FOREWORD INTRODUCTION

DIPHENYL CARBONATE

CAS N°: 102-09-0

SIDS Initial Assessment Report

For

SIAM 19

19–22 October 2004, Berlin, Germany

1. Chemical Name:	Diphenyl carbonate
2. CAS Number:	102-09-0
3. Sponsor Country:	Germany Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn
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 Building 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): 13 April 2004 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 18 March 2004 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search terms
8. Quality check process:	As basis for the SIDS-Dossier the IUCLID was used. All data have been checked and validated by BUA. A final evaluation of the human health part has been performed by the Federal Institute for Risk Assessment (BfR) and of the ecotoxicological part by the Federal Environment Agency (UBA).

9. Date of Submission: Deadline for circulation: 23 July 2004

10. Date of last Update: Last literature search: IUCLID Chapters 1-4: 2003-10-08

Chapter 5: 2004-01-22

11. Comments:

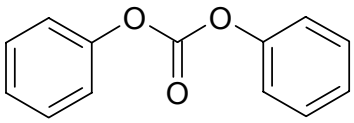
OECD/ICCA - The BUA* Peer Review Process

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 to robust summary requirements; completeness and correctness is checked against original reports (including unpublished internal company reports) and 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.	102-09-0
Chemical Name	Diphenyl carbonate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute dermal toxicity of diphenyl carbonate is relatively low with LD_{50} values exceeding 2000 mg/kg bw in rats and rabbits (no clinical signs noted). The acute oral LD_{50} in rats was 1500 mg/kg bw, with clonic convulsions as main clinical sign appearing at doses near to or exceeding the LD_{50} value. There are no acute inhalation studies available.

Diphenyl carbonate was not irritating to the skin and eye of rabbits (OECD TG 404, 405). Diphenyl carbonate showed no skin sensitisation potential in a Buehler patch test on 10 guinea pigs, limited by the small number of treated animals.

Repeated oral dosing of rats with diphenyl carbonate over 11 weeks (males) or 18 weeks (females) led to increases in liver weight and to hepatocellular hypertrophy and histopathological changes in the adrenals in males at a dietary concentration of 5000 ppm (about 427 mg/kg bw/day), and in females of 1500 ppm (about 219 mg/kg bw/day). At 1500 ppm, females exhibited also morphological changes in the ovaries (increased number and mononuclear infiltration of corpora lutea, granulated luteal cells, hypertrophic ovarian interstitial cells). The NOAEL in males was 1500 ppm (about 132 mg/kg bw/day) and in females about 50 mg/kg bw/day.

Diphenyl carbonate showed no mutagenic properties in bacterial and mammalian cell gene mutation assays performed according to current guidelines. In the *in vitro* chromosome aberration assay diphenyl carbonate led to increased frequencies of structural chromosomal aberrations in V79 cells both in the absence and in the presence of metabolic activation. This positive result could not be confirmed *in vivo* by two mouse bone marrow micronucleus assays performed according to current guidelines and with evidence of target cell exposure. An *in vivo/in vitro* UDS assay on rat liver, also performed according to current guidelines with oral doses up to the MTD, gave negative results. It is concluded that the genotoxic properties observed *in vitro* are not expressed *in vivo*.

In repeated dose toxicity studies on rats, diphenyl carbonate led to increased organ weights and morphological alterations in adrenals and ovaries. These effects did not influence reproductive performance in a one-generation dietary study on rats (OECD TG 415/416; NOAEL for fertility: 15 000 ppm = about 1561/2432 mg/kg bw/day for males/females; highest tested dose).

In a developmental toxicity study on rats according to OECD TG 414, daily gavage administration of 750 mg diphenyl carbonate/kg bw/day to pregnant rats on gestation days 6 to 19, led to severe maternal toxicity (mortality, convulsions, piloerection, body weight loss). Fetuses of this dose group showed reduced body weights and increased incidences of unspecific malformations (mainly dysplastic forelimb bones). The NOAEL for maternal toxicity and developmental toxicity of diphenyl carbonate in rats was 50 mg/kg bw/day. At 200 mg/kg bw/day slight maternal toxicity occurred and a retarding effect on fetal skeletal ossification of toes and cervical vertebral bodies could not be completely excluded.

Environment

Diphenyl carbonate is a white solid (flakes) with a melting point of 78.8 °C, and a boiling point of 302 °C. The density of the solid is 1.272 g/cm^3 at 14 °C. The vapour pressure is 0.014 Pa at 20 °C. The log K_{ow} is 3.21 - 3.28. The solubility of the substance in water is ca. 13 mg/l at 20 °C. The flash point is 168 °C.

Diphenyl carbonate hydrolyses under environmental conditions forming phenol and carbon dioxide. A study on the abiotic degradation of diphenyl carbonate in water predicted that the test substance has a $t_{1/2}$ of 39.9 h at pH 7 and 25 °C.

According to a Mackay Level I calculation the favourite target compartment of the substance is water with 72.2 % (soil 11 %, sediment 11 % and air 6 %). Henry's law constants of 8.59 Pa × m^3 mol^{-1} (calculated according to the Bond method) and 0.23 Pa × m^3 mol^{-1} respectively (derived from water solubility and vapour pressure) indicate that the compound has a slight to moderate potential for volatilization from surface waters. These results should only be considered of theoretical interest since the calculation programs are adequate for substances which show stability in water. The calculated half-life of diphenyl carbonate in air due to indirect photodegradation is $t_{1/2}$ = 4.0 days. Due to the low absorption in the UV-B range, no direct photodegradation is expected.

