test system (light schedule not in compliance with the OECD TG recommendation).
Result : EC50 (96h) value is reported as log 1/EC50 = 3.88 mol/l (corresponding to 21.5 mg/l).
Reliability : (3) invalid
Significant methodological deficiences

02.09.2005 (110)

Species : other algae: (species not specified)
Endpoint :
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : 1.27
Method : other: calculated with QSAR
Year : 2001
GLP :
Test substance : other TS: p-chlorotoluene

Remark : A set of 125 chemicals (derived from the European priority list in compliance with Directive 76/464/EEC) for which toxicological data on Daphnia, algae and fish were available, were taken to develop QSAR-classification models, based on

traditional and non-traditional molecular descriptors.
The classification results were good in agreement with the "a priori" classification as well as with the original water quality objectives classification (it is unclear whether the data concerning p-chlorotoluene are experimentally determined values or predicted ones by using QSAR's).

Reliability : (4) not assignable
Secondary literature

27.11.2004 (98)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	other protozoa: Spirostomum ambiguum
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	110.8
Analytical monitoring	:	no data
Method	:	other: Spirotox test
Year	:	2002
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity: analytical grade

Result : Results were given in mmol/l after 24 and 48 h:
For the deformation differences:
24 h-EC50 = 0.85 mmol/l = 107.0 mg/l
48 h-EC50 = 0.76 mmol/l = 95.8 mg/l
For lethality:
24 h-LC50 = 0.96 mmol/l = 120.9 mg/l
48 h-LC50 = 0.88 mmol/l = 110.8 mg/l

Test condition : Spirostomum ambiguum was used as test organism (big protozoa: 2-3 mm long). Diluent: Tyrod solution: 125 mg NaCl, 3.1 mg KCl, 3.1 mg CaCl2, 1.55 mg MgCl2, 15.6 mg NaHCO3 and 0.78 mg NaH2PO4 per liter of deionised water. Total hardness = 2.8 mg CaCO3/l and pH = 7.4 +/- 0.2. A five steps dilution series was prepared in triplicate directly in the microplate, which were than tightly closed. Incubation took place in darkness at 25 °C. 2 kinds of test responses were observed: a) different deformations and b) lethal response.

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

Flag : Critical study for SIDS endpoint

27.11.2004 (111)

Type	:	aquatic
Species	:	Pseudomonas putida (Bacteria)
Exposure period	:	18 hour(s)
Unit	:	mg/l
EC10	:	> 25
Analytical monitoring	:	yes
Method	:	other: Cell multiplication inhibition test
Year	:	1982
GLP	:	no
Test substance	:	other TS: p-chlorotoluene, purity not specified

Method : Method in most parts in accordance to DIN 38412 part 8.
300 ml test vessels filled with 100 ml test solution (bacterial suspension; distinct test substance

concentrations; bacterial growth medium); cell density was determined and adjusted by measuring the extinction/turbidity of the bacterial stock solution (monochromatic light Hg at 436 nm; 10 mm light path); test vessels were loosely closed with metal caps; tests were performed in triplicate; test cultures were kept at 25°C. EC10 values were determined graphically (semi-logarithmic; test concentration versus extinction values. A 10% deviation in extinction of the treated bacteria versus control was defined as toxicological threshold (TT) which is equivalent to the EC10 value.

Remark : Measured concentration of the stock solution was 15% of originally weighed in substance.

Result : Since the measured concentration in the stock solution was only 15% of the initial amount weighed in, the estimated EC10-value of >25 mg/l should be considered rather than the nominal concentration of >160 mg/l.

Reliability : (2) valid with restrictions
Basic data given, Test procedure in accordance with national standard method with acceptable restrictions

Flag : Critical study for SIDS endpoint

27.11.2004 (103)

Type : aquatic
Species : Pseudomonas putida (Bacteria)
Exposure period : 30 minute(s)
Unit : mg/l
EC0 : 250
Analytical monitoring : no
Method : other: Oxygen consumption inhibition test (Robra test)
Year : 1979
GLP : no
Test substance : other TS: p-chlorotoluene, purity not specified

Remark : emulsifier: Emulgator W , CAS No. 68130-72-3
Reliability : (4) not assignable
Documentation insufficient for assessment

27.11.2004 (112)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 15 minute(s)
Unit : mg/l
EC50 : 16.69
Analytical monitoring : no
Method : other: Microtox-test
Year : 1993
GLP : no
Test substance : other TS: p-chlorotoluene, purity >95%

Method : - Test substance was diluted with 3% NaCl solution
- Tests were performed at 20 +/-2 °C in closed systems
- Bioluminescence was measured after 15 and 30 min. with the toxicity analyzer.

Result : Ecotoxicological descriptors were the concentration values causing 50 % inhibition of bioluminescence after 15 minutes exposure (15 min-EC50, mol/l).
Only values for 15 minutes incubations are reported, since the results were similar for both time periods.
-log EC50 = 3.88 mol/l (corresponding to EC50 = 16.69 mg/l)

Reliability : (3) invalid
Unsuitable test system. Organisms are of marine origin. Method is not

appropriate for the hazard assessment of chemicals.

02.09.2005 (83) (97) (31) (34) (35)

Type	:	aquatic
Species	:	Photobacterium phosphoreum (Bacteria)
Exposure period	:	30 minute(s)
Unit	:	mg/l
EC50	:	6.49
Analytical monitoring	:	no data
Method	:	other: Microtox-test
Year	:	1987
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity: best grade available
Method	:	The acute toxicities to Photobacterium phosphoreum were determined with the Microtox (trade mark) toxicity analyzer. In some cases, up to 5% methanol was used to increase substrate solubility.
Result	:	Toxicity values reported (pTmr) as negative base ten logarithms of the millimolar concentrations at which 50% light reduction was observed on 30 min. exposure. The values are the mean of three independent determinations. EC50 value obtained for p-chlorotoluene: pTmr = 1.29 mmol (corresponding to an EC50 value of 6.49 mg/l)
Reliability	:	(3) invalid Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

02.09.2005 (113)

Type	:	aquatic
Species	:	Photobacterium phosphoreum (Bacteria)
Exposure period	:	
Unit	:	
Method	:	other: Microtox test
Year	:	1993
GLP	:	no
Test substance	:	other TS: p-chlorotoluene, purity not specified
Method	:	The Microtox bacterial luminescence assay was performed on sediment pore waters, collected from the Grand Calumet River, Indiana, with the standard procedure and the alternate osmotic adjustment procedure (NaCl and sucrose). The calculated ratio of corrected light emitted to emitted light remaining after 5, 15, 30 min was determined for each sample dilution. All results are reported as the percentage pore water causing a 50 % inhibition of bioluminescence (EC50). EC50 values were calculated with the linearized gamma distribution. Organic chemical analyses were conducted at test initiation. Identification and quantification of chemical analytes were performed with GC/MS.
Remark	:	The given EC values were not based on test substance concentrations. The effects cannot be attributed to p-chlorotoluene
Result	:	The following results are reported for a blend of organic chemicals including p-chlorotoluene in sediment pore waters from the Grand Calumet River, Indiana Harbor (% indicates % pore water in incubation medium): EC50, adjusted with NaCl: 5 min: 0.6 - 93 % 15 min: 0.3 - 93.8 % 30 min: 0.3 - >100 %

EC50, adjusted with sucrose:
5 min: 0.4 - >100 %
15 min: 0.2 - >100 %
30 min: 0.2 - 70.4 %

Analytically determined p-chlorotoluene concentrations in sediment pore water: 5.4 - 54.6 µg/l.

Test substance : Blend of organic chemicals including p-chlorotoluene in sediment pore waters from the Grand Calumet River, Indiana Harbor

Reliability : (3) invalid
Unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

02.09.2005 (104)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 15 minute(s)
Unit : mg/l
EC50 : 8.17
Method : other: calculated with QSAR
Year : 1996
GLP :
Test substance : other TS: p-chlorotoluene

Method : The concentration values causing 50% inhibition of bioluminescence at 20°C was tested as toxicity index. The Microtox test was performed using DXY-2 toxicity analyzer (Institute of Soil Science, Academia Sinica, Nanjing).

Remark : LC50 value was obtained from Zhao, 1993.
QSAR development for unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

Result : Experimental value reported:
-log EC50 observed = 3.88 mol/l (corresponding to 16.69 mg/l)

Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (99)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 15 minute(s)
Unit : mg/l
EC50 : 12.95
Method : other: calculated with QSAR
Year : 2002
GLP :
Test substance : other TS: p-chlorotoluene

Method : QSAR models were developed for 43 aromatic compounds to Photobacterium phosphoreum and Daphnia magna using octanol/water partitioning coefficient, linear solvation energy relationship (LSER), molecular connectivity index and group contribution. LSER fit best to the experimental values.

Remark : QSAR was developed for unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.

Result : Experimental value concerning p-chlorotoluene was received from literature: -logEC50 = 3.88 mol/l (corresponding to 16.69 mg/l).

Calculated value based on LSER: -logEC50 = 3.99
(corresponding to 12.95 mg/l).

Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (114)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 30 minute(s)
Unit : mg/l
EC50 : 8
Method : other: calculated with QSAR
Year : 1995
GLP :
Test substance : other TS: p-chlorotoluene

Method : QSAR models were developed using quantum chemical descriptors. Best fit for non-polar narcotics was achieved when using descriptors like molecular polarizability, LUMO energy, and a shape descriptor.
The experimental Microtox data were taken from the COMPUTOX database reported as log 1/EC50 = 1.29 [mmol/l]
(corresponding to EC50 = 6.49 mg/l).
Remark : QSAR was developed for unsuitable test system. Organisms are of marine origin. Method is not appropriate for the hazard assessment of chemicals.
Result : The calculated value reported was log 1/EC50 = 1.2 [mmol/l]
(corresponding to EC50 = 8.0 mg/l).
Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

02.09.2005 (115) (116)

Type : aquatic
Species : Vibrio fisheri (Bacteria)
Exposure period : 5 minute(s)
Unit : mg/l
EC50 : 4.9
Analytical monitoring : no data
Method : other: Microtox-test
Year : 1997
GLP : no data
Test substance : other TS: p-chlorotoluene, purity not specified

Remark : Value was obtained from Kaiser and Palabrica (1991), Res. J. Canc. 26, 361-431. It was reported by Cronin as negative logarithm of the mmol concentration required to elicit 50% reduction in light emission in Vibrio fisheri in 5 minutes.
log pT5 = 1.41 mmol (corresponding to 4.9 mg/l).
Reliability : (4) not assignable
Secondary literature

02.09.2005 (117)

Type : aquatic
Species : anaerobic bact. from a domestic water treatment plant
Exposure period : 24 hour(s)
Unit : mg/l
toxicological threshold : ca. 12
Analytical monitoring : no

Method	:	ETAD Fermentation tube method "Determination of damage to effluent bacteria by the Fermentation Tube Method"
Year	:	1982
GLP	:	no
Test substance	:	other TS: p-chlorotoluene, purity not specified
Reliability	:	(4) not assignable Original reference not available

27.11.2004 (73) (74)

4.5.1 CHRONIC TOXICITY TO FISH

Species	:	Brachydanio rerio (Fish, fresh water)
Endpoint	:	length of young fish
Exposure period	:	28 day(s)
Unit	:	mg/l
NOEC	:	1.9
LC50	:	4.4
Analytical monitoring	:	yes
Method	:	other: see method
Year	:	1990
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity: 99%
Method	:	Method is in most parts in accordance with OECD TG 210, 1992. 40 fertilized eggs/concentration (blastula stage, <6h after spawning) were exposed to 7-8 test concentrations (ratio: 1.8) and a control. After completion of hatching (4-5 days) the fry were transferred into two vessels/concentration. The rotifer Brachiunus rubens was offered as food. After 7 days the food was displaced by 48-h old nauplii of Artemia salina enriched with Selco, a commercial concentrate for nutritional enrichment of live food for fish. Dead eggs and larvae were counted and removed daily. At term final fish length and malformations were determined. The test solutions were renewed 3 times a week and analyses (HPLC/UV) were performed before and after renewal of the test solutions; pH and O2 concentrations were measured regularly. LC50 and confidence limits were determined according to Kooyman (1981). NOLC was determined by chi square test and NOEC was determined according to Williams (1971). Tests were discharged in the case that the number of viable eggs in the control was below 25 after 48 h.
Remark	:	Only 40 eggs/concentration were used (60 eggs/conc. are recommended by the OECD TGD 210).
Result	:	The mean concentrations were below the nominal concentrations. Therefore, results are based on mean actual concentrations. Retardation of growth was shown to be the most sensitive endpoint. No observed lethal concentration (NOLC) = 3.4 mg/l No observed effect concentration (NOEC) = 1.9 mg/l LC50 (28-d) = 4.4 (1.9-6.0) mg/l
Test condition	:	Reconstitute water prepared from groundwater was used: hardness: ca. 120 mg/l CaCO3; mean dissolved oxygen during the test: 7.7 mg/l (lowest measured conc. was 5.1 mg/l); pH of the medium from 8.0-8.2; concentrations of macronutrients were: 1.19 mmol/l Na+, 0.20 mmol/l K+, 1.36 mmol Ca2+, 0.73

mmol/l Mg2+, 2.72 mmol/l Cl-, 0.73 SO4- and 1.39 mmol/l HCO3-. The groundwater contained several trace elements at concentrations << 1 mg/l.
Test were carried out at 24+/-2°C, photoperiod was 12 hours.
Test solutions were not aerated.

