

[FOREWORD](#)

[INTRODUCTION](#)

[\$\alpha,\alpha,\alpha\$ -Trichlorotoluene \(Trichloromethylbenzene\)](#)

CAS N°:98-07-7

SIDS Initial Assessment Report

For

SIAM 18

Paris, France, 20 – 23 April 2004

1. **Chemical Name:** α,α,α -Trichlorotoluene (Trichloromethylbenzene)
2. **CAS Number:** 98-07-7
3. **Sponsor Country:** Contact Point:
BMU (Bundesministerium fuer Umwelt, Naturschutz und Reaktorsicherheit)
Contact person:
Prof. Dr. Ulrich Schlottmann
Postfach 12 06 29
D- 53048 Bonn-Bad Godesberg
4. **Shared Partnership with:**
5. **Roles/Responsibilities of the Partners:**
 - Name of industry sponsor /consortium Bayer AG, Germany
Contact person:
Dr. Burkhardt Stock
D-51368 Leverkusen
Gebaeude 9115
 - Process used The BUA Peer Review Process : 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):
08 October 2003 (Human Health): databases medline, topline;
search profile CAS-No. and special search terms
29 September 2003 (Ecotoxicology): databases CA, biosis;
search profile CAS-No. and special search terms OECD/ICCA Human
8. **Quality check process:** As basis for the SIDS-Dossier the IUCLID was used. All data have been checked and validated by BUA.
9. **Date of Submission:** Deadline for circulation: 23 January 2004
10. **Date of last Update:**

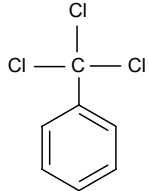
11. Comments:**OECD/ICCA - The BUA* Peer Review Process**

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

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

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	98-07-7
Chemical Name	α,α,α -Trichlorotoluene (Trichloromethylbenzene)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

α,α,α -Trichlorotoluene hydrolyzes to hydrochloric acid and benzoic acid upon contact with moisture. It is readily absorbed from the gastrointestinal tract, distributed within the body, and excreted after metabolic transformation to hippuric acid mainly via the urine. The 4-hour inhalation LC_{50} in rats was 530 mg/m^3 for females, and $>600 \text{ mg/m}^3$ for males. 5 of 6 rats died after a 4-hour exposure to about $1,000 \text{ mg/m}^3$. Clinical signs included ocular and respiratory tract irritation, dyspnea, and weight loss. The dermal LD_{50} value for rats was greater than $5,000 \text{ mg/kg bw}$, with sedation and poor general health from days 1 to 10 after exposure. Depending on the vehicle used, the acute oral LD_{50} values in rats were between about 700 mg/kg bw (when applied in corn oil) and $2,200 \text{ mg/kg bw}$ (when applied as aqueous suspension). Clinical signs like sedation, dyspnea, polyuria, and weight loss were observed for several days after the oral administration of the chemical.

Under occlusive conditions, α,α,α -trichlorotoluene was irritating to the skin of rabbits. The chemical may cause severe eye irritation. The vapors are irritating to the respiratory tract.

In mice, the repeated inhalation of α,α,α -trichlorotoluene (12.8 mg/m^3 for 12 months) resulted in a high incidence of bronchitis and bronchopneumonia. In rats, repeated inhalation exposure to concentrations $\geq 48.2 \text{ mg/m}^3$ for 4 weeks led to death, depressed weight gain, dyspnoea and gasping. Microscopically, inflammation and/or squamous metaplasia of the cells lining the nasal, tracheal, bronchial and bronchiolar epithelia were observed. No significant changes occurred in the 5.1 mg/m^3 group (NOAEL). Skin irritation up to necrosis was seen after dermal treatment of rabbits with 50, 100 or 200 mg/kg bw/day of the undiluted chemical for three weeks. Histopathologically, an increased incidence of portal inflammatory cell infiltrates in the liver, and, at 200 mg/kg bw/day , bile duct proliferation was found. Pathological changes were also seen in the seminiferous tubules at 100 and 200 mg/kg bw/day . Irritation of the eyes, the skin and the respiratory tract were the main clinical signs after repeated painting of mice skin with α,α,α -trichlorotoluene. In a 28-day feeding study on rats, a NOAEL could not be determined, as mild histopathological effects on liver, kidney and the thyroid gland were still present at the lowest test concentration of 0.5 ppm in the diet (corresponding to about $0.05 \text{ mg/kg bw/day}$).

α,α,α -Trichlorotoluene has demonstrated a genotoxic potential in bacterial and mammalian cell systems. In non-standard *in vivo* tests, the chemical induced micronuclei in bone marrow cells of mice. Chromosomal aberrations in bone marrow cells and sister chromatid exchanges in peripheral lymphocytes have been reported in rats after repeated inhalation exposure.

α,α,α -Trichlorotoluene has induced lung tumors, skin tumors, leukemia and lymphomas in animals by the inhalative, dermal and oral routes of exposure. The available human data for α,α,α -trichlorotoluene are limited because the studies included small numbers of cancer deaths and were confounded by exposure to mixtures of chlorinated compounds. Based on the limited human data and sufficient evidence from animal studies, the combined exposures to α -chlorinated toluenes and benzoyl chloride are probably carcinogenic to humans (IARC Group 2A).

There were no fertility studies available. In a 3-week dermal study on rabbits, degeneration of the tubules in

seminiferous ducts, and an increased incidence of multinucleated giant cells in the seminiferous tubules were reported at dose levels of 100 and 200 mg/kg bw/day, but not for 50 mg/kg bw/day. Pathological changes in reproductive organs were not reported in any of the carcinogenicity studies. Sufficient documentation with regard to the scope of the examinations relating to the reproductive organs was however not available, and therefore a lack of effect cannot be deduced from these studies. The effects on male reproductive organs observed in the 3-week dermal study in rabbits give some indications that α,α,α -trichlorotoluene might be toxic to reproduction. As results from further testing would not affect the most stringent exposure control measures already in place, no further tests are warranted.

In a poorly documented study, developmental effects were reported in rats at non-maternally toxic dose levels (LOAEL, fetal development = 12.5 mg/kg bw/day; NOAEL maternal toxicity = 12.5 mg/kg bw/day). Further testing is not warranted because exposure to the chemical is already strictly controlled due to its mutagenic and carcinogenic properties. Although not fully tested for reproductive and developmental toxicity, α,α,α -trichlorotoluene should be regarded as potentially toxic to reproduction because it is a genotoxic carcinogen.

Environment

α,α,α -Trichlorotoluene is a moisture/water sensitive fluid with a melting point of -4.8 °C, a boiling point of 220.7 °C, and a density of 1.37 g/cm³ at 20 °C. The vapour pressure of the substance is 0.2 hPa at 20 °C. The log Kow cannot be determined due to hydrolysis. The solubility in water is 0.1 g/l at 20 °C. The flash point is ca. 108 °C, the auto flammability (ignition temperature) 420 °C. An atmospheric half-life of about 45 days is estimated due to the reaction with hydroxyl radicals.

α,α,α -Trichlorotoluene reacts completely with water within a few minutes at 20 °C, forming benzoic acid and hydrochloric acid. Any emission into the air or into the terrestrial compartment would be affected by humidity and also results in the formation of the hydrolysis products. However, several aquatic toxicity tests have been undertaken with α,α,α -trichlorotoluene. The observed toxicity effects in these studies can be attributed to the degradation products benzoic acid and hydrochloric acid. For assessment of the environmental impact of the hydrolysis products it is referred to the validated results of the hazard assessments on benzoates and hydrochloric acid within the OECD SIDS-Program.

Hydrochloric acid is a strong mineral acid that dissociate readily in water to the hydrated protons. Hydrochloric acid will not adsorb on particulate matters or surfaces and will not accumulate in living tissues. Benzoic acid is not expected to hydrolyse.

The hydrolysis products benzoic acid and hydrochloric acid have been tested with aquatic species. Especially hydrochloric acid caused a pH shift in water which determined the impact on aquatic life. The tolerance of water organisms towards pH margin and variation is diverse. Recommended pH values for test species listed in OECD guidelines are between 6.0 and almost 9. Acute testing with fish showed 96h-LC₅₀ at about pH 3.5 (equals about 20 mg α,α,α -trichlorotoluene), chronic testing with early life stages of fish NOECs at pH 6.0 and 5.56. Benzoic acid is not toxic (LC₅₀ or EC₅₀ >100 mg/l) towards aquatic organisms. The substance is readily biodegradable and non-bioaccumulative.

Acute toxicity of α,α,α -trichlorotoluene to fish (*Leuciscus idus*) was 4140 mg/l (48 h-LC₅₀). With *Daphnia magna* an EC₅₀ (24 h) of > 100 mg/l was determined. For the blue-green alga *Microcystis aeruginosa* an 8 day-EC₃ of 34 mg/l was obtained in a cell multiplication inhibition test (test solution was not neutralized). It is not expected that an algal EC₅₀ obtained in a neutralized test solution would be lower than the EC₅₀ for *Daphnia*. Since there are acute tests for α,α,α -trichlorotoluene from three trophic levels, an assessment factor of 1000 is applied according to EU Technical Guidance Document to the lowest acute effect concentration (*Daphnia magna*, 24 h-EC₅₀ of 100 mg/l). The following value is obtained: PNEC_{aqua} = 0.1 mg/l

Exposure

In 2000, the world wide production capacity of α,α,α -trichlorotoluene is estimated to 80,000 metric tons by about 10 producers: Western Europe 56,000 t/a, USA 16,000 t/a, Japan 5,500 t/a, and others 2,400 t/a. α,α,α -Trichlorotoluene is an intermediate, used exclusively in the industrial production of other intermediates such as benzoylchloride, benzotrifluoride, 2,4-dihydroxybenzophenone. These intermediates are further used in the synthesis of pesticides, dyestuffs, UV absorbers and pharmaceuticals.

At the sponsor company α,α,α -trichlorotoluene is manufactured and processed in closed systems. The exhausts from manufacturing and processing (including filling) of α,α,α -trichlorotoluene are connected to absorbing units,

thermal exhaust purification plants and air washing units. Thus, at the sponsor company during production and processing virtually no α,α,α -trichlorotoluene is emitted into the atmosphere. Due to the water-free production and processing processes emissions into the wastewater were not detected. The exposure of workers is below the German Technical Exposure Limit (TRK) value of 0.012 ppm (0.1 mg/m³) for α,α,α -trichlorotoluene.

A direct use of α,α,α -trichlorotoluene is not known, and α,α,α -trichlorotoluene is not listed in the Nordic and Swiss product registers as being contained in consumer products. Exposure of consumers to α,α,α -trichlorotoluene is considered negligible.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

The chemical possesses properties indicating a hazard for human health (e.g. acute and repeated dose toxicity, irritation, mutagenicity, carcinogenicity, reproduction and developmental toxicity). In the sponsor country, the substance is solely used as an isolated intermediate with controlled transport, and exposure in occupational settings is controlled. There is no exposure of consumers. Countries may desire to investigate any exposure scenarios that were not presented by the sponsor country.

Environment:

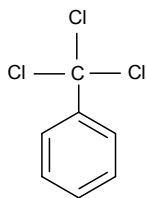
The chemical is currently of low priority for further work due to its low hazard profile. The degradation products benzoic acid and hydrochloric acid have already been assessed within the OECD SIDS-Program.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 98-07-7
IUPAC Name: Trichloromethylbenzene (Chemical Name)
Molecular Formula: $C_7H_5Cl_3$
Structural Formula:



Molecular Weight: 195.48 g/mol
Synonyms: Benzotrichloride
Benzene (trichloromethyl)
 α,α,α -Trichlorotoluene
Phenyltrichloromethane
Toluenetrichloride

1.2 Purity/Impurities/Additives

The purity of the commercial product is at least 99.8 % w/w for “benzotrichloride, pure” and at least 97 % w/w for the technical grade product of the sponsor company. The following impurities are reported for “benzotrichloride, pure” (Bayer Chemicals, 2003):

Benzylchloride max. 0.02 % w/w

Benzalchloride max. 0.2 % w/w

Benzoylchloride max. 0.2 % w/w

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference	IUCLID
Substance type	organic compound	BUA, 1991	1.1.1
Physical state	colourless to yellowish liquid	Verschuere, 1996	1.1.1
Melting point	-4.8 °C (Solidification point)	Auergesellschaft 1988	2.1
Boiling point	220.7 °C	Auergesellschaft, 1988	2.2
Density at 20 °C	ca. 1.37 g/cm ³	Auergesellschaft, 1988	2.3
Vapour pressure at 20 °C	0.2 hPa	Auergesellschaft, 1988	2.4
Partition coefficient n-octanol/water (log value)	2.92 (calculated)*	Leo, Hansch and Elkins, 1971	2.5
Water solubility at 20 °C	ca. 0.1 g/l*	Verschuere, 1996	2.6.1
Flash point	108 °C	Auergesellschaft, 1988	2.7
Auto flammability (ignition temperature)	420 °C	Auergesellschaft, 1988	2.8
Explosive properties	Explosive limits by volume: lower: 2.1 % higher: 6.5 % at 160 °C	Auergesellschaft, 1988	2.10
Viscosity	ca. 2.4 mPa s ⁻¹	Bayer AG, 2002	2.13
pH value at 23 °C	aqueous solution reacts acidic due to hydrolysis products	Bayer AG, 2002	2.14
Refractive index at 20 °C	1.5580	Elf Atochem, 1992	2.14

*In water, α,α,α -trichlorotoluene hydrolyses with a half-life of few minutes (Laughton and Robertson, 1959; Reusche, 1989)

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

α,α,α -Trichlorotoluene is produced by total side-chain chlorination of toluene or of residual products from benzal chloride production (BUA, 1991).

In 2000, the world wide production capacity of α,α,α -trichlorotoluene is estimated to 80,000 metric tons by about 10 producers (Srou, 1999).

Table 2 Worldwide manufacturing capacity 2000 (Srour, 1999)

Region	Estimated manufacturing capacity (t/a)
Western Europe	56,000
USA	16,000
Japan	5,500
Others	2,400

At Bayer AG, the total production capacity of α,α,α -trichlorotoluene is about 24,000 metric t/a (Srour, 1999).

α,α,α -Trichlorotoluene is an intermediate, used exclusively in the industrial production of other intermediates such as

- Benzoylchloride
- Benzotrifluoride
- 2,4-Dihydroxybenzophenone.

These intermediates are further used in the synthesis of pesticides, dyestuffs, UV absorbers and pharmaceuticals (Maki and Takeda, 2002).

A direct use of α,α,α -trichlorotoluene is not known (Bayer Chemicals, 2003).

α,α,α -Trichlorotoluene is not listed in the Danish, Finnish, Norwegian, Swiss and Swedish Product Registers as being contained in products (SPIN Database, 2003; Swiss Product Register, 2003).

2.2 Environmental Exposure and Fate

If α,α,α -trichlorotoluene is released to water, degradation occurs through hydrolysis (see chapter 2.2.3). A half-life for α,α,α -trichlorotoluene hydrolysis of 2.4 minutes was determined (Reusche 1989). Due to the rapid hydrolysis any emission to the air or to the terrestrial compartment would be affected by humidity. Therefore it is not expected that α,α,α -trichlorotoluene will remain stable in the environment (BGVV/UBA 1995).

For assessment of the environmental impact of the hydrolysis products, it is referred to the validated results of the hazard assessments on benzoic acid and hydrochloric acid within the OECD SIDS-Program:

Benzoic acid (CAS-No. 65-85-0):

Benzoic acid is readily biodegradable (*cf* Chapter 2.2.5) and not bioaccumulative (*cf* Chapter 2.2.6). Under environmental relevant conditions the acute environmental toxicity of benzoic acid is low (*cf* Chapter 4.1) (OECD SIAP/SIAR Benzoates Category 2001).

Hydrochloric acid (CAS-No. 7647-01-0):

Hydrochloric acid is a strong mineral acid that dissociates readily in water to chloride ions and hydrated protons, and is miscible with water. Being diluted hydrochloric acid is practically totally dissociated (OECD SIAP/SIAR Hydrogen chloride, 2002). This total ionization will imply also that hydrochloric acid will not adsorb on particulate matters or surfaces and will not accumulate in living tissues.

2.2.1 Sources of Environmental Exposure

Releases into the environment may occur from production and processing of the chemical.

Information on exposure from manufacturing and processing of the chemical is available for the Bayer Chemicals production plant in Germany (Bayer Chemicals, 2003).

At the Bayer manufacturing site α,α,α -trichlorotoluene is manufactured and processed in a closed system (Bayer Chemicals, 2003).

The exhausts from manufacturing and processing of α,α,α -trichlorotoluene are connected to absorbing units, thermal exhaust purification plants and air washing units. Thus, at the Bayer AG during production and processing virtually no α,α,α -trichlorotoluene is emitted into the atmosphere. α,α,α -Trichlorotoluene is not listed in the Emission Declaration of 2000 (Bayer Chemicals, 2003).

Due to the water-free production and processing processes emissions into the wastewater are not expected. Furthermore α,α,α -trichlorotoluene will rapidly hydrolyze in water (Bayer Chemicals, 2003).

During manufacturing there is no generation of α,α,α -trichlorotoluene containing wastes. The wastes from processing are burnt in a special incineration plant (Bayer Chemicals, 2003).

24 h/d, 365 d/a, the air and water emissions of the Bayer production site 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 air emissions. It also operates a station with measuring and sampling devices for water. Within their surveillance program α,α,α -trichlorotoluene was not detected in the wastewater with a detection limit of 20 $\mu\text{g/l}$ (Bayer Chemicals, 2003).

2.2.2 Photodegradation

There are no experimental data on the stability of α,α,α -trichlorotoluene in the atmosphere. A half-life of about 45 d is estimated due to reaction with photochemically produced hydroxyl radicals (mean OH concentration: $5 \cdot 10^5$ radicals/ cm^3) (Bayer, 2003). Direct photolysis is not expected to occur (Howard, 1989).

2.2.3 Stability in Water

α,α,α -Trichlorotoluene hydrolyses rapidly in the presence of water (BGVV/UBA, 1995). Reusche (1989) determined experimentally a half-life for α,α,α -trichlorotoluene hydrolysis of 2.4 minutes. In this test 10 mg/l test substance were dissolved in phosphate buffer of pH 7 at 20 °C containing 1 % v/v acetonitrile. At a higher concentration of acetonitrile (50 % v/v), the half-life of α,α,α -trichlorotoluene was prolonged to 2.1 hours (Table 3). An intermediate of the α,α,α -trichlorotoluene hydrolysis is benzoyl chloride. Benzoyl chloride also hydrolyses rapidly in water ($t_{1/2} < 2.4$ minutes at 20 °C) forming benzoic acid and hydrochloric acid (Reusche, 1989).

At 5 °C and neutral pH, a hydrolysis rate constant of $k = 0.00387 \text{ sec}^{-1}$ was determined (Laughton and Robertson, 1959). Based on the equation $t_{1/2} = \ln 2/k$, a half-life of 3 minutes was calculated.

Dietz (1981) observed a very fast hydrolysis of α,α,α -trichlorotoluene ($t_{1/2} = 14$ sec at 25 °C). The partial degradation product benzoyl chloride was degraded to benzoic acid and hydrochloric acid even faster ($t_{1/2} < 15$ sec) .

The rapid hydrolysis means that α,α,α -trichlorotoluene discharged into the environment will be abiotically degraded forming benzoic acid and hydrochloric acid.

Table 3 Hydrolysis of α,α,α -trichlorotoluene and benzoyl chloride (IUCLID 3.1.2)

Test substance	Procedure	Result	Source
α,α,α -trichlorotoluene	1 % acetonitrile in water 50 % acetonitrile in water	at pH 7, 20 °C: $t_{1/2} = 2.4$ min $t_{1/2} = 2.1$ h	Reusche, 1989*
α,α,α -trichlorotoluene	Calculation on base of measured reaction rate constants	at pH 7, 5 °C: $t_{1/2}$ ca. 3 min degradation products: benzoic acid, hydrochloric acid	Laughton and Robertson, 1959*
α,α,α -trichlorotoluene	100 % water; HPLC analysis, observation of pH decrease, calculation of rate constants	$t_{1/2} = 6.7$ min (0 °C) $t_{1/2} = 14$ sec (25 °C)	Dietz, 1981*
benzoyl chloride	1 % acetonitrile in water 50 % acetonitrile in water	at pH 7, 20 °C: $t_{1/2}$: not measurable because of very rapid hydrolysis $t_{1/2}$ ca. 3.6 min	Reusche, 1989*
benzoyl chloride	100 % water, 30 % acetone in water, HPLC analysis, observation of pH decrease, calculation of rate constants	at 25 °C $t_{1/2} < 15$ sec in 100 % water $t_{1/2} = 16$ sec in 30 % acetone in water degradation products: benzoic acid, hydrochloric acid	Dietz, 1981*

*studies flagged as robust summary studies

2.2.4 Transport between Environmental Compartments

In the aquatic environment, α,α,α -trichlorotoluene will undergo hydrolysis to benzoic acid and hydrochloric acid (BGVV/UBA 1995). In the atmosphere, α,α,α -trichlorotoluene will be affected by air humidity, which leads to hydrolysis of the substance (Howard 1989). Due to the rapid hydrolysis of α,α,α -trichlorotoluene a transport of the substance between environmental compartments is unlikely (Howard, 1989).

A calculation of the Henry constant and also of the distribution of α,α,α -trichlorotoluene between the environmental compartments according to the Mackay fugacity model level 1 is not suitable. For the degradation product benzoic acid the hydrosphere was identified as target compartment (OECD, 2001).

2.2.5 Biodegradation

Based on the available experimental biodegradation data for α,α,α -trichlorotoluene, the substance is classified as readily biodegradable (Table 4).

In a modified OECD screening test according to OECD TG 301E the biodegradation of α,α,α -trichlorotoluene was investigated with test substance concentrations of 5.4 and 22 mg/l, respectively. After three days degradation reached 95 %, after one week 96 - 97 % (Steinhaeuser, Ammann and Polenz, 1986).

Results of a Bayer study using the closed bottle test method (comparable to OECD TG 301D) showed a α,α,α -trichlorotoluene biodegradation of 63 % after 20 days (Bayer AG, 1976a).

It has to be considered that due to the very fast hydrolysis of α,α,α -trichlorotoluene the available biodegradation tests examine in fact the biodegradation behaviour of the hydrolysis products.

Table 4 Biodegradation of α,α,α -trichlorotoluene (IUCLID 3.5)

Inoculum	Procedure	Result	Source
Predominantly domestic sewage	Modified OECD Screening Test according to OECD TG 301E	96-97 % degradation after 7 days	Steinhaeuser, Ammann and Polenz, 1986*
Activated sludge	Closed Bottle Test	63 % degradation after 20 days	Bayer AG, 1976a*

*studies flagged as robust summary studies

Benzoic acid (CAS-No. 65-85-0):

Based on the results of biodegradation tests for the degradation product benzoic acid, the substance is classified as readily biodegradable, too (OECD SIAP/SIAR Benzoates Category, 2001). Sodium benzoate is used as a reference substance in OECD biodegradation tests.

2.2.6 Bioaccumulation

Measured bioconcentration factors (BCF) for α,α,α -trichlorotoluene are not available.

The calculation of log K_{ow} for α,α,α -trichlorotoluene is unsuitable. The calculated theoretical log K_{ow} values reflect the undissociated molecule without influence of water. Despite the calculated log K_{ow} values of 3 to 4, the rapid hydrolysis of α,α,α -trichlorotoluene results in a very short life time of the substance in the environment and causes a very low probability of bioaccumulation (BUA, 1991).

For the hydrolysis product benzoic acid a log K_{ow} value of 1.88 is reported (OECD, 2001). Freitag, Lay and Korte (1984) found BCF values below 10 for the accumulation of benzoic acid in *Leuciscus idus* and *Chlorella fusca*.

These data indicate that there is no bioaccumulation potential for α,α,α -trichlorotoluene and benzoic acid.

2.2.7 Geoaccumulation

There are no experimental data on the geoaccumulation of α,α,α -trichlorotoluene. Due to the rapid hydrolysis any emission to the terrestrial compartment would result in an exposure to the final hydrolysis products benzoic acid and hydrogen chloride.

Lokke (1984) investigated the adsorption of the degradation product benzoic acid in three different soils in a laboratory batch test. After an equilibration time of 72 hours no adsorption of benzoic acid to melt water sand and clayey till was observed. Very low adsorption was observed in sandy till with an adsorption constant of $K = 0.23$.

It is concluded that geoaccumulation α,α,α -trichlorotoluene and benzoic acid is unlikely to occur.

2.2.8 Environmental Monitoring

No monitoring data are available for α,α,α -trichlorotoluene.

2.3 Human Exposure

2.3.1 Occupational Exposure

At occupational settings, the potential routes of exposure are inhalation and skin contact.

In Germany, Bayer Chemicals AG is the only producer of α,α,α -trichlorotoluene.

At the Bayer manufacturing site, α,α,α -trichlorotoluene is manufactured and processed in closed systems (*cf* Chapter 2.2.1.1). For on-site processing, α,α,α -trichlorotoluene is transported in pipelines (Bayer Chemicals, 2003).

To customers α,α,α -trichlorotoluene is transported in rolling channel drums with plastic or stove coated inliner, and also in rail or road tankers made from nickel or stainless steel, enamelled. The drums are only used once and are disposed of by Bayer Chemicals after use (Bayer Chemicals, 2003).

To protect workers from exposure, several precautionary and protective measures are taken. Sampling uses dedicated closed systems with vacuum exhaust devices connected to the thermal exhaust purification plant. The filling and drumming station is operated with special vacuum exhaust pipes which are connected to the thermal exhaust purification plant. Occupational exposure is therefore not expected to occur (Bayer Chemicals, 2003).

Repair and maintenance work is only carried out on parts of the manufacturing system which have been emptied. Prior to repair and maintenance the parts are flushed with nitrogen or solvent to remove residual product. Special permits are required which include a detailed description of the protective measures (e.g. full protective clothing and gas filter masks (ABEK)) (Bayer Chemicals, 2003).

Surveys of the 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 a dangerous substance at different work situations and appropriate control measures (Bayer Chemicals, 2003).

Downstream users of α,α,α -trichlorotoluene are informed by way of a material safety data sheet on the recommended safety measures (Bayer Chemicals, 2003).

In Germany for occupational settings, an Technical Exposure Limit (TRK) of 0.012 ppm (0.1 mg/m³) is set for α,α,α -trichlorotoluene. At Bayer Chemicals, the exposure of workers is below this limit (Bayer Chemicals, 2003).

Residual levels of α,α,α -trichlorotoluene in the only Bayer downstream product (benzoyl chloride) are below the detection limit (< 5 ppm; data from routine quality control) (Bayer Chemicals, 2003).

Information on other than Bayer products was not readily available. However, residues in other end-products also appear to be negligible, because α,α,α -trichlorotoluene is used to produce other intermediates which are used in synthesis chains. Due to the reactivity of the product, relevant residual levels are not expected to occur.

Because of its hazardous properties α,α,α -trichlorotoluene is regulated and occupational exposure is strictly controlled in the sponsor country. This includes also downstream users, transport-related events, and accidents.

α,α,α -Trichlorotoluene is included in chapter 3.3.1 and Appendix 1 of the EU Seveso II Directive (Directive 2003/105/EC of the European Parliament and of the Council of 16 December 2003). This Directive aims at the prevention of major-accident hazards involving dangerous substances, and at the limitation of the consequences of such accidents for man and for the environment.

2.3.2 Consumer Exposure

A direct use of α,α,α -trichlorotoluene in consumer products is not known (Bayer Chemicals, 2003). α,α,α -Trichlorotoluene is not listed in Nordic and Swiss product registers as being contained in consumer products (Swiss Product Register, 2003; SPIN Database, 2003). Exposure through consumer products is considered to be negligible (Bayer Chemicals, 2003).

Based on the very low emissions of α,α,α -trichlorotoluene into air and water by the manufacturing plant in Germany (*cf* Chapter 2.1), and the low stability in environmental compartments, an indirect exposure of the general public via the environment is not expected.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Upon contact with moisture, α,α,α -trichlorotoluene hydrolyzes forming hydrochloric acid and benzoic acid (see 2.2.3; Reusche, 1989).

When radiolabelled [^{14}C]- α,α,α -trichlorotoluene was administered as single dose (40 mg/kg bw) to Sprague-Dawley rats (4-5 weeks old, about 200 g bw) the [^{14}C]-labelled α,α,α -trichlorotoluene was absorbed from the gastrointestinal tract. The absorption half-life was determined to be 3 h. Blood concentration peaked at 4 h reaching 6.5 ppm and decreased steadily to 2.6 ppm after 24 h. The elimination half-life in blood was 22 h. Elimination (48 h) proceeded to 90 % in urine and 10 % in faeces. After a rapid distribution in the body the renal elimination (elimination half-life in urine: 8 h) of the chemical proceeds according to an apparent first order kinetics. Total radiocarbon residue in tissue 72 hrs after dosing was 1.5 % of the dose given. Higher residues levels were present in fat, kidney and liver (muscle: lowest level), however no significant difference in the elimination rate from all tissues (one compartment model, first order kinetics) was observed. α,α,α -Trichlorotoluene was assumed to be rapidly metabolised via hydrolysis to benzoic acid and subsequently glycinilated to yield hippuric acid. More than 90 % of the recovered radiolabel in urine was actually hippuric acid. Small amounts of benzoic acid (0.7 %) and phenyl acetic acid (0.8 %), as well as four unidentified metabolites (5.5 %) were also found in urine (Yu and Nietschmann, 1980).

Conclusion

α,α,α -Trichlorotoluene hydrolyzes to hydrochloric acid and benzoic acid upon contact with moisture. It is readily absorbed from the gastrointestinal tract, distributed within the body and excreted after metabolic transformation to hippuric acid mainly via the urine.

3.1.2 Acute Toxicity

There are no studies of *in vivo* application of α,α,α -trichlorotoluene performed according to OECD test guidelines mainly because they were undertaken about 20 and more years ago. The studies however, are well documented and are considered to possess adequate quality to allow the evaluation of the endpoint.

Studies in Animals

Inhalation

The acute inhalation toxicity depended on duration of exposure (Bayer AG, 1978b). At about 1,000 mg/m³ the 7 h exposure of male or female rats resulted in the rapid death (within 24h) of all animals. In contrast, a short exposure period of 30 minutes at approximately 750/790 mg/m³ resulted in no death of animals. Nevertheless already in this group the weight gain within the 14 d post-exposure observation time was higher for males than females, indicating a higher susceptibility of female rats against α,α,α -trichlorotoluene. The intermediate exposure times (1 or 3 h; 750/790 – 1,000 mg/m³) confirmed this observation, giving rise to 4/6 deaths for female and 1/6 for male rats, respectively. In contrast to the 0.5 h exposed animals in the groups with the longer exposure times apparent oral and ocular mucosal irritations were noted. For up to 13 days breathing difficulties and behavior alterations were observed (see Table 5).

Table 5 Acute inhalation toxicity (Bayer AG, 1978b)

Conc. [mg/m ³]	exposure time	Deaths		symptoms/total	Average weight loss (14 d)
		number	time		
	[h]				[g]
Males					
1067	7	6	< 24h	6/6	Not determined
1147	3	1	3 d	6/6	-21
797	1	0		6/6	+9
790	0.5	0		0/6	+55
Females					
1193	7	6	< 24h	6/6	Not determined
995	3	4	3-13 d	6/6	-40
795	1	0		6/6	-4
747	0.5	0		0/6	+8

In another study, rats were exposed for 4 hours to 3 concentrations of α,α,α -trichlorotoluene (258/300, 550/530 or 600/654 mg/m³ for males/females, respectively). Again, the before mentioned gender specific difference in susceptibility was noted. The LC₅₀ values for female and male Wistar rats were 530 mg/m³ and >600 mg/m³ respectively. Body weights determined 21 d after exposure revealed a dose dependent weight reduction in all groups except the male group exposed to

258 mg/m³. In all 3 female treatment groups, weight loss was noticed being more pronounced than in the male comparison groups (see Table 6; Bayer AG, 1978b).

Table 6 Acute inhalation toxicity (Bayer AG, 1978b)

Conc. [mg/m ³]	Deaths		symptoms	average weight [g]	
	Number	time to death	total	pre	post (21 d)
Males					
258	1	16 d	6/6	188	195
550	2	1-2 d	6/6	195	171
600	2	2-21 d	6/6	187	143
Females					
300	2	13-18 d	6/6	167	149
530	3	17-21 d	6/6	169	110
654	4	1-21 d	6/6	175	108

In both mid- and high dose groups the visible mucous membranes of the animals were irritated. The gross pathology inspection of the rats at the end of the experiment revealed lung emphysema, atrophy of livers and dark colored spleens.

In another study a 1-hour LC₅₀ value of 8,390 mg/m³ was reported for rats (Cavender, 1979). Female and male rats (n=5) were exposed to α,α,α -trichlorotoluene for 1 h to 2,000, 4,010, 4,820, 6,010, 10,860, 20,300 mg test compound/m³ resulting in 0, 0, 5, 5, 4, 9 deaths. A dose dependent weight reduction was seen in all treatment groups ranging from moderate till severe. During exposure the animals showed nasal discharge, salivation and eye squint. These toxicological signs were only transient. Most animals suffered from dyspnea and retained this symptom for the 14 d observation period. In some animals exposed to the higher concentrations of α,α,α -trichlorotoluene, a decreased activity, as well as ataxia and gasping were noted. The gross pathological examination of the rats revealed occasional dark pink lungs with red patches or foci. In the highest concentration exposure group dark foci on the stomach mucosa and black-orange-streaked intestines were apparent.

The mortality of rats exposed for 4 h to 125 ppm (1,014 mg/m³) benzotrichloride was 5/6 (83.3%). The maximal exposure time where no deaths occurred was 0.5 h when the animals were exposed to saturated vapor (Smyth and Carpenter, 1951).

Conclusion

The 4-hour inhalation LC₅₀ in rats was 530 mg/m³ for females, and >600 mg/m³ for males. 5 of 6 rats died after a 4-hr exposure to about 1,000 mg/m³. Clinical signs included ocular and respiratory tract irritation, dyspnea, and weight loss.

Dermal

The acute dermal toxicity of α,α,α -trichlorotoluene was investigated in 5 male and 15 female Wistar rats. Animals were exposed for 24 hours under occlusive conditions to either 2,500 or 5,000 mg/kg bw (5 or 10 females, respectively) or 5,000 mg/kg bw (males). All animals survived, except for 1 female rat of the 5,000 mg/kg group indicating an LD₅₀ of >5,000 mg/kg bw. The animals started to show sedation and a compromised general health 1 day after exposure. These

symptoms lasted for 8 to 10 d of the 14 d observation period. The dermal areas of contact with test substance were slightly swollen and hardened after removal of the bandages (Bayer AG, 1978b).

Conclusion

The dermal LD₅₀ value for rats was greater than 5,000 mg/kg bw, with sedation and poor general health condition being observed from days 1 to 10 after exposure.