Diphenyl carbonate is not readily biodegradable but biodegraded by adapted microorganisms. After 28 days 37 % of the test substance had been degraded in a closed bottle test (Directive 92/69/EEC, C.4-E). With adapted domestic sewage, more than 99 % of the test substance had been degraded after 20 days in another closed bottle test (OECD TG 301 D).

According to the bioconcentration factor BCF = 66.9, calculated from the octanol-water partition coefficient the substance has a low potential to bioaccumulate in aquatic organisms. With a calculated K_{oc} value of 3926, diphenyl carbonate could be regarded as a substance with high geoaccumulation properties. However, due to hydrolysis geoaccumulation is not expected.

For fish (*Danio rerio)* the acute toxicity (LC_{50}, 96 h) of diphenyl carbonate (Directive 92/69/EEC, C.1) was 3.9 mg/l (effective concentration; nominal concentration: 10.0 mg/l). The acute toxicity (EC_{50}, 48 h) of diphenyl carbonate to the invertebrate *Daphnia magna* (Directive 92/69/EEC, C.2) was 6.5 mg/l (effective; nominal: 14.2 mg/l). Concerning the algal toxicity (Directive 92/69/EEC, C.3), for *Desmodesmus subspicatus* a 72 h-E_rC_{50} of 0.9 mg/l (effective; nominal: 2.4 mg/l) for the growth rate and a 72 h-E_bC_{50} 0.5 mg/l (effective; nominal: 1.4 mg/l) for the integral of biomass were determined. The corresponding 72 h-NOEC obtained from growth rate and biomass were 0.22 mg/l and 0.11 mg/l, respectively (effective; nominal 0.63 mg/l and 0.31 mg/l, respectively). The corresponding 72 h-LOEC obtained from growth rate and biomass were 0.44 mg/l and 0.22 mg/l, respectively (effective; nominal 1.25 mg/l and 0.63 mg/l, respectively).

Based on the lowest effect concentration observed for the algae a Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 1000. Using the effective 72 h-E_rC_{50} of 0.9 mg/l (growth rate) found for the algae species *Desmodesmus subspicatus* a $PNEC_{aqua}$ of 0.9 µg/l was determined.

Exposure

Phosgenation of phenol is the most important method for producing diphenyl carbonate. In 2002, the world wide production capacity of diphenyl carbonate is estimated to be 254 000 metric tonnes (Western Europe 141 000, Japan 61 000, Far East (excl. Japan) 52 000) by about 10 producers. The total manufacturing capacity of the sponsor company amounts to 10 000 - 50 000 tonnes/a in 2002 in Belgium (no production in the Sponsor country).

Diphenyl carbonate is a chemical intermediate mainly used for the synthesis of aromatic polycarbonates. It is also used for the synthesis of aliphatic polycarbonates and some aliphatic mono-isocyanates. Diphenyl carbonate is listed in the Danish, Finnish, Norwegian, and Swedish product registers as a product with industrial applications. No consumer applications are listed. Based on this data no exposure of the environment due to releases from consumer products occurs.

At the Sponsor company, diphenyl carbonate is manufactured and processed in closed systems. The exhausts from manufacturing and processing of diphenyl carbonate are connected to absorbing units, thermal exhaust

purification plants and air washing units, thus virtually no emissions of diphenyl carbonate occurred into the atmosphere.

Due to the water-free processing processes emissions into wastewater may occur only in the case of cleaning procedures. The wastewater of the production plant is treated with activated carbon and subsequently in a biological wastewater treatment plant. For the biological wastewater treatment plant an effluent concentration of < 2 µg/l is calculated. Using the local dilution factor of 554, this results in a local PEC of <0.0036 µg/l. Emissions of diphenyl carbonate from polycarbonate resins were 0.14 - 4.94 mg/m^3 exhaust stream during experimental extrusion.

There are no environmental monitoring data available for diphenyl carbonate.

Occupational exposure at production and processing sites of the Sponsor company is controlled and the concentration of diphenyl carbonate is currently below the detection limit of 0.003 mg/m^3 (time weighted average). Based on data presented by the Sponsor company, consumer exposure to diphenyl carbonate via the environment is anticipated to be low.

Diphenyl carbonate is used for the manufacturing of food contact material. Based on a very low migration from the food contact material into food, and based on the toxicological data, the European Scientific Committee on Food classified diphenyl carbonate in “List 3”, i.e. substances for which an ADI or TDI could not be established, but where the present use could be accepted. In the EU, the use is restricted to a maximum limit of 0.05 mg/kg of food.

No consumer preparations containing diphenyl carbonate are listed in the Nordic product registers.

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

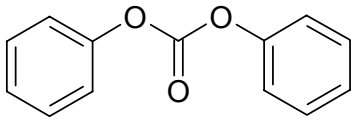
Human Health: The chemical is currently of low priority for further work because of its low hazard profile.