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

Flag : Critical study for SIDS endpoint

02.09.2005 (118)

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species : Daphnia magna (Crustacea)
Endpoint : reproduction rate
Exposure period : 16 day(s)
Unit : mg/l
NOEC : .32
EC50 : .58
Analytical monitoring : yes
Method : other: tests were performed according to: Concept NEN 6502 (1980). Determination of the chronic toxicity with Daphnia magna. Dutch Standard Organization, Delft
Year : 1984
GLP : no data
Test substance : other TS: p-chlorotoluene, purity not specified

Method : Daphnids used in the tests were <1 days-old; 15 daphnids/test group (deviation from Concept NEN 6502); test volume/group: 1 l; temperature: 19+/-1°C; test medium: Dutch standard water; ratio of concentrations: 3.2 (nominal concentrations not specified); all tests were carried out in duplicate under semi-static conditions (water was renewed 3 times a week); Chlorella spec. served as food.
Analysis was performed (GC). EC50 values were determined by log/Probit plots.

Result : Results are based on nominal concentrations. Analysis showed that more than 70% of the added quantities were recovered at test start. The decrease in concentration during the test, till renewing the solutions was max. 20%).

Results reported for mortality:

LC50 (16 d, mortality): 1.59 mg/l
NOEC (16 d, mortality): 1.0 mg/l

Reliability : (2) valid with restrictions
Guideline study without detailed documentation

Flag : Critical study for SIDS endpoint

27.11.2004 (102)

Species : Daphnia magna (Crustacea)
Endpoint : other: growth
Exposure period : 16 day(s)
Unit : mg/l
NOEC : .32
EC50 : 1.71
Analytical monitoring : yes
Method : other: tests were performed according to: Concept NEN 6502 (1980). Determination of the chronic toxicity with Daphnia magna. Dutch Standard Organization, Delft

Year	:	1985
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity not specified
Method	:	Daphnids used in the tests were <1 days-old; 15 daphnids/test group (deviation from Concept NEN 6502); test volume/group: 1 l; temperature: 19+/-1°C; test medium: Dutch standard water; ratio of concentrations: 1.8 (nominal concentrations not specified); all tests were carried out in duplicate under semi-static conditions (water was renewed 3 times a week); Chlorella spec. served as food. Lengths of 30 daphnids were determined at test start and at term. Analyses were performed for the lowest and highest concentration just before and after renewal of the solutions (GC). EC50 values were determined by log/Probit plots. NOEC was determined using the Student's t-test ($p < 0.001$).
Result	:	Results are based on nominal concentrations. Recovery of the test solution concentrations was between 80-110%. Criteria for EC50: concentration which reduce growth with 50%
Reliability	:	(2) valid with restrictions Guideline study without detailed documentation
Flag	:	Critical study for SIDS endpoint

27.11.2004 (119)

Species	:	Daphnia magna (Crustacea)
Endpoint	:	
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	.88
Method	:	other: calculated with QSAR
Year	:	1999
GLP	:	
Test substance	:	other TS: p-chlorotoluene
Remark	:	The acute-chronic ratio was discussed on base of QSAR models. The results show, that for Daphnia an equation of -logNOEC = 1.21(0.03)log EC50 [n=13, r=0.998; SE=0.39] is applicable to turn acute toxicity data from 24-h immobility test into chronic toxicity data for 3 week reproduction toxicity test for the tested compounds. Reported values concerning p-chlorotoluene were calculated according QSAR estimations adopted from literature (Van Leeuwen et al (1992), Env. Tox. Chem.11, 267-282: -logNOEC = 5.16 mol/l (corresponding to 0.88 mg/l)
Reliability	:	(4) not assignable Development of QSAR correlation. Currently, not commonly used calculation method

27.11.2004 (120)

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rabbit
Number of animals
Males :
Females :
Doses
Males : 300 mg/kg bw
Females :
Vehicle : no data
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
Year : 1955
GLP : no
Test substance : other TS: p-Chlorotoluene: no data on purity

Result : study on the metabolism of p-chlorotoluene via oxidation: rabbits received a single oral administration of 300 mg/ kg bw of p-chlorotoluene: 64-83 % of the dose was excreted with the urine as ether-soluble p-chlorobenzoic acid derivatives; 1 % of the dose was found in the urine as ester glucuronides.
Reliability : (2) valid with restrictions
short description but provides sufficient information to be taken into account
Flag : Critical study for SIDS endpoint
10.09.2004 (121)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : dog
Number of animals
Males :
Females :
Doses
Males : 5000 mg
Females :
Vehicle : no data
Route of administration : other: capsule
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 : 1903
GLP : no
Test substance : other TS: p-chlorotoluene, no data on purity

Remark : After a single oral administration of p-chlorotoluene to a dog, the corresponding hippuric acid was identified in the urine.
Reliability : (2) valid with restrictions
short description but provides sufficient information to be taken into account
Flag : Critical study for SIDS endpoint
10.09.2004 (122)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rabbit
Number of animals
Males :
Females :
Doses
Males : no data
Females :
Vehicle : no data
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
Year : 1903
GLP : no
Test substance : other TS: p-chlorotoluene, no data on purity

Remark : Following oral application of p-chlorotoluene to rabbits, the corresponding benzoic acid could be detected as urinary metabolite (no further data)
Reliability : (2) valid with restrictions
short description but provides sufficient information to be taken into account
Flag : Critical study for SIDS endpoint
10.09.2004 (122)

In Vitro/in vivo : In vivo
Type : Distribution
Species : rat
Number of animals
Males :
Females :
Doses
Males : 0, 500, 1000, 1500 mg/kg bw in soybean oil
Females :
Vehicle : other: soybean oil
Route of administration : i.p.
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: single i.p. application
Year	:	1997
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity: 98 %
Result	:	When p-chlorotoluene was given to rats , blood and lung levels rose rapidly at 1 h and reached near maximal values at 4 hours. Liver levels reached maximum levels at 1 hour and started to decline at 4 hour. Lowest tissue level was observed at 12 hours post dosing.
Reliability	:	(2) valid with restrictions short description but provides sufficient information to be taken into account
Flag	:	Critical study for SIDS endpoint

13.09.2004 (123) (124)

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 2100 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: none
Doses	:	1700, 2300, 3300, 4600 mg/kg bw
Method	:	other: see freetext ME
Year	:	1980
GLP	:	yes
Test substance	:	other TS: undiluted p-chlorotoluene; composition of the test substance: 97.6 % p-chlorotoluene, 2.4 % o-chlorotoluene
Method	:	single application by gavage to 5 rats/sex/dose, post application observation time: 14 d record of signs of intoxication; necropsy of all animals at the termination of the study LD50 calculation according to Weil (1952). Biometrics 8, 249
Remark	:	overt signs of toxicity: onset: 0.9 hours post application decreased motor activity, body tremors, cyanosis, salivation; mortality: 1700 mg/kg bw: 2/10 on day 1-2; 2300 mg/kg bw: 7/10 on day 1-2; 3300 mg/kg bw: 10/10 on day 1 4600 mg/kg bw: 10/10 on day 1-2 necropsy: all findings increased in severity with increasing dosage extreme salivation, signs of irritation to the gastrointestinal tract, lungs bright red
Reliability	:	(2) valid with restrictions in compliance with guideline, carefully reported
Flag	:	Critical study for SIDS endpoint

22.11.2004 (125)

Type	:	LD50
Value	:	= 2389 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	female
Number of animals	:	10
Vehicle	:	other: sesame oil
Doses	:	1600, 2000, 2240, 2500, 4000 mg/kg bw
Method	:	other: FDA-Guideline, see freetext ME
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	10 female rats/dose, body weights: 94-132 g 16 hours before application of the substance and 2 hours afterwards rats received no feed. lateron feed and water ad libitum observation time post application: 14 d animals that died during the experiment and survivors were macroscopically examined. LD50-value was calculated according to Lindner and Weber: Probit-Analysis
Remark	:	signs of toxicity: disorders of balance, accelerated breathing, and palmospasms Dosis//no of death rats/no of rats in test//time of death 1600 mg/kg bw// 0/10// - 2000 mg/kg bw// 0/10// - 2240 mg/kg bw// 4/10//d 2-6 2500 mg/kg bw// 6/10//d 1-3 4000 mg/kg bw//10/10//2.5hrs-d3 macroscopic evaluation of decedents and survivors yielded no pathological findings.
Reliability	:	(2) valid with restrictions female only
Flag	:	Critical study for SIDS endpoint

22.11.2004 (126)

Type	:	LD50
Value	:	ca. 2273 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	10
Vehicle	:	other: none
Doses	:	1, 1.5, 2.0, 2.5, 3.1 ml/kg bw (approx. 1070, 1610, 2140, 2680, 3320 mg/kg bw [d=1.0677g/l])
Method	:	other: see freetext ME
Year	:	1977
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	single oral application by gavage of undiluted substance to 10 male Wistar rats per dose; post exposure observation time: 14 d. Calculation of LD50 value according to Fink and Hund (1965) Arzneimittel-forschung 15, 624.
Result	:	signs of toxicity: palmospasms, sedation, at high doses flaccid paralysis of the extremities [d=1.0677g/l]

Dose[mg/kg bw] // No of rats dead / No of rats with signs of toxicity / No of rats used // time of death

1070 // 0/ 0/10 // -
1610 // 1/ 1/10 // d 2-3
2140 // 3/10/10 // d 2-3
2680 // 8/10/10 // d 2-3
3320 // 10/10/10 // d 2-3

LD50-value: 2.10 ml/kg bw

Reliability : (2) valid with restrictions
males only, no gross or histopathological evaluation
Flag : Critical study for SIDS endpoint
22.11.2004 (127) (128)

Type : LD50
Value : = 3600 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: single oral application by gavage (no further information)
Year : 1982
GLP : no
Test substance : other TS: p-chlorotoluene: no data on purity

Reliability : (4) not assignable
Documentation insufficient for assessment
12.08.2004 (129)

Type : LD50
Value : = 1920 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no data
Year : 1977
GLP : no
Test substance : other TS: p-chlorotoluene, no data on purity

Reliability : (3) invalid
not to identify in the original literature
23.11.2004 (130)

Type : LD50
Value : = 5500 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no data
Year : 1980
GLP : no data

Test substance : other TS: p-chlorotoluene, no data on purity

Remark : Signs of intoxications:
onset: 15-20 min post application: exciting, then depression, staggering gait, rough fur
Reliability : (4) not assignable
Documentation insufficient for assessment

22.11.2004 (131) (132)