Oral

The acute oral toxicity was investigated using male and female Wistar rats (n=15 per sex and dose group) treated by gavage with α,α,α -trichlorotoluene (in water containing Cremophor EL). LD₅₀ values of 2,188 and 1,590 mg/kg bw were found for male and female rats, respectively. The animals were observed for 14 days. Reduced activity, scrubby fur, labored breathing, and polyuria with sanguineous urine were observed as toxicological symptoms. Symptoms started within 15 minutes after treatment and persisted for 7 to 9 days. The gross pathology of deceased animals revealed empty intestinal tracts and white stipples on the stomach mucosa (Bayer AG, 1978b).

A study, in which undiluted α,α,α -trichlorotoluene was given by gavage to male Wistar rats resulted in a LD₅₀ of 1,249 mg/kg bw. The observation period was 14 days. The recorded symptoms were: increased diuresis, weight loss, scrubby fur, ataxia, shivers accompanied by cramps, and bloody eyes (Bayer AG, 1978a).

LD₅₀ values of 770 and 702 mg/kg bw were reported for male and female rats, respectively, in another study with α,α,α -trichlorotoluene, applied in corn oil. Toxic signs included hypoactivity, ataxia, decreased limb tone, piloerection and urine stained abdomen. At necropsy, pathological changes found were lung congestion, fluid filled intestines, thymus with red foci, and yellow stained urogenital region were found (Velsicol Chem. Corp., 1979).

Conclusion

Depending on the vehicle used, the acute oral LD₅₀ values in rats were between about 700 mg/kg bw (when applied in corn oil) and 2,200 mg/kg bw (when applied as aqueous suspension). Clinical signs like sedation, dyspnea, polyuria, and weight loss were observed for several days after the application of the chemical.

3.1.3 Irritation

A number of studies have been conducted, all according to old protocols and none in agreement with OECD guidelines. Though limited, they allow, however, to assess the irritant properties of α,α,α -trichlorotoluene.

Skin Irritation

Studies in Animals

A skin irritation study was conducted with 6 white New Zealand rabbits. The skin of the animals was treated with the test compound for 24 h under occlusive conditions. The volume applied was 0.5 ml. The animals were inspected 1, 3 and 7 days after application and the erythema and edema formation scored according to the Draize method. Reddening and edema of the skin were observed in all animals. Erythema (grades 1-2) and edema (grade 1) persisted until study termination at day 7 in 6/6 and 5/6 animals, respectively (Bayer AG, 1978b).

No irritation was found in a further study with three male and three female New Zealand white rabbits, exposed to 0.5 ml (approx. 0.69 g) α,α,α -trichlorotoluene of unknown purity for 4 h under

occlusion. Examinations after the 4 h exposure and thereafter 24, 48 and 72 h revealed no skin irritation. The combined irritating score for erythema and edema was 0 (Velsicol Chem. Corp., 1979).

Conclusion

Under occlusive conditions, α,α,α -trichlorotoluene was irritating to rabbit skin.

Eye Irritation

Studies in Animals

Three male and three female white New Zealand rabbits received 0.1 ml of α,α,α -trichlorotoluene (purity not reported) into the conjunctival sac. The lids were held together for about one second and no washout was made. Effects on cornea, iris and conjunctivae were observed for 14 days (see Table 7; Velsicol Chem. Corp., 1979a).

Table 7 Eye irritation scores (ranges) according to Draize (Velsicol Chem. Corp., 1979)

Score ranges:	1h	24h	48h	72h	7 days	14 days
cornea						
opacity	0	0	0-1	0-1	0	0
area	0	0	0-1	0-1	0-1	0
iris	0	0	0-1	0-1	0-1	0
conjunctiva						
redness	1-2	1-2	1-2	1-3	0-1	0
chemosis	1-2	1	1-1.5	1-2	2-3	0

A further eye irritation study was conducted using six white New Zealand rabbits. The animals were treated with 0.1 ml of α,α,α -trichlorotoluene (purity not reported). Again, the inspection of the treated eyes up to 7 days revealed an irritant effect. The not very marked opacities of the cornea were restricted to confined areas (lower inner corneal area) and were resolved at day 7. The effects on the conjunctivae were not fully reversible within 7 days, with grade 1 redness and/or chemosis persisting in 5 of the 6 animals. The scores obtained are given in the following table (see Table 8; Bayer AG 1978b).

Table 8 Eye irritation scores (ranges) according to Draize (Bayer AG, 1978b)

Score ranges:	1h	24h	48h	72h	7 days
cornea					
opacity	0	0-1	0-1	0-1	0
area	0	0-1	0-1	0-1	0
iris	0	0	0	0	0
conjunctiva					
redness	1-2	1-2	1-2	1-3	0-1
chemosis	0-3	0-1	0-2	0-1	0-1

In a publication by Smyth et al. (1951), a severe eye irritation was reported after treatment of rabbits with α,α,α -trichlorotoluene of unknown purity. The results reported fell into the highest injury grade in their score system.

Conclusion

α,α,α -Trichlorotoluene may cause severe eye irritation.

Respiratory Tract Irritation

Studies in Animals

In studies on acute inhalation toxicity, α,α,α -trichlorotoluene was shown to be a respiratory tract irritant. The symptom observed during exposure was irritation of visible mucous membranes at concentrations of $\geq 530 \text{ mg/m}^3$ after 4 hours exposure in rats (Bayer AG, 1978b) or at concentrations of $\geq 795 \text{ mg/m}^3$ after ≥ 1 hours exposure (Bayer AG, 1978b).

Conclusion

α,α,α -Trichlorotoluene is a respiratory tract irritant.

3.1.4 Sensitisation

No data available.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Inhalation

Thirty seven 5-week-old male ICR-JCL mice were exposed to an average concentration of 1.6 ppm (12.8 mg/m^3) α,α,α -trichlorotoluene of unknown purity vaporized at room temperature, twice weekly for 30 minutes for 12 months (Yoshimura et al., 1979, 1986). Surviving animals were observed for an additional 0 to 3 months. Thirty control animals were maintained for 12 months only. All treated animals had severe bronchitis and bronchial pneumonia.

Albino CD rats (10 males + 10 females/group) were exposed for 6 hours/day, 5 days/week to 0, 5.1, 48.2 and 460 mg/m^3 of α,α,α -trichlorotoluene for 4 weeks. All animals exposed to 460 mg/m^3 died or were sacrificed in moribund state during the first week. Gasping and dyspnea were observed in the animals exposed to 460 and 48.2 mg/m^3 . This latter group of animals also showed decreased body weight gains. Histopathological examination revealed exposure related findings in the animals of the 460 and 48.2 mg/m^3 groups like desquamation of superficial lining cells of bronchi and bronchioles. In nasal turbinates and trachea infiltrates of acute inflammatory cells, as well as loss and/or squamous metaplasia of superficial epithelial cells were seen in the medium and high dose groups. No such observations were made in the 5.1 mg/m^3 exposed animals. Therefore, a NOAEL of 5.1 mg/m^3 was defined (Velsicol Chem. Corp., 1981).

Conclusion

In mice, the repeated inhalation of α,α,α -trichlorotoluene (12.8 mg/m^3 for 12 months) resulted in a high incidence of bronchitis and bronchopneumonia. In rats repeated inhalation exposure to concentrations $\geq 48.2 \text{ mg } \alpha,\alpha,\alpha$ -trichlorotoluene $/\text{m}^3$ for 4 weeks led to death, depressed weight gain, dyspnoea and gasping. Microscopically, inflammation and/or squamous metaplasia of the cells lining the nasal, tracheal, bronchial and bronchiolar epithelia were observed. No significant changes occurred in the 5.1 mg/m^3 group (NOAEL).

Dermal

In a three week dermal toxicity study with four male and four female white New Zealand rabbits per dose group, undiluted α,α,α -trichlorotoluene (purity 96.4%) was administered to the shaved animal backs at dosage levels of 50, 100 and 200 mg/kg bw/day for 6 hours/day, 5 days/week. The skin of 2 male and 2 female animals of each dose group was abraded. One animals of the high-dose

group died. No effects were found on body weights, general behavior, and blood and urine parameters. Dose-dependent erythema, edema, desquamation, coriaceousness, fissuring, eschar formation, exfoliation, necrosis, blanching (only 200 mg/kg bw/day-group) and enlargement of the regional lymph nodes as well as atonia was observed in all doses. The histopathological examination showed an increased incidence of portal inflammatory cell infiltrates in the liver in all groups and bile duct proliferation at 200 mg/kg bw/day. In seminiferous tubules of the 100 and 200 mg/kg bw/day groups multinucleated giant cells and degeneration of the tubules were seen (Velsicol Chem. Corp., 1980).

Limited information on this endpoint is also available from a series of dermal carcinogenicity studies conducted on ICR mice (*cf* also section on Carcinogenicity for study details) (Fukuda et al., 1981). Irritation of the eyes, the skin and the respiratory tract as well as an increase in motor activities were the main clinical signs after repeated painting of mice skin with α,α,α -trichlorotoluene. First, erythema and swelling were noted, later-on alopecia, induration, marked keratinization, ulceration and/or epidermal necrosis were observed at treated skin.

Conclusion

Skin irritation up to necrosis was seen after dermal treatment of rabbits with 50, 100 or 200 mg/kg bw/day of the undiluted chemical for three weeks. Histopathologically, an increased incidence of portal inflammatory cell infiltrates in the liver, and, at 200 mg/kg bw/day, bile duct proliferation was found. Pathological changes were also seen in the seminiferous tubules at 100 and 200 mg/kg bw/day. Irritation of the eyes, the skin and the respiratory tract were the main clinical signs after repeated painting of mice skin with α,α,α -trichlorotoluene.

Oral

Oral toxicity of trichlorotoluene isomers including α,α,α -trichlorotoluene was examined in a 28-day feeding study in Sprague-Dawley rats. The doses given to the 10 animals/sex per group were 0.5, 5.0, 50.0, 500 ppm of α,α,α -trichlorotoluene in the diet. Based on food consumption data the amount of chemical ingested was 0.048 - 46 mg/kg bw/day for male rats and 0.053 - 53 mg/kg bw/day for female rats. No deaths and no clinical signs of toxicity were observed. The growth rate, food consumption, and hematological parameters were not affected by the treatment. Furthermore only mild serum biochemical changes in male rats were noticed, i.e. an increase in sorbitol dehydrogenase activity (in the 5.0 and 50.0 ppm dose group) and elevated lactic dehydrogenase activity (in the 500 ppm dose group). Mild histopathologic changes in liver, kidney and thyroids were observed in all treated groups, becoming progressively more severe and more frequent as dose levels increased. No residual compound was measured in liver and fat (detection limit: 0.1 ppm) (Chu et al., 1984).

Conclusion

In a 28-day feeding study on rats, a NOAEL could not be determined, as mild histopathological effects on liver, kidney and the thyroid gland were still present at the lowest test concentration of 0.5 ppm (corresponding to about 0.05 mg/kg bw/day).

3.1.6 Mutagenicity

Sufficient data has been generated. The animal data consist of inhalation study in male rats. The in vitro data are reverse mutation, chromosomal aberration and sister chromatid exchange tests.

In vitro Studies

Results of mutagenicity testing of α,α,α -trichlorotoluene in bacterial systems are equivocal. Positive results were obtained in a rec assay (assay for differential growth inhibition) in *Bacillus subtilis* and in reverse mutation assays in *Escherichia coli* and *Salmonella typhimurium* when a metabolic activation system was present (Yasuo et al., 1978). In another study, negative results were found for reverse mutation in *S. typhimurium* and for forward mutation in *Saccharomyces cerevisiae* in the absence and presence of metabolic activation (Jagannath, 1978). In an *in vitro* micronucleus test developed by Suzuki (1985b) using cultured bone marrow cells from Balb/c mice, α,α,α -trichlorotoluene induced micronuclei.

In vivo Studies

In a study, that is only reported in the form of an abstract and which therefore cannot be judged for its reliability, slight increases in chromosomal aberrations in bone marrow cells of rats exposed to 1 ppm α,α,α -trichlorotoluene for 6 hours/day, 5 days/week, during 1-, 3- and 6-month periods were reported. Additionally, a significant increase in the frequency of sister chromatid exchanges in peripheral lymphocytes was observed (Koshi and Fukuda, 1986).

In non-standard *in vivo* micronucleus assays using Balb/c mice, α,α,α -trichlorotoluene was tested positive. The mice were pre-treated with polychlorinated biphenyl (12.5 mg in 0.2 ml corn-oil) five days prior to the intraperitoneal administration of α,α,α -trichlorotoluene at doses of 50, 100 and 200 mg/kg bw. In an additional experiment, the α,α,α -trichlorotoluene was incubated with mouse-S9-liver fraction before it was administered by intraperitoneal injection at dose levels of 100, 200 and 300 mg/kg bw. The latter treatment resulted in an even higher incidence of micronucleated cells as compared to the treatment with the non-incubated α,α,α -trichlorotoluene (Suzuki, 1985a).

Conclusion

α,α,α -Trichlorotoluene has demonstrated a genotoxic potential in bacterial and mammalian cell systems. In non-standard *in vivo* tests, the chemical induced micronuclei in bone marrow cells of mice. Chromosomal aberrations in bone marrow cells and sister chromatid exchanges in peripheral lymphocytes have been reported in rats after repeated inhalation exposure.

3.1.7 Carcinogenicity

In vivo Studies

In a short term lung adenoma assay, α,α,α -trichlorotoluene (at least 99% purity) in tricaprylin was administered to both sexes of A/J mice (11 to 15/group) by intraperitoneal injection at doses of 12, 30, or 60 mg/kg bw, 3 times/week for 8 weeks. Total doses were 287, 719, or 1440 mg/kg bw. The mice were observed for 16 weeks following the exposure period. Lung adenomas were observed in 4/15 vehicle- treated controls of each sex, while 100% of the animals in all treated groups developed lung adenomas. The tumour incidence was significantly increased in each group compared with controls, and there was a significant dose-related trend in the average number of tumours per mouse. In other organs, only tumours observed as gross lesions at necropsy were further examined. In the highest dose group, three lymphomas and two kidney sarcomas, which reportedly occur rarely in this strain, were observed (Stoner et al., 1986).

Inhalation

37 5-week-old female ICR-JCL mice were exposed to an average concentration of 1.6 ppm (12.8 mg/m³) α,α,α -trichlorotoluene of unknown purity vaporized at room temperature, twice weekly for 30 minutes for 12 months (Yoshimura et al., 1979; 1986). Surviving animals were observed for an

additional 0 to 3 months. Thirty control animals were maintained for 12 months only. In the 10 treated mice that died before 12 months, the following tumor incidences were observed: 7 lung adenomas, 1 lung adenocarcinoma, and 1 skin papilloma. Ten treated mice were sacrificed at 12 months; lung adenoma was found in 5, adenocarcinoma in 4, skin papilloma in 3 and skin carcinoma in 1. Lung adenoma was observed in 3/30 of the control animals that died or were killed at 12 months. Of 8 treated mice that died from 12 to 15 months, 3 had lung adenoma, and 3 adenocarcinoma. None had skin tumors. The remaining 9 mice were killed at 15 months; 2 had lung adenomas, 5 had adenocarcinomas, 2 had skin papillomas, and 3 had skin carcinomas. Thus, the proportion of malignant tumors at these sites increased with time. During the first 12 months, 3 malignant lymphomas were observed, and 1 was observed between 12 and 15 months. The overall incidence of tumors was 30/37 (81 %) for the lung (compared to 3/30 in controls), 10/37 (27 %) for the skin (0/30 in controls), and 4/37 (11 %) for malignant lymphoma (0/30 in controls). The incidence at each of these sites was significantly elevated compared to the control incidence. Yoshimura et al. (1979) noted that all treated animals had severe bronchitis and bronchial pneumonia.

In a related study, 32 5-week-old female ICR mice were exposed by inhalation to an average concentration of 6.8 ppm (54.8 mg/m³) α,α,α -trichlorotoluene of unknown purity, vaporized at 50°C (Takemoto, Yoshimura and Matsushita, 1978; Yoshimura et al., 1986). The animals were exposed twice weekly for 30 minutes for 5 months, followed by a 1- to 5-month observation period. The control group of 30 animals was observed for 12 months; no results were reported. Of 12 treated mice that died during the exposure period, 2 had lung adenomas; 6 had malignant lymphoma. At the end of the treatment, 6/11 mice had developed lung adenomas and 1/11 had squamous-cell carcinoma of the skin. After 10 months, 8/9 had lung adenomas, 1/9 had lung adenocarcinoma, 3/9 had skin carcinoma, 4/9 had skin papillomas, and 2/9 had malignant lymphoma. The overall tumor incidence was 17/32 (53%) for the lung, 8/32 (25%) for the skin, and 8/32 (25%) for malignant lymphoma, compared with 3/30 lung adenomas and no other tumors in the controls.

Inhalation studies on Sprague-Dawley rats were reported by Fukuda and Takemoto (1980, 1984). The seven week old female rats were exposed to 2, 1, 0.4 and 0.1 ppm α,α,α -trichlorotoluene (16; 8; 3.2; 0.8 mg/m³) for 6 hours/day on 5 days/week for 104 weeks and autopsied at 107 weeks. In the 2 ppm group, the concentration of α,α,α -trichlorotoluene was decreased stepwise because of the progressive deaths observed. Nevertheless, all these animals died until week 39. The death rates for all groups, except the 0.1 ppm group, were significantly higher than the control values. Tumors of the respiratory system occurred in 92-12% of the animals, and more than half of them were malignant. Tumors of the nasal cavity appeared in 64-28% of the treated animals. Nasal tumors in the 2 ppm group were squamous cell carcinomas, and in the lower dose groups more than 60% of the nasal tumors were adenocarcinomas. Most of the tumors of the larynx (noted in 24-18%) and trachea (noted in 12-6%) were squamous cell carcinomas. Pulmonary tumors appeared in 35-10% of the animals, including squamous cell carcinomas at 2 ppm and adenocarcinomas in about 50% of the tumors at the lower concentrations. The exposed animals also developed tumors of the skin and the external ear duct.

Dermal

A series of three skin-painting studies on specific pathogen-free ICR mice, using α,α,α -trichlorotoluene (reagent grade) at successively smaller doses for longer periods was conducted (see table 10). The compound was administered undiluted or dissolved in benzene. In the first experiment, three groups of 19 to 22 14-week-old female ICR mice received skin applications of 25 μ l benzene (vehicle control), 25 μ l α,α,α -trichlorotoluene (34.3 mg), or 25 μ l of a 50% solution of α,α,α -trichlorotoluene (17.1 mg) in benzene. The doses were given twice weekly for 3 weeks,

then once weekly until the mice were killed at 7.2 months. Assuming a total of 34 doses, the high dose corresponded to a total of approximately 1,165 mg (average dose rate of 5.4 mg/day) and the low dose to 582.4 mg (average dose rate of 2.7 mg/day). Mortality at the termination of the experiment was 0, 10, and 46% in the control, low- and high-dose groups, respectively. The number of mice with tumours was 0/20, 17/19, and 21/22 in the control, low-dose, and high-dose groups, respectively. The reported incidence of tumours at specific sites for low- and high-dose groups was 6/19 and 12/22 for skin carcinomas, 10/19 and 9/22 for lung adenoma/carcinoma, and 1/19 and 6/22 for thymus lymphoma (Fukuda et al., 1981).

Similar results were obtained in the second experiment in which three groups of 9 to 10 3-week-old female ICR mice received dermal application of 10 μ l of benzene (vehicle control), 10 μ l α,α,α -trichlorotoluene or 10 μ l of a 50% α,α,α -trichlorotoluene:benzene solution 3 times/week for 4 weeks then twice weekly thereafter until sacrifice at 9.8 months. The mice in the high-dose group were sacrificed at 5.7 months because of high mortality and morbidity. The high dose thus represented a total of 740 mg and the low dose 603 mg (4.3 and 2.1 mg/day, respectively). Mortality at termination was 0, 60, and 80% for the control, low-dose, and high-dose groups, respectively. The number of mice with tumours was 0/10, 10/10, and 8/9 in the control, low-dose, and high-dose groups, respectively. Reported tumour incidences at specific sites for the low- and high-dose groups was 7/10 and 4/9 for skin carcinomas, 10/10 and 3/9 for lung adenoma/adenocarcinoma, and 3/10 and 5/9 for thymus lymphoma. In addition, two squamous-cell carcinomas of the lips and one squamous-cell carcinoma of the forestomach were reported in the low-dose mice. These tumors were assumed to result from the ingestion of α,α,α -trichlorotoluene caused by licking of the skin (Fukuda et al., 1981).

In the third experiment, 2 groups of 20 7-week-old female ICR mice received skin applications of 25 μ l benzene (controls) or 25 μ l of a 9.2% solution of α,α,α -trichlorotoluene in benzene twice weekly for 11.7 months. The total dose was approximately 315 mg (0.9 mg/day). Surviving mice were sacrificed at 18.7 months (controls) or at 13.3 months (α,α,α -trichlorotoluene-treated). Mortality at termination was 20% in the controls compared with 35% in the treated group. In the control group, 2/20 mice had lung adenomas while in the treated group, 13/19 had skin carcinoma and 11/19 had lung adenoma/carcinoma. Nineteen other tumors, attributed to licking, were observed in the lips, tongue, esophagus, forestomach and glandular stomach of the treated mice (see Table 9) (Fukuda et al., 1981).

Table 9 Dermal carcinogenicity (Fukuda et al., 1981)

Mouse age	dose [μ l]	treatment	total dose [mg]	end of experiment [month]	deaths [%]	all tumours	skin carc.	lung adenoma adenocarc	thymoma
14 w	0	2/w 3w; 1/w	0	7.2 m	0	0/20			
14 w	12.5		582.4	7.2 m	10	17/19	6/19	10/19	1/19
14 w	25		1165	7.2 m	46	21/22	12/22	9/22	6/22
3 w	0	3/w 4w; 2/w	0	9.8 m	0	0/10			
3 w	5		603	9.8 m	60	10/10	7/10	10/10	3/10
3 w	10		740	5.7 m	80	8/9	4/9	3/9	5/9
7w	0	2/w 11.7 m	0	18.7 m	20	2/20	0/20	2/20	0/20
7w	2.3		315	13.3 m	35	18/19	13/19	11/19	19 others

Oral

Groups of 40 nine-week-old female ICR mice were gavaged with 0.043, 0.17, 0.7, or 2.7 mg α,α,α -trichlorotoluene of 99.5% purity in 0.1 ml sesame oil twice weekly for 25 weeks (Fukuda,

Matsushita and Takemoto, 1978; Fukuda et al., 1993). The 40 control animals were untreated. Surviving animals were killed and examined histologically 18 months after the start of treatment. Mortality was significantly increased in the two highest dose groups, reaching 50% at 6.5 months in the highest dose group and at 16.5 months in the second highest dose group. Forestomach squamous cell carcinoma was observed in 0/35, 0/37, 2/38, 22/40, and 24/35 animals in the control to high-dose groups, respectively. The incidence was significantly increased at the two highest dose levels. Lung adenocarcinoma was reported in 0/35, 1/37, 9/38, 16/40, and 10/35 animals; the incidences were significantly increased in the three highest dose groups. Lung adenoma was observed in approximately equal proportions to carcinoma (1/35, 0/37, 6/38, 17/40, and 10/35; significantly increased at the two highest dose levels). Thymoma incidence (0/35, 0/37, 1/38, 2/40, and 7/35) was significantly increased only at the highest dose (see Table 10).

Table 10 Oral carcinogenicity (Fukuda, Matsushita and Takemoto, 1978; Fukuda et al., 1993)

	Control	0.043 mg/kg/d	0.17 mg/kg/d	0.7 mg/kg/d	2.7 mg/kg/d
No. of mice with tumor/ Effective number of animals	4/39 (10%)	10/39 (26%)	30/39 (77%)**	39/40 (98%)**	36/38 (95%)**
LD50 (months)				16.5	6.5
Forestomach papilloma	0/39 (0%)	0/39 (0%)	0/39 (0%)	2/40 (5%)	1/38 (3 %)
Forestomach squamous cell carcinoma	0/39 (0%)	0/39 (0%)	2/39 (5%)	21/40 (53%)	24/38 (63%)
Forestomach tumors	0/39 (0%)	0/39 (0%)	2/39 (5%)	23/40 (58%)**	25/38 (68%)**
Lung adenoma	1/39 (3%)	6/39 (15%)	17/39 (44%)	19/40 (48%)	14/38 (37%)
Lung adeno-carcinoma	1/39 (3%)	1/39 (3%)	9/39 (23%)	16/40 (40%)	10/38 (26%)
Lung tumors	2/39 (5%)	7/39 (18%)	26/39 (67%)**	35/40 (88%)**	24/38 (63%)**
Hematopoietic system	1/39 (3%)	2/39 (5%)	1/39 (3%)	3/40 (8%)	8/38 (21%)**
Other tumors	1/39 (3%)	2/39 (5%)	3/39 (8%)	5/40 (13%)	4/38 (11%)

**) Statistically significant difference from the control (p <0.01) (Fisher's exact probability test)

Conclusion:

α,α,α -Trichlorotoluene has induced lung tumors, skin tumors, leukemias and lymphomas in animals by the inhalative, dermal and oral routes of exposure.

Human Experience

Three cancer deaths among 41 workers employed in a benzoyl chloride production plant in Japan between 1954 and 1972 were reported. Two of the deaths were from lung cancer, both in smokers in their forties. The third cancer death was from maxillary malignant lymphoma in a 50-year-old worker not specified as a smoker or non-smoker. A fourth case of cancer diagnosed as squamous cell carcinoma of the lung was identified in a non-smoking worker still living at the time the analysis was undertaken in 1973. The number of years these four workers were employed in benzoyl chloride production ranged from 6 to 15 years. The number of deaths from lung cancer (2)

was significantly higher than the number expected (0.06), based on the Japanese national rates for death from lung cancer in males. In addition to α,α,α -trichlorotoluene and benzoyl chloride, these workers were exposed to toluene, chlorine gas, hydrogen chloride, benzyl chloride, benzal chloride, other chlorinated toluenes and polymerized products from the process. However, the authors considered it likely that the four cancer cases were produced by exposure to α,α,α -trichlorotoluene or benzoyl chloride since these are the major products of the two chemical reactions in the production process (Sakabe, Matsushita and Koshi, 1976).

In a subsequent report, two lung cancer deaths were identified among workers engaged in benzoyl peroxide and benzoyl chloride production at another plant, in which the total number of workers ranged from 13 in 1952 to 40 in 1963 (Sakabe and Fukuda, 1977). The two individuals, one of whom was a smoker, were in their forties and had worked in benzoyl chloride production for 6 to 18 years. The number of deaths expected among these workers was not reported.

A study of cancer mortality among 953 workers at a British factory engaged in production of chlorinated toluenes was conducted. As in the Japanese plants, there was exposure to toluene (the starting material), α,α,α -trichlorotoluene and benzoyl chloride (the major reaction products), as well as benzyl chloride, benzal chloride and other materials. The cohort of exposed workers consisted of 163 males employed for at least six months between 1961 and 1970. Some of these individuals started employment as early as 1923. Of the 10 deaths from cancer (25 total deaths) reported in this group, 5 were due to digestive system cancers and 5 to respiratory cancers, compared with 1.24 and 1.78 expected, respectively. The standardised mortality ratio for each of these sites was significantly higher than expected, based on mortality rates for England and Wales. A survival analysis using the Cox Proportional Hazards model, adjusting for age at entry to the survey and the time period when employment began, was also conducted. This analysis showed a statistically significant association between estimated cumulative exposure and deaths from cancer at all sites (but neither digestive nor respiratory cancers individually), for persons first employed before 1951. The association was not significant for all entry cohorts combined. Interpretation of this study is limited by several factors, including possible bias in assignment of exposure categories, exposure to multiple compounds and lack of data on smoking (Sorahan et al., 1983).

Another retrospective mortality study reported on a cohort of 697 male workers who were exposed to benzyl chloride, α,α,α -trichlorotoluene and benzoyl chloride at a chlorination plant. The length of employment at the plant ranged from 1 year to >35 years. Seven deaths from respiratory cancer (6 lung, 1 larynx) were found in the total cohort compared with 2.84 expected deaths based on U.S. mortality rates for males. Five of these deaths occurred in workers employed for at least 15 years. This was significantly greater than the 1.32 deaths expected for this subgroup. The results of this study were confounded by multiple exposures and lack of data on smoking (Wong, 1988).

Conclusion

The available human data for α,α,α -trichlorotoluene are limited because the studies included small numbers of cancer deaths and were confounded by exposure to mixtures of chlorinated compounds. Based on the limited human data and sufficient evidence from animal studies, the combined exposures to α -chlorinated toluenes and benzoyl chloride are probably carcinogenic to humans (IARC Group 2A).

3.1.8 Toxicity for Reproduction

Effects on Fertility

α,α,α -Trichlorotoluene has not been tested for its effects on reproduction.

In a 3-week dermal study on rabbits, degeneration of the tubules in seminiferous ducts, and an increased incidence of multinucleated giant cells in the seminiferous tubules were reported at dose levels of 100 and 200 mg/kg bw/day but not for 50 mg/kg bw/day (Velsicol Chem. Corp., 1980).

Pathological changes in reproductive organs were not reported in any of the carcinogenicity studies. Sufficient documentation with regard to the scope of the examinations relating to the reproductive organs was however not available.

Developmental Toxicity

In a study that is only available as an abstract (Ruddick et al., 1982) and which cannot therefore be evaluated as to its reliability, rats were treated by gavage on days 6-15 of gestation with α,α,α -trichlorotoluene of unspecified purity at dose levels of 12.5, 25 and 50 mg/kg bw/day (vehicle not reported). An increased number of resorption sites and reduced numbers of fetuses per litter at the dose of 50 mg/kg bw/day were reported. All doses induced a reduction in the mean fetal weight and skeleton anomalies in pups were evident (no further data reported; fetal LOAEL = 12.5 mg/kg bw). Maternal toxicity was recorded with significantly reduced weight gain at doses equal or greater than 25 mg/kg bw/day and changes in clinical and hematological parameters as well as organ weights at 50 mg/kg bw/day. Therefore the NOAEL for maternal toxicity is 12.5 mg/kg bw/day and for developmental toxicity the LOAEL is 12.5 mg/kg bw/day.

Conclusion

There were no fertility studies available. In a 3-week dermal study on rabbits, degeneration of the tubules in seminiferous ducts, and an increased incidence of multinucleated giant cells in the seminiferous tubules were reported at dose levels of 100 and 200 mg/kg bw/day, but not for 50 mg/kg bw/day. Pathological changes in reproductive organs were not reported in any of the carcinogenicity studies. Sufficient documentation with regard to the scope of the examinations relating to the reproductive organs was however not available, and therefore a lack of effect cannot be deduced from these studies. The effects on male reproductive organs observed in the 3-week dermal study in rabbits give some indications that α,α,α -trichlorotoluene might be toxic to reproduction. As results from further testing would not affect the most stringent exposure control measures already in place, no further tests are warranted.

In a poorly documented study, developmental effects were reported in rats at non-maternally toxic dose levels (LOAEL, fetal development = 12.5 mg/kg bw/day; NOAEL maternal toxicity = 12.5 mg/kg bw/day). Further testing is not warranted because exposure to the chemical is already strictly controlled due to its mutagenic and carcinogenic properties. Although not fully tested for reproductive and developmental toxicity, α,α,α -trichlorotoluene should be regarded as potentially toxic to reproduction because it is a genotoxic carcinogen.

3.2 Initial Assessment for Human Health

α,α,α -Trichlorotoluene hydrolyzes to hydrochloric acid and benzoic acid upon contact with moisture. It is readily absorbed from the gastrointestinal tract, distributed within the body, and excreted after metabolic transformation to hippuric acid mainly via the urine. The 4-hour inhalation LC₅₀ in rats was 530 mg/m³ for females, and > 600 mg/m³ for males. 5 of 6 rats died after a 4-hour exposure to about 1,000 mg/m³. Clinical signs included ocular and respiratory tract irritation,

dyspnea, and weight loss. The dermal LD50 value for rats was greater than 5,000 mg/kg bw, with sedation and poor general health from days 1 to 10 after exposure. Depending on the vehicle used, the acute oral LD50 values in rats were between about 700 mg/kg bw (when applied in corn oil) and 2,200 mg/kg bw (when applied as aqueous suspension). Clinical signs like sedation, dyspnea, polyuria, and weight loss were observed for several days after the oral administration of the chemical.

Under occlusive conditions, α,α,α -trichlorotoluene was irritating to the skin of rabbits. The chemical may cause severe eye irritation. The vapors are irritating to the respiratory tract.

In mice, the repeated inhalation of α,α,α -trichlorotoluene (12.8 mg/m³ for 12 months) resulted in a high incidence of bronchitis and bronchopneumonia. In rats, repeated inhalation exposure to concentrations ≥ 48.2 mg/m³ for 4 weeks led to death, depressed weight gain, dyspnoea and gasping. Microscopically, inflammation and/or squamous metaplasia of the cells lining the nasal, tracheal, bronchial and bronchiolar epithelia were observed. No significant changes occurred in the 5.1 mg/m³ group (NOAEL). Skin irritation up to necrosis was seen after dermal treatment of rabbits with 50, 100 or 200 mg/kg bw/day of the undiluted chemical for three weeks. Histopathologically, an increased incidence of portal inflammatory cell infiltrates in the liver, and, at 200 mg/kg bw/day, bile duct proliferation was found. Pathological changes were also seen in the seminiferous tubules at 100 and 200 mg/kg bw/day. Irritation of the eyes, the skin and the respiratory tract were the main clinical signs after repeated painting of mice skin with α,α,α -trichlorotoluene. In a 28-day feeding study on rats, a NOAEL could not be determined, as mild histopathological effects on liver, kidney and the thyroid gland were still present at the lowest test concentration of 0.5 ppm in the diet (corresponding to about 0.05 mg/kg bw/day).

α,α,α -Trichlorotoluene has demonstrated a genotoxic potential in bacterial and mammalian cell systems. In non-standard in vivo tests, the chemical induced micronuclei in bone marrow cells of mice. Chromosomal aberrations in bone marrow cells and sister chromatid exchanges in peripheral lymphocytes have been reported in rats after repeated inhalation exposure.

α,α,α -Trichlorotoluene has induced lung tumors, skin tumors, leukemia and lymphomas in animals by the inhalative, dermal and oral routes of exposure. The available human data for α,α,α -trichlorotoluene are limited because the studies included small numbers of cancer deaths and were confounded by exposure to mixtures of chlorinated compounds. Based on the limited human data and sufficient evidence from animal studies, the combined exposures to α -chlorinated toluenes and benzoyl chloride are probably carcinogenic to humans (IARC Group 2A).

There were no fertility studies available. In a 3-week dermal study on rabbits, degeneration of the tubules in seminiferous ducts, and an increased incidence of multinucleated giant cells in the seminiferous tubules were reported at dose levels of 100 and 200 mg/kg bw/day, but not for 50 mg/kg bw/day. Pathological changes in reproductive organs were not reported in any of the carcinogenicity studies. Sufficient documentation with regard to the scope of the examinations relating to the reproductive organs was however not available, and therefore a lack of effect cannot be deduced from these studies. The effects on male reproductive organs observed in the 3-week dermal study in rabbits give some indications that α,α,α -trichlorotoluene might be toxic to reproduction. As results from further testing would not affect the most stringent exposure control measures already in place, no further tests are warranted.