Environment: The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by one producer which accounts for approximately 4 % to 20 % of global production and relating to the use pattern in several OECD countries), exposure to the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number:	102-09-0
IUPAC Name:	Diphenyl carbonate
Molecular Formula:	$C_{13}H_{10}O_3$
Structural Formula:	
Molecular Weight:	214.22 g/mol
Synonyms:	Carbonic acid, diphenyl ester DPC

1.2 Purity/Impurities/Additives

Purity of the commercial product:	≥ 99.5 % (Bayer AG, 2000a)
Impurities:	≤ 0.2 % (w/w) phenol; ≤ 0.02 g/kg ash (Bayer AG, 2000a)

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference	IUCLID
Substance type	Organic compound		1.1.1
Physical state	White solid (flakes)		1.1.1
Melting point	78.8°C**	Buysch, 2002a	2.1
Boiling point at 1013 hPa	302°C**	Buysch, 2002a	2.2
Density at 14 °C	1.272 g/cm^3	Beilstein, 2003	2.3
Vapour pressure at 20 °C	0.014 Pa	Bayer AG, 1998	2.4
Octanol/water partition coefficient* (log K_{ow}) at 25 °C	3.21- 3.28	Ostergaard et al., 2003; Sangster, 1989	2.5
Water solubility* at 20 °C	ca. 13 mg/l	Bayer AG, 2000b	2.6.1
Flash point (Closed cup)	168 °C	Buysch, 2002a	2.7
Auto flammability (ignition temperature)	ca. 620 °C	Bayer MaterialScience, 2004a	2.8

*Uncertainty due to hydrolysis. **Data from peer-reviewed handbook, weight of evidence approach.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Phosgenation of phenol is the most important method for producing diphenyl carbonate.

$COCl_2 + 2\ C_6H_5OH \rightarrow C_6H_5OCOOC_6H_5 + 2\ HCl$

Various modifications of the above reaction are known (Buysch, 2002b):

- Phosgenation of aqueous sodium phenolate in the presence of diphenyl carbonate as solvent for newly formed diphenyl carbonate.
- Phosgenation in toluene and homogeneously catalyzed phenol phosgenation with metal salts, quarternary ammonium salts, heterocyclic N bases or phosphorous compounds.
- Phenol can also be phosgenated in the liquid phase and in the gas phase in a fully continuous reaction at 250 - 350 °C.

A phosgene-free process for diphenyl carbonate is the oxidative carbonylation of phenol using carbon monoxide and Pd compounds as catalysts (Buysch, 2002b).

The catalysed transesterification of dimethyl carbonate with phenol is also used to produce diphenyl carbonate, but requires the use of complex process technology since transesterification is an equilibrium reaction (Buysch, 2002b).

In 2002, the world wide production capacity of diphenyl carbonate is estimated to be 254 000 metric tonnes by about 10 producers (Table 2). The total manufacturing capacity of Bayer Antwerp N.V. amounts to 34 000 tonnes/a in 2002. There is no production of diphenyl carbonate in the Sponsor country, but some processing by the Sponsor company (Bayer MaterialScience, 2004b).

Table 2 Estimated diphenyl carbonate production capacity in 2002 (Bayer MaterialScience, 2004b)

Region	Estimated production capacity (tonnes/a)
Western Europe	141 000
Japan	61 000
Far East (excl. Japan)	52 000

Diphenyl carbonate is a chemical intermediate. It is mainly used for the synthesis of thermoplastic aromatic polycarbonates through transesterification of bisphenols (Buysch, 2002c; Duffy et al., 2000; Shaikh and Sivaram, 1996; Kirk-Othmer, 1993 and 2003). Beside this it is an intermediate for the production of aliphatic polycarbonates and of carbonates (Duffy et al., 2000; Buysch, 2002c). Lower-mass aliphatic mono-isocyanates, especially methyl isocyanate, which is further used in the synthesis of crop protection agents, are produced by treating diphenyl carbonate with aliphatic amines, followed by cleavage of the obtained phenyl urethane (Buysch, 2002c; Duffy et al., 2000; Shaikh and Sivaram, 1996). It is estimated that more than 98 % of the manufacturing volume are used for aromatic polycarbonates (Bayer MaterialScience, 2004b).

Diphenyl carbonate is reportedly used as a solvent for cellulose ethers and esters (Buysch, 2002c) or especially nitrocellulose (Merck Index, 2001). No (valid) reference for this information was presented by the authors, and the reliability of this statement remains therefore unclear. Other authors (Kirk-Othmer, 2003; Shaikh and Sivaram, 1996) report the use of diethyl carbonate and higher dialkyl carbonates, but not of diphenyl carbonate as solvents for (nitro-)cellulose ethers and esters.

Diphenyl carbonate is listed in the Danish, Finnish, Norwegian, and Swedish Product Registers as product with industrial applications. For Denmark, four industrial preparations with a consumption of 0.0 tonnes/a are listed in 2001. No consumer application is registered (SPIN, 2004). The Danish Product Register (2002) cited for diphenyl carbonate five industrial products with a content of diphenyl carbonate of 0 – 2 % and a quantity of < 1 tonne/a. Diphenyl carbonate is used in closed systems (SPIN, 2004).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Releases into the environment may occur during production and processing of diphenyl carbonate.

Information on exposure is available for the Bayer Antwerp N.V. manufacturing and processing plant in Belgium and the Leverkusen processing plant in Germany (Bayer MaterialScience, 2004b).

At the Sponsor company diphenyl carbonate is manufactured and processed in closed systems (Bayer MaterialScience, 2004b).

The exhausts from manufacturing and processing of diphenyl carbonate are connected to absorbing units, thermal exhaust purification plants and/or air washing units. At the Bayer Antwerp site during production and processing no emissions of diphenyl carbonate into the atmosphere were detectable with a detection limit of 0.1-0.6 mg/m^3. In Leverkusen, according to the current Official Emission Declaration, < 25 kg of diphenyl carbonate were emitted into the atmosphere in 2000 (Bayer MaterialScience, 2004b).