Type : other: estimated median lethal dose (MLD)
Value : ca. 1901 mg/kg bw
Species : rat
Strain : Sprague-Dawley
Sex : male
Number of animals : 2
Vehicle : other: corn oil
Doses : 10 µl/kg bw (1%), 31.6 µl/kg bw (1%), 100 µl/kg bw (10%), 316 µl/kg bw (10%), 1000 µl/kg bw, 3160 µl/kg bw.
Method : other: see freetext ME
Year : 1964
GLP : no
Test substance : other TS: purity not given but cosidered to be free of impurities

Method : single oral application by gavage to 2 rats/dose either as a 1.0 or 10% volume/volume solution in corn oil or in undiluted form at dosage levels of 10 µl/kg bw (1%), 31.6 µl/kg bw (1%), 100 µl/kg bw (10%), 316 µl/kg bw (10%), 1000 µl/kg bw, 3160 µl/kg bw.
The animals were closely observed for mortality and toxic effects immediately and at 1, 4, 24, and 48 hours post application. At the end of the obseervation period necropsies were performed on all animals.
Remark : principal toxic effects:
depression, lacrimation, labored respiration, ataxia, tremors, depressed righting and placement reflexes and prostration;
mortality:
0/2 at a dosage level up to 1000 ul/kg bw (= ca. 1068 mg/kg bw) and
2/2 at a dosage level of 3160 ul/kg bw (= ca. 3374 mg/kg bw)
major necropsy findings:
congestion of the lungs, kidneys and adrenals and inflammation of the gastrointestinal tract at death; none following sacrifice of survivors

estimated median lethal dose: 1780 ul/kg bw
Reliability : (4) not assignable
number of animals to small, observation period to short, no exact data on purity

22.11.2004 (133)

Type : LD50
Value : = 1900 mg/kg bw
Species : mouse
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: single application by gavage (no further information)
Year : 1982
GLP : no
Test substance : other TS: p-chlorotoluene: no data on purity

Reliability : (4) not assignable
Documentation insufficient for assessment
12.08.2004 (129)

Type : LD50
Value : = 4000 mg/kg bw
Species : mouse
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no data
Year : 1980
GLP : no data
Test substance : other TS: no data on purity

Remark : Signs of intoxications:
onset: 15-20 min post application: exciting, then depression, staggering gait, rough fur
Reliability : (4) not assignable
Documentation insufficient for assessment
22.11.2004 (131) (132)

Type : other
Value :
Species : cat
Strain : no data
Sex : female
Number of animals : 2
Vehicle : other: sesame oil
Doses : 100 mg/kg bw
Method : other: see freetext ME
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Single oral application of 100 mg/kg bw diluted in sesame oil was given to 2 female cats after determination of normal values of hemoglobin, number of erythrocytes, leucocytes, hematocrit, blood picture, methemoglobin and heinz bodies. these data were then determined 1, 3, 7, 24 and 48 hours post application.
Result : 1 hour post application slight increase in Heinz bodies and 3 hours post application increase in leucocytes and neutrophiles and decrease in lymphocytes. 48 hours post application all values had returned to normal. All other parameters did not show any change.
Reliability : (4) not assignable
number of animals to small, no GLP only females used
22.11.2004 (134)

Type : LD50
Value : = 3750 mg/kg bw
Species : guinea pig
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no data

Year	:	1980
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, no data on purity
Remark	:	Signs of intoxications: onset: 15-20 min post application: exciting, then depression, staggering gait, rough fur
Reliability	:	(4) not assignable Documentation insufficient for assessment

22.11.2004 (131)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other: Inhalation-hazard test
Value	:	
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	6
Vehicle	:	other: air
Doses	:	see freetext ME
Exposure time	:	hour(s)
Method	:	other: see freetext ME
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	6 male Wistar rats/Exposure-period were exposed to saturated vapor atmosphere (whole body exposure) for 4, 5, 6 or 8 hours, respectively. Generation of the test atmosphere was carried out at room temperature (24-25 °C) by a stream of air being bubbled through the testsubstance. Concentration of the test atmosphere was determined. Animals were carefully observed during exposure and up to 14 days post exposure with feed and water ad libitum. After termination of the test animals were sacrificed and gross pathologically examined.
Result	:	Signs of intoxication: disturbed balance, slightly closed eye lids, lowered reflex answer to acoustic stimuli, tremor, tachypnea, hypopnea, anestesia, death occured from 5 hour-exposure test onwards ---4-hour-exposure, test atmosphere approximately 4182.6 ppm: No animal died during exposure; rats recovered 24 hours post exposure gross pathology: no finding ---5-hour-exposure, test atmosphere approximately 4103.4 ppm: 3/6 rats died within the first night post exposure; 3/6 rats survived and recovered 24 hours post exposure gross pathology: decedents showed lungs slightly red colored; survivors: no findings ---6-hour-exposure, test atmosphere approximately 3950.9 ppm: 3/6 rats died during exposure; 2/6 rats died within the first night post exposure; 1/6 rats died 24 hours later gross pathology: 5/6 dead rats had red colored lungs ---8-hour-exposure,

test atmosphere approximately 4304.2 ppm:
6/6 rats died within the first night post exposure
gross pathology: all rats had marked red lungs

Reliability : (2) valid with restrictions
although no LC50 value was calculated there is sufficient information to characterize the effects on animals when exposed by inhalation.

Flag : Critical study for SIDS endpoint

22.03.2005 (135)

Type	:	LC50
Value	:	= 26.9 mg/l
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Exposure time	:	
Method	:	other: no data
Year	:	1982
GLP	:	no
Test substance	:	other TS: p-chlorotoluene, no data on purity

Remark : exposure time not specified, probably 1 hour,
Log LC50 =1.43

Reliability : (4) not assignable
special study: documentation insufficient for assessment

22.11.2004 (136)

Type	:	LC50
Value	:	= 34 mg/l
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Exposure time	:	2 hour(s)
Method	:	other: inhalation period: 2 hours
Year	:	1982
GLP	:	no
Test substance	:	other TS: p-chlorotoluene: no data on purity

Reliability : (4) not assignable
Documentation insufficient for assessment

12.08.2004 (129)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	2
Vehicle	:	other: none
Doses	:	2000 mg/kg bw
Method	:	other: see freetext ME
Year	:	1980

GLP : yes
Test substance : other TS: undiluted p-chlorotoluene; composition of the test substance: 97.6 % p-chlorotoluene, 2.4 % o-chlorotoluene

Method : 2000 mg/kg bw undiluted TS was applied to shaved (abraded and intact) areas of the back of each of 2 rabbits/sex und covered under occlusive conditions (gauze pad, rubber dam and several wrappings of Elastoplast) for 24 hours. Afterwards the restrainer and wrappings were removed and the TS was removed with a wet towel. pst exposure observation time 14 days, death and surviving animals were necropsied. LD50 value was calculated according tzo the method of Weil (1952).
Evaluation of skin reaction:
Erythema:
0 -none; 1 - slight (barely perceptible); 2 - moderate (well defined); 3 - severe (beet red)
Edema:
0 - none; 1 - slight (barely perceptible to well defined by definite railing); 2 - moderate (raised approximately 1 mm); 3 - severe raised more than 1 mm)
Atonia (not including eschar area):
0 - normal; 1 - slight (slight impairment of elaxticity); 2 - moderate (slow return to normal); 3 - marked (no elasticity)
Desquamation:
0 - none; 1 - slight (slight scaling); 2 - moderate (scabs and flakes); 3 - marked (pronounced flaking with denuded areas)
Fissuring:
0 - none; 1 - slight (definite cracks in epidermis); 2 - moderate (cracks in dermis); 3 - marked (cracks with bleeding)
Eschar
N = no; Y = yes

Result : no death occurred; 1 animal suffered from diarrhea; all other were unremarkable

skin reactions:
abraded skin:
-----male:
no erythema, no edema no atonia no desquamation, no fissuring and no eschar formation
------female:
erythema: score: 1 from d3-13; d14 score 0
edema: score: 1 from d3-13; d14 score 0
atonia: score 1 from d6-8, score 2 from d9-10, score 1 d11-13; d14 score 0
Fissuring: score 1 from d5-7; score 2 d8-13; score 1 d14
Eschar formation from d9 onwards and from d11 exfoliation

intact skin:
-----male
Erythema from d10-14 score 1
edema from d4-14 score 1
atonia from d5-8 score 1; d9-12 score 2; d13-14 score 1
Desquamation from d13-14 score 1
Fissuring from d5-13 score 2; d14 score 1
Eschr formation fron d 9 onwards and exfoliation at d 14
-----female
no erythema
edema: from d4-9 score 1
atonia: from d7-9 score 1; d9-14 score 0
Desquamation: from d10-14 score 1
Fissuring: at d 5 score 2; d 6-11 score 1; from d 12 score 0
no eschar formation and no exfoliation

At necropsy,
there were no remarkable findings in males whereas females showed dark red mottled lungs.

Reliability : (2) valid with restrictions
no typical acute toxicity study but provides sufficient information

Flag : Critical study for SIDS endpoint

22.11.2004 (137)

Type : LD50
Value : > 5000 mg/kg bw
Species : rat
Strain : Wistar
Sex : female
Number of animals : 6
Vehicle : other: undiluted
Doses : undiluted testsubstance: 5000 mg/kg bw
Method : other: FDA-Guideline, see freetext ME
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : 6 female SPF-Wistar rats, body weight: 170-192 g
Single application of 5000 mg/kg bw of the shaved back, covered by alu foil and elastic bandage for 24 hours. Afterwards the treatment area was carefully cleaned with warm water. Post exposure observation time was 14 days. At termination rats were sacrificed and pathologically evaluated.

Remark : reduced food consumption during the duration of exposure
(24 hours) and little weight loss immediately after ap-
plication were observable; no deaths occurred; no other signs of intoxication were observed; pathological evaluation revealed no finding.

Reliability : (2) valid with restrictions
females only, no GLP

Flag : Critical study for SIDS endpoint

10.08.2004 (138)

Type : LD50
Value : > 5000 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 5
Vehicle : other: none
Doses : 5000 mg/kg bw
Method : other: see freetext ME
Year : 1977
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : 5 Wistar rats /sex received single dermal application of undiluted test substance: 5000 mg/kg bw and covered with a bandage. The observation time was 14 days.

Result : No animal died during the experiment, but all animals displayed symptoms of intoxication (details not mentioned). The treatment area showed corrosive effects.

Reliability : (2) valid with restrictions
short but sufficient information

Flag : Critical study for SIDS endpoint

09.09.2004 (127)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	other: see freetext ME
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6
Vehicle	:	other: sesame oil
PDII	:	
Result	:	not irritating
Classification	:	
Method	:	other: FDA-Guideline, see also freetext ME
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : 6 rabbits with shaved flancs (each site with intact and scarificed areas) received gauze patches containing 0.5 ml undiluted testsubstance (right flanc) or a 10 % sesame oil solution (left flanc) fixed with a tape and PVC foil (occlussive dressing) for 24 hours.
Reading was done immediately after removal of the dressing(24 hour value) and 48 hrs and 72 hrs after start of the experiment.
Evaluation of the findings according to Federal Register 38,No.187,1973, § 1500.41

Result : undiluted Testsubstance:
----intact area, reading:
24 hrs: 2/6 with edema, score 1 of max 3; no erythema
48 hrs: 1/6 with edema, score 1 of max 3; no erythema
72 hrs: 0/6 with edema; no erythema
----scarificed area, reading:
24 hrs: 3/6 with edema, score 1 of max 3; no erythema
48 hrs: 0/6 with edema; no erythema
72 hrs: 0/6 with edema; no erythema

irritation index (24 and 72 hours): 0.21 of max 8.0

10% sesame oil solution:
-----intact area, reading:
24 hrs: 1/6 with edema, score 1 of max 3, no erythema
48 hrs: 0/6 with edema, no erythema
72 hrs: 0/6 with edema, no erythema
-----scarificed area
24 hrs: 0/6 with edema, no erythema
48 hrs: 0/6 with edema, no erythema
72 hrs: 0/6 with edema, no erythema

irritation index (24 and 72 hours): 0.04 of max 8.0

Reliability : (2) valid with restrictions
in compliance with guideline

Flag : Critical study for SIDS endpoint

23.11.2004 (139)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	24 hour(s)

Number of animals : 6
Vehicle : other: none
PDII :
Result : slightly irritating
Classification :
Method : other: exposure time: 24 hours; site of application: back (two test sites selected per rabbit in the clipped area: one is left intact and one is abraded); dose: 0.5 ml/test site; observation period: 48 h after exp.: also freetext ME
Year : 1980
GLP : yes
Test substance : other TS: undiluted p-chlorotoluene; composition of the test substance: 97.6 % p-chlorotoluene, 2.4 % o-chlorotoluene

Method : reading directly after removing the wrap (24 hour reading) and 48 hours later (72 hour reading).
Draize Skin reactions:
erythema amd eschar formation
score 0: no erythema
score 1: very slight erythema barely perceptible)
score 2: well defined erythema
score 3: moderate to severe erythema
score 4: severe erythema (beet redness) to slight eschar formation (injuries in depth)

edema formation:
score 0: no edema
score 1: very slight edema (barely perceptible)
score 2: slight edema (edges of area well defined by definite raising)
score 3: moderate edema (raised approximately 1 mm)
score 4: severe edema (raised more than 1 mm and extending beyond the area of exposure)

Result : -----intact skin :
--erythema:
score 1 in 6/6 rabbits at 24-hour reading and in 4/6 rabbits at the 72-hour reading
--edema:
0/6 rabbits at 24-hour reading and in 0/6 rabbits at the 72-hour reading
Corrosivity was not observed.