In a poorly documented study, developmental effects were reported in rats at non-maternally toxic dose levels (LOAEL, fetal development = 12.5 mg/kg bw/day; NOAEL maternal toxicity = 12.5 mg/kg bw/day). Further testing is not warranted because exposure to the chemical is already strictly controlled due to its mutagenic and carcinogenic properties. Although not fully tested for

reproductive and developmental toxicity, α,α,α -trichlorotoluene should be regarded as potentially toxic to reproduction because it is a genotoxic carcinogen.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Since α,α,α -trichlorotoluene reacts with water rapidly, forming benzoic acid and hydrochloric acid, α,α,α -trichlorotoluene itself indicates no hazard to the aquatic environment (*cf* Chapter 2.2.3).

However, several aquatic toxicity tests have been undertaken with α,α,α -trichlorotoluene (see Table 12).

It has to be considered that due to the very fast hydrolysis of α,α,α -trichlorotoluene the effects observed in these studies can be attributed to the degradation products benzoic acid and hydrochloric acid.

Acute Toxicity Test Results

Acute toxicity of α,α,α -trichlorotoluene to fish (*Leuciscus idus*) has been tested under static conditions in accordance to the German standard method for water, wastewater and sludges DIN 38412 Part 15 in neutralised test medium. A 48 h-LC₅₀ of 4140 mg/l was measured (Juhnke and Luedemann, 1978). In a limit test with *Leuciscus idus melanotus* in a static system an acute toxicity (72 h-LC₅₀) of > 1000 mg/l was observed (Bayer AG, 1976b). Although the available fish studies are shorter in duration than required by the OECD guideline, they are nevertheless regarded as sufficient to cover the SIDS endpoint for this substance.

Two static *Daphnia* acute tests were performed by Bringmann and Kuehn (1977a, 1982) according to the immobilisation test procedure of the authors. For both tests the authors give the information that the pH of the test solutions was not changed. The first test (Bringmann and Kuehn, 1977a) on *Daphnia magna* resulted in an 24 h-EC₅₀ > 100 mg/l. In the second test Bringmann and Kuehn (1982) reported an EC₅₀ (24 h) of 50 mg/l. Although it is stated in these studies that the pH was monitored, the pH values are not reported. In comparison to α,α,α -trichlorotoluene, benzoic acid is about 1 order of magnitude less toxic (Bringmann and Kuehn, 1982). Thus, it is assumed that the toxicity may solely be related to the pH shift caused by formation of hydrochloric acid (see below). Although the available *Daphnia* studies are shorter in duration than required by the OECD guideline, they are nevertheless regarded as sufficient to cover the SIDS endpoint for this substance.

With the blue-green alga *Microcystis aeruginosa* an 8 day-EC₃ of 34 mg/l was obtained in a cell multiplication inhibition test Bringmann and Kuehn (1978). No information on pH is given. It is only stated that the test solution was not neutralised. Therefore, toxic effects may be due to pH changes. No tests with algae with a test duration of 72 h is available from which an EC₅₀ can be derived. However, the available information is regarded as sufficient to cover the SIDS endpoint for this substance.

The results of the aquatic toxicity testing of α,α,α -trichlorotoluene on fish, *Daphnia* and algae are compiled in Table 11.

Table 11 Acute and chronic toxicity of α,α,α -trichlorotoluene to fish, *Daphnia* and algae

Trophic level	Species	Test type	Result	Source	IUCLID
Fish	<i>Leuciscus idus</i>	Static, acute	48 h-LC ₅₀ = 4140 mg/l (n)	Juhnke and Luedemann, 1978*	4.1
Fish	<i>Leuciscus idus melanotus</i>	Static, acute	72 h-LC ₅₀ > > 1000 mg/l (n)	Bayer AG, 1976b	4.1
<i>Daphnia</i>	<i>Daphnia magna</i>	Static, acute	24 h-EC ₅₀ > > 100 mg/l (n)	Bringmann and Kuehn, 1977a	4.1
<i>Daphnia</i>	<i>Daphnia magna</i>	Static, acute	24 h-EC ₅₀ = = 50 mg/l (n)	Bringmann and Kuehn, 1982*	4.2
Blue-Green Algae	<i>Microcystis aeruginosa</i>	Static, chronic	8 d-EC ₃ = 34 mg/l (n)	Bringmann and Kuehn, 1978*	4.3

(n): nominal concentration

*studies flagged as robust summary studies

Other chronic data for aquatic toxicity of α,α,α -trichlorotoluene are not available. Regarding the rapid hydrolysis of the substance a chronic aquatic exposure is not expected.

Determination of PNEC_{aqua}

Valid acute fish and *Daphnia* tests plus an 8d algal test (EC₃ = 34mg/l) are available for trichlorotoluene. As it is concluded that the effect values of 50 mg/l (derived from one *Daphnia* study) and 34 mg/l (from the *Microcystis* study) are influenced by pH shifts, the 24h-EC₅₀ of > 100 mg/l found in the second *Daphnia* study is used as basic value for the PNEC. It is not expected that an algal EC₅₀ obtained with a neutralized test solution would be lower than the EC₅₀ for *Daphnia*. Applying an assessment factor of 1000 according to the EU Technical Guidance Document results in a PNEC_{aqua} of:

$$\text{PNEC}_{\text{aqua}} = 100 \text{ mg/l} / 1000 = 0.1 \text{ mg/l}$$

Due to the fast hydrolysis this PNEC covers the hydrolysis products benzoic acid and hydrochloric acid.

Toxicity to Microorganisms

Regarding the toxicity to microorganisms, several cell multiplication inhibition tests were performed with different species (Table 12) by Bringmann (1978), Bringmann and Kuehn (1977b, 1980a, 1980 b, 1981), and Bringmann et al. (1980).

Table 12 Toxicity of α,α,α -trichlorotoluene to microorganisms

Trophic level	Species	Test type	Result	Source	IUCLID
Bacteria	<i>Pseudomonas putida</i>	Cell multiplication inhibition test, static, pH neutral	16 h-EC ₃ > 100 mg/l (n)	Bringmann and Kuehn, 1977b*, 1980b*	4.4
Protozoa	<i>Chilomonas paramecium</i>	Cell multiplication inhibition test, static, pH 6.9	48 h-EC ₅ = 27 mg/l (n)	Bringmann and Kuehn, 1981, Bringmann et al. 1980	4.4
Protozoa	<i>Entosiphon sulcatum</i>	Cell multiplication inhibition test, static, pH 6.9	72 h-EC ₅ = 56 mg/l (n)	Bringmann, 1978	4.4
Protozoa	<i>Uronema parduzci</i>	Cell multiplication inhibition test, static, pH 6.9	20 h-EC ₅ > 80 mg/l (n)	Bringmann and Kuehn, 1980b	4.4

(n): nominal concentration

*studies flagged as robust summary studies

Toxicities of benzoic acid and hydrochloric acid

The hydrolysis products benzoic acid and hydrochloric acid have been tested with aquatic species. Especially hydrochloric acid caused a pH shift in water (Table 13). The resulting pH determined the impact on aquatic life as shown with buffered test substance solution. Thus toxic effects are not due to substance inherent properties but a function of the pH (OECD-SIDS on Hydrochloric Acid, 2002). Regarding natural systems, the impact of dissociated acids depends on the buffer capacity of the system. Buffer function is attributed to humic substances, carbonates, clay minerals, silicates, as well as sesquioxides.

Table 13 Theoretical concentrations of benzoic acid and hydrochloric acid after degradation of α,α,α -trichlorotoluene in neutral water (pH = 7) without buffer and resulting pH-values

α,α,α -trichlorotoluene concentration	resulting benzoic acid concentration	resulting hydrochloric acid concentration	resulting pH-value due to hydrochloric acid
10 mg/l	6.2 mg/l	5.5 mg/l	3.8
50 mg/l	31.7 mg/l	28.1 mg/l	3.1
100 mg/l	62.2 mg/l	55.1 mg/l	2.8

Natural waters, as well as reconstituted waters for testing purposes, stipulated within the OECD test guidelines, are normally composed of substances serving as buffers. However natural waters in boreal areas with subsurfaces consisting of granite or gneiss may have low buffer capacities and may therefore be susceptible to acidification.

The tolerance of water organisms towards pH margin and variation is diverse. According to OECD guidelines recommended pH-values for testing issues are:

- Fish: 6.0 to 8.5 is preferable
- *Daphnia*: within the range of 6 to 9
- Algae: approximately 8

Ellgaard and Gilmore (1984) showed the acute toxicity (96 h-LC₅₀) of hydrochloric acid as well as other acids to be the same on *Lepomis macrochirus* as soon as a pH of 3.5 to 3.25 was reached. In a second test the authors showed the pH to be the cause of the lethal effect by setting up a test with the lethal acid dosis of the first test but adding the needed concentration of NaOH to obtain a pH of 7. No effects were observed in this test.

Craig and Baski (1977) tested the effect of depressed pH on *Jordanella floridae* larvae on reproduction, growth, and survival. After 45 days a LOEC (20 % effect on growth) at pH 6.0 and a NOEC at pH 6.5 were determined.

Hurley, Foyle and White(1989) conducted early life stage tests with brook trout (45 d) in order to find an acid resistant strain for stocking purposes. *Salvelinus fontinalis* is known to be tolerant to low pH (Johansson, Runn and Milbrink 1977). Strains, gathered from an acid watershed (pH 4.7 to 5.3), a neutral watershed (pH 7) and a hatchery (pH 7), were investigated. Significant differences in mortality between the strains at low pH were observed and these suggested a genetic component to acid tolerance, according to the authors. The hatchery strain showed to be most sensitive towards low pH values; no statistically significant effect on survival and time for hatching at neither of the strains was observed down to pH 5.2. Tam and Payson (1986) showed the most sensitive endpoint with *Salvelinus fontinalis* was the weight of the young fish with a 10-month NOEC at pH 5.56.

Selected characteristic test results of aquatic toxicity of benzoic acid taken from OECD (2001) are summarized in Table 14 and indicate only a low acute toxicity in the aquatic compartment.

Table 14 Acute toxicity of benzoic acid to fish, *Daphnia* and algae

Trophic level	Species	Test type	Result	Source
Fish	<i>Leuciscus idus</i>	static	48 h-LC ₅₀ = 460 mg/l (n)	Juhnke and Luedemann, 1978
<i>Daphnia</i>	<i>Daphnia magna</i>	static; with/without neutralisation	24 h-EC ₅₀ = 500 / 102 mg/l (n)	Bringmann and Kuehn, 1982
Algae	<i>Scenedesmus quadricauda</i>	static	8 d-EC ₃ = 1630 mg/l (n)	Bringmann and Kuehn, 1977,

(n): nominal concentration

4.2 Terrestrial Effects

No data available.

4.3 Other Environmental Effects

No data available.

4.4 Initial Assessment for the Environment

α,α,α -Trichlorotoluene hydrolyzes completely in water within a few minutes at 20 °C, forming benzoic acid and hydrochloric acid. Any emission into the air or into the terrestrial compartment would be affected by humidity and also results in the formation of the hydrolysis products. However, several aquatic toxicity tests have been undertaken with α,α,α -trichlorotoluene. The observed toxicity effects in these studies can be attributed to the degradation products benzoic acid and hydrochloric acid.

Hydrochloric acid is a strong mineral acid that dissociates readily in water. Hydrochloric acid will not significantly adsorb on particulate matters or surfaces and will not accumulate in living tissues. Benzoic acid is not expected to hydrolyse.

The hydrolysis products benzoic acid and hydrochloric acid have been tested with aquatic species. Especially hydrochloric acid causes a pH shift in water which determined the impact on aquatic life. The tolerance of water organisms towards pH margin and variation is diverse. Recommended pH values for test species listed in OECD guidelines are between 6.0 and almost 9. Acute testing with fish showed 96h-LC₅₀ at about pH 3.5 (equals about 20 mg α,α,α -trichlorotoluene), chronic testing with early life stages of fish NOECs at pH 6.0 and 5.56. Benzoic acid is not toxic (LC₅₀ or EC₅₀ >100 mg/l) towards aquatic organisms. The substance is readily biodegradable and non-bioaccumulative.

Acute toxicity of α,α,α -trichlorotoluene to fish (*Leuciscus idus*) was 4140 mg/l (48 h-LC₅₀) [DIN 38412 Part 15]. With *Daphnia magna* an EC₅₀ (24 h) of > 100 mg/l was determined. With the blue-green alga *Microcystis aeruginosa* an 8 day-EC₃ of 34 mg/l was obtained in a cell multiplication inhibition test (test solution was not neutralized). It is not expected that an algal EC₅₀ obtained in a neutralized test solution would be lower than the EC₅₀ for *Daphnia*. Since there are test results on α,α,α -trichlorotoluene from three different trophic levels, an assessment factor of 1000 is applied according to EU Technical Guidance Document to the lowest acute effect concentration (*Daphnia magna*, 24h-EC₅₀ of 100 mg/l). The following value is obtained:

$$\text{PNEC}_{\text{aqua}} = 0.1 \text{ mg/l}$$

5 RECOMMENDATIONS

The chemical is currently of low priority for further work.

Environment: The chemical is currently of low priority for further work due to its low hazard profile. The degradation products benzoic acid and hydrochloric acid have already been assessed within the OECD SIDS-Program.

Human Health: The chemical possesses properties indicating a hazard for human health (e.g. acute and repeated dose toxicity, irritation, mutagenicity, carcinogenicity, reproduction and developmental toxicity). In the sponsor country, the substance is solely used as an isolated intermediate with controlled transport, and exposure in occupational settings is controlled. There is no exposure of consumers. Countries may desire to investigate any exposure scenarios that were not presented by the sponsor country.

6 REFERENCES

- Auergesellschaft (1988). Auer Technikum. Berlin, 12th ed.
- Bayer AG (1976a). Biodegradability of Benzotrichloride. Unpublished report, written 2001-02-28.
- Bayer AG (1976b). Acute Fish Toxicity of Benzotrichloride. Unpublished report, written 2001-03-29.
- Bayer AG (1978a). Akute orale Toxizitaet. Short report dated March 21, 1978.
- Bayer AG (1978b). Benzotrichlorid akute toxikologische Untersuchungen. Study report No. 7839 dated September 29, 1978.
- Bayer AG (2002). Safety Data Sheet Benzotrichloride pure, Benzotrichloride technical. 2002-01-07.
- Bayer Chemicals (2003). α,α,α -Trichlorotoluene - Internal Data on Production, Processing, Use Pattern, and Workplace Exposure (Unpublished).
- BGVV/UBA (Eds.) (1995). Bewertung der Gefaehrung von Mensch und Umwelt durch ausgewaehlte Altstoffe. Umweltbundesamt, UBA Texte 38/95.
- Bringmann G (1978). Bestimmung der biologischen Schadwirkung wassergefaehrdender Stoffe gegen Protozoen. I. Bakterienfressende Flagellaten (Modellorganismus: Entosiphon sulcatum Stein). Z. Wasser- Abwasser-Forsch. **11** (6), 210-215.
- Bringmann G and Kuehn R (1977a). Befunde der Schadwirkung wassergefaehrdender Stoffe gegen Daphnia magna. Z. Wasser- Abwasser-Forsch. **10** (5), 161-166.
- Bringmann G and Kuehn R (1977b). Grenzwerte der Schadwirkung wassergefaehrdender Stoffe gegen Bakterien (*Pseudomonas putida*) und Gruenalgen (*Scenedesmus quadricauda*) im Zellvermehrungshemmtest. Z. Wasser- Abwasser-Forsch. **10** (3/4), 87-98.
- Bringmann G and Kuehn R (1978). Grenzwerte der Schadwirkung wassergefaehrdender Stoffe gegen Blaualgen (*Microcystis aeruginosa*) und Gruenalgen (*Scenedesmus quadricauda*) im Zellvermehrungshemmtest. Vom Wasser **50**, 45-60.
- Bringmann G and Kuehn R (1980a). Comparison of the toxicity thresholds of water pollutants to bacteria, algae and protozoa in the cell multiplication inhibition test. Water Res. **14**, 231-241.
- Bringmann G and Kuehn R (1980b). Determination of the biological effect of water pollutants in protozoa. II. Bacteriovorous ciliates. Z. Wasser- Abwasser-Forsch. **1**, 26-31.
- Bringmann G and Kuehn R (1981). Vergleich der Wirkung von Schadstoffen auf flagellate sowie ciliate bzw. auf holozoische bakterienfressende sowie saprozoische Protozoen. GWF-Wasser/Abwasser **122** (7), 308-313.
- Bringmann G and Kuehn (1982). Results of toxic action of water pollutants on daphnia magna Straus tested by an improved standardised procedure. Z. Wasser- Abwasser-Forsch. **15** (1), 1-6.
- Bringmann G, Kuehn R and Winter A (1980). Determination of the biological effect of water pollutants in protozoa III. Saprozoic flagellates. Z. Wasser- Abwasser-Forsch. **13** (5), 170-173.
- BUA (Advisory Committee on Existing Chemicals of Environmental Relevance) (1991). BUA Report No. 72. Benzotrichloride. Stuttgart, S. Hirzel Verlag.

Cavender FL (1979). Acute inhalation toxicity study in rats. Report No 163-662 dated April 27, 1979 with cover letter dated 7/27/82. Velsicol Chem Corp. FYI Submission FYI-OTS-1180-0107, Washington, DC: Office of Toxic Substances, U.S. Environmental Protection Agency.

Chu I, Shen SY, Villeneuve DC, Secours VE and Valli VE (1984). Toxicity of trichlorotoluene isomers: A 28-day feeding study in the rat. *J. Environ. Sci. Health B***19**, 183 - 191.

Craig GR and Baski WF (1977). tested the effect of depressed pH on flagfish reproduction, growth, and survival. *Water Res.* **11**, 621-626.

Dietz EA (1981). Hydrolytic stability of trichloromethylbenzene. Internal report (4852-122-136), unpublished.

Elf Atochem UK (1992). Safety Data Sheet. November 1992 (not available).

Ellgaard EG and Gilmore JY (1984). Effects of different acids on the bluegill sunfish, *Jordanella macrochirus*. *J. Fish Biol.* **25**, 133-137.

Freitag D, Lay JP and Korte F (1984). Environmental Hazard Profile - Test Results as related to Structures and Translation into the Environment. In: Kaiser KLE (ed.) *QSAR in Environmental Toxicology. Proceedings of the Workshop on Quantitative Structure-Activity Relationships (QSAR) in Environmental Toxicology*, MacMaster University, Hamilton, Ontario, Canada, August 16-18, 1983. D. Reidel Publishing Company, 111-136.

Fujita T, Iwasa J and Hansch C (1964). A new substituent constant, π , derived from partition coefficient. *J. Am. Chem. Soc.* **86**, 5175-5180.

Fukuda K, Matsushita H and Takemoto K (1978). Carcinogenicity of benzotrichloride by the oral route of administration (J-4774). In: *Proceedings of the 52nd Annual Meeting of the Japanese Industrial Health Association* pp. 516 - 517, cited in: IARC (International Agency for Research on Cancer) (1982) *Monographs on the evaluation of the carcinogenic risk of chemicals to human* 29: 73 - 82 and: TSCA 8e Submission 8EHQ-0980-0360 Document No. 86-8000116, Washington, DC: Office of Toxic Substances, U.S. Environmental Protection Agency.

Fukuda K, Matsushita H, Sakabe H and Takemoto K (1981). Carcinogenicity of benzyl chloride, benzal chloride, benzotrichloride and benzoyl chloride in mice by skin application. *Gann* **72**, 655 - 664.

Fukuda K, Matsushita H, Takemoto K and Toya T (1993). Carcinogenicity of benzotrichloride administered to mice by gastric intubation. *Ind. Health* **31**, 127 - 131.

Fukuda K and Takemoto K (1984). Erzeugung von Tumoren im Respirationssystem von Ratten und Mausem durch Inhalation von Benzotrichlorid (BTC). *Haigan, Chiba-Shi* **24**, 673.

Fukuda K and Takemoto K (1984). Inhalations-Karzinogenitaet von Benzotrichlorid (II). *Proc 57th Annual Meeting Japan Association of Industrial Health*, 380 - 381.

Howard PH (1989). *Handbook of Environmental Fate and Exposure Data. Vol. 1 Large Production and Priority Pollutants*, 73-77. Lewis Publ. Chelsea.

Hurley GV, Foyle TP and White WJ (1989). Difference in acid tolerance during the early life stages of three strains of Brook Trout, *Salvelinus fontinalis*. *Water Air Soil Pollut.* **46**, 387-398.

Jagannath DR (1978). Mutagenicity evaluation of benzotrichloride in the Ames Salmonella/microsome plate test. Final report. LBI project No 20988. Genetics assay No 3566 dated December

1978 with cover letter dated 7/27/82. Velsicol Chem Corp FYI Submission FYI-OTS-1180-0107, Washington, DC: Office of Toxic Substances, U.S. Environmental Protection Agency.

Johansson N, Runn P and Milbrink G (1977). Early development of three salmonid species in acidified water. *Zoon* **5**, 127-132.

Juhnke I and Luedemann D (1978). Ergebnisse der Untersuchung von 200 chemischen Verbindungen auf akute Fischtoxizitaet mit dem Goldorfentest. *Z. Wasser- Abwasser-Forsch.* **11** (5), 161-164.

Koshi K and Fukuda K (1986). Cytogenetic and morphological findings in rats exposed to benzotrichloride. *Mutat Res* **164**, 272.

Laughton PM and Robertson RE (1959). Solvolysis in hydrogen and deuterium oxide. *Can. J. Chem.* **37**, 1491 - 1497.

Leo A, Hansch C and Elkins D (1971). Partition coefficients and their uses. *Chemical Rev.* **71** (6), 525-616.

Levin AA (1981). Benzotrichloride sub-chronic inhalation study. FYI Submission FYI-OTS-0981-0122 Washington, DC: Office of Toxic Substances, U.S. Environmental Protection Agency, cited in: Chemical Hazard Information Profile. Draft Report "Benzotrichloride" dated march 3, 1982

Lokke H (1984). Leaching of ethylene glycol and ethanol in subsoils. *Water, Air Soil Pollut.* **22**, 373-387.

Mabey W and Mill T (1978). Critical review of hydrolysis of organic compounds in water under environmental conditions. *J. Phys. Chem.* **7**, 383-415.

Maki T and Takeda K (2002). Benzoic acid derivatives. 8.4 Benzoyl Chloride. *Ullmanns Encyclopedia of Industrial Chemistry*, Electronic Version.

MITI (Ministry of International Trade and Industry) (1992). Biodegradation and Biaccumulation Data of Existing Chemicals Based on the Chemical Substances Control Law (CSCL). Japan. Chemicals Inspection and Testing Institute (CITI, ed); Japan Chemicals Industry Ecology-Toxicology and Information Center, p. 3-99.

OECD SIAP/SIAR Benzoates Category, 2001.

OECD SIAP/SIAR Hydrogen chloride, 2002.

Reusche (1989). Hydrolysedaten fuer seitenkettenchlorierte Stoffe. Unpublished report.

Ruddick JA, Villeneuve DC, Secours V, Valli VE (1982). A transplacental and teratological evaluation of three trichlorotoluene congeners in the rat. *Teratology* **25**, 72A - 73A.

Sakabe H, Matsushita H and Koshi S (1976) Cancer among benzoyl chloride manufacturing workers. *Ann NY Acad Sci* **271**, 67 - 70.

Sakabe H and Fukuda K (1977). An updating report on cancer among benzoyl chloride manufacturing workers. *Ind. Health* **15**, 173 – 174.

Smyth HF, Carpenter CP and Weil CS (1951). Range-finding toxicity data: list IV. *Arch. Ind. Hyg. Occup. Med.* **4**, 119 – 122.

Sorahan T, Waterhouse JAH, Cooke MA, Smith EMB, Jackson JR and Temkin L (1983). A mortality study of workers in a factory manufacturing chlorinated toluenes. *Ann. Occup. Hyg.* **27**, 173 - 182.

SPIN Database (2003). Substances in Preparations in Nordic Countries. www.spin2000.net/spin.html.

Srour (1999). Benzotrichloride.

Steinhaeuser KG, Ammann W and Polenz A (1986). Biodegradability testing of chloroorganic compounds. *Vom Wasser* **67**, 147-154.

Stoner GD, You M, Morgan MA and Superczynski MJ (1986). Lung tumor induction in strain A mice with benzotrichloride. *Cancer Letters* **33**, 167 – 173.

Stratton GW and Corke CT (1982). Toxicity of the insecticide Permethrin and some degradation products towards algae and cyanobacteria. *Environ. pollution (Series A)* **29**, 71-80.

Suzuki Y (1985a). Studies on development of the sensitive micronucleus test (Part I) methods of induction by polychlorinated biphenyl and of metabolic activation. *Tokyo Jikeikai Med. J.* **100**, 695 - 705.

Suzuki Y (1985b) Studies on development of the sensitive micronucleus test (Part II) the in vitro method using cultured bone marrow cells. *Tokyo Jikeikai Med. J.* **100**, 707 - 719.

Swiss Product Register (2003).

Takemoto K, Yoshimura H and Matsushita S (1978). Experiment of pulmonary tumorigenicity of benzotrichloride. *Proceedings of the 51st Annual Meeting of the Japan Assoc. Ind. Health*, 514 - 515.

Tam WH and Payson PD (1986). Effects of chronic exposure to sublethal pH on growth, egg production and evaluation in brook trout, *Salvelinus fontinalis*. *Can. J. Fish Aquat. Sci.* **43**, 275-280.

Umweltbundesamt (2003). Wasser - Oberflaechengewaesser. <http://www.umweltbundesamt.de/wasser/themen/>.

U.S. EPA (1987). Health and Environmental Effects Document for Benzoic Acid. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

Velsicol Chem. Corp. (1979). Acute Toxicity Studies in Rabbits and Rats. Report 163-661. 13 February 1979. As submitted to U.S. EPA under TSCA on 20 Nov. 1980, U.S. EPA TSCA FYI-OTS-1180-0107 IN.

Velsicol Chem. Corp. (1980) Benzotrichlorid: three-week dermal toxicity study in rabbits. 4 April 1980. As submitted to U.S. EPA under TSCA on 20 Nov 1980, U.S. EPA TSCA FYI-OTS-1180-0107 IN.

Velsicol Chem. Corp. (1981). Benzotrichloride - four-week subacute inhalation toxicity study in rats with amendment. 26 May 1981. As submitted to U.S. EPA under TSCA on 25 August 1981, U.S. EPA TSCA FYI-OTS-0000122-0 IN.

Verschuere K (1996). *Handbook of Environmental Data on Organic Chemicals*, 3rd ed., New York, Van Nostrand Reinhold, p 1793.

Wong O (1988). A Cohort mortality study of employees exposed to chlorinated chemicals. *Am. J. Ind. Med.* **14**, 417 - 431.

Yasuo K, Fujimoto S, Katoh M, Kikuchi Y and Kada T (1978). Mutagenicity of benzotrichloride and related compounds. *Mutat Res.* **58**, 143 - 150.

Yoshimura H, Katayama H, Takemoto K and Matsushita S (1979). Experimental lung tumors induced by exposure to benzotrichloride (2). *Proc. of Japan. Assoc. of Ind. Health* 332 - 333. TSCA 8e Submission 8EHQ-0980-0360 Document No. 86-8000116, Washington, DC: Office of Toxic Substances, U.S. Environmental Protection Agency.

Yoshimura H, Takemoto K, Fukuda K and Matsushita H (1986). Carcinogenicity in mice by inhalation of benzotrichloride and benzoyl chloride. *Jpn. J. Ind. Health* **28**, 352 – 359.

Yu CC and Nietschmann DA (1980). Pharmacokinetics and metabolism of benzotrichloride in rats. Abstract. FYI submission FYI-OTS-1180-0170 Washington DC: Office of Toxic Substances, U.S. Environmental Protection Agency.

Zahn R and Wellens H (1980). Examination of biological degradability through the batch method - further experience and new possibilities of usage. *Z. Wasser- Abwasser-Forsch.* **13** (1), 1-7.

I U C L I D

Data Set

Existing Chemical : ID: 98-07-7
CAS No. : 98-07-7
EINECS Name : alpha,alpha,alpha-trichlorotoluene
EC No. : 202-634-5
TSCA Name : Benzene, (trichloromethyl)-
Molecular Formula : C₇H₅Cl₃

Producer related part
Company : Bayer AG
Creation date : 29.07.1992

Substance related part
Company : Bayer AG
Creation date : 29.07.1992

Status :
Memo : X AKTUELL EG-Abgabe / ICCA

Printing date : 09.09.2004
Revision date : 01.09.1993
Date of last update : 09.09.2004
Number of pages : 90

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**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 : Trichloromethylbenzene
Smiles Code : c1ccccc1CCl3
Molecular formula : C7H5Cl3
Molecular weight : 195.48
Petrol class :

25.09.2003

(1) (2)

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : typical for marketed substance
Substance type : organic
Physical status : liquid
Purity : 98.5 % w/w
Colour :
Odour :

25.09.2003

(1)

Purity type : typical for marketed substance
Substance type : organic
Physical status : liquid
Purity : 99.8 % w/w
Colour : colourless to yellowish
Odour :

25.09.2003

(3)

1.1.2 SPECTRA**1.2 SYNONYMS AND TRADENAMES**

alpha,alpha,alpha-Trichlorotoluene

26.09.2003

(4) (1)

Benzene, (Trichloromethyl)-

Remark	: CAS name	(1)
19.09.2003		
Benzenyltrichloride		
19.09.2003		(5)
Benzoic trichloride		
19.09.2003		(6) (5)
Benzotrichloride		
26.09.2003		(4) (1)
Benzylidene chloride		
19.09.2003		(1)
Benzyltrichloride		
19.09.2003		(5)
Phenylchloroform		
19.09.2003		(1)
Phenyltrichloromethane		
19.09.2003		(1)
Toluenetrichloride		
19.09.2003		(5)
Trichloromethyl benzene		
26.09.2003		(4) (1)
Trichloromethylbenzene		
26.09.2003		(6) (5)

1.3 IMPURITIES

Purity	: typical for marketed substance
CAS-No	:
EC-No	:
EINECS-Name	:
Molecular formula	:
Value	:
Result	: The purity of the commercial product is ≥ 99.8 % w/w for "benzotrichloride, pure" and ≥ 97 % w/w for the technical grade product of the Sponsor company. The following impurities are reported for "benzotrichloride, pure": Benzyl chloride ≤ 0.02 % w/w Benzal chloride ≤ 0.2 % w/w

Flag : Benzoyl chloride <= 0.2 % w/w
23.09.2003 : Critical study for SIDS endpoint (3)

Purity : typical for marketed substance
CAS-No : 98-87-3
EC-No : 202-709-2
EINECS-Name : alpha,alpha-dichlorotoluene
Molecular formula : C₇H₆Cl₂
Value : <= .02 % w/w

14.11.2003 (3)

Purity : typical for marketed substance
CAS-No : 100-44-7
EC-No : 202-853-6
EINECS-Name : alpha-chlorotoluene
Molecular formula : C₇H₇Cl
Value : < .2 % w/w

14.11.2003 (3)

Purity : typical for marketed substance
CAS-No : 98-88-4
EC-No : 202-710-8
EINECS-Name : benzoyl chloride
Molecular formula : C₇H₅ClO
Value : < .2 % w/w

14.11.2003 (3)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : - tonnes in 2000

Remark : In 2000, the world wide production capacity of alpha,alpha,alpha-trichlorotoluene is estimated to 79900 tons by about 10 producers.

Worldwide manufacturing capacity estimated for 2000

Region	Manufacturing capacity
Western Europe	56000
USA	16000
Japan	5500
Others	2400

At Bayer AG, the total production capacity of alpha,alpha,alpha-trichlorotoluene is about 24000 t/a

14.11.2003 (7)

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits :

Symbols : T, , ,
Nota : , ,
R-Phrases : (45) May cause cancer
 (22) Harmful if swallowed
 (23) Toxic by inhalation
 (37/38) Irritating to respiratory system and skin
 (41) Risk of serious damage to eyes
S-Phrases : (45) In case of accident or if you feel unwell, seek medical advice
 immediately (show the label where possible)
 (53) Avoid exposure - obtain special instructions before use

25.09.2003

(8)

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC
Class of danger : carcinogenic, category 2
R-Phrases : (45) May cause cancer
Specific limits :

28.03.2000

Classified : as in Directive 67/548/EEC
Class of danger : harmful
R-Phrases : (22) Harmful if swallowed
Specific limits :

28.03.2000

Classified : as in Directive 67/548/EEC
Class of danger : irritating
R-Phrases : (37/38) Irritating to respiratory system and skin
 (41) Risk of serious damage to eyes
Specific limits :

28.03.2000

Classified : as in Directive 67/548/EEC
Class of danger : toxic
R-Phrases : (23) Toxic by inhalation
Specific limits :

28.03.2000

1.6.3 PACKAGING**1.7 USE PATTERN**

Type of use : type
Category : Non dispersive use

18.09.2003

(1)

Type of use	: industrial
Category	: Chemical industry: used in synthesis
Remark	: alpha,alpha,alpha-Trichlorotoluene is a basic chemical, used exclusively industrial in the production of intermediates such as . Benzoylchloride . Benzotrifluoride . 2,4-dihydroxybenzophenone The intermediates are further used in the synthesis of pesticides, dyestuffs, UV absorbers and pharmaceuticals. A direct use of alpha,alpha,alpha-trichlorotoluene is not known.
26.09.2003	(9)
Type of use	: industrial
Category	: Chemical industry: used in synthesis
Remark	: alpha,alpha,alpha-Trichlorotoluene is not listed in the Danish, Finnish, Norwegian, and Swedish Product Registers as being contained in consumer products
09.12.2003	(10)
Type of use	: industrial
Category	: Chemical industry: used in synthesis
Remark	: alpha,alpha,alpha-Trichlorotoluene is used exclusively as a chemical intermediate. By far its most important derivative is benzoyl chloride, which is the subject of a separate monograph by IARC. About 18 million kg alpha,alpha,alpha-trichlorotoluene are estimated to be used annually in the US for the production of benzoyl chloride.
09.12.2003	(11)
Type of use	: use
Category	: Intermediates
18.09.2003	(1)

1.7.1 DETAILED USE PATTERN**1.7.2 METHODS OF MANUFACTURE**

Origin of substance	: Synthesis
Type	: Production
Remark	: Benzotrichloride is produced by means of side-chain chlorination of toluene in the presence of UV light or with the exclusion of light at elevated temperature. Residues from other areas of toluene chlorination (e.g. benzal chloride synthesis) are also used as starting materials to a limited extent. The synthesis product formed from toluene has a purity of > 95 % and is mostly processed downstream without purification. If downstream processing requires a higher degree of purity, then a product with a content of > 98.5 % is obtained by distillation.
19.09.2003	(1)

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : TRK (DE)
Limit value : .1 mg/m³

Remark : TRGS 900 limit value is 0,012 ml/m³ (ppm) = 0,1 mg/m³.
The 15 min average value is not permitted to exceed the limit value by more than a factor of 4.