Due to the water-free processing processes emissions into wastewater may occur only in the case of cleaning procedures. The wastewater of the production plant is treated via adsorption with activated carbon columns. The concentration of diphenyl carbonate at the outlet of this treatment is < 0.5 mg/l (detection limit of the analytical monitoring method). The wastewater is then led to the wastewater treatment plant (WWTP) of the site, where the concentration decreases to < 0.02 mg/l through dilution. Based on several elimination processes

- biodegradation with adapted organisms (99.5 % in dilute adapted sewage in 20 d)
- adsorption to sewage sludge (calculated K_{oc} value of 3926) and
- hydrolysis to carbon dioxide and the readily biodegradable phenol.

the total elimination is assumed to be > 90 %. The effluent of the WWTP passes into the river Scheldt. Taking into account the river flow of 77 m^3/s (mean: 231 m^3/s, minimum: 70 m^3/s in 2001), the dilution factor (554), and the effluent concentration of < 0.002 mg/l, for the receiving water a

Predicted Environmental Concentration (PEC) of < 0.0036 µg/l

is calculated. For the Leverkusen processing site, no significant releases of diphenyl carbonate are expected due to the waterfree processing (Bayer MaterialScience, 2004b).

Emissions factors for selected volatile and semi-volatile organic compounds during polycarbonate processing (extrusion) were investigated for several commercial polycarbonates. Based on the resin type for diphenyl carbonate values between 0.14 and 4.94 µg of diphenyl carbonate per liter (= mg/m3) of manifold exhaust flow were detected under the experimental conditions applied (Rhodes et al., 2002).

2.2.2 Photodegradation

There are no experimental data on the stability of diphenyl carbonate in the atmosphere (Table 3). The calculated half-life of diphenyl carbonate in air due to indirect photodegradation is 4.0 days, considering a daily mean OH-radicals concentration of 500 000 radicals cm^{-3} (Bayer Industry Services, 2003).

Due to the low absorption of diphenyl carbonate in the UV-B range (Hoyle, Rufus and Shah, 1995), no significant direct photodegradation is expected.

Table 3 Photodegradation of diphenyl carbonate (IUCLID 3.1.1)

Parameter	Method	Result	Reference
Indirect photodegradation in air	Calculation for 24 h-day, 500 000 OH/cm^3	$t_{1/2}$ = 4.0 days	Bayer Industry Services, 2003*

*Key study for the endpoint

2.2.3 Stability in Water

Diphenyl carbonate hydrolyses in the presence of water forming phenol and carbon dioxide. In a preliminary study on the abiotic degradation of diphenyl carbonate in water the test substance had a half-life ($t_{1/2}$) of 73.5 h at 23 °C (Bayer AG, 2000c).

Due to the above mentioned result a study on the abiotic degradation of diphenyl carbonate according to the Directive 92/69/EEC, C.7, was performed. It was concluded that at pH 7 a half-life ($t_{1/2}$) of 39.9 hours at 25 °C was expected (Bayer AG, 2001).

Table 4 Hydrolysis of diphenyl carbonate (IUCLID 3.1.2)

Test substance	Procedure	Result	Reference
Diphenyl carbonate	Directive 92/69/EEC, C.7	at pH 7, 25 °C $t_{1/2}$=39.9 h	Bayer AG, 2001*
Diphenyl carbonate	Abiotic degradation	at 23 °C $t_{1/2}$=73.5 h	Bayer AG, 2000c*

*Key study for the endpoint

2.2.4 Transport between Environmental Compartments

According to the Mackay Fugacity Model Level I (v. 2.11), the main target compartment for diphenyl carbonate is water with 72.2 %, followed by sediment with 11.0 %, soil with 10.9 %, and air with 5.9 % (Table 5, Bayer Industry Services, 2003). These results should be only considered of theoretical interest since the Mackay Fugacity Model is just adequate for substances which show stability in water.

Table 5 Input parameters and results of the Mackay Fugacity Model Level I

Input Parameters	Value
Temperature	20 °C
Vapour Pressure	0.014 Pa
Water Solubility	13 mg/l
Log K_{ow}	3.28
Melting point	78.8°C

Results pro Compartment	Calculated distribution
Air	5.86 %
Water	72.18 %
Soil	10.88 %
Sediment	11.00 %
Suspended Sediment	0.0706 %
Fish	0.0069 %
Aerosol	0.0129 %

The distribution of diphenyl carbonate between aqueous solutions and air was calculated by two methods. A Henry´s law constant (HLC) of 8.59 Pa × m^3/mol at 25 °C was obtained using the Bond Method and a HLC of 0.23 Pa × m^3/mol at 20 °C from the ratio of the vapour pressure to the water solubility (Bayer Industry Services, 2003) indicating that diphenyl carbonate is slightly to moderately volatile from waters according to the scheme of Thomas (1990).

Table 6 Distribution in the environment (IUCLID 3.3.2)

Parameter	Method	Result	Source
Distribution throughout environmental compartments	Calculated according to Mackay Fugacity Model Level I at 20 °C	Air: 5.86 % Water: 72.18 % Soil: 10.88 % Sediment: 11.0 % Suspended sediment: 0.0706 % Fish: 0.0069 % Aerosol: 0.0129 %	Bayer Industry Services, 2003*
Fugacity Water – air Henry´s law constant	Bond-Method (calculated) Calculation from the ratio of the vapour pressure to the water solubility	8.59 Pa × m^3 mol^{-1} 0.23 Pa × m^3 mol^{-1}	Bayer Industry Services, 2003*

*Key study for the endpoint

2.2.5 Biodegradation

According to the available biodegradation results diphenyl carbonate is not readily biodegradable. However diphenyl carbonate is biodegraded by adapted microorganisms..