-----abraded skin:
--erythema:
score 1 in 6/6 rabbits at 24-hour reading and in 4/6 rabbits at the 72-hour reading
--edema:
0/6 rabbits at 24-hour reading and 0/6 rabbits at the 72-hour reading
Corrosivity was not observed.

Irritation index (24 and 72 hours): 0.85 of max 8.0
Reliability : (2) valid with restrictions
post exposure observation time was rather short
Flag : Critical study for SIDS endpoint
23.11.2004 (140)

Species : rabbit
Concentration : undiluted
Exposure : Semiocclusive
Exposure time :
Number of animals : 1
Vehicle : other: none

PDII	:	
Result	:	corrosive
Classification	:	
Method	:	other: see freetext ME
Year	:	1977
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	500 µl/ 1 animal/exposure time was applied to one inner surface of the ear per animal per exposure time; exposure time was 1,2 and 4 hours. The testsubstance was fixed by a plaster. After exposure the treated areas were cleaned with water (soap and plant oil). The post exposure observation time was 7 days.
Result	:	---Following the 4-hour exposure slight erythema and corrosive effects were observed: redness score 1 of max 4 for about 7 days corrosive: score 1 of max 3 ---Exposure time: 2 hours redness score 2 of max 3 for up to 7 days ---Exposure time: 1 hour redness score 1 of max 3 for up to 7 days
Reliability	:	(3) invalid only 1 animal/reading, observation time only 7 days

14.01.2005 (127)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Semiocclusive
Exposure time	:	24 hour(s)
Number of animals	:	2
Vehicle	:	other: none
PDII	:	
Result	:	not irritating
Classification	:	
Method	:	other: see freetext ME
Year	:	1977
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	500 µl/animalwas applied to one inner surface of the ear per animal; exposure time was 24 hours. The testsubstance was fixed by a plaster. After exposure the treated areas were cleaned with water (soap and plant oil. The post exposure observation time was 7 days.
Result	:	RABBIT 1: Following the 24-hour exposure slight erythema was observed: redness score 1 of max 4 At the second day post reading skin of the ear had returned to normal appearance RABBIT 2: no skin reaction was reported
Reliability	:	(2) valid with restrictions at least 3 animals should be used, observation time only 7 days

23.11.2004 (128)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	24 hour(s)
Comment	:	rinsed after (see exposure time)
Number of animals	:	6
Vehicle	:	none
Result	:	slightly irritating
Classification	:	
Method	:	other: FDA-Guideline, see freetext ME
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : 0.1 ml of the undiluted Ts was applied into the conjunctival sac of one eye of each of the 6 rabbits. reading was carried out1, 7, 24, 48 and 72 hrs and 7 and 14 days post application. After the 24 hour reading the eyes were rinsed and additionally examined by addition of 1 drop of fluorescein.
The total observation period was 14 days.
The findings were evaluated according to federal Register 38, No.187, 1973

Result : Number of animals with changes:
cornea // iris // conjunc. redness // conjunc. swelling
1 hr : 0/6 //0/6 //6/6(grade 1 of 3)// 4/6(grade 1 of 4)
7 hrs: 0/6 //0/6 //6/6(grade 1 of 3)// 3/6(grade 1 of 4)
24 hrs: 0/6 //0/6 //6/6(grade 1 of 3)// 3/6(grade 1 of 4)
48 hrs: 0/6 //0/6 //4/6(grade 1 of 3)// 3/6(grade 1 of 4)
72 hrs: 0/6 //0/6 //3/6(grade 1 of 3)// 3/6(grade 1 of 4)
7 d : 0/6 //0/6 //0/6 // 0/6
14 d : 0/6//0/6//0/6 // 0/6

Total irritation index is not given.

Reliability : (2) valid with restrictions
in compliance with guideline, but no GLP

Flag : Critical study for SIDS endpoint

23.11.2004 (139)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	
Comment	:	other: eyes of 3 rabbits were rinsed, 6 rabbits eyes were not rinsed
Number of animals	:	9
Vehicle	:	none
Result	:	slightly irritating
Classification	:	
Method	:	other: dose: 0.1 ml/animal, observation period: 7 or 14 days; the eyes of 3 animals were rinsed with water(group 2) ca. 5 sec. after dosing, the eyes of further 6 animals (group 1) remained unwashed.
Year	:	1980
GLP	:	yes
Test substance	:	other TS: undiluted p-chlorotoluene; composition of the test substance: 97.6 % p-chlorotoluene, 2.4 % o-chlorotoluene

Method : Reading was performed according to Draize J.H. et al (1944) J. Pharm Exp. ther. 82.337-390
time of reading: day 1, 2, 3, 7, 14

Result : Group 1:
6 rabbits , no rinse
1 rabbit was found dead on day 5

Cornea and iris showed no pathological changes in any of the rabbits
Conjunctivae was affected in 6/6 rabbits
Redness (6/6 rabbits):
score 2 (more diffuse deeper crimson red, individual vessels not easily discernible) and score 1 (vessels definitela injected above normal) from d1-d3 or d7; at d 14 conjunjctiva had returned to normal.
Chemosis (6/6 rabbits):
Score 2 (obviously swelling with partial eversion of the lids) and score 1 (Any swelling above normal includes nictitating membrane)from d1-2 or d 3, afterwards no swelling was observed
Discharge:
2/6 rabbits d1-d2 or d7: score 1 (any amount different from normal), afterwards no discharge was observed

Maximum score (day 1) = 5.7 of 110

Group 2:
3 rabbits, rinsing
Cornea and iris were not affected by treatment
Conjunctiva was affected in 3/3 rabbits
Redness (3/3 rabbits):
Score 1 and score 2 from d1- d3 or d7; at d 14 conjunctiva had returned to normal.
Chemosis (3/3 rabbits):
Score 1 from d1-d3; afterwardsno swelling was observed
Discharge: 1/3 rabbit score 1 at d1, afterwards no discharge was observed.

Maximum score (day 1 and 2) = 4.7 of 110

Reliability : (2) valid with restrictions
in compliance with guideline

Flag : Critical study for SIDS endpoint

23.11.2004 (141)

Species : rabbit
Concentration : undiluted
Dose : .1 ml
Exposure time :
Comment : no data
Number of animals : 2
Vehicle : none
Result : slightly irritating
Classification :
Method : other: 100 µl (= 107 mg)/animal was applied into the conjunctival sac of one eye of each of 2 rabbits, observation period: 7 days
Year : 1977
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : 1 HR POST TREATMENT:
RABBIT 1: redness of conjunctiva score 2(max 3), edema score 2(max 4)
RABBIT 2: redness of concunctiva score 2(max 3) and edema score 2
24 HR POST TREATMENT:
RABBIT1: redness of conjunctiva score 2(max 3), edema score 1(max 4)
RABBIT 2: redness of conjunctiva; score 2(max 3), edema score 1(max 4)
2 DAYS POST TREATMENT:
RABBIT 1: redness of conjunctiva score 1(max 3), edema was not

observed
RABBIT 2: redness of conjunctiva score 2(max 3) edema score 1(max 4)
3 DAYS POST TREATMENT:
RABBIT 1: no signs of irritation
RABBIT 2: redness of conjunctiva score 1(max 3), no edema

From day 4 both rabbits did not show any signs of occular irritation.

Reliability : (2) valid with restrictions
at least 3 animals should be used, observation time only 7 days

14.09.2004 (127)

Species : rabbit
Concentration : undiluted
Dose : .1 ml
Exposure time :
Comment : no data
Number of animals : 2
Vehicle : other: none
Result : not irritating
Classification :
Method : other: 100 µl (= 107 mg)/animal was applied into the conjunctival sac of one eye of each of 2 rabbits, observation period: 7 days
Year : 1977
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result :

24 HR POST TREATMENT:
RABBIT1: redness of conjunctiva score 2(max 3)
RABBIT 2: redness of conjunctiva; score 2(max 3)
2 DAYS POST TREATMENT:
RABBIT 1: redness of conjunctiva score 1(max 3)
RABBIT 2: redness of conjunctiva score 1(max 3)

From day 3 both rabbits did not show any signs of occular irritation.

Reliability : (2) valid with restrictions
at least 3 animals should be used, observation time only 7 days

14.09.2004 (128)

5.3 SENSITIZATION

Type : Guinea pig maximization test
Species : guinea pig
Concentration : 1st: Induction 5 % intracutaneous
2nd: Induction undiluted occlusive epicutaneous
3rd: Challenge other: see freetext ME semiocclusive
Number of animals : 20
Vehicle : other: Cremophor E1 in physiological saline
Result : sensitizing
Classification :
Method : other: OECD Guide-line 406, see freetext ME
Year : 1992
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : 20 male guinea pigs/test group:
vehicle control: 10 male guinea pigs
body weight: 314-409 g

Dosages were chosen based on the results of dose-finding experiments
Experimental procedure:
1. Induction: Intradermal application into the back of 0.1 ml p-Chlorotoluene;
one week later:
2. Induction: topical application of a plaster containing 0.5 ml undiluted p-chlorotoluene which was fixed by alu fole (occlussive condition)
3 weeks after intradermal induction:
Challange with 0.5 ml of 12%- and 0.5 ml of 25%-solution of p-chlorotoluene by dermal application, covered with a plaster, for 24 hours.
Afterwards treatment areas were rinsed with physiological saline-solution.
Evaluation:
reading was carried out 48 and 72 hours post start of the challenge;
evaluation by comparison of the reacting animals between test and control group.