14.11.2003 (8)

1.8.2 ACCEPTABLE RESIDUES LEVELS**1.8.3 WATER POLLUTION**

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 3 (strongly water polluting)

25.09.2003 (8)

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung (DE)
Substance listed : yes
No. in Seveso directive : 40

Remark : Stoerfallnr. 40
25.09.2003 (8)

1.8.5 AIR POLLUTION

Classified by : TA-Luft (DE)
Labelled by : TA-Luft (DE)
Number : 2.3 (carcinogenic substances)
Class of danger :

14.11.2003 (8)

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES**1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS**

Type : degradation product in water
CAS-No : 65-85-0
EC-No : 200-618-2
EINECS-Name : benzoic acid
IUCLID Chapter : 5.0

14.11.2003 (9)

Type : degradation product in water
CAS-No : 7647-01-0
EC-No : 231-595-7
EINECS-Name : hydrogen chloride
IUCLID Chapter : 5.0

14.11.2003 (9)

Type : degradation product in water
CAS-No : 98-88-4
EC-No : 202-710-8
EINECS-Name : benzoyl chloride
IUCLID Chapter : 3.1.2

14.11.2003 (9)

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 : 08.07.2003

22.09.2003

Type of search : Internal and External
Chapters covered : 2
Date of search : 08.07.2003

22.09.2003

Type of search : Internal and External
Chapters covered : 3, 4
Date of search : 08.07.2003

22.09.2003

1.13 REVIEWS

Memo : BUA Report Benzotrichloride

18.09.2003 (1)

Memo : BUA Report Benzoic acid

19.09.2003 (12)

2.1 MELTING POINT

Value	:	-4.8 °C	
Sublimation	:		
Method	:		
Year	:	1988	
GLP	:		
Test substance	:		
Remark	:	Beilstein's reports several melting point values in the range of -3.15 till -5.8 °C	
Test substance	:	alpha,alpha,alpha-trichlorotoluene	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	
Flag	:	Critical study for SIDS endpoint	
04.09.2003			(13) (4) (14)
Value	:	-7.5 °C	
Sublimation	:		
Method	:	other: not specified	
Year	:	2003	
GLP	:	no data	
Test substance	:	no data	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	
14.11.2003			(5)
Value	:	ca. -5.5 °C	
Sublimation	:		
Method	:	other: no data	
Year	:	2002	
GLP	:	no data	
Test substance	:		
Remark	:	Point of solidification	
Result	:	Solidification point: approx. -5.5 °C (pure substance) approx. -8.0 °C (technical substance)	
Test substance	:	alpha,alpha,alpha-trichlorotoluene	
Reliability	:	(4) not assignable Not assignable/manufacturer data without proof	
19.09.2003			(8)
Value	:	= -5 °C	
Sublimation	:		
Method	:	other: not specified	
Year	:	2003	
GLP	:	no data	
Test substance	:	other TS: alpha,alpha,alpha-trichlorotoluene	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	
22.09.2003			(15) (16)

2.2 BOILING POINT

Value	:	= 220.7 °C at 1013 hPa	
Decomposition	:		
Method	:		
Year	:	1988	
GLP	:		
Test substance	:	other TS: alpha,alpha,alpha-trichlorotoluene	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	
Flag	:	Critical study for SIDS endpoint	
18.11.2003			(13)
Value	:	= 220.7 °C at	
Decomposition	:		
Method	:		
Year	:	1996	
GLP	:	no data	
Test substance	:		
Test substance	:	alpha,alpha,alpha-trichlorotoluene	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	
29.08.2003			(14)
Value	:	= 219 - 223 °C at	
Decomposition	:		
Method	:	other: not specified	
Year	:	1992	
GLP	:	no data	
Test substance	:		
Test substance	:	alpha,alpha,alpha-trichlorotoluene	
Reliability	:	(2) valid with restrictions Original reference not available	
19.09.2003			(17)
Value	:	220.6 °C at	
Decomposition	:		
Method	:	other: not specified	
Year	:	2003	
GLP	:	no data	
Test substance	:	no data	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	
22.07.2003			(5)
Value	:	= 220.8 °C at 1013 hPa	
Decomposition	:		
Method	:	other: not specified	
Year	:	1989	
GLP	:	no data	
Test substance	:	other TS: alpha,alpha,alpha-Trichlorotoluene	
Remark	:	Pressure given as 760 mm Hg	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	

22.09.2003

(15)

Decomposition :
Method : other: not specified
Year : 2003
GLP : no data
Test substance : no data

Result : Beilstein's reports several boiling point values:
 Boiling point (pressure in Torr)
 220.7 (761)
 220.9 (760)
 218 (750)
 146.9 (100)
 121.5 (39)
 105 (25)
 110.7 (23)
 106.7-106.9 (20)
 96 (18)
 95.4 (14)
 93 (12)
 84-85 (9)
 89-89.5 (10)
 114 (10)
 85-86 (8)

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

22.07.2003

(4)

2.3 DENSITY

Type : density
Value : 1.3723 g/cm³ at 20 °C

Test substance : alpha,alpha,alpha-trichlorotoluene
Reliability : (2) valid with restrictions
 Data from handbook or collection of data
Flag : Critical study for SIDS endpoint

19.09.2003

(13)

Type : density
Value : = 1.38 at °C
Method :
Year : 1996
GLP : no data
Test substance :

Test substance : Benzotrichloride
Reliability : (2) valid with restrictions
 Data from handbook or collection of data

02.09.2003

(14)

Type : density
Value : 1.3756 at 20 °C
Method : other: not specified
Year : 2003
GLP : no data
Test substance : no data

Reliability : (2) valid with restrictions
Data from handbook or collection of data
22.07.2003 (16)

Type : density
Value : at °C
Method : other: not specified
Year : 2003
GLP : no data
Test substance : no data

Result : Beilstein's reported density values are in the range of 1.3667 till 1.38 g/cmE+3 (at 14 - 25 °C)

Reliability : (2) valid with restrictions
Data from handbook or collection of data
22.07.2003 (4)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .2 hPa at 20 °C
Decomposition :
Method :
Year : 1988
GLP : no data
Test substance :

Test substance : alpha,alpha,alpha-trichlorotoluene
Reliability : (2) valid with restrictions
Data from handbook or collection of data

Flag : Critical study for SIDS endpoint
19.09.2003 (13) (14)

Value : .49 hPa at 30 °C
Decomposition :
Method : other (measured): not specified
Year :
GLP : no data
Test substance : no data

Reliability : (2) valid with restrictions
Data from handbook or collection of data
25.09.2003 (13)

Value : 1.8 hPa at 50 °C
Decomposition :
Method : other (measured): not specified
Year :
GLP : no data
Test substance : no data

Reliability : (2) valid with restrictions
Data from handbook or collection of data
25.09.2003 (13)

Value : = .16 hPa at 20 °C

Remark : Vapour pressure:
0.16 hPa at 20 °C,
1.46 hPa at 50 °C

Test substance : alpha,alpha,alpha-trichlorotoluene

Reliability : (4) not assignable
Original reference not yet available

25.09.2003 (18)

Value : = .3 hPa at 20 °C

Decomposition :

Method : other (measured): not specified

Year : 1992

GLP : no data

Test substance :

Test substance : alpha,alpha,alpha-trichlorotoluene

Reliability : (4) not assignable
Original reference not available

25.09.2003 (17)

Value : = .31 hPa at 20 °C

Decomposition :

Method : other (measured): not specified

Year : 1989

GLP : no data

Test substance : other TS: alpha,alpha,alpha-Trichlorotoluene

Remark : Vapor pressure given as 0.23 mm Hg

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

22.09.2003 (19)

Value : .552 hPa at 25 °C

Decomposition :

Method : other (measured): not specified

Year :

GLP : no data

Test substance : no data

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

25.07.2003 (16)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water

Log pow : = 2.92 at °C

pH value :

Method : other (calculated)

Year : 1971

GLP : no

Test substance : other TS: alpha,alpha,alpha-Trichlorotoluene

Remark : Calculation of log Kow unsuitable. The calculated theoretical value reflects the undissociated molecule without influence of water (hydrolysis).

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

Flag : Critical study for SIDS endpoint

2. PHYSICAL-CHEMICAL DATA

ID: 98-07-7

DATE: 09.09.2004

14.11.2003

(20) (21) (22)

Partition coefficient : octanol-water
Log pow : = 1.81 - 1.88 at 25 °C
pH value :
Method : other (measured)
Year : 1964
GLP : no
Test substance : other TS: Benzoic acid

Method : For partitioning, octanol saturated with distilled water and distilled water saturated with octanol were used. Usually, 50-150 ml portions of octanol were used with 50-400 ml portions of water. The volume ratio of the two phases and the amount of sample were chosen ensuring that the absorbance of a sample from the water layer after partitioning had a value between 0.2 and 0.9 using a 1 cm cell. Only the concentration of benzoic acid in the water layer was determined, and that in the octanol layer was obtained by difference. The analysis of the concentration was made using a Cary Model 14 spectrophotometer. The absorbance at 230-250 nm was measured.

Test condition : - Each determination was done in at least duplicate at two different volume ratios,
 - Temperature during the work was about 25 +/- 5 °C

Test substance : Benzoic acid is the major organic degradation product of alpha,alpha,alpha-trichlorotoluene hydrolysis.

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

26.09.2003

(23)

Partition coefficient : octanol-water
Log pow : = 3.9 at °C
pH value :
Method : other (calculated): with SRC-KOWWIN v1.66, 2000
Year : 2003
GLP :
Test substance : other TS: alpha,alpha,alpha-Trichlorotoluene

Remark : Calculation of log Kow unsuitable for alpha,alpha,alpha-trichlorotoluene. The calculated theoretical value reflects the undissociated molecule without influence of water.

Reliability : (2) valid with restrictions
 Accepted calculation method

26.09.2003

(24)

Partition coefficient : octanol-water
Log pow : = 4.1 at °C
pH value :
Method : other (calculated)
Year : 1996
GLP : no data
Test substance : other TS: alpha,alpha,alpha-Trichlorotoluene

Remark : Calculation of log Pow unsuitable. The calculated theoretical value reflects the undissociated molecule without influence of water (hydrolysis).

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

26.09.2003

(14)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
 Value : = 100 mg/l at 20 °C
 pH value :
 concentration : at °C
 Temperature effects :
 Examine different pol. :
 pKa : at 25 °C
 Description :
 Stable :
 Deg. product :
 Method :
 Year : 1996
 GLP : no data
 Test substance : other TS: alpha,alpha,alpha-Trichlorotoluene

Reliability : (2) valid with restrictions
 Data from handbook or collection of data
 Flag : Critical study for SIDS endpoint
 26.09.2003

(14)

Solubility in : Water
 Value : = 53 mg/l at 5 °C
 pH value :
 concentration : at °C
 Temperature effects :
 Examine different pol. :
 pKa : at 25 °C
 Description :
 Stable :
 Deg. product :
 Method : other: calculated
 Year : 1971
 GLP :
 Test substance : other TS: alpha,alpha,alpha-Trichlorotoluene

Method : Results were calculated utilizing kinetic data from literature
 Remark : The solubility of benzal chloride and benzotrichloride was calculated similarly by the present method utilizing kinetic data. With the increase of the number of chlorines of chlorinated phenylmethanes, their hydrolysis rate increases, but solubility decreases.
 Reliability : (4) not assignable
 Basic data given

14.11.2003

(25)

2.6.2 SURFACE TENSION**2.7 FLASH POINT**

Value : ca. 108 °C
 Type :
 Method : other: measured
 Year : 1988
 GLP : no data
 Test substance : other TS: alpha,alpha,alpha-Trichlorotoluene

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
14.11.2003 (13)

2.8 AUTO FLAMMABILITY

Value : = 420 °C at
Method :
Year : 1988
GLP : no data
Test substance : other TS: alpha,alpha,alpha-Trichlorotoluene
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
26.09.2003 (13)

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Method :
Year : 1988
GLP : no data
Test substance :
Result : explosive limits:
lower 2.1 % by vol.;
upper 6.5 % by vol. at 160 °C
Test substance : alpha,alpha,alpha-trichlorotoluene
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
19.09.2003 (13)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

Value : ca. 2.4 - mPa s (dynamic) at °C
Result :
Method : other: no data
Year : 2002
GLP : no data
Test substance :
Test substance : alpha,alpha,alpha-trichlorotoluene

Reliability	:	(4) not assignable Manufacturer data without proof	
Flag	:	Critical study for SIDS endpoint	
19.09.2003			(8)

2.14 ADDITIONAL REMARKS

Memo	:	pH value	
Remark	:	year: 2001	
Result	:	The aqueous solution reacts acidic due to hydrolysis products	
Reliability	:	(4) not assignable Manufacturer data without proof	
Flag	:	Critical study for SIDS endpoint	
26.09.2003			(8)

Memo	:	Refractive index	
Remark	:	Refractive index at 20 °C = 1.55789 year: 1989	
Reliability	:	(4) not assignable Original reference not available	
25.08.2003			(16)

02.03.1998

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/cm ³	
Rate constant	: .00000000000036 cm ³ /(molecule*sec)	
Degradation	: 50 % after 44.9 day(s)	
Deg. product	:	
Method	: other (calculated): with SRC-AOPWin v1.90, 2000	
Year	: 2003	
GLP	:	
Test substance	:	
Remark	: The calculated half-life is based on a mean OH concentration of 0.5E+6 OH radicals/cm ³ as 24 h average.	
Reliability	: (2) valid with restrictions Accepted calculation method	
Flag	: Critical study for SIDS endpoint	
19.11.2003		(24)
Type	: air	
Light source	:	
Light spectrum	: nm	
Relative intensity	: based on intensity of sunlight	
INDIRECT PHOTOLYSIS		
Sensitizer	: OH	
Conc. of sensitizer	: 800000 molecule/cm ³	
Rate constant	: cm ³ /(molecule*sec)	
Degradation	: = 50 % after 2 day(s)	
Deg. product	: not measured	
Method	:	
Year	: 1986	
GLP	: no data	
Test substance	:	
Remark	: Cited according to US-EPA, GEMS (1986)	
Result	: The ultraviolet absorption spectrum for alpha,alpha,alpha-trichlorotoluene in methanol solution shows no absorption above 290 nm, therefore direct photolysis in the environment is not expected to occur (Sadtler 1966, Sadtler Research Laboratory).	
	Absorption coefficient	
	450 at 274 nm	
	558 at 267 nm	
	499 at 260.5 nm	
	691 at 225 nm	
Test substance	: alpha,alpha,alpha-trichlorotoluene	
Reliability	: (4) not assignable Original reference not available	
26.09.2003		(26)
Type	: air	

Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Remark	:	If released to atmosphere, alpha,alpha,alpha-trichlorotoluene will react in vapor phase with photochemically produced hydroxyl radicals with an estimated half-life of 2 days in a typical atmosphere. Atmospheric hydrolysis may occur in the presence of moisture; however, direct photolysis is not expected to occur.
Reliability	:	(2) valid with restrictions Data from handbook or collection of data
Flag	:	Critical study for SIDS endpoint
22.09.2003		(15)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	= 2.4 minute(s) at 20 °C
t1/2 pH9	:	at °C
Deg. product	:	yes
Method	:	
Year	:	1989
GLP	:	no data
Test substance	:	other TS: alpha,alpha,alpha-trichlorotoluene, benzoylchloride
Deg. products	:	65-85-0 200-618-2 benzoic acid 7647-01-0 231-595-7 hydrogen chloride 98-88-4 202-710-8 benzoyl chloride
Method	:	10 mg/l test substance in phosphate buffer pH 7, 1 % or 50 % acetonitrile in water, respectively.
Remark	:	The environmental behaviour of alpha,alpha,alpha-trichlorotoluene is determined by the rapid hydrolysis of the substance (t1/2 ca. 2 minutes at 20 degree C). The first degradation product is benzoyl chloride which degrades very rapidly (t1/2 not measurable due to rapid degradation) to benzoic acid and hydrochloric acid. The fast hydrolysis of alpha,alpha,alpha-trichlorotoluene results in a very small half-life of the substance in the environment. Despite the calculated log Kow value of 3 to 4, the quick hydrolysis also reduces the probability of a relevant bioaccumulation.
Result	:	Degradation products: benzoyl chloride (CAS: 98-88-4, EINECS: 202-710-8); hydrogen chloride (CAS: 7647-01-0, EINECS: 231-595-7); benzoic acid (CAS: 65-85-0, EINECS: 200-618-2) : Half-life at 20 degree C: t1/2 (1 % v/v acetonitrile in water): alpha,alpha,alpha-trichlorotoluene: 2.4 min, benzoylchloride: not detectable (very rapid). t1/2 (50 % v/v acetonitrile in water): alpha,alpha,alpha-trichlorotoluene: 2.1 h, benzoylchloride: 3.6 min.
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles

Flag : Critical study for SIDS endpoint
18.11.2003 (27)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : ca. 2 minute(s) at 20 °C
t1/2 pH9 : at °C
Deg. product : yes
Method :
Year : 1995
GLP : no data
Test substance : other TS: alpha,alpha,alpha-Trichlorotoluene
Deg. products : 65-85-0 200-618-2 benzoic acid
 7647-01-0 231-595-7 hydrogen chloride
 98-88-4 202-710-8 benzoyl chloride

Remark : The environmental behaviour of alpha,alpha,alpha-trichlorotoluene is determined by the rapid hydrolysis of the substance (t1/2 ca. 2 minutes at 20 degree C).
 The first degradation product is benzoyl chloride which degrades very rapidly (t1/2 not measurable due to rapid degradation) to benzoic acid and hydrochloric acid.
 The fast hydrolysis of alpha,alpha,alpha-trichlorotoluene results in a very small half-life of the substance in the environment.
 Despite the calculated log Kow value of 3 to 4, the quick hydrolysis also reduces the probability of a relevant bioaccumulation.

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

Flag : Critical study for SIDS endpoint
18.11.2003 (28) (1)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method : other: HPLC and pH shift measurement
Year : 1981
GLP : no
Test substance : other TS: alpha,alpha,alpha-trichlorotoluene, benzoylchloride

Method : A. HYDROLYSIS OF ALPHA,ALPHA,ALPHA-TRICHLOROTOLUENE:
 HPLC-analysis with a Micromeritics 7000 instrument operating with C18 column (30 cm by 4.6 mm). Specific operating parameters were:
 I. at 0 °C:
 Elution solvent: 15 % H2O in methanol at 1.5 ml/min,
 Detector: Micromeritics model 785 variable ultraviolet operating at 240 nm and 0.02 absorbance setting.
 II. at 25 °C:
 Same as I. except using 10 % H2O in methanol as the eluting solvent.
 For HPLC studies, a 40 µl aliquot of stock solution (prepared immediately before starting the experiment) was injected into 4 ml of water and the resulting mixture was gently swirled. After an elapsed time, a 25 µl aliquot of reacting mixture was injected into the HPLC for examination.

	To represent a time zero response for the system, a 40 μl inject of stock solution into 4 ml of acetonitrile was used. Studies were conducted at ambient conditions (25 °C) and at 0 °C. In the latter case, only the 4 ml of water was cooled to 0 °C. HPLC retention times for each starting reagent and resulting carboxylic acid were established via injections of authentic reference materials which were dissolved in acetonitrile.
Result	B. HYDROLYSIS OF BENZOYL CHLORIDE Hydrolysis of benzoyl chloride was followed at 25 °C by measuring the decrease in solution pH values as HCl and carboxylic acids formed. Alpha,alpha,alpha-trichlorotoluene was included in these experiments as a control. Hydrolysis of benzoyl chloride is expected to be very rapid in the initial stages (0.1 min) and thus not observable by HPLC since a minimum sample preparation and HPLC injection time of 20 sec was needed. pH measurement studies were carried out using a Metrohm Herisau E 536 potentiograph. : alpha,alpha,alpha-trichlorotoluene: Half-life $t_{1/2}$: 6.7 min at 0 °C, 14 sec at 25 °C Benzoyl chloride, the partial hydrolysis product of alpha,alpha,alpha-trichlorotoluene, rapidly hydrolyses to HCl and benzoic acid in 70:30 water-acetone ($t_{1/2}$ = 16 sec at 25 °C). $t_{1/2}$ of benzoyl chloride in 100 % water: < 15 sec at 25 °C.
Reliability	: (2) valid with restrictions
Flag	: Study meets generally accepted scientific principles
18.11.2003	: Critical study for SIDS endpoint (29)
Type	: abiotic
$t_{1/2}$ pH4	: at °C
$t_{1/2}$ pH7	: ca. 3 minute(s) at 5 °C
$t_{1/2}$ pH9	: at °C
Deg. product	: yes
Method	: other: hydrolysis in light and heavy water
Year	: 1959
GLP	: no
Test substance	: other TS: alpha,alpha,alpha-trichlorotoluene
Deg. products	: 65-85-0 200-618-2 benzoic acid 7647-01-0 231-595-7 hydrogen chloride
Method	: Kinetic rates for the hydrolysis of alpha,alpha,alpha-trichlorotoluene in light and heavy water were measured and compared.
Result	: Hydrolysis of alpha,alpha,alpha-trichlorotoluene - In water: At 5.1 degree C and neutral pH, the hydrolysis rate was found to be 0.00387 1/sec, which corresponds to a half-life of 3 minutes - In deuterium: At 5.1 degree C and neutral pH, the hydrolysis rate was found to be 0.00307 1/sec, which corresponds to a half-life of 3.76 minutes. Relation of rate ratios: $k(D_2O) / k(H_2O) = 0.79$. The major factor determining the rate ratio appears to be the relative stability of the initial solvation shell.
Reliability	: (2) valid with restrictions
Flag	: Study meets generally accepted scientific principles
18.11.2003	: Critical study for SIDS endpoint (30)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : ca. 2 hour(s) at 25 °C
t1/2 pH9 : at °C
Deg. product :
Method :
Year : 1971
GLP : no
Test substance : other TS: alpha,alpha,alpha-Trichlorotoluene

Method : Measurement of chemical reaction constants at 25 °C with the method of simultaneous assays. Reaction stages of 10 to 30 % were investigated. The free chloride was determined after two subsequent extractions of the unreacted substrate with cooled dimethylether. A pseudo first-order rate constant was calculated ($t_{1/2} = \ln 2/K$; with K = rate constant of the reaction).

Remark : Calculated values for log K:
 At neutral pH: log K = -2.26
 at acid conditions (0.05 M H₂SO₄): log K = -2.18
 at basic conditions (0.1 M NaOH): log K = -2.17.

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

18.11.2003

(31)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : ca. .2 minute(s) at 25 °C
t1/2 pH9 : at °C
Deg. product : yes
Method :
Year : 1978
GLP : no
Test substance : other TS: alpha,alpha,alpha-Trichlorotoluene
Deg. products : 65-85-0 200-618-2 benzoic acid
 7647-01-0 231-595-7 hydrogen chloride

Method : Estimated rate constants were presented for benzotrichloride. Half-lives were calculated according to the equation:
 $t_{1/2} = \ln 2/K = 0.693/K$
 K = rate constant of the reaction.

Remark : At 25 °C and neutral pH, hydrolysis rate is 0.063/sec. This corresponds to a half-life of ca. 0.2 min. Hydrolysis products are benzoic acid and hydrochloric acid.

Reliability : (4) not assignable
 Secondary literature

18.11.2003

(32)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : ca. 3 minute(s) at 5 °C
t1/2 pH9 : at °C
Deg. product : not measured
Method :
Year : 1971
GLP : no
Test substance :

Method	:	The method consists of measurements of the hydrolysis rate below or at saturation solubility, the rate constants and order of reaction, and analysis of kinetic data. K-value of Laughton and Robertson (1959) was used for calculations.
Remark	:	The solubility of benzotrichloride was calculated similarly by the present method utilizing kinetic data. With the increase of the number of chlorines of chlorinated phenylmethanes, their hydrolysis rate increases, but solubility decreases.
Test substance	:	alpha,alpha,alpha-trichlorotoluene
Reliability	:	(4) not assignable Secondary literature
17.11.2003		(25)

3.1.3 STABILITY IN SOIL

Remark	:	Due to the rapid hydrolysis of alpha,alpha,alpha-trichlorotoluene in water, leaching in moist soil should not be significant, due to its degradation to benzoic and hydrochlorid acid.
Reliability	:	(2) valid with restrictions Data from handbook or collection of data
22.09.2003		(15)

3.2.1 MONITORING DATA

Type of measurement	:	background concentration
Media	:	surface water
Concentration	:	
Method	:	
Remark	:	Given the rapid hydrolysis the occurrence of benzotrichloride in surface waters in substantial concentrations is not expected. No data are available on its occurrence in air or soil.
Reliability	:	(2) valid with restrictions Data from handbook or collection of data
26.09.2003		(1)
Type of measurement	:	background concentration
Media	:	other: all media
Concentration	:	
Method	:	
Remark	:	alpha,alpha,alpha-Trichlorotoluene has not been reported to occur in nature.
Reliability	:	(2) valid with restrictions Data from handbook or collection of data
17.11.2003		(11)

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	:	
Year	:	1984
Method	:	14C-labelled benzoic acid (767 MBq mmol ⁻¹) of radiochemical purity greater than 98.5 % was prepared in 0.01 M calcium nitrate in concentrations of 0.01, 0.1, 1.0, and 10 mg/l. The solutions (10 ml) were added to three types of autoclaved, dry soils (2 g) and allowed to equilibrate on a mechanical shaker for 72 h at 6 °C. The soil types were sandy till, clayey till and melt water sand. The suspension was allowed to settle and the supernatant liquid was tested for 14C activity.
Result	:	No adsorption was observed for benzoic acid in melt water sand and clayey till; very low adsorption was observed in sandy till (K = 0.23).
Test substance	:	other TS: benzoic acid Benzoic acid is the major organic degradation product of α,α,α -trichlorotoluene hydrolysis.
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles
Flag	:	Critical study for SIDS endpoint
27.11.2003		

(33)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	predominantly domestic sewage
Concentration	:	5.4 mg/l related to Test substance 22 mg/l related to Test substance
Contact time	:	28 day(s)
Degradation	:	= 96 - 97 (±) % after 7 day(s)
Result	:	readily biodegradable
Kinetic of testsubst.	:	3 day(s) = 95 % % % % %
Control substance	:	other: benzoic acid
Kinetic	:	% %
Deg. product	:	yes
Method	:	OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year	:	1986
GLP	:	no data
Test substance	:	other TS: α,α,α -trichlorotoluene

Remark	: Results for test substance (5.5 mg/l) without inoculum: DOC removal after 3 days: 1 % DOC removal after 7 days: 11 %.
	Degradation product: chloride
	Mineralization of test substance to chloride incubated with and without inoculum after 3 days: 100 %
	alpha,alpha,alpha-trichlorotoluene shows a rapid abiotic hydrolysis in water. The formed metabolites are eliminated quickly by microorganisms.
	Method for the determination of chloride not mentioned in report.
Test condition	: The Modified OECD-Screening Test was altered in order to observe not only the DOC-value but also the chloride formation by degradation of chloroorganic compounds. By this way the biodegradability of nine substances was investigated. As degradation parameter the removed DOC was determined. For determination of possible precipitation, adsorption and volatilisation abiotic degradation of alpha,alpha,alpha-trichlorotoluene a test substance control without inoculum was performed.
Reliability	: (2) valid with restrictions Study meets generally accepted scientific principles
Flag 19.01.2004	: Critical study for SIDS endpoint
	(34)
Type	: aerobic
Inoculum	: activated sludge
Concentration	: 24 mg/l related to Test substance related to
Contact time	: 20 day(s)
Degradation	: = 63 (±) % after 20 day(s)
Result	: readily biodegradable
Kinetic of testsubst.	: 5 day(s) = 59 % 10 day(s) = 63 % % % %
Control substance	: other: no data available
Kinetic	: % %
Deg. product	: not measured
Method	:
Year	: 1976
GLP	: no
Test substance	: other TS: alpha,alpha,alpha-trichlorotoluene
Method	: Closed Bottle Test, comparable to OECD TG 301 D
Remark	: It is assumed by the time of incubation that all alpha,alpha,alpha-trichlorotoluene was hydrolysed to benzoic acid.
Test substance	: Test substance stock solution: 1015 mg/l COD of the stock solution: 1060 mg/l, BOD calculated for the stock solution after 5 days: 625 mg/l,

	after 10 days: 670 mg/ after 20 days: 670 mg/l.	
Reliability	: (2) valid with restrictions Comparable to guideline study with acceptable restrictions	
Flag 18.11.2003	: Critical study for SIDS endpoint	(35)
Type	: aerobic	
Inoculum	: activated sludge	
Contact time	:	
Degradation	: ($\pm$) % after	
Result	: under test conditions no biodegradation observed	
Deg. product	:	
Method	:	
Year	: 1994	
GLP	: no data	
Test substance	: other TS: alpha,alpha,alpha-Trichlorotoluene	
Method	: The dissimilation of alpha,alpha,alpha-trichlorotoluene was examined in laboratory-scale wastewater treatment plants and in respirometers (Sapromat). The laboratory-scale wastewater treatment plant corresponding to the "Confirmatory Test" (OECD TG 303 A) consisted of an influx vessel, an aerobic treatment vessel containing an aeration system and activated sludge (from an industrial wastewater treatment plant), and a final clarification vessel. The test solution was added continuously to the wastewater by pumps. The test duration was 1 d. The sapromat is a closed respirometer. It consists of 3 vessels, which are connected: one vessel for incubation, one for CO₂ absorption, and one vessel containing a electrolytic solution (CuSO₄) for the electrolytic generation of oxygen to compensate for the respiratory oxygen consumption. In both experiments the inoculum was adapted to the test substance for up to 6 weeks: A undescribed organic substrate was continuously substituted by the test substance within 3-6 weeks, until the test substance became the only source of carbon. The adaptation and degradation process was reported to be checked by determination of BOD₅, COD (oxidation by potassium dichromate), sludge dry matter, and by microscopic examination of the microorganism populations (species composition and organisms numbers). The results were classified in four groups: A: (BOD/COD) > 0,6: readily biodegradable B: 0,6 = (BSB/CSB) > 0,2: biodegradable C: 0,2 = (BSB/CSB) > 0,05: slowly biodegradable D: (BSB/CSB) = 0,05: not biodegradable E: (BSB/CSB) = 0: theoretically not biodegradable	
Remark	: It is stated that the limit of solubility was 30 mg/l COD according to the COD chromate method. Since a theoretical COD of 1.23 g oxygen/g alpha,alpha,alpha-trichlorotoluene (240/195.5) was expected, the solubility limit of 30 mg/l COD means a test substance solubility (24 mg/l alpha,alpha,alpha-trichlorotoluene) far less than that reported by others (see IUCLID 2.6.1). There is also no report on the pH although hydrolysis could have released enough hydrogen chloride to decrease the pH to about 3.4.	
Result	: Results for alpha,alpha,alpha-trichlorotoluene: COD: 30 mg/l BOD: 0 mg/l (after adaption) alpha,alpha,alpha-trichlorotoluene was assigned to the Biodegradation group "D" (non biodegradable).	
Reliability	: (3) invalid Documentation insufficient for assessment	

03.12.2003

(36)

3.6 BOD5, COD OR BOD5/COD RATIO**3.7 BIOACCUMULATION**

BCF : 98
 Elimination :
 Method : other: calculation
 Year : 1990
 GLP :
 Test substance :

Method : The BCF of alpha,alpha,alpha-trichlorotoluene was estimated by using the following equation:

$$\log \text{BCF} = 0.76 \log K_{ow} - 0.23$$

according to Bysshe SE (1990). Bioconcentration Factors in Aquatic Organisms. In: Lyman WJ, Reehl WF and Rosenblatt DH (1990).

Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. McGraw-Hill, NY.

The widely published K_{ow} of 2.92 [Leo A, Hansch C and Elkins D (1971). Partition coefficients and their uses. Chemical Reviews 71 (6), 525-616] was used for calculation.

Remark : Based on the log K_{ow} , the BCF for alpha,alpha,alpha-trichlorotoluene can be estimated to be 98. Due to the rapid hydrolysis of alpha,alpha,alpha-trichlorotoluene in water bioconcentration in aquatic organisms is not expected to occur.

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

16.11.2003

(15)

Elimination :
 Method :
 Year : 1984
 GLP : no
 Test substance : other TS: Benzoic acid

Method : The bioaccumulation in green algae (*Clorella fusca*) and fish (*Leuciscus idus*) was tested. For this purpose, ^{14}C -labelled substance was used; chemical concentration: 50 $\mu\text{g/l}$.

Result : Bioaccumulation factors:
Leuciscus idus (golden orfe): < 10 (3 d exposure),
Clorella fusca (green algae): < 10 (1 d exposure)

Test substance : Benzoic acid is the major organic degradation product of alpha,alpha,alpha-trichlorotoluene hydrolysis.

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

16.11.2003

(37)

3.8 ADDITIONAL REMARKS

Memo : Stability in air

Remark : Atmospheric hydrolysis may occur in the presence of moisture.