A closed bottle test (Directive 92/69/EEC, C.4-E) was performed with a concentration of diphenyl carbonate of 3.3 mg/l. After 28 days 37 % of the test substance had been degraded (Bayer AG, 2000d).

A closed bottle test, comparable to the OECD TG 301 D was performed with a concentration of diphenyl carbonate of 2.4 mg/l and adapted domestic sewage. After 20 days 99.5 % of the test substance had been degraded (Bayer AG, 1979a).

In a test carried out with adapted activated sludge, 100 % of diphenyl carbonate in an initial concentration of 833 mg/l was primary degraded after 3 days (Andreoni et al., 1990). The authors identified the strain *Acinetobacter calcoaceticus* to grow well in the presence of diphenyl carbonate.

The key data of the biodegradation studies are listed in Table 7.

Table 7 Tests on biodegradation of diphenyl carbonate (IUCLID 3.5)

Inoculum	Procedure	Result	Reference
Aerobic activated sludge	Dir. 92/69/EEC, C.4-E	37 % after 28 d	Bayer AG, 2000d*
Domestic sewage, adapted	Comparable to OECD TG 301 D	99.5 % after 20 d	Bayer AG, 1979a*
Activated sludge, adapted	Microbial degradation	100 % after 3 d (primary degradation)	Andreoni et al., 1990*

*Key study for the endpoint

2.2.6 Bioaccumulation

There are no measured bioconcentration factors (BCF) available for diphenyl carbonate (Table 9). Taking in account the octanol-water partition coefficient, a bioconcentration factor (BCF) can be calculated with the BCF Program (v 2.15). Using log K_{ow} = 3.28, the calculated BCF was 66.9 (log BCF = 1.83) (Bayer Industry Services, 2003) indicating that the substance has a low potential to bioaccumulate in aquatic organisms.

Table 8 Bioaccumulative properties of diphenyl carbonate (IUCLID 3.7)

Parameter	Method	Result	Source
Bioconcentration factor	Calculated	BCF = 66.9	Bayer Industry Services, 2003*

*Key study for the endpoint

2.2.7 Geoaccumulation

There are no experimental data on the geoaccumulation of diphenyl carbonate. Carrying out a QSAR calculation with the PCKOC program (v1.66), a K_{oc} value of 3926 is obtained (Bayer Industry Services, 2003). According to Litz (1990) this value indicates that diphenyl carbonate is supposed to have a high geoaccumulation potential. However, due to the hydrolysis ($t_{1/2}$: 40 h) geoaccumulation is not expected.

2.2.8 Environmental Monitoring

There are no environmental monitoring data available for diphenyl carbonate.

2.3 Human Exposure

2.3.1 Occupational Exposure

Exposure-related information was available on the Belgium and German facilities of the Sponsor company (Bayer MaterialScience (2004b). There is no production of diphenyl carbonate in the Sponsor country, but some processing by the Sponsor company.

At the Bayer site in Belgium, diphenyl carbonate is manufactured and directly processed in closed systems (Bayer MaterialScience, 2004b). Due to the use of closed systems, occupational exposure is limited to situations of maintenance and repair, and accidental spills. In those situations, the occupational exposure to diphenyl carbonate is most likely to occur through inhalation and dermal contact.

Following the principles of Responsible Care and Sustainable Development, the exposure of workers is reduced to the lowest technically practicable level in the Sponsor company. Surveys of the workplaces in Belgium and Germany are performed for any possible exposure to diphenyl carbonate and dangerous substances under all relevant work situations, and appropriate control measures are taken (Bayer MaterialScience, 2004b).

To protect workers from exposure, several precautionary and protective measures are taken, e.g., repair and maintenance work is only carried out on parts of the manufacturing or processing systems which have previously been emptied and flushed with solvent and water to remove residual substance. For the involved personnel, special permits are required which include a detailed description of the protective measures depending on the work to be done (e.g. full protective clothing and gas filter masks (classification ABEK)) (Bayer MaterialScience, 2004b).

In Belgium there is no exposure limit value designated for diphenyl carbonate. As part of the Bayer monitoring program, workplace air is sampled - in general – for longer than 4 h to obtain results representative of a time weighted average for an 8-h shift. Current results of this monitoring show diphenyl carbonate values below the limit of detection of 0.003 mg/m^3 (n = 6) during manufacturing and processing of diphenyl carbonate (Bayer MaterialScience, 2004b).

Diphenyl carbonate is listed in the Danish, Finnish, Norwegian, and Swedish product registers as a product with industrial application (SPIN, 2004). The Danish Product Register (2002) lists five industrial products containing diphenyl carbonate in concentrations of 0-2 %.

2.3.2 Consumer Exposure

Diphenyl carbonate is only used as an industrial intermediate and has no consumer application. Based on data presented by the Sponsor company, consumer exposure to diphenyl carbonate via the environment is anticipated to be low.

Diphenyl carbonate is also used as a monomer in the manufacturing of polycarbonate, which may be used as food contact material. In 2003, the European Scientific Committee on Food (SCF) evaluated the use of diphenyl carbonate in polycarbonate for food contact materials (SCF, 2003). Migration of diphenyl carbonate was determined in 3 % acetic acid, 10 % ethanol and HB 307. Diphenyl carbonate hydrolyses in aqueous food simulants into phenol and carbon dioxide. Migration of diphenyl carbonate was not detectable at levels of approximately 0.05 mg/kg food simulant (6 dm^2/kg). Phenol was detected in 3 % acetic acid (0.16 mg/kg) and in 10 % ethanol (0.2 mg/kg) after a contact period of 2 h at 100 °C. Most likely the polycarbonate is hydrolysed at the high temperature conditions.