Result : no mortality occurred
body weight development was comparable between test and control animals
Challenge with 25 % solution, positive reactions:
48 hour reading: 14/20 and 72 hour-reading 7/20
Challange with 12 % solution, positive reactions:
48 hour reading: 3/20 and 72 hour reading 1/20
Control animals showed no reaction at any time point.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
19.07.2004 (142)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	14 d
Frequency of treatm.	:	daily, 7 d/w
Post exposure period	:	no
Doses	:	0, 200, 600 or 1800 mg/kg bw/d in corn oil
Control group	:	yes, concurrent vehicle
NOAEL	:	= 600 mg/kg bw
Method	:	other: see freetext ME
Year	:	1990
GLP	:	no data
Test substance	:	other TS: the purity was determined to be greater than 98 %; 1-Chloro(4-chloromethyl)benzene at 0.5 % was identified by GC-MS as the only impurity

Method : dose-finding study for a 90-day study:

ANIMALS AND HOUSING:
10 rats/sex/group. Sprague-Dawley, 46 days of age at initiation,
Bodyweight at initiation: males: app. 227-276g; females: app. 153-195g
Acclimisation period: 2 weeks
food and tap water ad libitum
room temperature: 22-24°C; humidity: 40-60 %; 12 hour light-dark cycle
MATERIAL:
test solutions were prepared fresh weekly;
dosing volume: 3 ml/kg bw

SACRIFICE:
the day following completition of treatment

ANIMAL OBSERVATIONS:
for signs of mortality and morbidity, for overt signs of toxicityand clinical signs (general apprarance, behavior, excretion, respiration, respiration, skin pelage, eyes), physical examination weekly, abnormalities in housing, food or water intake
TERMINAL EVALUATION:
blood and urine collection prior necropsy
-----Heamtology:
leucocyte (differentials and cell morphology), erythrocyte, hematocrit, hemoglobin,
-----Clinical chemistry:
sodium, potassium, total protein, albumin, calcium, total bilirubin, creatinine, aspartate aminotransferase (AST), alanine aminotransferase(ALT), alkaline phosphatase(ALP), lactate dehydrogenase(LDH), and blood urea nitrogen(BUN),
-----Urinalysis
pH, glucose, protein, bilirubin, occult blood, urobilinogen

TERMINAL NECROPSY:
-----body weight determination
-----organ weight determination:
liver, kidneysm spleen, adrenal glands, thymus, brain, heart, lung, testes with epididymides, ovaries
-----Histopathological evaluation:
all animals of the 600-mg-group, and five animals /sex of the corn oil controls:
adrenals, thyroid, esophageusmtrachea, larynx, heart, spleen liver, kidney, stomach, duodenum, jejunum, colon, pancreasm and gross lesions

STATISTICAL ANALYSIS
Levene's test on homogenicity, analysis for variance, Dunnett's t-test

Result : DOSE-FINDING STUDY
Animal data were not shown

600 mg/kg bw/d:
ANIMAL OBSERVATION
males: decreased body weight gain and decreased food consumption (the authors state that the decreased body weight may be related to the decreased food consumption)
TERMINAL EXAMINATION:
---Clinical chemistry, hematology, urinalysis:
(data not shown)
no treatment-related effects were noted;
---Necropsy - histopathological evaluation:
organ weights:
comparison between dosed animals and control animals revealed a number of differences which were considered related to a lower terminal body weight (data not shown).
gross- and histopathology:
no treatment-related lesions were identified

1800 mg/kg bw/d, males and females:
ANIMAL OBSERVATION:
death of 8/10 animals for both, males and females, during the study;
Signs of intoxication: prostration, salivation, tremors;
decrease in body weight and body weight gain; food consumption decreased for males;
TERMINAL EXAMINATION:

---Clinical chemistry, hematology, urinalysis:
no treatment-related effects were noted;
---Necropsy - histopathological evaluation:
organ weights, gross and histopathology:
no findings were reported

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

26.11.2004 (143) (144)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	90 d
Frequency of treatm.	:	daily, 7 d/w
Post exposure period	:	no
Doses	:	0, 50, 200 or 800 mg/kg bw/d in corn oil
Control group	:	yes, concurrent vehicle
NOAEL	:	= 200 mg/kg bw
Method	:	other: see freetext ME
Year	:	1990
GLP	:	no data
Test substance	:	other TS: the purity was determined to be greater than 98 %; 1-Chloro(4-chloromethyl)benzene at 0.5 % was identified as the only impurity

Method :

DOSAGE:
Doses were choses on the basis of a preliminary dose-range finding study.
ANIMALS and HOUSING:
10 rats/sex/group. Sprague-Dawley, 46 days of age at initiation,
Bodyweight at initiation: males: 227.3-276.1g; females: 153.2-195.8 g
Acclimisation period: 2 weeks
food and tap water ad libitum
room temperature: 22-24°C; humidity: 40-60 %; 12 hour light-dark cycle
MATERIAL:
test solutions were prepared fresh weekly;
dosing volume: 3 ml/kg bw
SACRIFICE:
the day following completition of treatment

ANIMAL OBSERVATIONS:
for signs of mortality and morbidity, for overt signs of toxicityand clinical signs (general apprarance, behavior, excretion, respiration, respiration, skin pelage, eyes), physical examination weekly, abnormalities in housing, food or water intake
TERMINAL EXAMINATION:
-----Ophthalmoscopic examination
and
-----Hemtology:
blood collection prior necropsy: leucocyte (differentials and cell morphology), erythrocyte, hematocrit, hemoglobin,
-----Clinical chemistry:
sodium, potassium, total protein, albumin, calcium, total bilirubin, creatinine, aspartate aminotransferase (AST), alanine aminotransferase(ALT), alkaline phosphatase(ALP), lactate dehydrogenase(LDH), and blood urea nitrogen(BUN),
-----Urinalysis:
urine collection prior necropsy: pH, glucose, protein, bilirubin, occult blood, urobilinogen

TERMINAL NECROPSY:
-----body weight determination
-----organ weight determination:
liver, kidneys spleen, adrenal glands, thymus, brain, heart, lung, testes with epididymides, ovaries
-----Histopathological evaluation:
all animals of the 800-mg-group, and five animals/sex of the corn oil controls:
adrenals, thyroid, esophageus, trachea, larynx, heart, spleen liver, kidney, stomach, duodenum, jejunum, colon, pancreas, testes with epididymides and ovaries and gross lesions

STATISTICAL ANALYSIS:
Levene's test on homogenicity, analysis for variance, Dunnett's t-test

Remark : see also section 5.8.3
Result : 800 mg/kg bw/d:

-----ANIMAL OBSERVATIONS
mortality: death of 4/10 males and 2/10 females
signs of intoxication: languid behabior, prostration, sensitivity to touch, tremors, epistaxis, wheezing, dyspnea and/or polypnea, death
food consumption comparable to controls
body weight:
males: initiation to week 13: statistically significant decreased body weight gain, shown in a figure, mean terminal body weight was not significantly decreased: 489 g versus 571 g of control
females: body weight gain: not significnant different to control; mean terminal body weight was significantly decreased: 282 g vers. 321 g of controls
-----TERMINAL EVALUATIONS
ophthalmoscopic evaluation: no treatment-related effects observed
--Hematology:
values comparable to control values (data not shown)
--Clinical chemistry:
(significantly changed values vers. controls)
males:
BUN (33 vers. 11 mg/dl), Creatinine (1.0 vers. 0.5 mg/dl),
ALP (136 vers. 87 IU/L), Bilirubin (0.23 vers. 0.16mg/dl)
Sodium (139 vers. 143 mEq/L)
females:
female values comparable to respective control values
--Urinalysis:
pH-values:
significantly decreased in males (6.42 vers. 7.50 in controls) and in females (6.50 vers. 7.25 in controls)
all other parameteres were comparable to the respective control parameters (data not shown)
-----NECROPSY:
--Organ weights:
absolute organ weights [significant changes in organ-to-body weight ratios(%bw)] versus controls
-males:
brain: 2.18g [0.456 %bw] vers. 2.18g [0.386 %bw],
liver: 15.11g [3.134 %bw] vers. 14.97g [2.616 %bw]
kidneys: 4.12g [0.878 %bw] vers. 3.57g [0.628 %bw]
adrenal: 0.076g(sign.)[0.0164 %bw] vers. 0.059g[0.0104 %bw]
testes: no relevant changes:
control-high dose (rel weights): 5.26g (0.931 %bw) - 4.96g (1.016 %bw)

-females:
brain: 2.09g [0.742 %bw] vers. 2.05g [0.643 %bw]
liver: 9.82g [3.481 %bw] vers. 8.83g [2.748 %bw]
lungs: 1.24g(sign.)[0.439 %bw(not sign.)] vers. 1.41g [0.441 %bw] relative weights were unaffected
kidneys: 2.35g [0.835 %bw] vers. 2.22g [0.694 %bw]
heart: 1.05g [0.370 %bw] vers. 1.08g [0.377 %bw]
ovaries: no relevant changes:
control-high dose (rel weights): 0.163g (0.0512 %bw) - 0.0547g (0.0745 %bw)
-----gross- and histopathology:
--kidneys:
males:
depressed areas, pale areas, mottled appearance, dilated renal pelvis, and/or granular/pitted/rough texture,
males and females:
chronic progressive nephropathy (degeneration and regeneration of the tubular epithelial cells, interstititial fibrosis, mononuclear cell infiltrates) in 10/10 treated and in 2/10 control males and in 9/10 treated females but not in control females
--liver:
males and females:
centrilobular hypertrophy of hepatocytes
--adrenal gland:
males and females:
hyperplasia of the zona fasciculata
--stomach:
males and females:
dark areas in the glandular portion, minimal mucosal erosion in the glandular portion in 2/10 males and 3/10 females
--testes and ovaries:
no pathological findings.

200 mg/kg bw/d:
-----ANIMAL OBSERVATIONS
no mortality, no signs of intoxication were reported
food consumption comparable to controls
body weight development comarable to respective controls, including terminal body weights
-----TERMINAL EVALUATIONS
ophthalmoscopic evaluation: no treatment-related effects observed
--Hematology:
values comparable to control values (data not shown)
--Clinical chemistry:
values comparable to control values
--Urinalysis
pH-values:
significantly decreased in males (6.80 vers. 7.50 in controls) and in females (6.35 vers. 7.25 in controls)
all other parameteres were comparable to the respective control parameters (data not shown)
-----NECROPSY:
--Organ weights:
values comparable to respective control values
--gross- and histopathology:
stomach:
males and females:
dark areas in the glandular portion,
female only: 1/10 with minimal mucosal erosion in the glandular portion

50 mg/kg bw/d:

-----ANIMAL OBSERVATIONS
no mortality, no signs of intoxication were reported
food consumption comparable to controls
body weight development comarable to respective controls, including terminal body weights
-----TERMINAL EVALUATIONS
ophthalmoscopic evaluation: no treatment-related effects observed
--Hematology:
values comparable to control values (data not shown)
--Clinical chemistry:
values comparable to control values
--Urinalysis
pH-values:
increased in males (7.75 vers. 7.50 in controls) and decreased in females (6.85 vers. 7.25 in controls)
all other parameteres were comparable to the respective control parameters (data not shown)
-----NECROPSY:
--Organ weights:
female:
lungs abs weight significantly decreased when compared to the respective control:1.28g vers. 1.41g; relative weights were unaffected
all other values of organ weights were comparable to respective control values
--gross- and histopathology:
stomach:
males and females:
dark areas in the glandular portion,
female only: 1/10 with minimal mucosal erosion in the glandular portion

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
05.08.2005 (143) (144)

Type : Sub-acute
Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : gavage
Exposure period : 29 d
Frequency of treatm. : daily, 7 d/w
Post exposure period : no
Doses : 0, 50, 200 or 800 mg/kg bw/d dissolved in Polyethylenglycol 400
Control group : yes, concurrent vehicle
NOAEL : = 200 mg/kg bw
Method : OECD Guide-line 407 "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-d Study"
Year : 1991
GLP : yes
Test substance : other TS: purity: 99.8 %

Method : TEST SPECIES AND ANIMAL HUSBANDARY.
-Age at start of the study: 7-8 weeks
-Number of rats: 5 m/5 f per group
-Animal maintenance: air-conditioned rooms,
-----groups of 5 rats/cage
-Acclimatisation: 7 days
-Room temperature: 22 °C
-Relative Humidity: 50 %
-Lighting time: 12 hours daily
-Food: rat diet ad libitum

-Water: tap water ad libitum
ADMINISTRATION / EXPOSURE
-Dose selection based on priliminary experiments
-Vehicle: polyethyleneglycole 400
-Total volume applied: 5 ml/kg bw

CLINICAL OBSERVATIONS AND FREQUENCY
-Clinical signs: twice daily
-Body weight: deaily just before application of TS
-Food consumption: once per week
-Water consumption: once per week
-Ophthalmoscopic examination: weekly

CLINICAL LABORATORY EXAMINATIONS
-Hematology / Clinical chemistry/Urinalysis: at week 4 of the study on all animals
-HEMATOLOGY:
Differential blood picture, Erythrocyte count (Erys), hemoglobin (HG), hematocrit (HK), mean cellular volume (MCV), mean cellular hemoglobin (MCH), mean cellular hemoglobin concentration (MCHC), reticulocyte count, Leucocyte count (Leucos), Thromocyte count (Thrombos), Thromboplastin coagulation time
-CLINICAL CHEMISTRY:
Sodium, Potassium, Calcium, Chloride, Inorganic phophorus, glucose, bilirubin, Cholesterol, Creatinine, total protein, Urea, albumin, triglycerides, Alkaline phosphatase (AP), Alanine aminotransferase (ALAT/GPT), Aspartate aminotransferase (ASAT/GOT)
-URINALYSIS:
-a few days before determination of hematology values:
blood, ketone bodies, pH-value, glucose, protein, bilirubin, urobilinogen, sediment, specific weight, volume, protein

--Animals that died during treatment time were evaluated gross-pathologically and changes were noted.
--After termination of the feeding period all surviving animals were sacrificed and gross and histopathologically examined.