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

Flag	:	Critical study for SIDS endpoint	
17.11.2003			(15)
Memo	:	Stability in air	
Remark	:	It is expected that alpha,alpha,alpha-trichlorotoluene released into the atmosphere will be degraded rapidly due to hydrolysis in humid air.	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	
17.11.2003			(16)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	: static
Species	: <i>Leuciscus idus melanotus</i> (Fish, fresh water)
Exposure period	: 48 hour(s)
Unit	: mg/l
LC0	: = 2480
LC50	: = 4140
LC100	: = 8280
Limit test	: no
Analytical monitoring	: no
Method	:
Year	: 1978
GLP	: no
Test substance	: other TS: alpha,alpha,alpha-trichlorotoluene
Method	: Basis for the investigation was the static Golden Orfe test according to Mann, published in DEV L15: Fischtest (Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische). Preprint (1976) in: Vom Wasser 46, 291-295.
Remark	: 200 selected compounds were examined under comparable conditions in two different laboratories. Hydrolysis of alpha,alpha,alpha-trichlorotoluene leads to the acidification of the test solution (to about pH 1-2). It is not clearly stated whether the incubation solutions were neutralized before incubation. In the method description the user is informed that deviation from neutral pH (pH 7-8) will affect the results. Since the significant acidification resulting from the reported LC0 would be lethal to fish, it is assumed that the test solutions were neutralized before start of incubation.
Reliability	: (2) valid with restrictions Study meets generally accepted scientific principles
Flag	: Critical study for SIDS endpoint
16.11.2003	(38)
Type	: static
Species	: <i>Leuciscus idus</i> (Fish, fresh water)
Exposure period	: 3 day(s)
Unit	: mg/l
LC0	: > 1000
Limit test	: yes
Analytical monitoring	: no
Method	:
Year	: 1976
GLP	: no
Test substance	: other TS: alpha,alpha,alpha-trichlorotoluene
Method	: Basis for the investigation was the static Golden Orfe test according to Mann, published in DEV L15: Fischtest (Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische). Preprint (1976) in: Vom Wasser 46, 291-295.
Remark	: The test substance reacts hydrolytically with water to benzoic acid and hydrochloric acid. Hydrolysis of alpha,alpha,alpha-trichlorotoluene leads to the acidification of the test solution (to about pH 1-2). It is not clearly stated whether the incubation solutions were neutralized before incubation. In the method description the user is informed that deviation from neutral pH (pH 7-8) will affect the results. Since the significant acidification resulting from the reported LC0 would be lethal to fish, it is assumed that the test solutions

	were neutralized before start of incubation.	
Result	: After the study period of three days neither dead fish nor fish with adverse symptoms were observed.	
Test condition	: 1 l test medium, ventilated, static system, loading rate: 2 animals/vessel, nominal concentration: 1000 mg/l	
Reliability	: (2) valid with restrictions	
	Study meets generally accepted scientific principles	
16.11.2003		(39)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	: static	
Species	: Daphnia magna (Crustacea)	
Exposure period	: 24 hour(s)	
Unit	: mg/l	
EC0	: = 42	
EC50	: = 50	
EC100	: = 56	
Limit Test	: no	
Analytical monitoring	: no	
Method	: other: immobilisation test according to Bringmann (1978)	
Year	: 1982	
GLP	: no	
Test substance	: other TS: alpha,alpha,alpha-Trichlorotoluene	
Remark	: Effect endpoint: immobilisation	
Result	: - related to nominal concentration - reference substance: potassium dichromate, EC50 (average value) = 1.3 mg/l (required range: 0.9-1.9 mg/l) - the measured pH values were not documented. Since the test solutions were not neutralized, pH effects might have occurred	
Test condition	: - test organism: Daphnia magna Straus, standardized test strain IRCHA (age: max. 24 h, temperature: 20 °C (incubator) - testing was performed in a chemically and physically defined standardised culture medium according to DIN 38412 part 11 ("artificial fresh water"). Quality of the culture medium: sum of calcium and magnesium ions: 2.5 mmol/l; mol ratio sodium to potassium ions: 10:1; saturated with oxygen, pH 8.0 +/- 0.2. - duplicate parallel dilution series with 10 daphnids/vessel (= 10 organisms/20 ml) - stock cultures were fed standardized dry algae - oxygen content and pH were measured at the beginning and at the end of the test	
Reliability	: (2) valid with restrictions	
Flag	: Study meets generally accepted scientific principles	
19.01.2004	: Critical study for SIDS endpoint	(40)
Type	: static	
Species	: Daphnia magna (Crustacea)	
Exposure period	: 24 hour(s)	
Unit	: mg/l	
EC50	: > 100	
Analytical monitoring	: no	
Method	: other: immobilisation test according to Bringmann (1978)	
Year	: 1977	
GLP	: no	
Test substance	: other TS: alpha,alpha,alpha-Trichlorotoluene	

Remark	:	Effect endpoint: immobilisation
Result	:	- related to nominal concentration - the measured pH values were not documented. Since the test solutions were not neutralized, pH effects might have occurred
Test condition	:	- test organism: clone of <i>Daphnia magna</i> of wild population - cultures of <i>Daphnia magna</i> were fed daily with green algae (<i>Chlorella vulgaris</i>) - age of test organism: max. 24 h - temperature: 20-22 °C - quality of tap water used as test medium: free from chlorine, saturated with oxygen, hardness 16 ° d.H., pH 7.6-7.7 - triplicate parallel dilution series with 10 daphnids/vessel (= 10 organisms/20 ml)
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles
19.01.2004		

(41)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	<i>Microcystis aeruginosa</i> (Algae, blue, cyanobacteria)
Endpoint	:	growth rate
Exposure period	:	8 day(s)
Unit	:	mg/l
TT	:	= 34
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1978
GLP	:	no
Test substance	:	other TS: alpha,alpha,alpha-trichlorotoluene
Method	:	Cell multiplication inhibition test according to Bringmann & Kuehn
Result	:	TT (toxicity threshold) refers to nominal concentration and was determined at 3 % effect compared to the control (comparable to EC3). The measured pH values were not documented. Since the test solutions were not neutralized, pH effects might have occurred
Test condition	:	static test, nominal concentration, temperature: 27 °C, continuous artificial light, pH 7, measurement of turbidity
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint
19.01.2004		

(42)

Species	:	<i>Scenedesmus quadricauda</i> (Algae)
Endpoint	:	biomass
Exposure period	:	8 day(s)
Unit	:	mg/l
TT	:	> 100
Limit test	:	
Analytical monitoring	:	no
Method	:	
Year	:	1977
GLP	:	no
Test substance	:	other TS: alpha,alpha,alpha-Trichlorotoluene

Method	: Cell multiplication inhibition test according to Bringmann and Kuehn (1977). Due to the long duration of the assay and the rapid growth rate of <i>Scenedesmus quadricauda</i> , it is not clear whether the algae were still in the exponential growth phase at the end of the test.
Remark	: It is not clear whether the algae were still in the exponential growth phase at the end of incubation
Result	: TT (toxicity threshold) refers to nominal test substance concentration and was determined at 3 % effect compared to the control (comparable to EC3)
Test condition	: static test, nominal concentration, temperature: 27 °C, continuous artificial light, pH 7, measurement of turbidity
Reliability	: (3) invalid Unsuitable test system
16.11.2003	(43) (42) (44)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	: aquatic
Species	: <i>Pseudomonas putida</i> (Bacteria)
Exposure period	: 16 hour(s)
Unit	: mg/l
TT	: > 100
Analytical monitoring	: no
Method	:
Year	: 1977
GLP	: no
Test substance	: other TS: alpha,alpha,alpha-trichlorotoluene
Method	: Cell multiplication inhibition test according to Bringmann & Kuehn
Remark	: TT (toxicity threshold) comparable to EC3; value based on nominal concentration
Test condition	: static test, temperature: 25 °C, pH 7, measurement of turbidity
Reliability	: (2) valid with restrictions Study meets generally accepted scientific principles
Flag	: Critical study for SIDS endpoint
19.01.2004	(43) (44)
Type	: aquatic
Species	: <i>Chilomonas paramecium</i> (Protozoa)
Exposure period	: 48 hour(s)
Unit	: mg/l
TT	: = 27
Analytical monitoring	: no
Method	:
Year	: 1980
GLP	: no
Test substance	: other TS: alpha,alpha,alpha-Trichlorotoluene
Method	: Cell multiplication inhibition test according to Bringmann & Kuehn
Remark	: TT (toxicity threshold) comparable to EC5; value based on nominal concentration
Test condition	: Temperature: 20 °C, pH 6.9. The number of protozoa is determined by means of a cell counter (Coulter Counter) after addition of a suitable electrolyte (10 % of a 1.1 % NaNO ₃ solution in double-distilled water filtered through a membrane filter)

(pore size 0.2 μ m)).	
Test substance	: α,α,α -trichlorotoluene
Reliability	: (2) valid with restrictions
	Study meets generally accepted scientific principles
16.11.2003	(45) (46)
Type	: aquatic
Species	: Entosiphon sulcatum (Protozoa)
Exposure period	: 72 hour(s)
Unit	: mg/l
TT	: = 56
Analytical monitoring	: no
Method	:
Year	: 1980
GLP	: no
Test substance	: other TS: α,α,α -Trichlorotoluene
Method	: Cell multiplication inhibition test according to Bringmann and Kuehn (1978)
Remark	: TT (toxicity threshold) comparable to EC5; value based on nominal concentration
Test condition	: - Stock and preliminary cultures of protozoa are fed with viable bacteria (Escherichia coli), except during the test cultures are fed with killed bacteria to avoid a metabolism of α,α,α -trichlorotoluene by bacteria. - Temperature: 25 °C, pH 6.9 - The number of protozoa is determined by means of a cell counter (Coulter Counter) after addition of a suitable electrolyte (10 % of a 1.1 % NaNO ₃ solution in double-distilled water filtered through a membrane filter (pore size 0.2 μ m)).
Reliability	: (2) valid with restrictions
	Study meets generally accepted scientific principles
26.09.2003	(47) (44) (45)
Type	: aquatic
Species	: Uronema parduzci (Protozoa)
Exposure period	: 20 hour(s)
Unit	: mg/l
TT	: > 80
Analytical monitoring	: no
Method	:
Year	: 1980
GLP	: no
Test substance	: other TS: α,α,α -Trichlorotoluene
Method	: Cell multiplication inhibition test according to Bringmann and Kuehn (1980)
Remark	: TT (toxicity threshold) comparable to EC5; value based on nominal concentration
Test condition	: - Stock and preliminary cultures of protozoa are fed with viable bacteria (Escherichia coli), except during the test cultures are fed with killed bacteria to avoid a metabolism of α,α,α -trichlorotoluene by bacteria. - Temperature: 25 °C, pH 6.9 - The number of protozoa is determined by means of a cell counter (Coulter Counter) after addition of a suitable electrolyte (10 % of a 1.1 % NaNO ₃ solution in double-distilled water filtered through a membrane filter (pore size 0.2 μ m)).

Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles	
26.09.2003			(48) (45)
Type	:	aquatic	
Species	:	Photobacterium phosphoreum (Bacteria)	
Exposure period	:	30 minute(s)	
Unit	:	mg/l	
EC50	:	ca. 18	
Analytical monitoring	:	no data	
Method	:	other: Microtox	
Year	:	1986	
GLP	:	no data	
Test substance	:	other TS: alpha,alpha,alpha-trichlorotoluene	
Method	:	The acute toxicities to Photobacterium phosphoreum were determined with the Microtox toxicity analyzer according to the Microtox-test. Reference for the method: Bulich AA, Greene MW, Isenberg DL (1981) Reliability of the bacterial luminescence assay for determination of the toxicity of pure compounds and complex effluents. In: Branson DR, Dickson KL (Eds) Aquatic Toxicology and Hazard Assessment: Fourth Conference, American Society for Testing and Materials, ASTM STP 737, 338-347.	
Remark	:	The observed toxicity range of the investigated one hundred mono-substituted benzene derivatives is close to five orders of magnitude on a molar basis. Quantitative-structure-toxicity correlations with the octanol/water partition coefficient, the energy of the ultraviolet absorption band of the compounds, the substituents' molar refractivity in logarithmic units, and an indicator for acidic -OH groups, explains 61 % of the variation observed.	
Test condition	:	The toxicity values reported are the negative logarithms to base 10 ("p" values) of the millimolar concentrations at which a 50 % reduction was observed on 30 min. exposure. Each value is the mean of at least three independent determinations, usually performed with different bacterial suspensions to reduce any systematic errors or biases. The standard deviations of such triplicate analyses were normally in the order of 0.05 logarithmic toxicity units.	
Reliability	:	(3) invalid Unsuitable test system	
25.09.2003			(49)
Type	:	aquatic	
Species	:	Photobacterium phosphoreum (Bacteria)	
Exposure period	:	30 minute(s)	
Unit	:	mg/l	
EC50	:	= 19 measured/nominal	
Analytical monitoring	:	no	
Method	:	other: Microtox	
Year	:	1986	
GLP	:	no	
Test substance	:	other TS: alpha,alpha,alpha-trichlorotoluene	
Remark	:	It is not clear whether the pH of the test solution was effected by the HCl released during hydrolysis of alpha,alpha,alpha-trichlorotoluene.	

Test condition	: The toxicity of the test substances was photometrically measured in tests with Photobacterium phosphoreum after 30 minutes exposure time.	
Reliability	: (3) invalid Unsuitable test system	
25.09.2003		(34)
Type	: aquatic	
Species	: Photobacterium phosphoreum (Bacteria)	
Exposure period	: 30 minute(s)	
Unit	: mg/l	
EC50	: = 20	
Baseline Toxicity	: = 1.7	
Analytical monitoring	: no	
Method	: other: Microtox	
Year	: 1996	
GLP	: no	
Test substance	: other TS: alpha,alpha,alpha-trichlorotoluene	
Method	: The Microtox data were taken from the COMPUTOX database. The classification scheme of Verhaar et al. (1992) based on fish toxicity data was investigated as to whether it is applicable to photobacteria toxicity data (Microtox). For this purpose 240 diverse chemicals were classified according to this scheme into 3 classes: 1) nonpolar narcotics, 2) polar narcotics, and 3) reactive chemicals. Each molecule was characterized by a set of 31 descriptors accounting for the geometry, polarity, hydrogen binding, activity and reactivity of the compound. The descriptors were computed based on semiempirical quantum chemical calculations.	
Result	: The authors conclude that for Class 3 compounds (reactive chemicals) - as alpha,alpha,alpha-trichlorotoluene - no single toxicity mechanism can be postulated. With regard to the wide variety of mechanisms of action present in the Class 3 compounds, the determined poor QSAR is not surprising. For this class, further classification into reactive subclasses is required. The baseline equation for the Microtox data was found to be $\log 1/EC50 = 1.07 \log P - 2.36$.	
Reliability	: (4) not assignable Secondary literature	
26.09.2003		(50)
Type	: aquatic	
Species	: anaerobic bact. from a domestic water treatment plant	
Exposure period	: 24 hour(s)	
Unit	: mg/l	
EC0	: ca. 150	
Analytical monitoring	: no	
Method	: ETAD Fermentation tube method "Determination of damage to effluent bacteria by the Fermentation Tube Method"	
Year	: 1980	
GLP	: no	
Test substance	: other TS: alpha,alpha,alpha-trichlorotoluene, purity 99.5 %	
Remark	: SG = Limit of harmfulness, similar to EC0	
Reliability	: (4) not assignable Original reference not available	

16.11.2003

(51)

Type	: aquatic
Species	: <i>Pseudomonas putida</i> (Bacteria)
Exposure period	:
Unit	: mg/l
NOEC	: > 1.4
Analytical monitoring	: no data
Method	:
Year	: 1979
GLP	: no
Test substance	: other TS: alpha,alpha,alpha-trichlorotoluene
Method	: The influence of organo halogens on degradation of defined degradable substances was investigated with the method "Kreatinin-Degradation-Model" of the author.
Result	: alpha,alpha,alpha-Trichlorotoluene shows no toxic reaction to <i>Pseudomonas putida</i> under the conditions of this test. alpha,alpha,alpha-Trichlorotoluene shows a transient inhibition of the kreatinin biodegradation in the "subtoxic" dose range of the test substance which was determined in a growth-inhibition test. After this phase the kreatinin degradation in the alpha,alpha,alpha-trichlorotoluene treated group was not different from the degradation behaviour in the control group without the test substance.
Test condition	: Test substance concentrations: 0.0014 and 1.4 mg/l
Reliability	: (2) valid with restrictions Basic data given

16.11.2003

(52)

4.5.1 CHRONIC TOXICITY TO FISH**4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES****4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS****4.6.2 TOXICITY TO TERRESTRIAL PLANTS****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	:	Toxicokinetics
Species	:	rat
Number of animals		
Males	:	5
Females	:	17
Doses		
Males	:	39.9 mg/kg bw
Females	:	40.4 - 46.0 mg/kg bw
Vehicle	:	other: corn oil
Route of administration	:	gavage
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1 st . t _{1/2} = 22h 2 nd . 3 rd .
Toxic behaviour	:	
Deg. product	:	yes
Method	:	other:
Year	:	1980
GLP	:	no data
Test substance	:	other TS: radiochemical purity: > 98%
Deg. products	:	65-85-0 200-618-2 benzoic acid 7647-01-0 231-595-7 hydrogen chloride
Remark	:	Rat strain: Sprague-Dawley. Female animals were used throughout the study and only one group of male rats served for treatment comparison and one as vehicle treated control. In 0.4 ml corn oil 10.1 mg of [14C]-benzotrichlorid was given by gavage. The results obtained give a concise set of results regarding uptake, blood kinetics, metabolism and excretion in rats.
Result	:	[14C]-benzotrichloride was administered as single dose (ca. 40 - 46 mg/kg bw) to Sprague-Dawley rats (4-5 weeks old, about 200 g bw). The [14C]-labelled benzotrichloride is absorbed from the GI-tract. The absorption half-life was 3 h. Blood concentration peaked at 4 h reaching 6.5 ppm and decreased steadily to 2.6 ppm after 24 h. Elimination half-life in blood was 22 h. Elimination (48 h) proceeded to 90 % in urine and 10 % in faeces. After a rapid distribution in the body the renal elimination (elimination half-life in urine: 8 h) of the chemical proceeds according to an apparent first order kinetics. Total radiocarbon residue in tissue: 1.5 % of the dose present in the body 72 hrs after dosing; fat, kidney, liver had higher residues levels than other tissues (muscle: lowest level), however no significant difference in the elimination rate from all tissues (one compartment model, first order kinetics) was observed. Benzotrichloride was assumed to be rapidly metabolised via hydrolysis to hydrochloric acid and benzoic acid. Benzoic acid is thought to be subsequently glycinilated to yield hippuric acid. More than 90 % of radiolabel in urine was hippuric acid. Small amounts of benzoic acid (0.7 %) and phenyl acetic acid (0.8 %), as well as four unidentified metabolites (5.5 %) were found.
Test condition	:	Collection of samples: urine and feces were collected at 24, 48 and 72

	hours. Blood was collected through tail incision at 0.5 1, 2, 4, 8 hours. Organs analyzed: kidney liver, muscle, fat, brain, heart, spleen, gonads, uterus, lung and blood. Data processing: a curve best fit analysis of urine, blood and faeces as function of time was performed. Analysis of variance of the curves. WIdentification and separation of metabolites were done by mass spectrometry (direct inlet probe in the electron impact mode (EI 70 eV)) and thin layer chromatography (Sil G-25 UV-254 Macherey- Nagel precoated plates) using several solvent systems and visualising radioactive spots by autoradiography or UV detection.
Test substance	: The specific activity of radiolabelled substance was 10.2 mCi/mmol (14C-benzotrichloride[phenyl-UL-14C]). The radiochemical purity was >98%. Standard benzotrichloride was 97.7% pure and obtained from Velsicol Chemical Corp.
Reliability	: (1) valid without restriction
Flag	: Critical study for SIDS endpoint
27.11.2003	(53)
In Vitro/in vivo	: In vivo
Type	: Metabolism
Species	: rat
Number of animals	
Males	: 0
Females	: 10
Doses	
Males	:
Females	: 30 mg/m ³ , 2 h, 20 days
Vehicle	: no data
Route of administration	: other: repeated inhalation of 30mg/m ³ for 2 h/d on 20 d.
Exposure time	:
Product type guidance	:
Decision on results on acute tox. tests	:
Adverse effects on prolonged exposure	:
Half-lives	: 1 st . 2 nd . 3 rd .
Toxic behaviour	: no data
Deg. product	: yes
Method	: other: no data
Year	: 1963
GLP	: no data
Test substance	: no data
Deg. products	: 495-69-2 207-806-3 hippuric acid
Remark	: The rat strain was not specified. The same group of 10 rats served for preexposure and after treatment determination of hippuric acid in urine.
Result	: On 20 consecutive days rats (n=10) were exposed to 30 mg benzotrichloride/m ³ by inhalation. The amount of hippuric acid in urine increased from 14-20 mg (no volume or weight dimension indicated) to 47 mg in certain individuals. The authors conclude that benzotrichloride is metabolised to sodium benzoate which in turn is converted to hippuric acid and possibly other metabolites.
Conclusion	: First report demonstrating biochemically the renal elimination of benzotrichloride via hippuric acid.
Reliability	: (4) not assignable Insufficient data and documentation.
08.12.2003	(54)

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 1249 mg/kg bw
Species : rat
Strain : Wistar
Sex : male
Number of animals : 10
Vehicle : other: none
Doses : 0.1, 0.5, 0.7, 0.8, 0.9, 1.0, 1.3 ml/kg (= ca. 137, 686, 961, 1098, 1235, 1372, 1784 mg/kg bw)
Method : other: acute toxicity of benzotrichloride in male Wistar rats treated with undiluted substance by gavage
Year : 1978
GLP : no data
Test substance : other TS: "benzotrichloride pure", no purity indicated.

Remark : LD50 = 0.91 ml/kg (density 1.3723; 1249 mg/kg bw)
Test substance was administered undiluted by gavage.
Few experimental details given.
Gross pathological examination not mentioned.
Age of animals was not stated.

Result	dose [ml/kg bw]	dead animals (death time)	symptoms	total
	0.1	0 (-)	0	10
	0.5	1 (6d)	10	10
	0.7	1 (6d)	10	10
	0.8	2 (7-8d)	10	10
	0.9	5 (5-7d)	10	10
	1.0	6 (3-9d)	10	10
	1.3	10 (2-8d)	10	10

Wistar (specific pathogen free) male rats weighing 160 to 180 g were treated with undiluted test substance.
The LD50 was 0.91 ml/kg bw. (Confidence interval: 0.81 - 1.02 ml/kg bw)
Observation period was 14 days.
Recorded symptoms were: increased diuresis, weight loss, scrubby fur, balance problems, shivers accompanied by cramps, bloody eyes.

Reliability : (2) valid with restrictions
Few experimental details given
Flag : Critical study for SIDS endpoint

07.06.2004

(55)

Type : LD50
Value : = 2188 mg/kg bw
Species : rat
Strain : Wistar
Sex : male
Number of animals : 15
Vehicle : other: Cremophor EL/water
Doses : 50, 500, 1500, 2000, 2500, 3500 mg/kg bw
Method : other: acute toxicity of benzotrichloride after single oral treatment of male Wistar rats
Year : 1978
GLP : no data
Test substance : other TS: as provided by sponsor

Remark : Purity of test item and age of animals were not indicated
Result : dose dead animals symptoms total

[mg/kg bw]	(time of death)		
50	0 (-)	0	15
500	0 (-)	15	15
1500	1 (1d)	15	15
2000	3 (1-4d)	15	15
2500	12 (1-2d)	15	15
3500	15 (7-24h)	15	15

Male Wistar rats weighing 160 to 180 g were used for the study. The animals were fasted 16 h before treatment. Aqueous solutions of trichlorotoluene were prepared with Cremophor EL®. Treatment volume was 1 ml/100 g bw given by gavage. The animals were observed for 14 days. Reduced activity, scrubby fur, difficulties of breathing, polyuria with sanguineous urine was noticed. The symptoms started within 15 minutes after treatment and persisted till days 7 to 9. Gross pathology: empty intestinal tract, white stipples on stomach mucosa.

Reliability : (2) valid with restrictions
Purity of test item not given
Flag : Critical study for SIDS endpoint

27.11.2003

(56)

Type : LD50
Value : = 1590 mg/kg bw
Species : rat
Strain : Wistar
Sex : female
Number of animals : 15
Vehicle : other: Cremophor EL/water
Doses : 50, 500, 1000, 1500, 2000, 2500, 3500 mg/kg bw
Method : other: acute toxicity of benzotrichloride after single oral treatment of female Wistar rats
Year : 1978
GLP : no data
Test substance : other TS: as provided by sponsor

Remark : no weight control
Purity of test item and age of animals were not indicated

Result	dose	dead animals	symptoms	total
	[mg/kg bw]	(time of death)		
	50	0 (-)	0	15
	500	0 (-)	15	15
	1000	1 (3d)	15	15
	1500	5 (1-2d)	15	15
	2000	13 (1-2d)	15	15
	2500	14 (1-2d)	15	15
	3500	15 (7-24h)	15	15

Female Wistar rats weighing 160 to 180 g were used in the study. Rats were fasted for 16h prior treatment. Formulation of benzotrichloride (lot Nr. 1986) in water was aided by Cremophor EL®. All doses were applied by gavage in a volume of 1 ml/100 g bw. The animals were observed for 14 days. Reduced activity, scrubby fur, laboured breathing, polyuria with sanguineous urine was observed. Symptoms started within 15 minutes after treatment and persisted for 7 to 9 days. Gross pathology of deceased animals: empty intestinal tract, white stipples on stomach mucosa.

Reliability : (2) valid with restrictions
Purity of test item not given
Flag : Critical study for SIDS endpoint

27.11.2003

(56)

Type : LD50
Value : = 6000 mg/kg bw
Species : rat
Strain : Sherman
Sex : no data
Number of animals : 10
Vehicle : no data
Doses : no data
Method : other: according to Smyth HF and Carpenter CP J Ind Hyg Toxicol: 30, 63-68 (1948)
Year : 1951
GLP : no data
Test substance : no data

Remark : Observation period: 14 days
Reliability : (4) not assignable
Insufficient details given.

06.12.2003

(57)

Type : LD50
Value : = 770 mg/kg bw
Species : rat
Strain : Sprague-Dawley
Sex : male
Number of animals : 5
Vehicle : other: corn oil
Doses : 320.2, 508.4, 807.1, 1281, 2034, 3229 mg/kg bw
Method :
Year : 1979
GLP : no data
Test substance : other TS: as supplied by the sponsor on August 31, 1978 (Lot D8-195-1; transparent yellow liquid with white particles)

Remark : Observation period: 14 days
Result : Male rats mortality:

mg/kg bw	deaths
320.2	0/5
508.4	0/5
807.1	3/5
1281	5/5
2034	5/5
3229	5/5

Toxic signs:

Hypoactivity, ataxia, decreased limb tone, piloerection and urine stained abdomen.

Gross necropsy:

Yellow stained urogenital region, lung congestion, intestines filled with tan creamy or yellow or red fluid, thymus with red foci.

Reliability : (2) valid with restrictions
no information on substance purity
Flag : Critical study for SIDS endpoint

06.12.2003

(58)

Type : LD50
Value : = 702 mg/kg bw
Species : rat

Strain : Sprague-Dawley
Sex : female
Number of animals : 5
Vehicle : other: corn oil
Doses : 320.2, 508.4, 807.1, 1281, 2034, 3229 mg/kg bw
Method :
Year : 1979
GLP : no data
Test substance : other TS: as supplied by the sponsor on August 31, 1978 (Lot D8-195-1; transparent yellow liquid with white particles)

Remark : Observation period: 14 days
Result : Female rats mortality:

mg/kg bw	deaths
320.2	0/5
508.4	1/5
807.1	3/5
1281	5/5
2034	5/5
3229	5/5

Toxic signs:

Hypoactivity, ataxia, decreased limb tone, piloerection and urine stained abdomen, diarrhea.

Gross necropsy:

Yellow stained urogenital region, lung congestion, intestines filled with tan creamy or yellow or red fluid, thymus with red foci.

Reliability : (2) valid with restrictions
 No information on substance purity
Flag : Critical study for SIDS endpoint

06.12.2003

(58)

Type : LD50
Value : = 1300 mg/kg bw
Species : mouse
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data

Remark : No details reported
Reliability : (4) not assignable

26.11.2003

(59)

Type : LD50
Value : = 845 mg/kg bw
Species : mouse
Strain : CD-1
Sex : male
Number of animals : 5
Vehicle : other: corn oil
Doses : 320.2, 508.4, 807.1, 1281, 2034, 3229, 5126 mg/kg bw
Method :
Year : 1978
GLP : no data
Test substance : other TS: as supplied by the sponsor (lot D8-195-1)

Remark	:	Observation period: 14 days	
Result	:	Male mice mortality:	
		mg/kg bw	deaths
		320.2	0/5
		508.4	0/5
		807.1	2/5
		1281	5/5
		2034	5/5
		3229	5/5
		5126	5/5
			death time (d)
			-
			-
			2-3
			2
			2
			1-2
			1
		LD50 (calculated): 845 mg/kg bw (674-1060 mg/kg bw confidence interval)	
Reliability	:	(2) valid with restrictions	
		No clinical findings recorded	
07.12.2003			(60)
Type	:	LD50	
Value	:	= 770 mg/kg bw	
Species	:	mouse	
Strain	:	CD-1	
Sex	:	female	
Number of animals	:	5	
Vehicle	:	other: corn oil	
Doses	:	320.2, 508.4, 807.1, 1281, 2034, 3229, 5126 mg/kg bw	
Method	:		
Year	:	1978	
GLP	:	no data	
Test substance	:	other TS: as supplied by the sponsor (lot D8-195-1)	
Remark	:	Observation period: 14 days	
Result	:	Female mice mortality:	
		mg/kg bw	deaths
		320.2	0/5
		508.4	0/5
		807.1	3/5
		1281	5/5
		2034	5/5
		3229	5/5
		5126	5/5
			death time (d)
			-
			-
			3-4
			2
			1-2
			1
			1
		LD 50 (calculated): 770 (614-966) mg/kg bw	
Reliability	:	(2) valid with restrictions	
		No clinical findings recorded	
27.11.2003			(61)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	> .6 mg/l
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	6
Vehicle	:	other: none
Doses	:	258, 550, 600 mg/m ³
Exposure time	:	4 hour(s)
Method	:	other: see method

Year	:	1978																									
GLP	:	no data																									
Test substance	:	other TS: as supplied by the sponsor, no purity data given (appearance: colourless, pungent liquid)																									
Method	:	Male Wistar rats (n=6/group) were exposed to three doses of benzotrichloride (258, 550, 600 mg/m³) by inhalation. Exposure time was 4 h in a 10 l glass containment at 22°C. The exposure concentration of benzotrichloride in the air was determined (GC). Saturated vapor of benzotrichloride obtained by bubbling air through a test item sample was adjusted to lower concentrations by mixing with different amounts of clean air.																									
Remark	:	The study fulfils generally accepted scientific criteria and is therefore approved for assessment.																									
Result	:	<table><tr><th>conc. [mg/m³]</th><th>deaths (time)</th><th>symptoms</th><th colspan="2">average weight [g]</th></tr><tr><th></th><th></th><th></th><th>pre</th><th>post (21 d)</th></tr><tr><td>258</td><td>1 (16 d)</td><td>6</td><td>188</td><td>195</td></tr><tr><td>550</td><td>2 (1-2 d)</td><td>6</td><td>195</td><td>171</td></tr><tr><td>600</td><td>2 (2-21 d)</td><td>6</td><td>187</td><td>143</td></tr></table> LC50 >600 mg/m³ (determined at day 14) Symptoms during treatment: irritation of visible mucous membranes in both higher dosed groups. Gross pathology: pulmonary emphysema, atrophic liver and spleen being coloured darkly. The weight gain of the 258 mg/m³ group is far below normal weight development of male rats in three weeks.	conc. [mg/m³]	deaths (time)	symptoms	average weight [g]					pre	post (21 d)	258	1 (16 d)	6	188	195	550	2 (1-2 d)	6	195	171	600	2 (2-21 d)	6	187	143
conc. [mg/m³]	deaths (time)	symptoms	average weight [g]																								
			pre	post (21 d)																							
258	1 (16 d)	6	188	195																							
550	2 (1-2 d)	6	195	171																							
600	2 (2-21 d)	6	187	143																							
Reliability	:	(2) valid with restrictions Minor deviations from OECD guideline 403 (test item purity not stated, weight control interval, animal age not indicated)																									
Flag	:	Critical study for SIDS endpoint																									
27.11.2003		(56)																									
Type	:	LC50																									
Value	:	= .5 mg/l																									
Species	:	rat																									
Strain	:	Wistar																									
Sex	:	female																									
Number of animals	:	6																									
Vehicle	:	other: none																									
Doses	:	300, 530, 654 mg/m³																									
Exposure time	:	4 hour(s)																									
Method	:	other: see method																									
Year	:	1978																									
GLP	:	no data																									
Test substance	:	other TS: as supplied by the sponsor, no purity data given (appearance: colourless, pungent liquid)																									
Method	:	Female Wistar rats (n=6/group) were exposed to three doses of benzotrichloride (300, 530, 654 mg/m³) by inhalation. Exposure time was 4 h in a 10 l glass containment at 22°C. The exposure concentration of benzotrichloride in the air was determined. Saturated vapor of benzotrichloride obtained by bubbling air through a test item sample was adjusted to lower concentrations by mixing with different amounts of clean air.																									
Remark	:	The study is well documented and does fulfil scientific criteria for																									

Result	assessment.
	: conc. deaths symptoms average weight [g] [mg/m ³] (time) pre post (21 d)
	300 2 (13-18 d) 6 167 149
	530 3 (17-21 d) 6 169 110
	654 4 (1-21 d) 6 175 108
LC50 ~500 mg/m ³ (determined at day 14)	
Symptoms during treatment: irritation of visible mucous membranes in both higher dosed groups.	
Gross pathology: pulmonary emphysema, atrophic liver and spleen exhibiting dark coloured appearance.	
Reliability	The weight reduction in all treatment groups is very prominent.
	: (2) valid with restrictions
Flag 27.11.2003	Minor deviations from OECD guideline 403 (test item purity not stated, weight control interval, animal age not indicated).
	: Critical study for SIDS endpoint (56)
Type	: LC50
Value	: = .06 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: no data
Year	: 1964
GLP	: no data
Test substance	: no data
Result	: LC16=30 mg/m ³ , LC50=60 mg/m ³ , LC84=120 mg/m ³ (2 h exposition).
	The postexposure observation period was 2 weeks.
	Toxicological symptoms were excitation and irritation of conjunctiva and mucosal membranes of the respiratory tract.
	Furthermore hyperaemia of tail, ears and pads were noticed.
Histopathological examination revealed inflammation of the respiratory tract accompanied by bacterial superinfection, fat distrophy in liver cells, epithelial necrosis of renal tubules, dystrophic alterations of the cardiac muscle and cortical cell swelling in CNS.	
Reliability	: (4) not assignable
	Documentation is insufficient (62)
26.11.2003	
Type	: LC50
Value	: = 8.39 mg/l
Species	: rat
Strain	: other: Charles River CD
Sex	: male/female
Number of animals	: 5
Vehicle	: other: none
Doses	: 20.3, 10.86, 6.01, 4.82, 4.01, 2.00 mg/l
Exposure time	: 1 hour(s)
Method	: other: see method

Year	:	1979
GLP	:	no data
Test substance	:	other TS: as supplied by the sponsor (lot D8-195-1) on August 31, 1978 without data on purity (appearance: transparent yellow liquid with white particles)
Method	:	By use of an atomizer and dilution with clean air the desired concentration of benzotrichloride was adjusted. Animals were exposed in individual wire-mesh cages placed in a 160 l chamber.
Result	:	Post exposure and observation time was 14 days. One hour exposure of male and female rats (n=5) to 20.3, 10.86, 6.01, 4.82, 4.01, 2.00 mg benzotrichloride/ l air resulted in 9, 4, 5, 5, 0 and 0 deaths, respectively. The 1 h LC50 was calculated to be 8.39 mg/l. Toxicological signs during exposure: nasal discharge, salivation and eye squint, all only transient. Dyspnea persisted during observation period. At the higher exposure concentrations decreased activity, ataxia and gasping was observed in some animals. A slight to moderate body weight loss was observed for both male and female rats in all exposures. Gross pathology: dark pink lungs with red patches or red foci was noticed in some animals of all exposed groups. Dark foci on the stomach with black-orange streaked intestines was found in highest exposure dose animals.
Reliability	:	(2) valid with restrictions
Flag	:	No purity of the test item defined.
06.12.2003	:	Critical study for SIDS endpoint (63)
Type	:	LC50
Value	:	= .15 mg/l
Species	:	rat
Strain	:	no data
Sex	:	male
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Exposure time	:	2 hour(s)
Method	:	other: no data
Year	:	1964
GLP	:	no data
Test substance	:	no data
Result	:	LC16=90 mg/m³, LC50=150 mg/m³, LC84=240 mg/m³ (2 h exposition) The postexposure observation period was 4 weeks. Toxicological symptoms were excitation and irritation of conjunctivae and mucosal membranes of the respiratory tract. Furthermore hyperaemia of tail, ears and pads were noticed. Histopathological examination revealed inflammation of the respiratory tract accompanied by bacterial superinfection, fat dystrophy in liver cells, epithelial necrosis of renal tubules, dystrophic alterations of the cardiac muscle and cortical cell swelling in CNS.
Reliability	:	(4) not assignable
28.11.2003	:	Documentation is insufficient (62)

Type : LC50
Value : 150
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Exposure time : 2 hour(s)
Method : other: no data
Year : 1982
GLP : no data
Test substance : no data

Remark : No dimension given.
No details
Reliability : (4) not assignable
Insufficient detail given; secondary citation

28.11.2003

(59)

Type : other: acute inhalation study
Value :
Species : rat
Strain : no data
Sex : male
Number of animals : 10
Vehicle : no data
Doses : 0.1 mg/l
Exposure time : 2 hour(s)
Method : other: no data
Year : 1964
GLP : no data
Test substance : no data

Result : Male rats (n=10) were exposed to benzotrichloride at 100 mg/m³ for two hours. Follow up was 4 weeks. During this observation period 3 animals died (the cause for the animals death was not commented) and the remaining 7 showed initial weight loss. The animal's weight returned to the preexposure value at week four.
The animals were leukopenic 3 weeks after exposure.
A diminished daily volume of renal excretion and less protein excreted in urine was noticed.