Based on the results from the required tests on physical chemical properties, as well as on the migration and mutagenicity data, the Scientific Committee on Food classified diphenyl carbonate in “List 3”, i.e. substances for which an ADI or TDI could not be established, but where the present use could be accepted due to a very low migration. The use was, therefore, restricted to a maximum limit of migration of 0.05 mg/kg of food (SCF, 2003). This limit value has become a legal entity in the EU (EU 2004).

Diphenyl carbonate was not detectable in eluates from 12 out of 14 polycarbonate products. In two products (dishes, cups) diphenyl carbonate concentrations of 225 ± 6.8 mg/kg and 79 ± 4.6mg/kg were measured after elution with acetonitrile (Ozaki et al., 2003).

No consumer preparations are listed in the SPIN database (SPIN, 2004).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

No data available.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

No data available.

Dermal

Guideline studies on acute dermal toxicity of diphenyl carbonate in rats and rabbits are available. In rats, diphenyl carbonate was tested using the acute toxic class method, in rabbits a protocol according to OECD TG 402 was used. For a better skin contact, diphenyl carbonate was moistened with water in both studies and applied for 24 hours under occlusive conditions. The dermal LD_{50} was > 2000 mg/kg bw in both rats and rabbits. No local or systemic effects were observed (General Electric Plastics, 1990b; Bayer AG, 1999a).

Oral

An early acute oral toxicity study was conducted on rats with diphenyl carbonate (test substance not specified) in doses up to 2500 mg/kg bw (administered as aqueous emulsion in cremophor). Transient bad condition and convulsions became obvious at ≥ 1000 mg/kg bw and the LD_{50} was determined to be > 2500 mg/kg bw (Bayer AG, 1967). A further study, performed under GLP and following OECD TG 401 with rats gave an LD_{50} of 1500 mg/kg bw for diphenyl carbonate of known purity (99.95 %) (General Electric Plastics, 1990a). In this study 5 rats/sex were treated with diphenyl carbonate doses of 750, 1500, and 3000 mg/kg bw in corn oil. Mortality was 10/10 in the highest dose group, 5/10 at 1500 mg/kg bw and 0/10 at 750 mg/kg bw. Clonic convulsions became obvious at ≥ 1500 mg/kg bw. The LD_{50} was determined to be 1500 mg/kg bw in this study.

In a poorly documented study, the acute oral toxicity of diphenyl carbonate of unknown purity (administered as aqueous emulsion in cremophor) in male mice and dogs was shown to exceed 1000 mg/kg bw (Bayer AG, 1967).

Conclusion

The acute dermal toxicity of diphenyl carbonate is relatively low with LD_{50} values exceeding 2000 mg/kg bw in rats and rabbits (no clinical signs noted). The acute oral LD_{50} in rats was 1500 mg/kg bw, with clonic convulsions as main clinical sign appearing at doses near to or exceeding the LD_{50} value. There are no acute inhalation studies available.

3.1.3 Irritation

Skin Irritation

Studies in Animals

The skin irritating potential of undiluted, solid diphenyl carbonate (purity 99.95%) was investigated in a study according to current guideline (OECD TG 404) with 6 rabbits. No signs of erythema or edema were observed after 4 hours of semiocclusive contact with diphenyl carbonate (Draize scores for erythema and edema after removal of the patch and at 24, 48 and 72 hours thereafter: 0.0) (General Electric Plastics, 1990c).

Eye Irritation

Studies in Animals

The eye irritating potential of undiluted, solid diphenyl carbonate (purity 99.95%) was examined in a study according to current guideline (OECD TG 405). Fluorescein staining was used during each examination. Instillation of 0.1 grams of diphenyl carbonate into the left eye of 6 rabbits led to slight swelling (grade 1) of the conjuctivae at 1 hour (5/6 animals), however, no signs of irritation were obvious at 24, 48, and 72 hours after treatment (General Electric Plastics, 1990d). Therefore, diphenyl carbonate can be regarded as not irritating to the eyes of rabbits.

Conclusion

Diphenyl carbonate was not irritating to the skin and eye of rabbits (OECD TG 404, 405).

3.1.4 Sensitisation

Studies in Animals

Skin

Diphenyl carbonate showed no evidence of a skin sensitisation potential in guinea pigs in a Buehler Patch Test following GLP (General Electric Company, 1991a). In this test 10 guinea pigs were treated by occlusive topical patch technique (6 h) with 75 % diphenyl carbonate in petrolatum once weekly for 3 weeks. Two weeks after completion of this induction phase, an unused skin area of the animals was challenged with the same test concentration. No dermal reactions were observed in any of the animals subjected to diphenyl carbonate. In deviation of the OECD TG 406, only 10 (instead of 20 animals) were used in this test.

Conclusion

Diphenyl carbonate showed no skin sensitisation potential in a Buehler patch test on 10 guinea pigs, limited by the small number of treated animals.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Inhalation

No data available.

Dermal

No data available.