NECROPSY:
ORGAN WEIGHTS:
brain, heart, lung, liver, kidneys, spleen, adrenals, ovaries, testes
GROSS PATHOLOGY:
adrenals, aorta, auricles (tattooed), bone marrow of femur and sternum, conchae, epididymis, esophagus, extraorbital lacrimation gland, eyes, eye lids, femur with knee joint,
Hardrian gland, heart, intestine (colon, caecum, jejunum, ileum duodenum, rectum, remainder), kidneys, larynx, liver, lung, lymph nodes (mesenteric and mandibular), mammary gland, muscles (femur), nervus ischiadicus, nervus opticus,
ovaries, oviduct, pancreas, pituitary gland, prostate gland, salinary gland, seminal vesicles, skin, spinal cord (cervical, thoracal, lumbal), spleen, sternum, stomach,
testes, thyroid gland with parathyroids, tongue, trachea, thymus if present, ureters, urethra, urinary bladder,
uterus, vagina, Zymbal's gland
HISTOPATHOLOGY:
all control animals and all high dosed animals,
heart, liver, lung, spleen, kidneys, adrenals
but also macroscopically changed organs of animals in all dose groups

-STATISTICS:
U-test according to Mann and Whitney,

Wilcoxon test

Remark : see also section 5.8.3

Result : CLINICAL SIGNS OF INTOXICATION:
50 mg-group:
without any signs
200 mg-groups:
1/5 male: rough fur, reduced condition, difficulties in breathing
800 mg-group:
1/5 males (reduced body weight at week 3) and 1/5 females: both: rough fur, reduced condition, difficulties in breathing and distended abdomen
1/5 male and 4/5 females with transient increased salivation
MORTALITY OR MORIBUND SACRIFICED:
1/5 control male; 800 mg-group: 2/5 males, 1/5 female
BODYWEIGHT DEVELOPMENT:
females, all dose groups: comparable with control females
males:
50 mg-group. comparable with control males
200 mg-group: 1/5 reduced body weight gain (not treatment related because all other rats had normal weight gain and only this animal showed changes in clinical laboratory examination)
800 mg-group: body weights in general lower than that of control males
FOOD AND WATER INTAKE:
was comparable in all groups

CLINICAL LABORATORY EXAMINATIONS:
----HEMATOLOGY
200 mg-group, male:
significantly lowered mean thrombocyte count when compared to control value: 837 10[exp9]/l versus 1119 10[exp9]/l
(historical control range: 774-1295 10[exp9]/l)
200 mg-group female:
significantly lowered mean MCH when compared to control: 17.7 pg versus 18.3 pg
(HISTORICAL CONTROL RANGE: 15.9-20 pg)
all other parameters were comparable to control parameters
----CLINICAL CHEMISTRY
Enzymes were comparable between treated males and females and the respective control animals.
Electrolytes values were comparable between treated males and females and controls except the mean value for Calcium in males of the 50 mg-group: 2.49 mmol/l versus 2.57 mmol/l of control (significant, but:
HISTORICAL CONTROL VALUES: 2.43-2.68 mmol/l)
200 mg-group, females: significantly increased mean protein
value when compared to control: 63.9 g/l versus 60.9 g/l

All other clinical chemistry parameters were comparable to the respective controls. Therefore the reported changes which were not dose-related, were regarded to be incidential.

----URINALYSES
Urinary excretion rate and density was comparable between treated groups and respective control groups.
200 mg-group, male:
mean protein content was significantly lowered:
4.4 mg versus 8.4 mg
(HISTORICAL CONTROL RANGE: 3-23 mg)
200 mg-group, females:
mean protein excretion was significantly lower than in the respective control: 0.16 g/l versus 0.34 g/l
(mean historical control range: 0.05-0.45 g/l)

NECROPSY
----ORGAN WEIGHTS
800 mg-group, male and female: mean value of relative and absolute liver weight increased (female,n=5: absolute weight(sign.): 7710 mg versus 7125 mg - relative weight (sign.): 4702 versus 4192; male n=3: 12619 mg versus 11351 mg - relative weight: 5052 versus 4282)
----HISTOPATHOLOGY
800 mg-group, female:
1/5 with liver changes including moderate, inflammatory-cellular, focal infiltrates in the
liver and vacuoles in the hepatocytes

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
05.08.2005 (145)

Type : Sub-acute
Species : rat
Sex : no data
Strain : no data
Route of admin. : oral unspecified
Exposure period : 2 months
Frequency of treatm. : daily
Post exposure period : no data
Doses : 0.01 or 0.1 x LD50/d (= 55 or 550 mg/kg bw/d)
Control group : no data specified
Method : other: p-chlorotoluene was given probabely by gavage as oily solution to 150 rats (no further data)
Year : 1981
GLP : no
Test substance : other TS: p-chlorotoluene was administered as oily solution, no data on purity

Result : At a dose level of 550 mg/kg bw/d the following signs of toxicity were observable: stimulation of the haematopoiesis, central nervous depression, disturbances of the hepatic and renal functions, disturbed immune reactions; the administration of 55 mg/kg bw/d induced clearly weaker signs of toxicity (no further data)
Reliability : (4) not assignable
insufficient documentation:
26.11.2004 (131) (132)

Type : Sub-chronic
Species : rat
Sex : no data
Strain : no data
Route of admin. : oral unspecified
Exposure period : 6 months
Frequency of treatm. : daily
Post exposure period : no data
Doses : 0.01, 0.1 or 1 mg/kg bw/d
Control group : no data specified
NOAEL : = .01 mg/kg bw
Method : other: p-chlorotoluene was administered as oily solution, 190 rats were used (no further data)
Year : 1981
GLP : no

Test substance	:	other TS: p-chlorotoluene was administered as oily solution, no data on purity
Result	:	0.01 mg/kg bw/d: no toxic effects observable 0.1 mg/kg bw/d: about the same effects as observed after administration of 1.0 mg/kg bw/d, but less marked (see below) 1.0 mg/kg bw/d: changes of haematological parameters (increased haemoglobin content, increased red cell counts and leucocyte counts); changes of the phagocytic reaction of the neutrophils; decrease in the ascorbic acid content of the suprarenal bodies; indications of a disturbed hepatic function: changed enzyme activities in the blood (cholin-esterase, aspartate aminotransferase, alanine aminotrans-ferase), decreased blood-urea level, disturbances of the carbohydrate metabolism, markedly decreased glycogen con-tent of the hepatocytes; effects on the central nervous system: increased activity of cholinesterase and increased content of asparaginic acid and of glutaminic acid in the brain homogenates, disturbed compactness of the cerebral substance due to enlarged perivascular spaces, capillary hyperaemia and low-grade haemorrhages, enlargement of the nuclei and swelling of the cytoplasm in the brain cells; microscopic examination of the inner organs: various-grade dystrophia of the liver parenchyma (focal necrosis being a high-grade damage), granular dystrophia in the epithelium of the convolute renal tubules, atrophies and ruptures of the alveolar septa in the lung, marked plethora and thi-ckening of the arterial walls in the liver and the lung, marked narrowing of the zona fasciculata in the suprarenal bodies
Reliability	:	(4) not assignable the experimental results are insufficiently documented because no animal data are given.

26.11.2004 (131) (132)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA100, TA102, TA104, TA1535, TA1537, Escherichia coli WP2uvrA, WP2uvrA/pKM101
Test concentration	:	1) +/-S9: 0.0763, 0.305, 1.22, 4.88, 19.5, 78.1, 313, 1250, 5000 µg/plate; 2) +/-S9: 2.44(only S.typh strains -S9), 4.88(only S.typh strains -S9), 9.77, 19.539.1, 78.1, 156, 313, 625 µg/plate
Cycotoxic concentr.	:	from 313 µg/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: preincubation method according to Ames, Mutat. Res. 31, 347 (1975), Maron, Mutat. Res. 113, 173 (1983); Highest doses used: cytotoxic, positive controls, solvent (DMSO) control (see also freetext ME)
Year	:	1996
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity: 99 %
Method	:	Method: --preincubation: 20 min. --Controls: -------positive controls:

---without S9-mix:
2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (Salmonella typhimurium TA100, TA98, Escherichia coli WP2uvrA, WP2uvrA/pKM101)
Sodium azide (Salmonella typhimurium TA1535)
4-Nitroquinoline-N-oxide (Salmonella typhimurium TA1538)
9-Aminoacridine (Salmonella typhimurium TA1538)
Bleomycin (Salmonella typhimurium TA102)
Pyruvic aldehyde (Salmonella typhimurium TA104)
---with S9-mix
2-Aminoanthracene (for all strains)
-------negative control:
solvent (DMSO) control
-------Preparation of S9 Fraction:
Male Sprague-Dawley rats were used for the preparation of liver fractions. Sodium phenobarbital and 5,6-benzofravone were used as an inducer of the rat metabolic activation system. Sodium phenobarbital was injected intraperitoneally into the rats 4 days before killing and 1, 2 and 3 days before killing 5,6-benzoflavone was injected intraperitonally. From these rats liver S9 fraction was prepared according to Ames et al. (1975), Methods for detecting carcinogens and mutagens in the Salmonella /mammalian microsome mutagenicity test, Mutat. Res. 31, 347-364. S9 was dispensed into freezing ampules and stored at -80°C. Once the stock S9 had been thawed, remained S9 was not reused.

Evaluation criteria:
Twohold rule was used for data evaluation. the chemicals are considered to be mutagenic when dose-related increase in revertant colony count is observed and the number of revertant colonies per plate with the test substance is more than twice that of the negative control (solvent control) and when a reproducibility of test result is observed.

Result : The positive controls were functional.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
25.11.2004 (146)

Type : Ames test
System of testing : Salmonella typhimurium TA 97, TA 98, TA 100, TA 1535, TA 1537
Test concentration : 0.0, 3.3, 10.0, 33.0, 100.0, 150.0, 333.0, 666.0, 1000.0 µg/plate in DMSO
Cycotoxic concentr. : +/- S9-mix: from 150.0 µg/plate onwards
Metabolic activation : with and without
Result : negative
Method : other: preincubation procedure according to Haworth. 1983. Environ. Mutagen. 5 [Suppl. 1], 3-142, see also freetext
Year : 1992
GLP : no data
Test substance : other TS: p-Chlorotoluene: vendors purity: 98 %, analyzed purity: 87.7 %

Method : -----Preincubation procedure:
Preincubation time with TS: 20 min
TS was testes with and without S9-mix
-----Metabolic activation systems (S9-mix):
S9-mix was prepared from Aroclor 1254-induced male Sprague -Dawley rats(RLI) and males Syrian Hamster(HLI) in 10 % and 30 % concentrations:
Salmonella typhimurium TA97, TA98, TA100, TA 1535:
S9-mix RLI and HLI 10 and 30 % each
Salmonella typhimurium TA 1537: 30 % RLI and 30 % HLI
-------Controls:
Positive controls were used, but the name of the substances were not mentioned.
negative controls: solvent: DMSO

-----Evaluation of the results
A chemical was judged mutagenic or weakly mutagenic if it produced a reproducible dose-related response over the solvent control.

Result : p-Chlorotoluene did not induce point mutations in any tests neither with nor without any of the metabolic activation systems used.
The positve controls were functional.