Reliability : (4) not assignable
Documentation incomplete

28.11.2003

(62)

Type : other: acute inhalation toxicity
Value :
Species : rat
Strain : Wistar
Sex : male
Number of animals : 6
Vehicle : other: none
Doses : 0.79 -1.2 mg/l
Exposure time :
Method : other: single exposure for 0.5, 1.0, 3.0 and 7.0 h
Year : 1978
GLP : no data
Test substance : other TS: as supplied by the sponsor, purity of testitem not given
(appearance: colourless, pungent liquid)

Result	:	dose mg/m ³	expos. time [h]	death (time)	symptoms	weight loss (14 d) [g]
		1067	7	6 (< 24 h)	6	-
		1147	3	1 (3 d)	6	-21
		797	1	0	6	+ 9
		790	0.5	0	0	+55

Male Wistar rats showed behaviour disorders (lethargy, dirty fur) and respiratory embarrassment. These symptoms lasted for up to 13 days post-treatment.

The groups exposed for 1 h or more exhibited irritations of the ocular and respiratory mucous membranes.

Reliability	:	(2) valid with restrictions Insufficient details about test substance
Flag	:	Critical study for SIDS endpoint

28.11.2003

(56)

Type	:	other: acute inhalation toxicity
Value	:	
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	6
Vehicle	:	no data
Doses	:	125 ppm = about 1 mg/l
Exposure time	:	4 hour(s)
Method	:	other: see method
Year	:	1951
GLP	:	no
Test substance	:	no data

Method	:	The method is described by Smyth HF and Carpenter CP (J Ind Hyg Toxicol: 30, 63-68 (1948). Saturated vapour inhalation of known concentration which produces fractional mortality as a result of a 4-hour exposure.
--------	---	--

Result	:	The mortality of rats exposed 4 h to 125 ppm (1014 mg/m ³) benzotrichloride was 5/6 (83.3%). The maximal exposure time where no deaths occurred was 0.5 h when the animals were exposed to saturated vapor.
--------	---	--

Reliability	:	(2) valid with restrictions Few details given.
-------------	---	---

Flag	:	Critical study for SIDS endpoint
------	---	----------------------------------

09.12.2003

(57)

Type	:	other: time dependent acute inhalation toxicity
Value	:	
Species	:	rat
Strain	:	Wistar
Sex	:	female
Number of animals	:	6
Vehicle	:	other: none
Doses	:	747, 795, 995, 1193 mg/m ³
Exposure time	:	
Method	:	other: single exposure for 0.5, 1.0, 3.0 or 7.0 h
Year	:	1978
GLP	:	no data
Test substance	:	other TS: as supplied by the sponsor, purity of test item not given (appearance: colourless, pungent liquid)

Result	:	dose mg/m ³	expos. time [h]	death (time)	symptoms	weight loss (14 d) [g]
		1193	7	6 (< 24 h)	6	-
		995	3	4 (3-13 d)	6	-40
		795	1	0	6	-4
		747	0.5	0	0	+8

Rats showed behaviour disorders (lethargy, dirty fur) and respiratory embarrassment. These symptoms lasted for up to 13 days post-treatment. The groups exposed for 1 h or more exhibited irritations of the ocular and respiratory mucous membranes.

Reliability : (2) valid with restrictions
Not characterized test substance
Flag : Critical study for SIDS endpoint

28.11.2003

(56)

Type : LC50
Value : 60
Species : mouse
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 data
Test substance : no data

Remark : No dimension, no details given.

Same values for mouse and rat LC50 as from Mikhailova's study.

Reliability : (4) not assignable
Insufficient detail given; secondary citation

28.11.2003

(59)

Type : LC100
Value : <= 1 mg/l
Species : other: mouse and rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Exposure time : 2 hour(s)
Method : other: no data
Year : 1963
GLP : no data
Test substance : no data

Remark : No further details given.

Result : The single exposure of either mice or rats to 1 mg/l benzotrichloride for 2 h resulted in the death of all animals.

Single exposure of rats for 2 h to 0.1 mg/ml led to irritation of the respiratory tract, to inhibition of the motor activity, dyspnoea, vasodilatation of tail, paws, and ears.

Reliability	: Single exposure of rats for 2 h to 0.03 mg/ml had no effect (4) not assignable Insufficient documentation
08.12.2003	(54)

5.1.3 ACUTE DERMAL TOXICITY

Type	: LD50
Value	: > 5000 mg/kg bw
Species	: rat
Strain	: Wistar
Sex	: male/female
Number of animals	:
Vehicle	: other: Cellulose
Doses	: 2500, 5000 mg/kg bw (female), 5000 mg/kg bw (male)
Method	: other: occlusive application for 24 h
Year	: 1978
GLP	: no data
Test substance	: other TS: as supplied by the sponsor (Appearance: colourless, pungent liquid)
Remark	: Number of animals: see doses
Result	: MORTALITY: 5000 mg/kg bw/d: 0/5 (male); 1/10 (female) 2500 mg/kg bw/d: 0/5 (female) The cutaneously exposed animals survived all but 1 female of the 5000 mg/kg group (day 3). Therefore the LD50 is >5000 mg/kg bw. All animals showed sedation and a decreased general health status. These symptoms did not persist beyond days 8 to 10 after exposure. The onset of symptoms started at day 1 after exposure. The dermal areas of contact with benzotrichloride were slightly swollen and hardened after removal of the bandages. NECROPSY FINDINGS: not reported.
Test condition	: The study was conducted using male and female Wistar rats. The wrap method of Noakes and Sanderson (Brit. J. Int. Med.: 26, 59 (1969)) was followed. The dose of 2500 mg/kg was thickened with 150 mg cellulose and the dose of 5000 mg/kg thickened with 300 mg cellulose. Five male rats were treated with 5000 mg/kg bw whereas 10 female rats were treated with this amount Benzotrichloride and five female rats were treated with 2500 mg Benzotrichloride/kg bw. The cellulose thickened substance was applied to the shaved, non wounded backs of the animals. Their bodies were wrapped in bandages for 24 h and after removal the animals were washed free of test item. The animals were observed for 14 days.
Reliability	: (2) valid with restrictions limited documentation
Flag	: Critical study for SIDS endpoint
06.12.2003	(56)
Type	: LD50
Value	: = 4000 mg/kg bw
Species	: rabbit
Strain	: New Zealand white
Sex	: male/female
Number of animals	:
Vehicle	: no data
Doses	: 1000, 2000, 4000, 8000 mg/kg bw
Method	: other: see Test Condition
Year	: 1979

GLP	: no data
Test substance	: other TS: Benzotrichloride was received from the study's sponsor on August 31, 1978 (Velsicol Chemical Corporation) as lot: D8-195-1 appearing as transparent yellow liquid with white particles.
Result	: The LD50 was 4000 mg/kg bw irrespective of the gender (95% confidence interval 2000 - 8000 mg/kg bw for males and females, respectively; 2681 - 5968 mg/kg bw for males and females combined). Starting with 2000 mg/kg bw a weight reduction was observed for female rabbits and also for males and females at 4000 mg/kg bw. This symptom was more pronounced in females. In males and females of the 4000 mg/kg bw treatment group hypoactivity and ataxia were the most pronounced pharmacotoxic signs. They persisted for the observation period of 14 d. Mortality: 4000 mg/kg bw : 1 male (day 3), 1 female (day 6) 8000 mg/kg bw : 2 males (day 2), 2 females (day 3)
Test condition	: Gross necropsy (on dead animals): irritation at application site, mottled or pale coloration of livers, brown or green fluid in stomach, brown intestinal contents, lung congestion (females only) : The acute dermal toxicity was determined by using 2 male and 2 female rabbits per group. The skin of one male and one female per group was abraded. The test substance was applied for 24 hours under occlusive conditions. Vehicle: non reported, presumably applied undiluted.
Reliability	: (2) valid with restrictions Purity of test substance not given; small number of animals per group; method not complying with current standard (animals skin abraded)
06.12.2003	(58)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

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: Code of Federal Regulations, Title 16, Section 1500.41
Year	: 1978
GLP	: no data
Test substance	: other TS: as supplied by the sponsor (Appearance: colourless, pungent liquid).
Method	: The method described by the Code of Federal Regulations, title 16, section 1500.41 (Method of testing primary irritating substances) was applied. White New-Zealand rabbits of both sexes were treated with 0.5 ml (0.69 mg) of undiluted benzotrichloride under a 1x1 inch patch. The test item remained under occlusion on the skin for 24 hours. The skin was either clipped free of hair (normal skin) or was clipped free of hair and abraded (abraded skin).

		Treated animals (white New-Zealand rabbits) were inspected for skin effects (erythma, edema) after 24 and 72 h and after 7 days Total observation time was 7 d.						
Result	:	Benzotrichloride was found to possess a slightly irritant effect when applied for 24 h on normal and abraded rabbit skin.						
		animal symptom	normal skin			abraded skin		
			24 h	72 h	7d	24 h	72 h	7 d
		1 erythrema	1	2	2	2	2	2
		1 oedema	1	1	1	2	1	1
		2 erythrema	2	2	2	2	2	2
		2 oedema	2	1	1	2	1	1
		3 erythrema	2	2	2	1	2	2
		3 oedema	2	1	1	1	1	1
		4 erythrema	1	1	1	1	1	1
		4 oedema	1	1	1	1	1	1
		5 erythrema	2	1	1	2	1	1
		5 oedema	2	1	0	2	1	1
		6 erythrema	1	1	1	1	1	1
		6 oedema	1	1	1	2	1	1
		Total	18	15	14	19	15	15
		Primary irritation score = sum of all scores (24 + 72 h) / 24 = 2.8						
		The primary irritation score is 2.8 (= slightly irritant) The cutaneous alterations persisted after day 7.						
Reliability	:	(2) valid with restrictions Deviation from current guideline: occlusive application (instead of semi-occlusive), 24 hours exposure time (instead of 4 hours); observation time ended before all effects were reversible.						
Flag	:	Critical study for SIDS endpoint						
06.12.2003		(56)						
Species	:	rabbit						
Concentration	:	1.4 other: g/painting						
Exposure	:	no data						
Exposure time	:	no data						
Number of animals	:							
Vehicle	:	no data						
PDII	:							
Result	:	irritating						
Classification	:							
Method	:	other: shaved skin, 1ml/painting, 3 paintings/w						
Year	:	1963						
GLP	:	no data						
Test substance	:	no data						
Result	:	The 3 times weekly dermal painting with 1 ml benzotrichloride (about 1.4 g/ painting) onto the shaved rabbit skin produced dermal erosions. Although the treatment time is not stated, a slow healing of these erosions is reported. After one month eschar formed at the eroded skin. Leukocytes dropped from average normal levels of 14,000 cells/µl to 9000 - 8000 cells/µl indicating leukopenia.						
Reliability	:	(4) not assignable						

08.12.2003 Insufficient documentation (54)

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle : no data
PDII :
Result : irritating
Classification :
Method : other: according to Smyth HF and Carpenter CP J Ind Hyg Toxicol: 30, 63-68 (1948)
Year : 1951
GLP : no data
Test substance : other TS: no data

Remark : Details of test method not given.
Result : The author's score system (described in: Smyth HF et al. J Ind Hyg Toxicol 31, 60-62 (1949)) classified benzotrichloride as grade 5 (score grades: 0 to 10) or causing strong erythema, oedema or slight necrosis.
Reliability : (4) not assignable
Insufficient documentation

28.11.2003 (57)

Species : rabbit
Concentration : undiluted
Exposure : Occlusive
Exposure time : 4 hour(s)
Number of animals : 3
Vehicle : other: none, undiluted
PDII :
Result : not irritating
Classification :
Method : other: 0.5 ml/rabbit, 3 rabbits/sex, examination after 4, 24, 48, 72 h.
Year : 1979
GLP : no data
Test substance : other TS: as supplied by the sponsor on August 31, 1978 (Lot D8-195-1; transparent yellow liquid with white particles)

Result : Three male and three female New Zealand white rabbits were exposed to 0.5 ml (approx. 0.69 g) benzotrichloride under a 4 inch square gauze pad at their backs for 4 h under occlusion.
Examinations after the 4 h exposure and thereafter 24, 48 and 72 h for skin irritation revealed no indication of such.
Score=0
Reliability : (2) valid with restrictions
Deviation from current guideline: occlusive application (instead of semi-occlusive).
Flag : Critical study for SIDS endpoint

06.12.2003 (58)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration : undiluted
Dose : .1 ml
Exposure time :

Comment	: not rinsed																																																
Number of animals	: 6																																																
Vehicle	: other: none																																																
Result	: irritating																																																
Classification	:																																																
Method	: other: (Code of Federal Regulations, Title 16, Section 1500.42)																																																
Year	: 1978																																																
GLP	: no data																																																
Test substance	: other TS: other TS: as supplied by the sponsor (Appearance: colourless, pungent liquid).																																																
Method	: The method described by the Code of Federal Regulations, title 16, section 1500.42 (Test for eye irritants) was applied. A volume of 0.1 ml is placed into the cupped eye lid. For 1 second the eye lids are held together. At 24 h the eyes are inspected for ocular reactions. If flourescein is needed for further inspection the eyes are washed after the procedure with physiological saline. After 48 and 72 hours the eye examinations are repeated till healig of injuries are noticed.																																																
Result	: Inspection of the treated eyes at 1, 24, 48 and 72 h and after 7 days by examination of cornea, iris and conjunctiva revealed only a slight irritant property of benzotrichloride. The not very marked opacity of the cornea was restricted to confined areas (lower inner corneal area) and was resolved at day 7. Confined areas of the lower cornea showed sparse and only transient turbidity. Scores: <table><tr><td></td><td>1h</td><td>24h</td><td>48h</td><td>72h</td><td>7 days</td></tr><tr><td>cornea</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td> opacity</td><td>0</td><td>0-1</td><td>0-1</td><td>0-1</td><td>0</td></tr><tr><td> area</td><td>0</td><td>0-1</td><td>0-1</td><td>0-1</td><td>0</td></tr><tr><td>iris</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr><tr><td>conjunctiva</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td> redness</td><td>1-2</td><td>1-2</td><td>1-2</td><td>1-3</td><td>0-1</td></tr><tr><td> chemosis</td><td>0-3</td><td>0-1</td><td>0-2</td><td>0-1</td><td>0-1</td></tr></table>		1h	24h	48h	72h	7 days	cornea						opacity	0	0-1	0-1	0-1	0	area	0	0-1	0-1	0-1	0	iris	0	0	0	0	0	conjunctiva						redness	1-2	1-2	1-2	1-3	0-1	chemosis	0-3	0-1	0-2	0-1	0-1
	1h	24h	48h	72h	7 days																																												
cornea																																																	
opacity	0	0-1	0-1	0-1	0																																												
area	0	0-1	0-1	0-1	0																																												
iris	0	0	0	0	0																																												
conjunctiva																																																	
redness	1-2	1-2	1-2	1-3	0-1																																												
chemosis	0-3	0-1	0-2	0-1	0-1																																												
Reliability	: (2) valid with restrictions Limited documentation																																																
Flag	: Critical study for SIDS endpoint																																																
06.12.2003	(56)																																																
Species	: rabbit																																																
Concentration	: 1 %																																																
Dose	: 5 other: mg																																																
Exposure time	:																																																
Comment	: not rinsed																																																
Number of animals	: 5																																																
Vehicle	: other: see method																																																
Result	: highly irritating																																																
Classification	:																																																
Method	: other: see method																																																
Year	: 1951																																																
GLP	: no data																																																
Test substance	: no data																																																
Method	: The method and details of the score system are described by Carpenter C.P. and Smyth H.F., Am. J. Ophtal., 29, 1363-1372,(1946). Usually 5 rabbits are tested for each dose tested. The dose is applied in a volume of 0.005 ml to the center of the cornea while the lids are retracted.																																																

About one minute later the lids are released. After 18 to 24 hours later, the eyes are inspected in strong diffuse daylight, stained with fluorescein, and the injury scored. The individual numerical scores of each eye (total of 20 at maximum) treated with a given volume or concentration of test substance are added together and then divided by the number of eyes treated (usually 5) to obtain the score of the injury caused by the treatment. Where dilution of test item is necessary (score >5), the preferred solvent was propylene glycol (pretested to cause no harm). Next preference is given to water, and in some cases a deodorized kerosene has been used. The applied volume for the solution of benzotrichloride is not mentioned. No further details available.

Remark : The test item remains for one minute in the opened eye of the test animal. In the humid/watery eye environment benzotrichloride rapidly decomposes to benzoic acid and hydrochloric acid.

Result : A 1% solution of benzotrichloride yielded a score of >5 (a level of 5 is representative of severe injury, corresponding to necrosis, visible only after staining and covering about ¾ of the surface of the cornea, or a more serious necrosis covering a smaller area)

Reliability : (2) valid with restrictions
Precise number of animals, reading time, individual scores, observation period and reversibility of lesions was not indicated.

Flag : Critical study for SIDS endpoint
06.12.2003 (57)

Species : rabbit
Concentration : undiluted
Dose : .1 ml
Exposure time :
Comment : not rinsed
Number of animals : 6
Vehicle : none
Result : moderately irritating
Classification :
Method : other: 0.1 ml/eye/rabbit, into the cupped conjunctival sac
Year : 1979
GLP : no data
Test substance : other TS: as supplied by the sponsor on 31 August, 1978 (Lot: D8-195-1; transparent yellow liquid with white particles)

Result : Results obtained defined benzotrichloride as a moderate eye irritant.

Score ranges:

	1h	24h	48h	72h	7 days	14 days
cornea						
opacity	0	0	0-1	0-1	0	0
area	0	0	0-1	0-1	0	0
iris	0	0	0-1	0-1	0-1	0
conjunctiva						
redness	1-2	1-2	1-2	1-3	0-1	0
chemosis	1-2	1	1-1.5	1-2	2-3	0

After 14 d all rabbits showed hair loss around the eye, only one rabbit exhibited a weight loss between days 7 and 14.

Reliability : (2) valid with restrictions
Purity of test item not declared.

Flag : Critical study for SIDS endpoint
09.12.2003 (58)

5.3 SENSITIZATION**5.4 REPEATED DOSE TOXICITY**

Type : Sub-acute
Species : rat
Sex : no data
Strain : no data
Route of admin. : inhalation
Exposure period : up to 8 w
Frequency of treatm. : 2 h/d, no further information
Post exposure period : no data
Doses : 0.03, 0.1 mg/l
Control group : yes
Method :
Year : 1963
GLP : no data
Test substance : no data

Result : Rats (initial weight: 170 -200 g) were exposed daily by inhalation to bezotrichloride (30 or 100 mg bezotrichloride/m³) for up to 2 months. After one week of exposure body weight reduction, increased aggressiveness of the animals, decrease in blood pressure (90 mm Hg to 60 mm Hg) and leukopenia (14,000 to 8000 - 9000 cells/ μ l) was observed. The continued inhalation resulted in histopathological findings like putrid bronchitis, pneumonia, fatty degeneration of liver cells, karyolysis in cortical cells of the brain. Dystrophic effects on liver, kidney and adrenal glands were observed.

Reliability : (4) not assignable
Insufficient documentation

08.12.2003

(54)

Type : Sub-acute
Species : rat
Sex : male/female
Strain : other: Charles River CD
Route of admin. : inhalation
Exposure period : 4 w
Frequency of treatm. : 6 h/d, 5 d/w
Post exposure period : no
Doses : 0, 5.1, 48.2, 460 mg/m³
Control group : yes
NOAEL : = 5.1 mg/m³
Method : other: see method
Year : 1981
GLP : yes
Test substance : other TS: purity: 96.4% (GC); lot 08-195-1

Method : The effect of bezotrichloride inhalation for 6 h/day, 5 d/week for 4 weeks was examined in rats (10 male and 10 female/group, control group). The groups received 460, 48.2, 5.1 and 0 mg bezotrichloride/m³.

Result : 460 mg/m³-group: marked dyspnea, gasping, death during the first week or sacrifice in extremis at the end of the first week;
48.2 mg/m³-group: depressed body weight after one week which persisted throughout the study time, slight dyspnea after 4 weeks;
gross pathology revealed lung congestion primarily in the high dose group (7/10 males, 6/10 females);

	histopathological changes in the nasal turbinates, the trachea, the lungs of the 460 mg/m³- and 48.2 mg/m³-group (inflammation, desquamation, ulceration, degeneration, squamous metaplasia); no significant changes in the 5.1 mg/m³-group (NOAEL)	
Conclusion	: Benzotrichloride is a respiratory tract irritant after repeated inhalation exposure leading to dyspnea. Histopathology revealed nasal, tracheal and pulmonary changes. The NOAEL is 5.1 mg/m³.	
Reliability	: (1) valid without restriction	
Flag	: Critical study for SIDS endpoint	
08.01.2004		(64)
Type	: Chronic	
Species	: rat	
Sex	: female	
Strain	: Sprague-Dawley	
Route of admin.	: inhalation	
Exposure period	: 104 w	
Frequency of treatm.	: 6 h/d, 5 d/w	
Post exposure period	: 3 w	
Doses	: 0.1, 0.4, 1.0, 2.0 ppm	
Control group	: yes	
Method	: other: see Test Condition	
Year	: 1980	
GLP	: no data	
Test substance	: no data	
Remark	: Publication years: 1980 and 1984	
Result	: Due to high mortality in the 2 ppm group a dose reduction to 1.6 ppm after 10 weeks and to 1 ppm after 20 weeks was made. After 25 weeks this group received no further treatment. Nevertheless, the animals succumbed all by week 39. Death of rats was increased at doses >= 0.4 ppm and resulted from tumours and accompanying illnesses as well as lung inflammation and spontaneous diseases.	
	Cummulative mortality (%)	
	Exp. 2 1 0.4 0.1 0 [ppm]	
	Weeks	
	20 2 0 0 0 0	
	40 100 2 2 0 0	
	60 22 16 4 2	
	80 100 46 14 4	
	100 86 46 38	
	107 100 54 54	
Test condition	: See section 5.7 for carcinogenicity. : Seven week old female Sprague-Dawley rats were exposed to 2.0, 1.0, 0.4 and 0.1 ppm benzotrichloride by inhalation for 104 weeks. Exposure was 6h/day on 5 days/week for 104 weeks with a post-treatment observation period of 3 weeks.	
Reliability	: (2) valid with restrictions Purity of test item not given	
18.08.2004		(65) (66) (67)
Type	: Sub-acute	
Species	: rat	
Sex	: male/female	
Strain	: Sprague-Dawley	

Route of admin.	: oral feed
Exposure period	: 28 d
Frequency of treatm.	: daily
Post exposure period	: no
Doses	: 0.5, 5.0, 50.0, 500 ppm
Control group	: yes
LOAEL	: = .5 ppm
Method	: other: see method
Year	: 1984
GLP	: no data
Test substance	: other TS: 98% (Aldrich Chemical Co.)
Method	: Oral toxicity of trichlorotoluene isomers including benzotrichloride was examined in a 28-day feeding study in weanling (ca.60 g) Sprague-Dawley rats. The compound was dissolved in corn oil and then mixed to the diet. The doses given to the 10 animals/group/sex were 0.5, 5.0, 50.0, 500 ppm leading to 0.048 - 46 mg/ kg bw/day for male rats and 0.053 - 53 mg/kg bw/day for female rats of chemical ingested. Body weight and food consumption were determined weekly, clinical observations were made daily. After the 28 day feeding period the animals were lightly anesthetized with ether, exanguined and gross pathologically examined at necropsy. Bone marrow cytology, hematological parameters (hemoglobin concentration, packed cell volume, total and differential leukocyte cell counts), serum analysis and liver, brain, heart, spleen and kidney weights determined and prepared for microscopic inspection. Statistics: one-way multiple of variance and Duncan's multiple range test.
Result	: Based on food consumption data the amount of chemical ingested was 0.048 - 46 mg/ kg bw/day for male rats and 0.053 - 53 mg/ kg bw/day for female rats. Growth rate, food consumption, haematological parameters not affected by treatment; no deaths occurred; mild serum biochemical changes in male rats: significant increases in SDH (sorbitol dehydrogenase, indicative for liver injury) activities (5.0 and 50.0 ppm dose group), elevated LDH (lactate dehydrogenase) activities (500 ppm dose group); Mild histopathologic changes in the liver, kidney and thyroid of the treated rats were seen, males being more susceptible than females. The observed histological changes became progressively more severe and occurred more frequently as dose levels increased. Hepatocytes had mild anisokaryosis associated with pyknosis and occasionally necrotic hepatocytes were observed. Cytoplasmic vacuolation and increased eosinophilia was seen in portal areas of the hepatic lobe. Renal changes consisted of an accumulation of eosinophilic cytoplasmic inclusions in the epithelium of proximal tubules associated with focal glomerular adhesions and interstitial scarring due to spontaneous ageing process. Thyroids had a reduced follicular size and colloid density. The epithelium cells became columnar and thickened with focal and multifocal angular collapse of follicles. Additional changes included focal and multifocal papillary proliferations and focal vacuolations.
Conclusion	: Oral administration of 0.5 ppm was the LOAEL (histopathology)
Reliability	: No detectable residual compound in liver and fat (< 0.1 ppm).
Flag	: (1) valid without restriction
06.12.2003	: Critical study for SIDS endpoint (68)
Type	: Chronic
Species	: mouse
Sex	: male

Strain : ICR
Route of admin. : inhalation
Exposure period : 104 w
Frequency of treatm. : 6 h/d, 5 d/w
Post exposure period : 3 w
Doses : 0.1, 0.4, 1.0, 2.0 ppm
Control group : yes
Method : other: repeated dose inhalation
Year : 1980
GLP : no data
Test substance : no data

Method : Seven week old female ICR mice rats were exposed to 2.0, 1.0, 0.4 and 0.1 ppm benzotrichloride by inhalation for 104 weeks. Exposure was 6h/day on 5 days/week for 104 weeks with a post-treatment observation period of 3 weeks. Groups: 50 animals/dose

Remark : Publication years: 1980 and 1984

Result : Due to high mortality in the 2 ppm group a dose reduction to 1.6 ppm after 10 weeks and to 1 ppm after 20 weeks was made. Nevertheless, the animals succumbed all by week 45.

Death of rats was increased at doses $\geq$ 0.4 ppm and resulted from tumours and accompanying illnesses as well as lung inflammation and spontaneous diseases.

Cummulative mortality (%)

Exp.	2	0.4	0.1	0 [ppm]
Weeks				
20	2	2	2	0
40	90	8	2	4
60	100	26	10	14
80		90	18	26
100		100	56	46
107			68	60

Reliability : See section 5.7 for carcinogenicity.
(2) valid with restrictions
Purity of test substance not given.

18.08.2004

(65) (66) (67)

Type : Sub-chronic
Species : mouse
Sex : male
Strain : ICR
Route of admin. : inhalation
Exposure period : 5 m
Frequency of treatm. : 30 min/day, 2 days/week
Post exposure period : 1 m, 6 m
Doses : 6.7 ppm
Control group : yes
Method : other: carcinogenicity induced by repeated inhalation
Year : 1979
GLP : no data
Test substance : no data

Remark : Vapourisation at 50°C
Publication years: 1978 and 1986.

Result : For details of the tumorigenesis see chapter 5.7 carcinogenicity.

Death rate:

	Twelve exposed animals died within the 2nd and 5th month (36.4%) of exposure, a further 4 in the first month after exposure and a single mice until the 10th month. The remaining animals were in poor health conditions since the 9th month, therefore the experiment was terminated after the 10th month.
	Pulmonar lesions: Almost all animals showed severe bronchitis and bronchial pneumonia.
	Cutaneous lesions: Beginning with the 3rd month of exposure hair-loss, skin hardening as well as ulcerous lesions on ventral and dorsal skin were observed.
	Gross pathology: At necropsy many animals showed inflammatory lesions associated with hypertrophy of organs such as thymus, lymph nodes, and spleen.
Test condition	: The male ICR mice (5 week old) were exposed to benzotrichloride twice weekly for 30 minutes for 5 months, followed by a 1- to 5-month observation period. The control group of 30 animals was observed for 12 months. The exposure group consisted of 33 animals (32 were evaluated), whereas, all 30 control mice were evaluated. A volume of 0.5 ml of benzotrichloride in a 500 ml gas wash bottle held at 50°C was evaporated using a stream of dry air. The vapours were directed into a 100 l acrylic box which served as exposure chamber. To attain a even distribution of the test item in the exposure chamber, 2 small ventilators operated in the chamber during exposure. The concentration within the chamber was measured by GC determination (6.7 +/- 1.66 ppm; n=10).
Reliability	: (2) valid with restrictions Limited description of clinical signs, gross pathology, no weight development reported, no purity of test item stated
07.12.2003	(69) (70)
Type	: Sub-chronic
Species	: mouse
Sex	: male
Strain	: ICR
Route of admin.	: inhalation
Exposure period	: 12 m
Frequency of treatm.	: 30 min/day, 2 days/week
Post exposure period	: 2 m and 5 m
Doses	: 1.62 ppm
Control group	: yes
Method	: other: carcinogenicity induced by repeated inhalation
Year	: 1979
GLP	: no data
Test substance	: no data
Result	: For details of the tumorigenesis see chapter 5.7 carcinogenicity. Death rate: After 8 month of exposure first treated animals died. During the 10th month their number increased to 10/38 animals. At this time exposition was stopped. After 13 month animals started to die again (8 animals between month 12 and 15), therefore the experiment was terminated by the end of the 15th month (9 animals remaining). Ten animals were euthanized after month 12 and examined. Pulmonar lesions: Almost all animals examined after the 15th month were found to have

	proliferation of the trachea, bronchial, and terminal bronchiolar epithelia.
	Cutaneous lesions: Beginning with the 8th month neoplastic alterations of the skin were noticed.
	Gross pathology: At necropsy many animals showed inflammation of organs such as thymus, lymph nodes, and spleen. No metastasis of primary lung or dermal neoplasia was observed. Mild keratosis and hyperplasia of the gastric mucosa was seen.
Test condition	: The male ICR mice (5 week old) were exposed to benzotrichloride twice weekly for 30 minutes for 10 months, followed by a 2- to 5-month observation period. The control group of 30 animals was observed for 12 months. The exposure group consisted of 38 animals (37 were evaluated), whereas, all 30 control mice were evaluated. A volume of 0.5 ml of benzotrichloride in a 500 ml gas wash bottle held at room temperature (20 +/- 5°C) was evaporated using a stream of dry air. The vapours were directed into a 100 l acrylic box which served as exposure chamber. To attain a even distribution of the test item in the exposure chamber, 2 small ventilators operated in the chamber during exposure. The concentration within the chamber was measured by GC determination (1.62 +/- 0.43 ppm; n=8).
Reliability	: (2) valid with restrictions Limited description of clinical signs, gross pathology, no weight development reported, no purity of test item stated
Flag 08.12.2003	: Critical study for SIDS endpoint (71) (70)
Type	: Sub-chronic
Species	: mouse
Sex	: female
Strain	: ICR
Route of admin.	: dermal
Exposure period	: 30 w; 41 w; 50 w
Frequency of treatm.	: 2/w 3 w, 1/w 27 w; 3/w 4 w, 2/w 37 w; 2/w 50 w
Post exposure period	: 51.w - 57.w
Doses	: 12.5, 25 µl; 5, 10 µl; 2.3 µl /animal/painting
Control group	: yes
Method	: other: see method
Year	: 1981
GLP	: no data
Test substance	: other TS: reagent grade commercial material from Tokyo Kasei Co. Ltd., Tokyo
Method	: The backs of the ICR mice were clipped free of hair before treatment and clipping was repeated when necessary. Benzene solutions of the test material were prepared just prior to treatment. The dorsal skin application was done with a micropipette. Experiment I: 25 µl of benzotrichloride or 25 µl of 50% benzotrichloride solution in benzene (25 µl benzene only for controls) was administered to 14 week old mice twice a week for the initial 3 weeks, and thereafter once a week until 7.2 months, when the experiment ended. Experiment II: 10 µl of benzotrichloride or 10 µl of a 50% solution of benzotrichloride in benzene (10 µl benzene for control mice) was painted on the backs of 3 week old weanling mice 3/w for the initial 4 weeks, and thereafter 2/w until the mice were killed at 9.8 months. Mice treated with undiluted benzotrichloride were killed at 5.7 month because of the high mortality and

	poor health condition of the remaining mice. Experiment III: 2.3 µl benzotrachloride diluted to 25 µl was applied to the dorsal skin of 7 week old mice twice a week during 11.7 (50 weeks) months. The study was terminated after 13.3 months. Controls received 25 µl benzene only. When moribund or at the indicated time mice were ether killed and completely necropsied. After gross pathological inspection the organs and tumors were excised, fixed, paraffin embedded, 5 µm sections made and stained appropriately for histological evaluation.
Remark	: The study is not a guideline (OECD test guideline: 407, 410, 412 or 422) study, but fulfils general scientific criteria. Due to the small group size (n=20) no statistical evaluation was performed. Due to the study design a NOAEL was not determined.
Result	: During a few minutes after dermal painting of mice a marked irritation of the eyes, the skin and the respiratory system as well as elevated motor activities were seen. At the painted area first erythema and swelling were noted later alopecia, induration, marked keratinization, ulcers and/or necrosis of the epidermis were observed. The lesions were rather severe. Experiment I: Mortality at the termination of the experiment I was 0, 10, and 46% in the control, low- and high-dose groups, respectively. The high dose corresponded to a total of approximately 1165 mg (average dose rate of 5.4 mg/day) and the low dose to 582.4 mg (average dose rate of 2.7 mg/day). The number of mice with tumours was 0/20, 17/19, and 21/22 in the control, low-dose, and high-dose groups, respectively. Experiment II: The high dose represented a total of 740 mg and the low dose 603 mg (4.3 and 2.1 mg/day, respectively). Mortality at termination was 0, 60, and 80% for the control, low-dose, and high-dose groups, respectively. The number of mice with tumours was 0/10, 10/10, and 8/9 in the control, low-dose, and high-dose groups, respectively. Experiment III: The total dose was approximately 315 mg (0.9 mg/day). Mortality at termination was 20% in the controls compared with 35% in the treated group. In the control group, 2/20 mice had lung adenomas while in the treated group, 13/19 had skin carcinoma and 11/19 had lung adenoma/carcinoma. Nineteen other tumors, attributed to licking, were observed in the lips, tongue, esophagus, forestomach and glandular stomach of the treated mice. Systemic effects: leukemogenic and pulmonary tumourigenic activity was observed (see chapter 5.7 for carcinogenicity).
Reliability	: (2) valid with restrictions see remarks
Flag 06.12.2003	: Critical study for SIDS endpoint (72) (73)
Type	: Sub-acute
Species	: mouse
Sex	: no data
Strain	: C57BL
Route of admin.	: other: intradermal injection
Exposure period	: 4 d
Frequency of treatm.	: 1 / d
Post exposure period	: 24 w
Doses	: 5.0, 0.5, 0.05 mg/animal
Control group	: no data specified
Method	: other: no data
Year	: 1981
GLP	: no data