Oral

A repeated dose toxicity study was conducted on male Wistar rats over a period of 10 weeks. Groups of 15 animals were treated by gavage on 5 days per week with doses of 85, 165, 415, 550, 660, 830, and 1000 mg/kg bw/day. Observation parameters were clinical signs, development of body and organ weight, gross pathology and hematology. Up to and including a daily dose of 830 mg/kg bw/day, all investigated parameters remained within the normal range. At 1000 mg/kg bw/day, elevated liver weights (+ 18 %) were found. The NOAEL for repeated dose toxicity in male rats was 830 mg/kg bw/day in this study (Bayer AG, 1967).

Based on the results of a 13 week dose finding study with 5 rats/dose (Bayer AG, 2002a), a one-generation study with 25 male and female Wistar rats per group following OECD TG 416 (2001) was conducted, including open field observations, a macro- and microscopical examination of main organs, and a Functional Observation Battery. Animals were given 1500, 5000, or 15000 ppm diphenyl carbonate in the food for a period of 11 weeks prior to mating and then during the mating period for up to three weeks. Males were sacrificed after the mating period, females were further treated during pregnancy and weaning and were sacrificed when 28 day-old F1 offspring was weaned (after about 18 weeks of treatment). The calculated actual doses were 132, 427, and 1561 mg/kg bw/day for males, and 219, 710, and 2432 mg/kg bw/day for females (Bayer AG, 2003). Mortality and clinical appearance of treated animals were unchanged throughout all dose groups. Slightly reduced mean body weights (up to 8 %) became obvious in the high dose animals. Organ weight determination and histopathology revealed changes in liver, adrenals and ovaries. Significantly increased relative liver weights were seen in 5000 and 15000 ppm males (+10.1 and +13.5 %, respectively) and 15000 ppm females (+12 %). Hepatocellular hypertrophy was found in males of the mid and high dose group (n = 0, 0, 4, 6 for controls, low-, mid- and high-dose animals, respectively) and in females of the high dose group (0, 0, 0, 2) in low frequency and with low severity score. The incidence of Kupffer cell foci was slightly increased in females of the high dose group (6, 5, 5, 10). Significantly increased absolute (+11.5 %, +13.5 %, +17.3 %) and relative (+9.5 %, +14.3 %, +19 %) adrenal weights were found in females of all dose groups. In adrenals of mid and high dosed males the frequency of mixed-size vacuolation of the *zona fasciculata* cells and partly also of the *zona glomerulosa* cells was slightly and the severity moderately increased (incidence: 18, 21, 25, 25; grade 2: 5, 6, 13, 9; grade 3: 0, 0, 5, 15). In adrenals of females microvesicular vacuolation (0, 17, 23, 24) and hypertrophy (0, 17, 23, 25) of the *zona fasciculata* cells were found in high incidences in all dose groups. The severity score increased dose-dependently. Ovarian weights were significantly increased from 5000 ppm onwards (absolute: +22.8 %, +16.3 %; relative: +27.1 %, +22.9 %). The number of *corpora lutea* (severity score grade 2) increased slightly from 1500 ppm onwards (8, 12, 17, 16). The total number of *corpora lutea* per group was also slightly elevated (365, 391, 443, 428). At 1500 ppm and above, large *corpora lutea* exhibited an infiltration of predominantly mononuclear cells (0, 21, 24, 21). In addition, many of these corpora lutea contained granulated luteal cells (0, 20, 18, 9). Hypertrophic ovarian interstitial cells were increased in treated females (0, 16, 24, 24) with severity score increasing in a dose dependent manner. The NOAEL for parental males was 1500 ppm (about 132 mg/kg bw/day) in this study. The LOAEL was 5000 ppm (about 427 mg/kg bw/day) based on increased relative liver weights with hepatocellular hypertrophy, and histopathological changes in adrenals. For parental females a NOAEL could not be determined in this study because of histopathological changes in adrenals and ovaries in all dose groups. The LOAEL for parental females was 1500 ppm (about 219 mg/kg bw/day) in this study, based on increased relative and absolute adrenal weights with histopathological changes in the *zona fasciculata*, and morphological changes in the ovaries.

In a supplementary study doses of 2 to 200 mg/kg bw/day diphenyl carbonate were given to female rats (10/dose) over a similar period as in the one-generation study to establish a NOAEL for diphenyl carbonate in this gender. Because of instability of diphenyl carbonate at doses below 1500 ppm in food, diphenyl carbonate was administered by gavage in this 18-week study in doses of 2, 10, 50 and 200 mg/kg bw/day (Bayer HealthCare, 2003). This study was not conducted in accordance with a special guideline. Mortality, clinical appearance, body and organ weights of treated animals were unchanged throughout all dose groups. In the 200 mg/kg group histopathological changes became obvious in ovaries and adrenals similarly to those observed in females of the one-generation study at a comparable dose. Ovaries of 4 animals exhibited interstitial glands characterized by slight hypertrophy and pale cytoplasm (grade 2). Numbers of *corpora lutea* were not affected. Adrenal glands of 3 high dosed females showed hypertrophy of *zona fasciculata* cells with microvesicular vacuolation. No changes were observed at the other tested diphenyl carbonate doses of 50, 10, and 2 mg/kg bw/day. The NOAEL for repeated dose toxicity of diphenyl carbonate in female rats was therefore 50 mg/kg bw/day.

Studies in Humans

No data available.