Reliability : (2) valid with restrictions
E. coli and Salmonella typhimurium TA102 were not included

Flag : Critical study for SIDS endpoint

05.08.2005 (147)

Type : Ames test
System of testing : Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration : in this assay a wide range of doses was tested up to 5 mg/plate or a dose which gave a toxic response, whichever was lower (no further data)
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other
Year : 1977
GLP : no
Test substance : other TS: the purity of the test substance was not determined, but a reagent of the highest available purity was used (no further data)

Reliability : (4) not assignable
Results only mentioned in the text

11.08.2004 (148)

Type : Mitotic recombination in Saccharomyces cerevisiae
System of testing : Saccharomyces cerevisiae D3
Test concentration : in this assay a wide range of doses was tested up to 5 mg/plate or a dose which gave a toxic response, whichever was lower (no further data)
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method :
Year :
GLP : no
Test substance : other TS: the purity of the test substance was not determined, but a reagent of the highest available purity was used (no further data)

Reliability : (4) not assignable
Results only mentioned in the text

11.08.2004 (148)

Type : Ames test
System of testing : S. typhimurium (no further data)
Test concentration : no data
Cycotoxic concentr. :
Metabolic activation : no data
Result : negative
Method :
Year :
GLP : no data
Test substance :

Reliability : (4) not assignable
Documentation insufficient for assessment

11.08.2004 (149)

Type	:	other: umu test
System of testing	:	Salmonella typhimurium TA 1535/pSK 1002
Test concentration	:	100 ug/ml
Cycotoxic concentr.	:	no data
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: determination of ß-galacdosidase activity after a incubation time of 4 hours
Year	:	1992
GLP	:	no data
Test substance	:	other TS: p-chlorotoluene, purity not given
Reliability	:	(4) not assignable Documentation insufficient for assessment

11.08.2004 (150)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	NMRI
Route of admin.	:	i.p.
Exposure period	:	single administration
Doses	:	1000 mg/kg bw disssolved in corn oil, dosage based on a pilot test
Result	:	negative
Method	:	OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	TEST ANIMALS: young adult male and virgin female NMRI mice (Bor:NMRI), weighing between 28 and 44 grams at study begin (age between 8 and 12 weeks). 5 males and 5 females were used per group. EXPOSURE: Animals were dosed intraperitoneally with the test substance dissolved in corn oil and sacrificed 16 hours, 24 hours or 48 hours after the administration. DOSING VOLUME: 5 mL/kg bw (10 mL/kg bw in the positive controls) POSITIVE CONTROL: cyclophosphamid, 20 mg/kg bw, dissolved in deionised water, intraperitoneally. Animals were sacrificed 24 hours after the administration. PREPARATION OF SPECIMENS: at least one intact femur was prepared from each sacrificed animal, and smears were prepared according to the method as described by Schmid (Mut. Res. 31, 9-15, 1975). EVALUATION: Coded slides were evaluated using light microscopy. Generally, 1000 polychromatic erythrocytes were counted per animal. The incidence of cells with micronuclei was determined, as well as the ratio of polychromatic to normochromatic erythrocytes (number of normochromatic erythrocytes per 1000 polychromatic ones). In addition, also the number of micronucleated normochromatic erythrocytes was determined. STATISTICAL METHODs: Standard deviation, Wilcoxon`s non-parametric rank sum test at a 5% significance level, or one-sided chi-square-test, if the micronulei rate for polychromatic erythrocytes was increased in the negative controls. ASSESSMENT CRITERIA: a result was considered positive if, at any of the intervals, there was a relevant and significant increase in the number of polychromatic erythrocytes showing micronuclei in comparison to the negative control. A test was considered negative if there was no relevant or significant increase in the rate of micronucleated polychromatic

erythrocytes at any time. A test was also considered negative if there was no significant increase in that rate which according to the laboratory`s experience was within the range of negative controls.
ACCEPTANCE CRITERIA: a test was considered acceptable if the figures of negative and positive controls were within the expected range, in accordance with the laboratory`s experience and/or the available literature data.

Result : general toxicity:
compound-related signs of toxicity observable until sacrifice 16, 24 and 48 hours after the administration:
apathy, roughened fur, staggering gait, spasms, twitching, shivering and difficulty in breathing;
death of 2/40 treated animals during the test period; autopsy findings:
slightly inflated lungs, spotted livers

no indications of a clastogenic effect of p-chlorotoluene were found; the ratio of polychromatic to normochromatic erythrocytes was not altered.
The positive contol was functional.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
07.09.2004 (151)

Type : Cytogenetic assay
Species : rat
Sex : female
Strain : no data
Route of admin. : gavage
Exposure period : see freetext ME
Doses : see freetext ME
Result :
Method : other: see freetext ME
Year : 1981
GLP : no
Test substance : other TS: p-chlorotoluene: no data on purity

Method : dosing scheme:
single application: 1100 or 1833 mg/kg bw
repeated application:
--2 months: 55 or 550 mg/kg bw/day
--6 months: 0.01, 0.1 or 1 mg/kg bw/day

evaluation of mutagenicity:
Ford FE, Hammerton JH (1956). Stain. Technol. 31, 247-251

no further data

Result : within the scope of a study of reproductive toxicity,
a slight tendency to the formation of chromosomal fragments was observed in sexually mature female rats which had received a single administration of p-chlorotoluene

Reliability : (4) not assignable
Documentation insufficient for assessment
25.11.2004 (131)

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	other: CrL:COBS CD (SD) BR
Route of admin.	:	inhalation
Exposure period	:	days 6-19 of gestation
Frequency of treatm.	:	6 h/d
Duration of test	:	on day 20 of gestation the dams were killed
Doses	:	0.1.1, 3.1 or 9.0 mg/l
Control group	:	
NOAEL maternal tox.	:	ca. 1.1 mg/l
LOAEL Teratogenicity	:	ca. 1.1 mg/l
Method	:	other: 25 females/dose, whole-body exposure, animals were kept individually during exposure
Year	:	1982
GLP	:	yes
Test substance	:	other TS: purity: 96.5 %o-chlorotoluene, 3.4 % p-chlorotoluene and 0.1 % toluene
Remark	:	These are the data of o-chlorotoluene
Result	:	1.1 mg/l: no maternal effects being obviously attributable to treatment fetal effects: 4 malformed fetus compatred to 3 in the control group. One showing brachygnathia, one showing retro-oesophageal aortic arch, one showing cardiac ventricular septal defect and one showing brachydactyly and bachymelia of all four limbs. The last malformation was similiar with the observed malformation of six fetuses at 9 mg/l 3.1 mg/l: maternal effects: slight ataxia observable during the exposure periods fetal effects: no notable or significant deviations from control values among litter parameters and among indices of malformations, anomalies and skeletal variants of the offspring 3.1 and 9 mg/l: maternal effects: dosage-related reduction in food consumption and in bodyweight gain and dosage-related increase in water consumption 9 mg/l: maternal effects: ataxia, lachrymation and/or salivation among occasional animals during exposure, and brown fur staining; fetal effects: mean values for litter and mean fetal weight significantly reduced; increase in the incidence of fetal malformations mainly due to the occurrence of six fetuses (distributed among four litters) showing brachydactyly of a single fore- or hindpaw; for five of the 6 fetuses the brachydactyly was associated with a terminal haemorrhagic area on the affected paw; 3 other malformations (1 microphthalmia,1 anophthalmia amd 1 cardiac ventricular septal defect); correlating with the lower mean fetal weight, reduced skeletal ossification observable, providing an increased incidence of fetuses with sternebral variants and contributing to a significant increase in fetuses with skeletal anomaly; incidence of visceral anomalies unaffected
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

05.08.2005 (152) (153)

Species	:	rabbit
Sex	:	female
Strain	:	New Zealand white
Route of admin.	:	inhalation
Exposure period	:	days 6-28 of gestation
Frequency of treatm.	:	6h/d
Duration of test	:	on day 29 of gestation the dams were killed
Doses	:	0, 1.5, 4.0 or 10 mg/l
Control group	:	yes, concurrent no treatment
NOAEL maternal tox.	:	ca. 1.5 mg/l
NOAEL teratogen.	:	ca. 4 mg/l
Method	:	other: 16 females/dose, whole-body exposure, rabbits were held individually during exposure
Year	:	1983
GLP	:	yes
Test substance	:	other TS: purity: 96.5 % o-chlorotoluene, 3.4 % p-chlorotoluene and 0.1 % toluene
Remark	:	These are data of o-chlorotoluene
Result	:	There were 6 deaths associated with pulmonary disorder. Although four of these occurred at 10 mg/l, there was no conclusive association with treatment. all dose groups: no significant effect on litter size, pre- and post implantation loss, or litter and mean fetal weight; the mean percentage incidence of fetuses with skeletal anomaly was higher than the control incidence; the difference were neither statistically significant (P<0.05) nor dosage-related. In addition the incidences were within the range of historical control data. 1.5 mg/l: no maternal effects obviously attributable to treatment fetal effcts: 4 malformed fetuses, 3 occurred in a single litter and all showed vertebral defects. A fouth fetus in a second litter showed cebocephaly and hydrocephaly. 4 mg/l: maternal effects: partial ptosis observable in occasional animals fetal effects: 1 malformed fetus showed a major heart vessel defect. 4 and 10 mg/l: maternal effects: rapid respiration detectable shortly following exposure (at the 4 mg/l level, to a lesser extent); dosage-related reduction in food consumption and in bodyweight gain during the initial part of the treatment period 10 mg/l: maternal effects: lachrymation, salivation and ptosis observable during initial exposures fetal effects: 1 fetus showed unilateral microphthalmia, major heart defect and forelimb brachydactyly.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

05.08.2005 (154) (153)

Species	:	rat
Sex	:	female
Strain	:	no data
Route of admin.	:	unspecified
Exposure period	:	see remarks
Frequency of treatm.	:	see remarks
Duration of test	:	the dams were killed on day 20 of gestation
Doses	:	see remarks
Control group	:	yes
Method	:	other

Year	:	1981
GLP	:	no
Test substance	:	other TS: p-chlorotoluene was given as oily solution, purity not given
Method	:	the route of application is supposed to be intragastric application experimental design: three different dosage regimens were used: in the first, the animals received a single administration of 1100 or 1833 mg/kg bw (= 1/5 or 1/3 LD50); the second group received 55 or 550 mg/kg bw/d (= 1/100 or 1/10 LD50) for 2 months; according to the third dosage regimen, the animals received 0.01, 0.1 or 1.0 mg/kg bw/d for 6 months; the dams were killed on day 20 of gestation and the number of corpora lutea, of implantations, of malformed fetuses as well as the number of intra-uterine or postnatal deaths were determined; with regard to the pups, the course of the physical development, the organogenesis and the ossification were examined (time periods in relation to gestation not specified)
Result	:	Embryotoxic effects (not further specified) were found at 1100 and 1833 mg/kg bw following single application. only in the 2 months-experiment at a dose level of 550 mg/kg bw/d, an increased embryonal mortality (20.27 versus 8.7 in controls) due to preimplantation losses (19.80 versus 5.8 in controls) was observable; at the same dose level, hepatic hypertrophy was discernible in 12.7 % of the fetuses and hepatic hypotrophy was observed in 47 % of the fetuses; no teratogenic effects were observable (no further data)
Reliability	:	(4) not assignable Documentation insufficient for assessment (e.g. no individual animal data were shown)

14.01.2005 (131) (132)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type	:	other: subchronic toxicity
In vitro/in vivo	:	In vivo
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	90 d
Frequency of treatm.	:	daily: 7 d/w
Duration of test	:	90 d
Doses	:	0, 50, 200, 800 mg/kg bw/d in corn oil
Control group	:	yes, concurrent vehicle
Result	:	see freetext RS
Method	:	other: see freetext ME
Year	:	1990
GLP	:	no data
Test substance	:	other TS: the purity was determined to be greater than 98 %; 1-Chloro(4-chloromethyl)benzene at 0.5 % was identified by GC-MS as the only impurity
Method	:	Animals and Housing:

10 rats/sex/group. Sprague-Dawley, 46 days of age at initiation,
Bodyweight at initiation: males: 227.3-276.1g; females: 153.2-195.8 g
Acclimisation period: 2 weeks
food and tap water ad libitum
room temperature: 22-24°C; humidity: 40-60 %; 12 hour light-dark cycle
Material
test solutions were prepared fresh weekly;
dosing volume: 3 ml/kg bw
Experimental design and treatment:
Sacrifice of the animal: the day following completition of treatment