Test substance	:	no data																					
Result	:	Depigmentation was seen three or more weeks after repeated intradermal injection of 5 mg benzotrichloride (no further information).																					
Reliability	:	(4) not assignable insufficient detail reported																					
28.11.2003			(74)																				
Type	:	Sub-acute																					
Species	:	rabbit																					
Sex	:	male/female																					
Strain	:	New Zealand white																					
Route of admin.	:	dermal																					
Exposure period	:	3 w																					
Frequency of treatm.	:	5 d/w																					
Post exposure period	:	no																					
Doses	:	50, 100, 200 mg/kg/day																					
Control group	:	other: controls were taken through the same procedures																					
Method	:	other: see method																					
Year	:	1980																					
GLP	:	no data																					
Test substance	:	other TS: supplied by sponsor (lot 08-195-1), purity: 96.4% (GC), clear liquid																					
Method	:	A dermal toxicity study with four male and four female white New Zealand rabbits per dose group, in which undiluted benzotrichloride was administered to the shaved animal backs at dosage levels of 50, 100 and 200 mg/kg bw / day for 5 days/ week for 3 weeks. The skin of 2 male and 2 female animals of each dose group was abraded twice weekly. Ingestion of the compound was inhibited by applying collars to the animals. These were removed after 6 hours, when the application sites were washed. Once in the pre-test period and at 3 weeks of the study, blood (hematological determinations included hemoglobin, hematocrit, erythrocyte count and leucocyte count (total and differential)) and urine analyses were conducted. The animals were observed daily. The body weights were recorded weekly.																					
Result	:	During the study, one animal of the 200 mg/kg bw/day group was found dead. No treatment related changes were found relating to general behavior, body weight, blood chemistry and urinalysis. In all treatment groups erythema, oedema, atonia, desquamation, coriaceousness and fissuring were observed with increasing severity as the dose increased. Eschar formation, exfoliation and necrosis were observed at each dose level, and, blanching in the 200 mg/kg bw/day-group. Enlargement of the regional lymph nodes was seen in rabbits from all treatment groups. Histopathology: in the liver increased incidence of portal inflammatory cells in all groups and bile duct proliferation (200 mg-group) were attributed to the chemical. Reactive hyperplasia and/or inflammation was seen in the regional lymph nodes. In seminiferous tubules of the 100 and 200 mg/kg bw groups multinucleated giant cells were noted (0, 50, 100, 200 mg/kg bw 1/4, 1/4, 2/4, 4/4)and degeneration of the seminiferous tubules were seen (0, 50, 100, 200 mg/kg bw 0/4, 0/4, 1/4, 3/4). Reported incidences in abraded (n=4) and shaved-only (normal; n=4) rabbits: <table><tr><td>50 mg/kg bw</td><td></td><td>abraded</td><td></td></tr><tr><td></td><td>abraded</td><td>and normal</td><td>normal</td></tr><tr><td>edema</td><td></td><td>2</td><td></td></tr><tr><td>atonia</td><td></td><td>2</td><td></td></tr><tr><td>severe coriaceousness</td><td></td><td></td><td>4</td></tr></table>		50 mg/kg bw		abraded			abraded	and normal	normal	edema		2		atonia		2		severe coriaceousness			4
50 mg/kg bw		abraded																					
	abraded	and normal	normal																				
edema		2																					
atonia		2																					
severe coriaceousness			4																				

	desquamation	4	4	
	blanching	3		
	necrosis	4		
	eschar	5		
	exfoliation	3		
	100 mg/kg bw			
	severe edema	1		
	atonia	2	3	
	severe coriaceousness	2		3
	blanching	4	1	
	eschar	3	3	
	exfoliation	1	2	
	necrosis	1	3	
	200 mg/kg bw			
	severe edema		7	
	severe coriaceousness		4	4
	blanching	4	4	
	eschar	4	4	
	necrosis		5	
	exfoliation		4	
Test condition	: Observations:			
	Eight rabbits/dose group were treated; two animals/sex were shaved-only, and another two animals/sex were abraded. The rabbits were observed daily (7 days a week) for pharmacotoxic signs and for mortality. Dermal irritation was scored (score: 0-3, none-severe) and recorded daily, following the 6-hour exposure period and just prior to the next days application. On weekends the dermal irritation was scored and recorded only once. Individual body weights were recorded weekly.			
	Clinical Laboratory Tests:			
	Once in the pretest period and at 3 weeks of study, clinical laboratory tests were conducted on all the rabbits. The blood samples were obtained from the marginal ear vein of fasted rabbits. The urine samples were collected. over night when the rabbits were fasting. The clinical tests conducted were:			
	a. Hematology:			
	The hematological determinations included hemoglobin, hematocrit, erythrocyte count, and leucocyte count (total and differential).			
	b. Biochemistry:			
	The blood chemistry included the determination of fasting blood glucose, blood urea nitrogen (BUN) and the activities of serum alkaline phosphatase (SAP), serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT).			
	c. Urinalysis:			
	The urinalyses included the determination of volume, specific gravity, color, appearance and pH and qualitative tests for protein, glucose, occult blood and bilirubin. At 3 weeks of study ketones, nitrates, and urobilinogen were determined also.			
	Pathology:			
	a. Gross Pathology:			
	At the termination of the three week study period, all rabbits were sacrificed with an overdose of sodium pentobarbital and necropsied. Selected organs were weighed and representative tissues were preserved in neutral buffered 10% formalin.			
	One rabbit from the 200-mg/kg/day group that died during the course of the study was also necropsied and the organs and tissues were processed			

as stated above.

b . Histopathology:

The following tissues from the untreated control and the 200-mg/kg/day groups were paraffin embedded, sectioned, stained with hematoxylin and eosin and microscopically examined:

skin (treated and untreated)	urinary bladder
regional lymph node	ovaries/testes
spleen	nerve, peripheral
pancreas	skeletal muscle
stomach	bone marrow (sternum)
duodenum	thymus
colon	heart
mesenteric lymph node	thyroid/parathyroid
liver	eye
gallbladder	brain (cerebrum,
cerebellum and pons)	
adrenals (2)	pituitary
spinal cord	kidneys (2)
lung	any other tissue with lesions

In addition, skin (treated and untreated), regional lymph node, liver and testes from the 50 mg/kg/day and 100 mg/kg/day groups were also similarly processed and examined microscopically.

Statistical Analysis:

All statistical analyses compared the treatment groups with the control group, by sex.

Body weights (week 3), hematological, biochemical and urinalysis parameters (week 3) and absolute and relative organ weights (terminal sacrifice) were compared by analysis of variance (one-way classification), Bartlett's test for homogeneity of variances and the appropriate t-test (for equal or unequal variances) as described by Steel and Torrie using Dunncott's multiple comparison tables to judge significance of differences.

Reliability	: (2) valid with restrictions
Flag	: Critical study for SIDS endpoint
08.12.2003	(75)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	: Ames test
System of testing	: Salmonella typhimurium TA 98, TA 100, TA 1538
Test concentration	: no data
Cycotoxic concentr.	: no data
Metabolic activation	: with
Result	: positive
Method	: other: no details given, see method
Year	: 1985
GLP	: no data
Test substance	: no data

Remark	: No further data on the specific test using benzotrichloride. The study tested positive and negative controls together with BTC, determined cytotoxicity and indicated a positive mutagenic property only when a dose dependency of the mutagenic activity was noted.
---------------	--

Reliability	: (4) not assignable
28.11.2003	Insufficient detail reported (76) (77)

Type	: Micronucleus test in vitro
-------------	------------------------------

System of testing	: bone marrow cells from BALB/c mice
Test concentration	: 1, 5, 10 µg/ml
Cycotoxic concentr.	: no data
Metabolic activation	: without
Result	: positive
Method	: other: as described by Suzuki Y (1985) Tokyo Jikeikai Med J 100: 707 - 719
Year	: 1985
GLP	: no data
Test substance	: other TS: no data on purity; purchased from Tokyo Kasei Co. Ltd.
Result	: In a in vitro micronucleus test using cultured bone marrow cells from Balb/c mice benzotrichloride induced micronuclei.
Reliability	: (2) valid with restrictions Purity of test item not defined.
Flag	: Critical study for SIDS endpoint
28.11.2003	(78)
Type	: Ames test
System of testing	: Salmonella typhimurium TA98, TA100, TA1535
Test concentration	: 0, 0.5, 1, 2 µmol/plate
Cycotoxic concentr.	: no data
Metabolic activation	: with and without
Result	: positive
Method	: other: according to Ames, B.N. et al., Mutation Res. 31, 347-364 (1975)
Year	: 1978
GLP	: no data
Test substance	: other TS: purity of benzotrichloride not stated
Reliability	: (2) valid with restrictions Purity of test item not given, positive controls lacking.
Flag	: Critical study for SIDS endpoint
28.11.2003	(79) (80)
Type	: Bacterial reverse mutation assay
System of testing	: Escherichia coli WP2 try hcr, WP2 B/r try; Salmonella thyphimurium TA98, TA 100, TA 1535
Test concentration	: 0, 0.5, 1, (2, S. typhimurium TA 100)
Cycotoxic concentr.	: no data
Metabolic activation	: with and without
Result	: positive
Method	: other: close to OECD guideline 471
Year	: 1978
GLP	: no data
Test substance	: other TS: as purchased from Tokyo Kasei Co. Ltd.
Method	: 0.1 ml of overnight culture of each strain and 0.05 ml of sample in 0.5 ml reaction medium with or without 0.5 ml S-9 mixture was incubated at 37°C for 20 min with shaking and then spread over minimal medium plates with the aid of 2 ml soft agar. The plates were incubated for 48 h at 37°C, and revertant colonies counted.
Reliability	: (2) valid with restrictions No controls included.
Flag	: Critical study for SIDS endpoint
28.11.2003	(80)
Type	: Bacillus subtilis recombination assay
System of testing	: B. subtilis H17 (Rec+), M45 (Rec-)
Test concentration	: 1.5, 2.6, 3.6 µmoles/disk
Cycotoxic concentr.	: no data

Metabolic activation : with and without
Result : positive
Method : other: "rec-assay" according to Kada T, Tutikawa K, Sadaie Y (1972) In vitro host-mediated "rec-assay" procedures for screening chemical mutagens; and phloxine, a mutagenic red dye detected. Mutat Res 16: 165 - 174
Year : 1978
GLP : no data
Test substance : other TS: as purchased from Tokyo Kasei Co. Ltd.

Remark : Assay for differential growth inhibition as an indirect measure of DNA damage.

Reliability : (2) valid with restrictions
No controls were included

Flag : Critical study for SIDS endpoint

07.06.2004

(80)

Type : other: DNA strand break test
System of testing : human bronchial epithelial cells
Test concentration : 0.1 - 1 µg/ml
Cycotoxic concentr. : no data
Metabolic activation : no data
Result : positive
Method : other: no data
Year : 1986
GLP : no data
Test substance : no data

Remark : Benzotrichloride induced strand breaks in human bronchial epithelial cells at all concentrations tested (0.1-1 µg/ml) and was 3 - 4 times more active than benzo(a)pyrene.

Reliability : (4) not assignable
Abstract only

28.11.2003

(81)

Type : Ames test
System of testing : Salmonella typhimurium TA 98, TA100
Test concentration : 0, 1, 3, 6, 10, 16, 33, 66, 100, 166 µg/plate
Cycotoxic concentr. : 166 µg/plate
Metabolic activation : with and without
Result : positive
Method : other: see method
Year : 1988
GLP : no data
Test substance : other TS: > 98% purity

Method : The preincubation test was performed essentially as described by Haworth et al. (Environm Mutagen 6: 705-717 (1983)) using strains TA 98 and TA 100 of Salmonella typhimurium (triplicate plates tested). Preparation of Aroclor 1254 induced S-9 fractions from rat or hamster livers was as described in Haworth et al. (Environm Mutagen 6: 705-717 (1983)). Only positive results of replicate trials showing a dose dependency were considered as valid positives.
A panel of 34 chemicals was reported as being reproducibility markers of the test within and between laboratories involved in the study.
Solvent and positive controls were run with each trial. In the absence of metabolic activation positive controls were sodium azide (TA 100) and 4-nito-o-phenylenediamine (TA 98). The positive control for metabolic activation was 2- amino-anthracene.
Data evaluation was according to Zeiger et al. (Environ Mutagen 9 (Suppl

Result	: 9) 1-109 (1987)). : Salmonella typhimurium TA 100 showed positive reversion with (hamster or rat S-9) activation and without activation. The strain TA 98 showed no revertants or ambiguous results without activation but a positive mutagenic response upon activation by hamster or rat S-9. Positive controls reversed the histidine auxotrophy of both tester strains.
Reliability	: (1) valid without restriction
Flag	: Critical study for SIDS endpoint
28.11.2003	(82)
Type	: Ames test
System of testing	: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537
Test concentration	: 0.004 - 1.0 µl/plate
Cycotoxic concentr.	: no data
Metabolic activation	: with and without
Result	: positive
Method	: other: according to Ames, B.N. et al., Mutation Res. 31, 347-364 (1975)
Year	: 1977
GLP	: no data
Test substance	: no data
Result	: Benzotrichlorid tested with 4 Salmonella typhimurium strains (TA 98, TA 100, TA 1535, TA 1537) showed mutagenicity with and without enzymatic activation by rat liver preparation in the dosage range of 0,1 µl to 0,004 µl per plate.
Reliability	: (2) valid with restrictions test item purity not stated
14.01.2004	(83)
Type	: other: umu-test (DNA damage reporter test)
System of testing	: Salmonella typhimurium TA1535/pSK1002
Test concentration	: 0, 0.125, 0.25, 0.5, 1 µl/device
Cycotoxic concentr.	: no data
Metabolic activation	: with
Result	: positive
Method	: other: plural impinging exposure system for volatile compounds
Year	: 1994
GLP	: no data
Test substance	: other TS: no data on purity given
Reliability	: (2) valid with restrictions Purity of test item not reported.
28.11.2003	(84)
Type	: Ames test
System of testing	: Salmonella typhimurium TA98, TA100, TA1538, Saccharomyces D4
Test concentration	: 0.005 - 10 µl/plate
Cycotoxic concentr.	: 5, 10 µl/plate
Metabolic activation	: with and without
Result	: negative
Method	: other: according to Ames, B.N. et al., Mutation Res. 31, 347-364 (1975)
Year	: 1978
GLP	: no data
Test substance	: other TS: no data on purity provided by the sponsor
Result	: The Ames test was negative for all Salmonella strains tested, irrespective of microsomal activation. Positive controls and solvent controls were included and gave the expected results. At 5 and 10 µl compound/plate growth inhibition occurred with Salmonella

	thyphimurium and <i>Saccharomyces cerevisiae</i> . No mitotic recombination in <i>Saccharomyces cerevisiae</i> D4.
Reliability	: (2) valid with restrictions
Flag	: Purity of test item not indicated
28.11.2003	: Critical study for SIDS endpoint

(85)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	: Cytogenetic assay
Species	: rat
Sex	: male
Strain	: Sprague-Dawley
Route of admin.	: inhalation
Exposure period	: 4 w, 12 w, 24 w
Doses	: 1 ppm 6 h/d, 5 d/w
Result	: positive
Method	: other: cytogenetic assay with bone marrow cells after inhalation exposure of test animals
Year	: 1986
GLP	: no data
Test substance	: no data

Result : A slight but significant increase in chromosomal aberrations (mostly chromatid gaps) in bone marrow cells was observed in all exposure groups as compared to controls.

Reliability : (4) not assignable
Abstract

Flag : Critical study for SIDS endpoint

26.11.2003

(86)

Type	: Cytogenetic assay
Species	: rat
Sex	: male
Strain	: Sprague-Dawley
Route of admin.	: inhalation
Exposure period	: 4 w, 12 w, 24 w
Doses	: 1 ppm, 6 h/d, 5 d/w
Result	: positive
Method	: other: cytogenetic assay with peripheral blood lymphocytes after inhalation exposure of test animals
Year	: 1986
GLP	: no data
Test substance	: no data

Result : Chromosomal aberrations in peripheral blood lymphocytes were in the control level in the 4 w-exposure group, but aberrant metaphases were significantly higher in the 24-w exposure group than in the control. Within this group the first appearance of neoplastic changes of the respiratory tract were seen.

Reliability : (4) not assignable
Abstract

Flag : Critical study for SIDS endpoint

26.11.2003

(86)

Type	: Micronucleus assay
Species	: mouse
Sex	: no data
Strain	: Balb/c

Route of admin.	: i.p.
Exposure period	: once
Doses	: 200, 100, 50 mg/kg bw
Result	: positive
Method	: other: test substance injected 5 d after a single i.p. injection of corn oil-dissolved polychlorinated biphenyl (PCB) to 6 week old BALB/c mice
Year	: 1985
GLP	: no data
Test substance	: other TS: Benzotrichloride, not specified further? no purity of benzotrichloride indicated
Remark	: Micronucleated polychromatic erythrocytes (MPCE's) are counted 48 h after injection of the test chemical (with or without S9 liver homogenate activation). The Balb/c mice are pretreated once five days before with PCB (polychlorinated biphenyl). This pretreatment enhances the susceptibility of the micronucleus test.
Result	: Without PCB pretreatment the 100 and 200 mg/kg bw benzotrichloride treatment did not show elevated levels of MPCE's (MPCE's: 0.3 %, 0.3%; 0.2% for 100, 200 mg/kg bw; control). Benzotrichlorid gave significant positive results in the 100 mg- and in the 200 mg-dose group when given after the (- 5 days) PCB pretreatment. (MPCE's: 0.7%, 1.7%, 0.2% for 100, 200 mg/kg bw, control) When S-9 fraction was prepared from PCB pretreated mice, incubated with benzotrichloride and this in vitro metabolized test item injected to mice then a significant elevation of MPCE's were observed at 48 hours MPCE's: 1.4%, 1.3%, 0.7%, 0.3% for 300, 200, 100 mg/kg bw, control). MPCE's (%) control 100 200 300 mg benzotrichloride/kg bw; Without pretreatment: 0.2% 0.3 %, 0.3% With PCB pretreatment (- 5 days) 0.2% 0.7% 1.7% S-9 PCB stimulated 0.3% 0.7% 1.3% 1.4%
Reliability	: (2) valid with restrictions No purity of test item declared
Flag	: Critical study for SIDS endpoint
28.11.2003	(87)

5.7 CARCINOGENICITY

Species	: mouse
Sex	: female
Strain	: ICR
Route of admin.	: dermal
Exposure period	: 30 w
Frequency of treatm.	: 2/w 3 w, then 1/w 27 w
Post exposure period	: no
Doses	: 12.5 μ l (in 12.5 μ l benzene), 25 μ l/animal/painting
Result	: positive
Control group	: yes
Method	: other: carcinogenicity in vivo after repeated dermal application
Year	: 1981
GLP	: no data
Test substance	: other TS: reagent grade purchased from Tokyo Kasei Co. Ltd.
Method	: Fourteen week old specific pathogen free ICR female mice received 25 μ l paintings of benzene (vehicle control), 25 μ l benzotrichloride or a 50% solution of benzotrichloride in benzene. In the first 3 weeks mice were treated twice/week, then once/week until their sacrifice at 7.2 months.

Remark : control group: benzene
14 week old female ICR mice

Result : 12.5 µl-group: 19 animals, 153 d after the first application first skin papilloma;
25 µl-group: 22 animals, 70 d after the first application first skin papilloma;

				mice numbers			
	mg	dose	total mortality %	total tumor	skin carcin.	lung adenom	thymus lymph
contr.	0	0	0	0/20	0/20	0/20	0/20
12.5µl	17.1	582.4	10	17/19	6/19	10/19	1/19
25 µl	34.3	1165	46	21/22	12/22	9/22	6/22

Reliability : (2) valid with restrictions
Purity of test item not reported

Flag : Critical study for SIDS endpoint

28.11.2003

(72) (73)

Species : mouse

Sex : female

Strain : ICR

Route of admin. : dermal

Exposure period : 40 w

Frequency of treatm. : 3/w 4 w, 2/w 36 w

Post exposure period : no

Doses : 5 µl (in 5 µl benzene), 10 µl/animal/painting

Result : positive

Control group : yes

Method : other: carcinogenicity in vivo after repeated dermal application

Year : 1981

GLP : no data

Test substance : other TS: reagent grade purchased from Tokyo Kasei Co. Ltd.

Method : Three groups of 9 to 10 3-week-old female ICR mice received dermal application of 10 µl of benzene (vehicle control), 10 µl benzotrichloride or 10 µl of a 50% benzotrichloride:benzene solution 3 times/week for 4 weeks then twice weekly until sacrifice at 9.8 months.

Remark : control group: benzene
3 week old specific pathogen free ICR female mice
10 µl group was sacrificed at week 24

Result : 5 µl-group: 10 animals, 131 d after the first application first skin papilloma;
10 µl-group: 9 animals, 58 d after the first application first skin papilloma;
10/10 (5 µl) and 8/9 (10 µl) with tumors: skin-carcinoma and -papilloma, lung-carcinoma and -adenoma, lymphoma; only in the 5µl-group: carcinoma of the lip and the forestomach;
mortality at the end of experiment: 60 % (5µl), 80 % (10µl)

Reliability : (2) valid with restrictions
Purity of test item not reported

Flag : Critical study for SIDS endpoint

28.11.2003

(72) (73)

Species : mouse

Sex : female

Strain : ICR

Route of admin. : dermal

Exposure period : 50 w

Frequency of treatm. : 2/w

Post exposure period : 7 w

Doses : 2.3 µl/animal/painting in benzene

Result : positive

Control group	: yes
Method	: other: carcinogenicity in vivo after repeated dermal application
Year	: 1981
GLP	: no data
Test substance	: other TS: reagent grade purchased from Tokyo Kasei Co. Ltd.
Method	: Two groups of 20 seven-week-old female ICR mice received skin applications of 25 µl benzene (controls) or 25 µl of a 9.2% solution of benzotrichloride in benzene twice weekly for 11.7 months. The total dose was approximately 315 mg (0.9 mg/day). Surviving mice were sacrificed at 18.7 months (controls) or at 13.3 months (benzotrichloride treated).
Remark	: control group: benzene seven week old specific pathogen free female ICR mice post exposure time: 7 w treated animals; 32 w controls
Result	: 19 animals (treatment: 25µl painting of a 9.2% solution of benzotrichloride for 50 weeks, twice/week; total compound administered: 316 mg/animal), 210 d after the first application first skin papilloma; 18/19 with tumors: skin-carcinoma and -papilloma, lung-carcinoma and -adenoma, papillomas of the lip and the forestomach, carcinomas of the lip, the tongue, the oesophagus, the forestomach and adenocarcinoma of the glandular stomach; mortality: 35% at 13.3 month vs. 20% at 18.7 month (contr.)
Reliability	: (2) valid with restrictions Purity of test item not reported
Flag	: Critical study for SIDS endpoint
28.11.2003	(72) (73)
Species	: mouse
Sex	: female
Strain	: ICR
Route of admin.	: gavage
Exposure period	: 25 w
Frequency of treatm.	: 2/w
Post exposure period	: 28 w
Doses	: 0.0315, 0.125, 0.5, 2 µl/animal (= approx. 0.043, 0.17, 0.7, 2.7 mg)
Result	: positive
Control group	: yes
Method	: other: carcinogenicity after repeated (28 days) oral treatment
Year	: 1993
GLP	: no data
Test substance	: other TS: 99.5% purity
Method	: Groups of 40 nine-week-old female ICR mice were gavaged with 0.043, 0.17, 0.7, or 2.7 mg benzotrichloride of 99.5% purity in 0.1 ml sesame oil twice weekly for 25 weeks. The 40 control animals were treated with vehicle. Surviving animals were killed and examined histologically 18 months after the start of treatment. Mice receiving the highest dose were sacrificed after 12 month due to high mortality (95%) and poor general health status of survivors.
Remark	: Due to high mortality (95%) sacrifice of animals in highest dose group after 12 m (vs 18 m) Purity of BTC: 99.5% (GC analysis) No details of clinical signs during the experiment and of gross pathology given. Weight development not stated.
Result	: Mortality of the treated mice increased dose-dependently. Mortality was mostly due to lymphosarcoma and stomach cancer. Development of dose-related malignant tumours: squamous-cell carcinomas and papillomas of the forestomach, adenocarcinomas and

adenomas in the lung furthermore thymic lymphosarcoma and lymphatic leukemia of the haematopoietic system.

Contr	0.0315µl 0.043 mg	0.125µl 0.17 mg	0.5 µl 0.7 mg	2.0 µl 2.7 mg
-------	----------------------	--------------------	------------------	------------------

LD50 (month)	16.5	6.5
--------------	------	-----

Forestomach squamous
cell carcinoma

0/39	0/39	2/39	21/40	24/38
------	------	------	-------	-------

Forestomach squamous
cell papilloma

0/39	0/39	0/39	2/40	1/38
1/39	6/39	17/39	19/40	14/38
1/39	1/39	9/39	16/40	10/38

Lung adenoma
Lung adenocarcinoma
Haematopoietic

system	1/39	2/39	1/39	3/40	8/38
--------	------	------	------	------	------

Others	1/39	2/39	3/39	5/40	4/38
--------	------	------	------	------	------

Reliability : (2) valid with restrictions
Few details about clinical signs

Flag : Critical study for SIDS endpoint

07.06.2004

(88) (89)

Species : mouse
Sex : male/female
Strain : Strain A
Route of admin. : i.p.
Exposure period : 8 w
Frequency of treatm. : 3 inj./w
Post exposure period : 16 w
Doses : 60, 30, 12 mg/kg bw in tricaprylin /total dose 1440, 719, 287 mg/kg bw
Result : positive
Control group : yes
Method : other: carcinogenicity after repeated i.p. treatment
Year : 1986
GLP : no data
Test substance : other TS: > 99% purity of benzotrichloride (Aldrich Chemical Company)

Result : The maximum tolerated dose was determined and defined as the dose maximally tolerated by male and female A/J mice(n=4/sex) treated 3 times (in one week) without losing weight (1 month observation period). BTC given 3 times a week i.p. for 8 weeks (vehicle: tricaprylin, groups: n=30 males and females, total dose: 1440, 719 and 287 mg/kg bw) corresponding to 1, 0.5 and 0.2x maximum tolerated dose)) produced an average of 128, 43, 18 lung adenomas/mouse (tricaprylin controls: 0.46 lung tumors per A/J mouse). Additionally, in animals of the highest dose group 3 lymphomas and 2 sarcomas of the kidney were observed. Mortality was 7/30, 1/30 and 0/30 in the 60, 30, 12 mg/kg bw treatment groups.

The mode of action of benzotrichloride as a carcinogen in the A/J mouse lung tumor bioassay (7-fold stronger than urethan, the standard carcinogen in the model) was studied. Activated K-ras protooncogenes were detected in BTC-induced lung tumours from A/J mice. The activating mutation in the K-ras gene from all BTC induced lung tumours was a GC-AT transition in codon 12 of K-ras.

Reliability : (2) valid with restrictions
unphysiological route of exposure

Flag : Critical study for SIDS endpoint

07.12.2003

(90) (81) (91)

Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 4 w, 12 w, 24 w
Frequency of treatm. : 6 h/d 5 d/w
Post exposure period : 20 w
Doses : 1 ppm
Result : ambiguous
Control group : yes
Method : other: carcinogenicity after repeated inhalation exposure
Year : 1986
GLP : no data
Test substance : other TS: Benzotrichloride, not specified further

Result : 24 w - exposure group: squamous metaplasia or hyperplasia of the upper respiratory tract, papillomas in the nasal cavity at the end of the exposure; further 20 w later: malignant or benign tumours in the respiratory system, the skin, and the external ear duct.
No neoplastic changes in the 4 w - and the 12 w - exposure group.

Reliability : (4) not assignable
Abstract

26.11.2003

(86)

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 104 w
Frequency of treatm. : 6 h/d, 5 d/w
Post exposure period : 3 w
Doses : 2.0, 1.0, 0.4, 0.1 ppm
Result : positive
Control group : yes
Method : other: carcinogenicity after repeated inhalation exposure
Year : 1980
GLP : no data
Test substance : no data

Method : Seven week old female Sprague-Dawley rats were exposed to 2.0, 1.0, 0.4 and 0.1 ppm benzotrichloride by inhalation for 104 weeks. Exposure was 6h/day on 5 days/week for 104 weeks with a post-treatment observation period of 3 weeks.

Remark : 2 ppm group: dose reduction to 1.6 ppm after 10 w, to 1 ppm after 20 w and discontinued after 25 w due to high mortality.
Publication years: 1980 and 1984

Result : Due to high mortality in the 2 ppm group a dose reduction to 1.6 ppm after 10 weeks and to 1 ppm after 20 weeks was made. After 25 weeks this group received no further treatment. Nevertheless, the animals succumbed all by week 39.
Death of rats resulted from tumours and accompanying illnesses as well as lung inflammation and spontaneous diseases.

Cumulative mortality (%)

Exp.	2	1	0.4	0.1	0 [ppm]
Weeks					

20	2	0	0	0	0
40	100	2	2	0	0
60		22	16	4	2
80		100	46	14	4
100			86	46	38
107			100	54	54

Tumors of the respiratory system occurred in 92-12% of the animals, and more than half of them were malignant. Tumors of the nasal cavity appeared in 64-28% of the treated animals. Nasal tumors in the 2 ppm group were squamous cell carcinomas, and in the lower dose groups more than 60% of the nasal tumors were adenocarcinomas. Most of the tumors of the larynx (noted in 24-18%) and trachea (noted in 12-6%) were squamous cell carcinomas. Pulmonary tumors appeared in 35-10% of the animals, including squamous cell carcinomas at 2 ppm and adenocarcinomas in about 50% of the tumors at the lower concentrations.

Number of tumors induced by inhalation of benzotrichloride in rats

	2	1	0.4	0.1	0 [ppm]
effective no					
of rats	43	50	50	50	50
rats with tumors	28	49	45	41	42
resp. tract	28	46	38	6	0
nasal ca	12	32	17	0	0
nasal ad./pa	9	12	18	2	0
Larynx ca	0	12	9	0	0
Larynx pa	0	4	3	0	0
Lung ca	15	7	5	0	0
Lung ad/pa	0	5	0	0	0
Ear duct ca	0	14	12	2	0
Ear duct pa	0	3	2	0	0
Skin ca	0	17	17	2	2
Skin pa	0	1	3	2	1
Others	3	20	36	58	52

Skin tumors of different types were observed (sebaceous gland, hair follicle, basaliomas, acanthocytic)

The mean induction time (weeks) required to elicit respiratory tract neoplasms is summarised in the next table.

	Nasal cavity	Larynx	Trachea	Lung
2 ppm	28 (23-39)	---	32 (28-39)	28 (25-37)
1 ppm	69 (54-79)	69 (58-80)	71 (60-80)	73 (68-79)
0.4 ppm	82 (60-105)	96 (88-103)	93 (73-105)	--
0.1 ppm			106 (105-107)	

In all organs the tumour development progressed faster with increasing dose.

2 ppm-group: all rats died within 39 w, squamous cell carcinomas of the respiratory tract;

lower dosed groups:

dose related (up to 92 %) carcinomas in the respiratory tract (nasal cavity, larynx, trachea, lung).

Tumours of the skin and the external ear duct were observed frequently.

Reliability

- : (2) valid with restrictions
- Purity of test item not stated, sparse clinical observations.
- : Critical study for SIDS endpoint

Flag

07.06.2004

(65) (92) (67)

Species	: mouse
Sex	: male
Strain	: ICR
Route of admin.	: inhalation
Exposure period	: 20 w
Frequency of treatm.	: 30 min/d; 2 d/w
Post exposure period	: 5 m
Doses	: 6.7 ppm
Result	: positive
Control group	: yes
Method	: other: carcinogenicity induced by repeated inhalation
Year	: 1979
GLP	: no data
Test substance	: no data
Remark	: Vapourisation at 50°C Limited description of clinical signs, gross pathology, no weight development reported. Publication years: 1979 and 1986
Result	: Significant increased incidence of pulmonary tumours (53%), skin tumours (25%), and malignant lymphomas (25%) compared to controls at the end of the 10th month. Due to high mortality and poor general health condition of the animals the experiment was terminated after 10 m. At this time from 9 remaining mice 9 had lung tumours, 8 showed skin tumours and 8 had malignant lymphoma. The animals were exposed twice weekly for 30 minutes for 5 months, followed by a 1- to 5-month observation period. The control group of 30 animals was observed for 12 months; only 3/30 animals developed neoplasms. Of 12 treated mice that died during the exposure period, 2 had lung adenomas; 6 had malignant lymphoma. At the end of the treatment, 6/11 mice had developed lung adenomas and 1/11 had squamous-cell carcinoma of the skin. After 10 months, 8/9 had lung adenomas, 1/9 had lung adenocarcinoma, 3/9 had skin carcinoma, 4/9 had skin papillomas, and 2/9 had malignant lymphoma. The overall tumour incidence was 17/32 (53%) for the lung, 8/32 (25%) for the skin, and 8/32 (25%) for malignant lymphoma, compared with 3/30 lung adenomas and no other tumors in the controls.
Test condition	: The male ICR mice (5 week old) were exposed to benzotrichloride twice weekly for 30 minutes for 5 months, followed by a 1- to 5-month observation period. The control group of 30 animals was observed for 12 months. The exposure group consisted of 33 animals (32 were evaluated), whereas, all 30 control mice were evaluated. A volume of 0.5 ml of benzotrichloride in a 500 ml gas wash bottle held at 50°C was evaporated using a stream of dry air. The vapours were directed into a 100 l acrylic box which served as exposure chamber. To attain a even distribution of the test item in the exposure chamber, 2 small ventilators operated in the chamber during exposure. The concentration within the chamber was measured by GC determination (6.7 +/- 1.66 ppm; n=10).
Reliability	: (2) valid with restrictions limited documentation.
Flag	: Critical study for SIDS endpoint
07.12.2003	(71) (70)
Species	: mouse
Sex	: male
Strain	: ICR

Route of admin.	:	inhalation																																			
Exposure period	:	10 months																																			
Frequency of treatm.	:	30 min/d, 2 d/w																																			
Post exposure period	:	2 m, 5 m																																			
Doses	:	1.62 ppm																																			
Result	:	positive																																			
Control group	:	yes																																			
Method	:	other: carcinogenicity induced by repeated inhalation																																			
Year	:	1986																																			
GLP	:	no data																																			
Test substance	:	no data																																			
Remark	:	Vapourisation at room temperature. No description of body weight development. Yoshimura et al. (1979) noted that all treated animals had severe bronchitis and bronchial pneumonia.																																			
Result	:	Significant increased incidence of pulmonary tumours, skin tumours, and malignant lymphomas of benzotrichloride exposed mice compared to controls.																																			
		<table><tr><td>month</td><td>cases</td><td>lung tumour</td><td>skin tumour</td><td>mal. lymphoma</td></tr><tr><td></td><td>(%)</td><td>(%)</td><td>(%)</td><td></td></tr><tr><td><12</td><td>10</td><td>8 (80)</td><td>1 (10)</td><td></td></tr><tr><td>12</td><td>10</td><td>9 (90)</td><td>4 (40)</td><td>3 (15)</td></tr><tr><td>-15</td><td>8</td><td>6 (75)</td><td>0</td><td></td></tr><tr><td>15</td><td>9</td><td>7 (78)</td><td>5 (55)</td><td>1 (6)</td></tr><tr><td>total</td><td>37</td><td>30 (81)</td><td>10 (27)</td><td>4 (11)</td></tr></table>	month	cases	lung tumour	skin tumour	mal. lymphoma		(%)	(%)	(%)		<12	10	8 (80)	1 (10)		12	10	9 (90)	4 (40)	3 (15)	-15	8	6 (75)	0		15	9	7 (78)	5 (55)	1 (6)	total	37	30 (81)	10 (27)	4 (11)
month	cases	lung tumour	skin tumour	mal. lymphoma																																	
	(%)	(%)	(%)																																		
<12	10	8 (80)	1 (10)																																		
12	10	9 (90)	4 (40)	3 (15)																																	
-15	8	6 (75)	0																																		
15	9	7 (78)	5 (55)	1 (6)																																	
total	37	30 (81)	10 (27)	4 (11)																																	
Test condition	:	The male ICR mice (5 week old) were exposed to benzotrichloride twice weekly for 30 minutes for 10 months, followed by a 2- to 5-month observation period. The control group of 30 animals was observed for 12 months. The exposure group consisted of 38 animals (37 were evaluated), whereas, all 30 control mice were evaluated. A volume of 0.5 ml of benzotrichloride in a 500 ml gas wash bottle held at room temperature (20 +/- 5°C) was evaporated using a stream of dry air. The vapours were directed into a 100 l acrylic box which served as exposure chamber. To attain a even distribution of the test item in the exposure chamber, 2 small ventilators operated in the chamber during exposure. The concentration within the chamber was measured by GC determination (1.62 +/- 0.43 ppm; n=8).																																			
Reliability	:	(2) valid with restrictions limited documentation																																			
Flag	:	Critical study for SIDS endpoint																																			
07.12.2003		(71) (70)																																			
Species	:	mouse																																			
Sex	:	female																																			
Strain	:	ICR																																			
Route of admin.	:	inhalation																																			
Exposure period	:	104 w																																			
Frequency of treatm.	:	6 h/d, 5 d/w																																			
Post exposure period	:	3 w																																			
Doses	:	2.0, 0.4, 0.1 ppm																																			
Result	:	positive																																			
Control group	:	yes																																			
Method	:	other: carcinogenicity after repeated inhalation exposure																																			
Year	:	1980																																			
GLP	:	no data																																			
Test substance	:	no data																																			

Remark	: mouse strain: ICR 2 ppm group: dose reduction to 1.6 ppm after 10 w and to 1 ppm after 20 w due to high mortality.
Result	All three references were meeting abstracts only. Publication years: 1980 and 1984 : 2 ppm-group: all mice died (causes: tumours and its sequela, respiratory tract inflammation) within 45 w, squamous cell carcinomas of the respiratory tract; 1 ppm and lower dosed groups: up to 46% of the animals suffered from pulmonary carcinomas, squamous epithelial carcinoma was observed frequently on external ear duct, skin neoplasia developed dose dependently.
Reliability	: (2) valid with restrictions Purity of test item, sparse clinical observations.
07.12.2003	(65) (66) (67)
Species	: mouse
Sex	: female
Strain	: ICR
Route of admin.	: inhalation
Exposure period	: 5 m
Frequency of treatm.	: 30 min/d, 2 d/w
Post exposure period	: 1 m, 5 m
Doses	: 6.8 ppm
Result	: positive
Control group	: no data specified
Method	: other: carcinogenicity after repeated inhalation exposure
Year	: 1978
GLP	: no data
Test substance	: no data
Result	: Epithelial proliferation of trachea, bronchi and multiple development of adenomas in pulmonary parenchyma some with malignant changes. Skin papilloma and squamous cell carcinoma were observed. All animals displayed hypertrophic thymus, lymph nodes and spleens.
Reliability	: (2) valid with restrictions limited documentation; no data on control group.
07.12.2003	(93)

5.8.1 TOXICITY TO FERTILITY

Type	: Fertility
Species	: rabbit
Sex	: male/female
Strain	: New Zealand white
Route of admin.	: dermal
Exposure period	: 3 w
Frequency of treatm.	: 5 d/w
Premating exposure period	
Male	:
Female	:
Duration of test	: 21 d
No. of generation studies	: 0
Doses	: 50, 100, 200 mg/kg/day
Control group	: yes, concurrent no treatment
NOAEL parental	: = 50 mg/kg bw

Method	: other: repeated dose (21d) dermal toxicity
Year	: 1980
GLP	: no data
Test substance	: other TS: supplied by sponsor (lot 08-195-1), purity: 96.4% (GC), clear liquid
Remark	: post treatment observation period: none
Result	: At 100 and 200 mg/kg bw increased incidence of multinucleated giant cells in the seminiferous tubules (0, 50, 100, 200 mg/kg bw 1/4, 1/4, 2/4, 4/4) and increased incidence of degeneration of the seminiferous tubules was found (0, 50, 100, 200 mg/kg bw 0/4, 0/4, 1/4, 3/4).
Test condition	: See study details under IUCLID chapter on repeated dose toxicity (5.4)
Reliability	: (2) valid with restrictions not in accordance with current guideline (the skin of half of the animals was abraded).
Flag	: Critical study for SIDS endpoint
07.12.2003	(75)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	: rat
Sex	: female
Strain	: no data
Route of admin.	: gavage
Exposure period	: 10 d (6th-15th day of gestation)
Frequency of treatm.	: daily
Duration of test	: 10 d
Doses	: 0, 12.5, 25.0, 50.0 mg/kg bw
Control group	: yes
NOAEL maternal tox.	: = 12.5 mg/kg bw
LOAEL Fetotoxicity	: = 12.5 mg/kg bw
Method	: other: effect of oral treatment on the foetal development in rats
Year	: 1982
GLP	: no data
Test substance	: other TS: Benzotrichloride, not specified further
Result	: maternal toxicity: 25 mg-, 50 mg group: significant reduced weight gain 50 mg-group: changes in clinical and haematological parameters and organ weights, increased numbers of resorptions, reduced numbers of foetuses per litter histological alterations in the thyroid gland, bone marrow, kidney and liver, residues of BTC in the tissues foetal toxicity: all dosages: reduced mean foetal weight, an evident number of skeleton anomalies (no further information), liver damage, residues of BTC in the tissues
Test condition	: Number of animals: not reported Vehicle: not reported Parameters investigated: Dams: maternal weight gain, changes in organ weights, hematology, biochemistry parameters (15, not specified), residue analysis in organs, microscopic examination. Fetal toxicity: litter size, fetal weight, deciduoma, visceral and skeletal examination, residue analysis, microscopic examination.
Reliability	: (4) not assignable Abstract
Flag	: Critical study for SIDS endpoint

06.01.2004

(94)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES**5.9 SPECIFIC INVESTIGATIONS****5.10 EXPOSURE EXPERIENCE**

- Remark** : The study analyzed the cancer mortality among 953 workers at a British factory engaged in production of chlorinated toluenes. There was exposure to toluene (the starting material), benzotrichloride and benzoyl chloride (the major reaction products), as well as benzyl chloride, benzal chloride and other materials. The cohort of exposed workers consisted of 163 males employed for at least six months between 1961 and 1970. Some of these individuals started employment as early as 1923. Of the 10 deaths from cancer (25 total deaths) reported in this group, 5 were due to digestive system cancers and 5 to respiratory cancers, compared with 1.24 and 1.78 expected, respectively. The standardised mortality ratio for each of these sites was significantly higher than expected, based on mortality rates for England and Wales. A survival analysis using the Cox Proportional Hazards model, adjusting for age at entry to the survey and the time period when employment began, was also conducted. This analysis showed a statistically significant association between estimated cumulative exposure and deaths from cancer at all sites (but neither digestive nor respiratory cancers individually), for persons first employed before 1951. Interpretation of this study is limited by several factors, including possible bias in assignment of exposure categories, exposure to multiple compounds and lack of data on smoking.
- Conclusion** : Benzotrichloride should be considered to be a potential human carcinogen.
- Reliability** : (2) valid with restrictions
Exposure to multiple chlorinated toluenes, lack of smoking data of the cohort.
- Flag** : Critical study for SIDS endpoint
- 26.11.2003 (95)

- Remark** : The results of a cohort study among workers in a factory manufacturing chlorinated toluenes (follow up period: 1964-1984) showed an excess mortality from lung cancer. The calculated risks and the 95% confidence intervals were large, not approaching statistical significance.
- Reliability** : (2) valid with restrictions
Levels and length of exposure not stated. Exposure was to several chlorinated toluenes.
- 26.11.2003 (96)

- Remark** : It was reported on three cancer deaths among 41 workers employed in a benzoyl chloride production plant in Japan between 1954 and 1972. Two of the deaths were from lung cancer, both smokers in their forties. The third cancer death was from maxillary malignant lymphoma in a 50-year-old worker not specified as a smoker or non-smoker. A fourth case of cancer diagnosed as squamous cell carcinoma of the lung was identified in a non-smoking worker still living at the time of analysis. The number of years the four workers were employed in benzoyl chloride production was from 6 to

	15 years. Deaths from lung cancer (2) were significantly higher than the number expected (0.06), based on the Japanese national rates for death from lung cancer in males. In addition to benzotrichloride and benzoyl chloride, these workers were exposed to toluene, chlorine gas, hydrogen chloride, benzyl chloride, benzal chloride, other chlorinated toluenes and polymerized products from the process. Nevertheless, the authors considered it highly possible that the four cancer cases were produced by exposure to benzotrichloride or benzoyl chloride since these are the major products of the two chemical reactions in the production process. In addition, it was noted that these two chemicals have generally been used as synthetic reagents because of their high chemical reactivity.
Reliability	: (2) valid with restrictions
Flag 26.11.2003	: Very small cohort size. Exposure was to several chlorinated toluenes and corrosive chemicals (HCl, Cl ₂). : Critical study for SIDS endpoint (97)
Remark	: cohort study: 1943-1982, chlorination plant: mainly benzoyl chloride, benzylchloride, benzotrichloride; the data obtained suggest an association between the chlorination process at the plant and an increased risk of respiratory cancer, especially to male employees with 15 or more years of employment.
	A retrospective mortality study reported on a cohort of 697 male workers who were exposed to benzyl chloride, benzotrichloride and benzoyl chloride at a chlorination plant. The length of employment at the plant ranged from 1 year to >35 years. Seven deaths from respiratory cancer (6 lung, 1 larynx) were found in the total cohort compared with 2.84 expected deaths based on U.S. mortality rates for males. Five of these deaths occurred in workers employed for at least 15 years. This was significantly greater than the 1.32 deaths expected for this subgroup. The results of this study were confounded by multiple exposures and lack of data on smoking.
Reliability	: (2) valid with restrictions
Flag 26.11.2003	: Exposure to multiple chemicals and lack of data on smoking. : Critical study for SIDS endpoint (98) (99)
Result	: In the report two lung cancer deaths were identified among workers engaged in benzoyl peroxide and benzoyl chloride production at another plant, in which the total number of workers ranged from 13 in 1952 to 40 in 1963. The two individuals, one of whom was a smoker, were in their forties and had worked in benzoyl chloride production for 6 to 18 years. The number of deaths expected among these workers was not reported.
Reliability	: (2) valid with restrictions
Flag 28.11.2003	: Very small cohort varying in size from 13-40 individuals. The reported 2 fatal cases (one being a smoker) have been exposed to a variety of chlorinated toluenes. : Critical study for SIDS endpoint (100)

5.11 ADDITIONAL REMARKS

Remark	: Single injection of 1.1-1.2 mmol/100 g frog (= ca. 214-234 mg/100 g frog) into the pectoral lymph sac caused increasing paralytic symptoms, spontaneous movements, and
---------------	--

07.12.2003	finally the frogs death.	(101)
------------	--------------------------	-------

Remark	: Adult male Holzman rats received for 5 days a single i.p. injection of 50 mg/kg bw/d in corn oil and were sacrificed 24 h after the last dose. Benzotrichloride did not have an effect on any of the enzymes tested: phosphorothioate detoxification system, O-demethylase, and N-demethylase	(102)
26.11.2003		

-
- (1) BUA (Advisory Committee on Existing Chemicals of Environmental Relevance) (1991). BUA Report No. 72. Benzotrichloride. Stuttgart, S. Hirzel Verlag.
 - (2) ICS Naming, ACD/Name Batch (Network) ver. 6.06
 - (3) Bayer Chemicals (2003). α,α,α -Trichlorotoluene - Internal Data on Production, Processing, Use Pattern, and Workplace Exposure (Unpublished).
 - (4) Beilstein Handbook, Registry Number: 605574, Last Update: 2002.10.21
 - (5) Chemfinder Internet Database (2003) Data sheet for α,α,α -Trichlorotoluene. www.chemfinder.cambridgesoft.com
 - (6) Ariel, insight on the net, chemical database search
 - (7) Srour 1999 Benzotrichloride
 - (8) Bayer AG (2001). Safety Data Sheet Benzotrichloride pure, Benzotrichloride technical. Safety Data Sheet No. 018655, 2001-11-06.
 - (9) Maki T and Takeda K (2002) Benzoic acid derivatives. 8.4 Benzoyl Chloride. Ullmanns Encyclopedia of Industrial Chemistry, Electronic Version
 - (10) SPIN Database (2003) Substances in Preparations in Nordic Countries. www.spin2000.net/spin.html
 - (11) IARC Monographs (1982). Some Industrial Chemicals and Dyestuffs 29, 74. IARC, Lyon
 - (12) BUA (Advisory Committee on Existing Chemicals of Environmental Relevance) (1993). BUA Report No. 145. Benzoic acid/Sodium benzoate. Stuttgart, S. Hirzel Verlag.
 - (13) Auergesellschaft (1988) Auertechnikum (12. ed.) Berlin
 - (14) Verschueren K (1996). Handbook of Environmental Data on Organic Chemicals, 3rd ed. New York, Van Nostrand Reinhold, p 1793.
 - (15) Howard PH (1989) Handbook of Environmental Fate and Exposure Data. Vol. 1 Large Production and Priority Pollutants, 73-77. Lewis Publ. Chelsea
 - (16) HSDB (2003) Hazardous Substances Data Bank, data sheet for Benzotrichloride
 - (17) Elf Atochem UK (1992). Safety Data Sheet. November 1992.
 - (18) Hoechst AG (1996). EG-Sicherheitsdatenblatt Benzotrichlorid TTR. 1996-01-10.
 - (19) Weber RC et al. (1981) Vapour pressure distribution of selected organic chemicals. USEPA-600/2-81-021. Cited in: Howard PH (1989) Handbook of Environmental Fate and Exposure Data. Vol. 1 Large Production and Priority Pollutants, 73-77. Lewis Publ. Chelsea
 - (20) Hansch C and Leo A (1979). Substituent Constants for Correlation Analysis in Chemistry and Biology. John Wiley & Sons, New York Chichester Brisbane Toronto 1979, 213.
 - (21) Hansch C, Leo A and Hoekman D (1995). Exploring QSAR. Hydrophobic, Electronic, and Steric Constants. ACS Professional Reference Book, American Chemical Society, Washington, DC.
 - (22) Leo A, Hansch C and Elkins D (1971). Partition coefficients and their uses. Chemical Reviews 71 (6), 525-616.
-

-
- (23) Fujita T, Iwasa J and Hansch C (1964). A New Substituent Constant derived from Partition Coefficients. J. Am. Chem. Soc. 86, 5175-5180.
- (24) Bayer AG (2003). α,α,α -Trichlorotoluene, CAS-No. 98-07-7. Calculation of
- Log Octanol-Water Partition Coefficient with SRC-KOWWIN v1.66, 2000.
- Indirect Photodegradation with SRC-AOPWIN v1.90, 2000.
- (25) Ohnishi R and Tanabe K (1971). A new method of solubility determination of hydrolyzing solute - Solubility of benzyl chloride in water. Bull. Chem. Soc. Japan 41, 2647-2649.
- (26) US-EPA, GEMS (1986). Graphical Exposure Modeling System. Fate of atmospheric pollutants (FAP) data base. Office of Toxic Substances. Cited in: Howard PH (1989) Handbook of Environmental Fate and Exposure Data. Vol. 1 Large Production and Priority Pollutants, 73-77. Lewis Publ. Chel-sea.
- (27) Reusche (1989). Hydrolysedaten fuer seitenkettenchlorierte Stoffe. Bayer Report, 1989-09-21.
- (28) BGVV/UBA (Eds.) (1995). Bewertung der Gefaehrung von Mensch und Umwelt durch ausgewaehlte Altstoffe. Umweltbundesamt, UBA Texte 38/95.
- (29) Dietz (1981). Unveroeffentlichte Untersuchung (4852-122-136).
- (30) Laughton PM and Robertson RE (1959). Solvolysis in hydrogen and deuterium oxide. Can. J. Chem. 37, 1491-1497.
- (31) Quemeneur F, Bariou B and Kerfanto M (1971). Etude cinetique de l'hydrolyse des α,α -dichloro et des α,α,α -trichloro toluenes para-substitues, en milieu eau-acetone a 50 %. C. R. Acad. Sc. Paris, 272, Serie C, 497-499.
- (32) Mabey W and Mill T (1978). Critical review of hydrolysis of organic compounds in water under environmental conditions. J. Phys. Chem. 7, 383-415
- (33) Lokke H (1984). Leaching of ethylene glycol and ethanol in subsoils. Water Air Soil Pollut. 22, 373-387.
- (34) Steinhaeuser KG, Ammann W and Polenz A (1986). Biodegradability testing of chloroorganic compounds. Vom Wasser 67, 147-154.
- (35) Bayer AG (1976). Biodegradability of Benzotrichloride. Unpublished Report, written 2001-02-28.
- (36) Wotzka J, Pfitzner S and Giest B (1994). Biochemical degradability of selected organic compounds; Part 2. Deutsche Gewaesserkundliche Mitteilungen 38, 10-17.
- (37) Freitag D, Lay JP, and Korte F (1984). Environmental Hazard Profile - Test Results as related to Structures and Translation into the Environment. In: KLE Kaiser (ed.). QSAR in Environmental Toxicology. Proceedings of the Workshop on Quantitative Structure-Activity Relationships (QSAR) in Environmental Toxicology, Macmaster University, Hamilton, Ontario, Canada, August 16-18, 1983. D. Reidel Publ., Dordrecht, 111-136.
- (38) Juhnke I and Luedemann D (1978). Ergebnisse der Untersuchung von 200 chemischen Verbindungen auf akute Fischtoxizitaet mit dem Goldorfentest. Z. Wasser- Abwasser-Forsch. 11 (5), 161-164.
- (39) Bayer AG (1976). Acute Fish Toxicity of Benzotrichloride. Unpublished Report, written 2001-03-29.
-

-
- (40) Bringmann G and Kuehn (1982). Results of toxic action of water pollutants on *Daphnia magna* Straus tested by an improved standardized procedure. Z. Wasser-Abwasser-Forsch. 15 (1), 1-6.
- (41) Bringmann G and Kuehn R (1977). Befunde der Schadwirkung wassergefahrdender Stoffe gegen *Daphnia magna*. Z. Wasser- Abwasser-Forsch. 10 (5), 161-166.
- (42) Bringmann G and Kuehn R (1978). Grenzwerte der Schadwirkung wassergefahrdender Stoffe gegen Blaualgen (*Microcystis aeruginosa*) und Gruenalgen (*Scenedesmus quadricauda*) im Zellvermehrungshemmtest. Vom Wasser 50, 45-60.
- (43) Bringmann G and Kuehn R (1977). Grenzwerte der Schadwirkung wassergefahrdender Stoffe gegen Bakterien (*Pseudomonas putida*) und Gruenalgen (*Scenedesmus quadricauda*) im Zellvermehrungshemmtest. Z. Wasser- Abwasser-Forsch. 10 (3/4), 87-98.
- (44) Bringmann G and Kuehn R (1980). Comparison of the toxicity thresholds of water pollutants to bacteria, algae and protozoa in the cell multiplication inhibition test. Water Research 14, 231-241.
- (45) Bringmann G and Kuehn R (1981). Vergleich der Wirkung von Schadstoffen auf flagellate sowie ciliate bzw. auf holozoische bakterienfressende sowie saprozoische Protozoen. GWF-Wasser/Abwasser 122 (7), 308-313.
- (46) Bringmann G, Kuehn R, and Winter A (1980). Determination of the biological effect of water pollutants in protozoa III. Saprozoic flagellates. Z. Wasser- Abwasser-Forsch. 13(5), 170-173.
- (47) Bringmann G (1978). Bestimmung der biologischen Schadwirkung wassergefahrdender Stoffe gegen Protozoen.I. Bakterienfressende Flagellaten (Modellorganismus: *Entosiphon sulcatum* Stein). Z. Wasser- Abwasser-Forsch. 11 (6), 210-215.
- (48) Bringmann G and Kuehn R (1980). Determination of the biological effect of water pollutants in protozoa. II. Bacteriovorous ciliates. Z. Wasser- Abwasser-Forsch. 1, 26-31.
- (49) Kaiser KLE, Palabrica VS and Ribo JM (1987). QSAR of acute toxicity of mono-substituted benzene derivatives to *Photobacterium phosphoreum*. In: Kaier KLE (Ed.) QSAR in Environmental Toxicology II: D. Reidel Publ. Co, Dordrecht 153-168.
- (50) Sixt S and Altschuh J (1996). Prediction of luminescent bacteria toxicity using quantum chemical descriptors: Test of a classification scheme. Quantitative Structure-Activity Relationships in Environmental Sciences VII, D. Reidel Publ. Co, Dordrecht, 343-362.
- (51) Hoechst AG (1980). Unpublished Report, 1980-06-12.
- (52) Schubert R (1979). Toxizitaet von Organohalogenverbindungen gegenueber Bakterien und Abbaubarkeit. Forschungsbericht 037123, Bundesminister fuer Forschung und Technologie, Bonn.
- (53) Yu CC and Nietschmann DA (1980) Pharmacokinetics and metabolism of benzotrichloride in rats. Project No 482448. Report No 6 dated May 22, 1980 with cover letter dated 7/27/82 Velsicol Chem Corp. FYI submission FYI-OTS-1180-0170 Washington DC: Office of Toxic Substances, U.S. Environmental Protection Agency
- (54) Arkhipova OG, Kochetova TA, Shinkarenko BN (1963) Toxic properties and biotransformation of benzotrichloride. Gig Sanit 28: 30 - 34
- (55) Bayer AG (1978) Akute orale Toxizitaet. Short report dated March 21, 1978
- (56) Bayer AG (1978 b) Benzotrichlorid akute toxikologische Untersuchungen. Study report No. 7839 dated September 29, 1978
-

-
- (57) Smyth HF, Carpenter CP, Weil CS (1951) Range-finding toxicity data: list IV. Arch Ind Hyg Occup Med 4: 119 - 122
- (58) Velsicol Chem. Corp. (1979): Acute Toxicity Studies in Rabbits and Rats. Report 163-661. 13 February 1979. As submitted to U.S. EPA under TSCA on 20 Nov. 1980, U.S. EPA TSCA FYI-OTS-1180-0107 IN.
- (59) Izmerov NF, Sanotsky IV, Sidorov KK (1982) Toxicometric parameters of industrial toxic chemicals under single exposure. Centre of International Projects, GKNT, Moscow, p. 24
- (60) Velsicol Chem Corp (1978) Benzotrichloride acute oral toxicity (LD50) study in mice. Report No. 163-659 dated November 20, 1978 with cover letter dated 7/27/82. FYI Submission FYI-OTS-1180-0107. Washington, DC: Office of Toxic Substances, U.S. Environmental Protection Agency
- (61) Dean WP (1978) Benzotrichloride acute oral toxicity (LD50) study in mice. Report No. 163-659 dated November 20, 1978 with cover letter dated 7/27/82. Velsicol Chem Corp. FYI Submission FYI-OTS-1180-0107. Washington, DC: Office of Toxic Substances, U.S. Environmental Protection Agency
- (62) Mikhailova TV (1964) Comparative toxicity of chlorous toluene compounds - benzyl chloride, benzal chloride and benzotrichloride. Gig Tr Prof Zabol 8: 14 - 19
- (63) Velsicol Chem. Corp. (1979): Acute inhalation toxicity study in rats. Report No 163-662. 27 April 1979. As submitted to U.S. EPA under TSCA on 20 Nov. 1980, U.S. EPA TSCA FYI-OTS-1180-0107 IN.
- (64) Velsicol Chem. Corp. (1981) Benzotrichloride - four-week subacute inhalation toxicity study in rats with amendment. 26 May 1981. As submitted to U.S. EPA under TSCA on 25 August 1981, U.S. EPA TSCA FYI-OTS-0000122-0 IN.
- (65) Fukuda K and Takemoto K (1980) Species difference and concentration-effect relationship in cancers induced by inhalation of benzotrichloride (BTC). The 44th General Meeting of the Japanese Cancer Association
- (66) Fukuda K and Takemoto K (1984) Erzeugung von Tumoren im Respirationssystem von Ratten und Mäusen durch Inhalation von Benzotrichlorid (BTC). Haigan, Chiba-Shi 24: 673
- (67) Fukuda K and Takemoto K (1984) Inhalations-Karzinogenität von Benzotrichlorid (II). Proc 57th Annual Meeting Japan Association of Industrial Health pp 380 - 381
- (68) Chu I, Shen SY, Villeneuve DC, Secours VE (1984) Toxicity of trichlorotoluene isomers: A 28-day feeding study in the rat. J Environ Sci Health B19: 183 - 191
- (69) Takemoto K, Yoshimura H, Matsushita S (1978) Experiment of pulmonary tumorigenicity of benzotrichloride. Proc of 51st Annual Meeting of Japan Assoc of Ind Health 514 - 515. TSCA 8e Submission 8EHQ-0980-0360 Document No. 86-8000116, Washington, DC: Office of Toxic Substances, U.S. Environmental Protection Agency
- (70) Yoshimura H, Takemoto K, Fukuda K, Matsushita H (1986) Carcinogenicity in mice by inhalation of benzotrichloride and benzoyl chloride. Jpn J Ind Health 28: 352 - 359
- (71) Yoshimura H, Katayama H, Takemoto K, Matsushita S (1979) Experimental lung tumors induced by exposure to benzotrichloride (2). Proc of Japan Assoc of Ind Health 332 - 333. TSCA 8e Submission 8EHQ-0980-0360 Document No. 86-8000116, Washington, DC: Office of Toxic Substances, U.S. Environmental Protection Agency
-

- (72) Fukuda K (1981) Experimental carcinogenesis by the chemicals relating to benzoyl chloride production. *Ochanomizu Igaku Zasshi* 29: 69 - 81
- (73) Fukuda K, Matsushita H, Sakabe H, Takemoto K (1981) Carcinogenicity of benzyl chloride, benzal chloride, benzotrichloride and benzoyl chloride in mice by skin application. *Gann* 72: 655 - 664
- (74) Aw TC and Boyland E (1981) Depigmentation of hair in mice by chemicals. *IRCS Med Sci* 9: 29 - 30
- (75) Velsicol Chem. Corp. (1980) Benzotrichlorid: three-week dermal toxicity study in rabbits. Report No 163-673. 4 April 1980. As submitted to U.S. EPA under TSCA on 20 Nov 1980, U.S. EPA TSCA FYI-OTS-1180-0107 IN.
- (76) Khudoley VV, Mizgirev I, Pliss GB (1987) The study of mutagenic activity of carcinogens and other chemical agents with *Salmonella typhimurium* assay: Testing of 126 compounds. *Arch Geschwulstforsch* 57: 453 - 462
- (77) Khudoley VV, Mizgirev IV, Pliss GB (1986) Evaluation of mutagenic activity of carcinogens and other chemical agents with *Salmonella typhimurium* assays. *Voprosy Onkol* 32: 73 - 80
- (78) Suzuki Y (1985) Studies on development of the sensitive micronucleus test (Part II) the in vitro method using cultured bone marrow cells. *Tokyo Jikeikai Med J* 100: 707 - 719
- (79) Kier LE, Brusick DJ, Auletta AE, Von Halle ES, Brown MM, Simmon VF, Dunkel V, McCann J, Mortelmans K, Prival M, Rao TK, Ray V (1986) The *Salmonella typhimurium*/mammalian microsomal assay. A report of the U.S. Environmental Protection Agency Gene-Tox Program. *Mutat Res* 168: 69 - 240
- (80) Yasuo K, Fujimoto S, Katoh M, Kikuchi Y, Kada T (1978) Mutagenicity of benzotrichloride and related compounds. *Mutat Res.* 58: 143 - 150
- (81) You M, Hsu I-C, Morgan M, Stoner GD (1986) Induction of lung adenomas in strain A mice and DNA strand breaks in human bronchial epithelial cells with benzotrichloride. *Proceedings of AACR* 27: 94
- (82) Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K (1988) *Salmonella* mutagenicity tests: IV. Results from the testing of 300 chemicals. *Environ Mol Mutagen* 11 (Suppl.12): 1 - 158
- (83) Hoechst AG (1977) Gericke D Benzotrichloride Test for Mutagenicity in Bacteria Strains in the absence and presence of a Liver Preparation. Hoechst AG unpublished study No. 1020/77 A dated 1977-10-28
- (84) Goto S, Ohkubo T, Watanabe E, Endo O, Mochizuki H, Mizoguchi T, Mineki S, Tanabe K, Matsushita H (1994) Mutagenicity detection method for volatile compounds using plural impinging exposure system. *J Environ Chem (Kankyo Kagaku)* 4: 631 - 636
- (85) Jagannath DR (1978) Mutagenicity evaluation of benzotrichloride in the Ames salmonella/microsome plate test. Final report. LBI project No 20988. Genetics assay No 3566 dated December 1978 with cover letter dated 7/27/82. Velsicol Chem Corp FYI Submission FYI-OTS-1180-0107, Washington, DC: Office of Toxic Substances, U.S. Environmental Protection Agency
- (86) Koshi K and Fukuda K (1986) Cytogenetic and morphological findings in rats exposed to benzotrichloride. *Mutat Res* 164: 272
- (87) Suzuki Y (1985) Studies on development of the sensitive micronucleus test (Part 1) methods of induction by polychlorinated biphenyl and of metabolic activation. *Tokyo Jikeikai Med J* 100: 695 - 705

-
- (88) Fukuda K, Matsushita H Takemoto K (1978) Carcinogenicity of orally administered benzotrichloride. In: Proceedings of the 52nd Annual Meeting of the Japanese Industrial Health Association pp. 516 - 517, cited in: IARC (International Agency for Research on Cancer) (1982) Monographs on the evaluation of the carcinogenic risk of chemicals to human 29: 73 - 82
and: TSCA 8e Submission 8EHQ-0980-0360 Document No. 86-8000116, Washington, DC: Office of Toxic Substances, U.S. Environmental Protection Agency
- (89) Fukuda K, Matsushita H, Takemoto K, Toya T (1993) Carcinogenicity of benzotrichloride administered to mice by gastric intubation. Ind Health 31: 127 - 131
- (90) Stoner GD, You M, Morgan MA, Superczynski MJ (1986) Lung tumor induction in strain A mice with benzotrichloride. Cancer Letters 33: 167 - 173
- (91) You M, Wang Y, Nash B, Stoner GD (1993) K-ras mutations in benzotrichloride-induced lung tumors of A/J mice. Carcinogenesis 14: 1247 - 1249
- (92) Fukuda K and Takemoto K (1984) Erzeugung von Tumoren im Respirationssystem von Ratten und Mäusen durch Inhalation von Benzotrichlorid (BTC). Haigan, Chiba-Shi 24: 673
- (93) Takemoto K, Yoshimura H, Matsushita S (1978) Experiment of pulmonary tumorigenicity of benzotrichloride. Proceedings of the 51st Annual Meeting of the Japan Assoc Ind Health: 514 - 515
- (94) Ruddick JA, Villeneuve DC, Secours V, Valli VE (1982) A transplacental and teratological evaluation of three trichlorotoluene congeners in the rat. Teratology 25: 72A - 73A
- (95) Sorahan T, Waterhouse JAH, Cooke MA, Smith EMB, Jackson JR, Temkin L (1983) A mortality study of workers in a factory manufacturing chlorinated toluenes. Ann Occup Hyg 27: 173 - 182
- (96) Sorahan T and Cathcart M (1989) Lung cancer mortality among workers in a factory manufacturing chlorinated toluenes: 1961 - 84. Br J Ind Med 46: 425 - 427
- (97) Sakabe H, Matsushita H, Koshi S (1976) Cancer among benzoyl chloride manufacturing workers. Ann NY Acad Sci 271: 67 - 70
- (98) Velsicol Chem Corp (1984) A cohort mortality study of employees at the Velsicol Chattanooga Plant 1943-1982. (Authors: Wong O, Morgan RW) EPA-OTS0509690, Doc I.D. 88-8400672 (1986)
- (99) Wong O (1988) A Cohort mortality study of employees exposed to chlorinated chemicals. Am J Ind Med 14: 417 - 431
- (100) Sakabe H, Fukuda K (1977) An updating report on cancer among benzoyl chloride manufacturing workers. Ind Health 15: 173 - 174
- (101) Lehmann F (1928) Ueber Konstitution und Wirkung. Untersuchungen an aromatischen Fluorverbindungen. Naunyn-Schmiedeberg's Arch Exp Pathol Pharmacol 130: 250 - 255
- (102) Ehrich M and Carlson GP (1979) Hepatic microsomal enzyme induction by trifluoromethyl compounds and some halogenated and nonhalogenated analogs. Res Commun Chem Path Pharm 25: 333 - 342
-