Animal observations
for signs of mortality and morbidity, for overt signs of toxicityand clinical signs (general apprarance, behavior, excretion, respiration, respiration, skin pelage, eyes), physical examination weekly, abnormalities in housing, food or water intake
Terminal evaluation:
ophthalmoscopic examination
blood and urine collection prior necropsy
Heamtology: leucocyte (differentials and cell morphology), erythrocyte, hematocrit, hemoglobin,
clinical chemistry:
sodium, potassium, total protein, albumin, calcium, total bilirubin, creatinine, aspartate aminotransferase (AST), alanine aminotransferase(ALT), alkaline phosphatase(ALP), lactate dehydrogenase(LDH), and blood urea nitrogen(BUN),
Urinalysis
pH, glucose, protein, bilirubin, occult blood, urobilinogen

Terminal necropsy:
body weight determination and organ weight determination: liver, kidneysm spleen, adrenal glands, thymus, brain, heart, lung, testes with epididymides, ovaries
Histopathological evaluation:
all animals of the 800-mg-group, and five animals /sex of the corn oil controls:
adrenals, thyroid, esophageusmtrachea, larynx, heart, spleen liver, kidney, stomach, duodenum, jejunum, colon, pancreasm and gross lesions

Statistical analysis
Levene's test on homogenicity, analysis for variance, Dunnett's t-test

Remark : see also section 5.4

Result : For general toxicity see section 5.4
organ weights:
males:
There were no significant differences in testes weights: control-low, mid, high dose (rel weights):
5.26g (0.931 %bw) - 5.18g (0.898 %bw), 5.35g (0.45 %bw) 4.96g (1.016 %bw)
females:
There were no significant differences in ovaries weights: control-low, mid, high dose (rel weights):
0.163g (0.0512 %bw) - 0.0522g (0.063 %bw), 0.0531g (0.074 %bw), 0.0547g (0.074 5%bw)
gross and histopathology:
Evaluation revealed no pathological findings.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

05.08.2005 (143) (144)

Type : other: subacute

In vitro/in vivo	:	In vivo
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	29 d
Frequency of treatm.	:	daily: 7d/w
Duration of test	:	29 d
Doses	:	0, 50, 200 or 800 mg/kg bw/d dissolved in Polyethylenglycol 400
Control group	:	yes, concurrent vehicle
Result	:	see freetext RS
Method	:	other: see freetext ME
Year	:	1993
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4

Method :

TEST SPECIES AND ANIMAL HUSBANDARY.
-Age at start of the study: 7-8 weeks
-Number of rats: 5 m/5 f per group
-Animal maintenance: air-conditioned rooms,
-----groups of 5 rats/cage
-Acclimatisation: 7 days
-Room temperature: 22 °C
-Relative Humidity: 50 %
-Lighting time: 12 hours daily
-Food: rat diet ad libitum
-Water: tap water ad libitum
ADMINISTRATION / EXPOSURE
-Dose selection based on priliminary experiments
-Vehicle: polyethyleneglycole 400
-Total volume applied: 5 ml/kg bw

CLINICAL OBSERVATIONS AND FREQUENCY
-Clinical signs: twice daily
-Body weight: daily just before application of TS
-Food consumption: once per week
-Water consumption: once per week
-Ophthalmoscopic examination: weekly

CLINICAL LABORATORY EXAMINATIONS
-Hematology / Clinical chemistry/Urinalysis: at week 4 of the study on all animals
-HEMATOLOGY:
Differential blood picture, Erythrocyte count (Erys), hemoglobin (HG), hematocrit (HK), mean cellular volume (MCV), mean cellular hemoglobin (MCH), mean cellular hemoglobin concentration (MCHC), reticulocyte count, Leucocyte count (Leucos), Thromocyte count (Thrombos), Thromboplastin coagulation time
-CLINICAL CHEMISTRY:
Sodium, Potassium, Calcium, Chloride, Inorganic phophorus, glucose, bilirubin, Cholesterol, Creatinine, total protein, Urea, albumin, triglycerides, Alkaline phosphatase (AP), Alanine aminotransferase (ALAT/GPT), Aspartate aminotransferase (ASAT/GOT)
-URINALYSIS:
-a few days before determination of hematology values:
blood, ketone bodies, pH-value, glucose, protein, bilirubin, urobilinogen, sediment, specific weight, volume, protein

--Animals that died during treatment time were evaluated gross-pathologically and changes were noted.

--After termination of the feeding period all surviving animals were sacrificed and gross and histopathologically examined.

NECROPSY:
ORGAN WEIGHTS:
brain, heart, lung, liver, kidneys, spleen, adrenals, ovaries, testes
GROSS PATHOLOGY:
adrenals, aorta, auricles (tattooed), bone marrow of femur and sternum, conchae, epididymis, esophagus, extraorbital lacrimation gland, eyes, eye lids, femur with knee joint,
Hardrian gland, heart, intestine (colon, caecum, jejunum, ileum duodenum, rectum, remainder), kidneys, larynx, liver, lung, lymph nodes (mesenteric and mandibular), mammary gland, muscles (femur), nervus ischiadicus, nervus opticus,
ovaries, oviduct, pancreas, pituitary gland, prostate gland, salinary gland, seminal vesicles, skin, spinal cord (cervical, thoracal, lumbal), spleen, sternum, stomach,
testes, thyroid gland with parathyroids, tongue, trachea, thymus if present, ureters, urethra, urinary bladder,
uterus, vagina, Zymbal's gland
HISTOPATHOLOGY:
all control animals and all high dosed animals,
heart, liver, lung, spleen, kidneys, adrenals
but also macroscopically changed organs of animals in all dose groups

-STATISTICS:
U-test according to Mann and Whitney,
Wilcoxon test

ADDITIONAL HISTOPATHOLOGICAL EXAMINATIONS
on reproductive organs on all animals including control animals:
-male reproductive organs:
testes, epididymides, prostate, seminal vesicles
-female reproductive organs:
uterus, vagina, ovaries, oviduct

Remark : see also section 5.4

Result : NOAEL (general toxicity): 200 mg/kg bw/d

The histopathological investigations revealed no changes in testes, epididymides, prostrate, seminal vesicles, ovaries/oviduct, uterus and vagina which can be attributed to the treatment. Thus, from the viewpoint of pathology and based on the organs investigated and reported in this amendment the NOAEL is 800 mg/kg bw/d for both sexes.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

05.08.2005 (145) (155)

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Type of experience : Human

Remark : experience with occupational exposure to an unspecified mixture of o- and p-chlorotoluene or to the isomere:

400 ppm (= 2.106 mg/m³):

Mono-chlorotoluene causes severe toxic effects in persons exposed by inhalation for 60 min.;

200 ppm (= 1.053 mg/m³):
Mono-chlorotoluene may lead to symptoms of illness in persons, if the exposure continues for more than a short time;

75 ppm (= 0.395 mg/m³):
concentrations in general atmosphere of plant or greater may lead to unsatisfactory conditions (no further data)

Reliability : (2) valid with restrictions
exposure against chlorotoluene (isomer not specified)

Flag : Critical study for SIDS endpoint

13.09.2004 (156)

5.11 ADDITIONAL REMARKS

Type : Biochemical or cellular interactions

Remark : The inhibition of CYP2B activity by p-chlorotoluene (PCT) and its Phase I metabolites was measured through the o-dealkylation of benzoyloxyresorufin (BROD). The enzyme kinetic analyses suggest that PCT and its Phase I metabolites have potent inhibitory effects on BROD activity in the lung and to a lesser extent in the liver.

Reliability : (4) not assignable
abstract only: no details available

13.08.2004 (157)

Type : Biochemical or cellular interactions

Remark : Hepatocytes from male Wistar rats were cultured and then incubated with different amounts of p-chlorotoluene, dissolved in DMSO, for 24 hours to determine cytotoxcicity:

Effective concentration value for cytotoxicity:
EC50 value for p-chlorotoluene: 1.2 mM
EC10 value for p-chlorotoluene: 0.79 mM

Incubation with 0.71 mM:
---Slightly reduced EROD activity:
(12.1 versus 16.5 pmol/min/mg in controls)
---Slightly increased PROD activity:
(8.8 versus 5.1 pmol/min/mg in controls)

Reliability : (4) not assignable
special study

25.11.2004 (158)

Type : Biochemical or cellular interactions

Remark : Single intraperitoneal injection of p-chlorotoluene(pCT) to rats significantly decreased hepatic and pulmonary aryl hydrocarbon hydroxylase (AHH) activities at 500 mg/kg bw, 1 h. Maximum inhibition was attained at 1000 mg/kg bw, 1 h, and further increase in the dose did not enhance the enzyme inhibition.
In the time-course investigations, 1000 mg/kg bw pCT maximally inhibited hepatic and pulmonary AHH activities at 1 h and the decrease in enzyme activity was sustained through 12 h.

Administration of pCT also markedly decreased pulmonary P-450 content, while hepatic cytochrome P-450 content was only slightly reduced.
pCT significantly inhibited cytochrome P-4502B1 in the lung (50%) amd 2B1/2B2 in the liver (40%) while cytochrome P-4501A activity was not altered in either lung or liver.
pCT increased phospholipid levels (45%) and conjugated diene formation (58%) in lung but not in liver while membrane fluidity was increased in both organs. There was no apparent relationship between these membrane changes and alterations in mixed function oxidase (MFO) activity.

Reliability : (2) valid with restrictions
special study

13.09.2004 (123) (159) (160) (124)

Type : other

Remark : The c-mitotic activity of some benzene derivatives, including p-chlorotoluene, was studied in Allium cepa (onion); full c-mitosis was observed at a concentration of 1000 uM; partial disturbances in mitosis were observable at a concentration of 300 uM and normal mitosis was seen at a concentration of 100 uM

Reliability : (4) not assignable
special study, documentation insufficient for assessment

25.11.2004 (161)

Type : other

Remark : p-chlorotoluene given i.p. to rats at a dose level of 1000 mg/kg bw reduced pulmonary (37%) and hepatic (76%) arylhydrocarbon hydroxylase activity at 1 hour; lipid peroxidation was increased in lung (45%) and liver (13%); hepatic phospholipid content (13%) and membrane fluidity (5%) were also increased.

Reliability : (4) not assignable
abstract only

13.09.2004 (162) (163)

Type : other

Remark : By evaluating sensory irritation potential of volatile organic chemicals from carpets the RD50 of p-chlorotoluene in male Swiss-Webster mice was determined to be 100-1000 ppm.

Reliability : (4) not assignable
special study

25.11.2004 (164)

Type : other

Remark : 4-Chlorotoluene is one of the chemicals in the list of suspected endocrine disrupturs (EDs) published by the Japan Environment Agency. 4-chlorotoluene was therefore tested in a screening assay using Yeast Two-Hybrid system based on the ligand-dependent interaction of nuclear hormone receptors with coactivators. 4-chlorotoluene was judged to be negative [positive Control: 17ß-Estradiol(E2)].

Reliability : (4) not assignable
no validated test method.

12.08.2004 (165)

Type : other: cytotoxicity

Remark : To a suspension of Human hepatoblastoma cells, Hep G2, a definitive

amount of labelled LDL was added, then this suspension was incubated with TS for 48 hours. Afterwards the cells were washed, cell membrans destroyed and the uptake of LDL measured. The result was compared with uptake of untreated cells to evaluate the toxicity of the TS on the hpatoblastoma cells:
2,62 Mol/liter(approx. 331g/l) reduced the LDL-uptake about 50 %.

Reliability : (4) not assignable
special study

13.08.2004 (166)

Type : other: haemotoxicity in vitro

Remark : The effect of p-chlorotoluene on heme synthesis in vitro was determined by studying its influence on delta-amino-levulinic acid synthetase (ALAS) and ferrochelatase (FC) activities in rat liver homogenates;
at a final concentration of 0.001 mol/l (= 126 ug/ml), p-chlorotoluene induced a very slight inhibition of ALAS activity (activity, expressed as percentage of control: 97 %), whereas the activity of FC remained unaffected by p-chlorotoluene.

Reliability : (4) not assignable
special study

12.08.2004 (167)

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