Conclusion

Repeated oral dosing of rats with diphenyl carbonate over 11 weeks (males) or 18 weeks (females) led to increases in liver weight and to hepatocellular hypertrophy and histopathological changes in the adrenals in males at a dietary concentration of 5000 ppm (about 427 mg/kg bw/day), and in females of 1500 ppm (about 219 mg/kg bw/day). At 1500 ppm, females exhibited also morphological changes in the ovaries (increased number and mononuclear infiltration of corpora lutea, granulated luteal cells, hypertrophic ovarian interstitial cells). The NOAEL in males was 1500 ppm (about 132 mg/kg bw/day) and in females about 50 mg/kg bw/day.

3.1.6 Mutagenicity

Studies in Animals

In vitro Studies

The mutagenicity of diphenyl carbonate was investigated in well-performed *in vitro* guideline studies with bacterial and mammalian cell test systems.

Diphenyl carbonate did not induce gene mutations in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 in two independently performed Ames tests under GLP, and according to OECD TG 471 and EPA guideline. Concentrations of up to 5 mg/plate were used, leading to cytotoxicity in high dose cultures without S9-mix. In one laboratory the cultures with metabolic activation showed no signs of toxicity even at a concentration of 5 mg/plate (Bayer AG, 1989), whereas in the other laboratory cytotoxicity became obvious at this concentration (General Electric Company, 1991b). In both studies diphenyl carbonate gave negative results with and without metabolic activation (Bayer AG, 1989; General Electric Company, 1991b). Also in *E. coli* strain WP 2 negative results were obtained for diphenyl carbonate with and without S9-mix. No cytotoxicity became obvious for this strain up to a concentration of 5 mg/plate (General Electric Company, 1991b). Appropriate reference mutagens were used as positive controls and showed the expected results throughout all tested strains.

Diphenyl carbonate gave no indication of a mutagenic potential in the in vitro gene mutation HPRT test performed according to OECD TG 476 using Chinese hamster V79 cells (General Electric

Plastics, 1996a). Concentrations of up to 150 µg/ml without S9-mix (cytotoxicity at ≥ 60 µg/ml) and up to 2000 µg/ml with S9-mix (cytotoxicity at ≥ 600 µg/ml) were tested. Appropriate reference mutagens were used as positive controls and showed the expected results.

Diphenyl carbonate was tested in the chromosome aberration assay with Chinese hamster V79 cells *in vitro* according to OECD TG 473 (General Electric Plastics, 1996b). In two independent experiments diphenyl carbonate induced structural chromosomal aberrations in V79 cells. In the absence of S9-mix up to 9.5 % aberrant cells (at 30 µg diphenyl carbonate/ml) and in the presence of S9-mix up to 21.5 % (at 500 µg/ml) aberrant cells were obtained.

In vivo Studies

Two mouse bone marrow micronucleus assays done according to OECD TG 474 and under GLP were performed with diphenyl carbonate.

In the first assay with diphenyl carbonate of 99% purity, groups of 10 NMRI mice (5/sex/dose) were treated with single intraperitoneal doses of 30, 100, and 300 mg diphenyl carbonate/kg bw. 24 hours after dosing, and for the highest dose group also 48 hours after dosing, the animals were sacrificed (General Electric Plastics, 2000). In pilot tests 300 mg/kg bw diphenyl carbonate (i.p.) were determined as MTD for both genders. Females appeared to be little more susceptible than males. In the main experiment, 300 mg/kg bw led to a distinct reduction (>40 %) of the PCE/NCE ratio in the bone marrow, indicating cytotoxicity. This dose led to a statistically significant ($p < 0.05$) incidence of 0.19 % micronucleated PCEs (MNPCE) compared to 0.065 % MNPCE in control animals. However, the statistical significance was mainly influenced by enhanced micronucleus frequencies of individual animals with exceptional high numbers of 15 (24 h) or 10 (48 h) MNPCE. Since these values were clearly different from the other findings in these groups (0 - 6 MNPCE, 24 h; 0-7 MNPCE, 48 h), they were interpreted as outliers. In conclusion, the results of this assay were considered as equivocal (General Electric Plastics, 2000). Additionally, it has to be considered that no dose dependent micronucleus increase occurred and that the mean value of the incidence (0.19 %) was well within the range of the laboratory's historical negative control range of the concurrent time window of 0.03 - 0.26 % MNPCE. An appropriate reference mutagen (cyclophosphamide, single i.p. injection of 40 mg/kg bw) was used as positive control and showed the expected results.

In the second micronucleus test with diphenyl carbonate of 99.98 % purity, groups of 5 male NMRI mice were treated with two intraperitoneal doses of 75, 150, and 300 mg diphenyl carbonate/kg bw, separated by 24 hours. Preparation of bone marrow cells were made 24 hours after the last dosing (Bayer AG, 1999b). In a pilot experiment two-fold i.p. dosing with 300 mg diphenyl carbonate/kg bw was determined as the MTD for males and females. In the main experiment, the highest dose led to a distinct reduction (> 30 %) of the PCE/NCE ratio in the bone marrow. Throughout all doses no statistically significant increase of MNPCE occurred (control: 0.18 % MNPCE; 300 mg/kg: 0.28 % MNPCE). The slightly enhanced value in the highest dose group is caused by one animal showing an exceptional high number of 16 MNPCE. Since this value is clearly different from the other findings in this group (1 - 5 MNPCE), it is interpreted as outlier. An appropriate reference mutagen (cyclophosphamide, single i.p. injection of 20 mg/kg bw) was used as positive control and showed the expected results.

Based on the evaluation of both micronucleus tests, diphenylcarbonate is regarded to be negative in the mouse micronucleus assay *in vivo*.

An *in vivo/in vitro* UDS test performed according to OECD TG 486 and following GLP gave negative results for diphenyl carbonate (purity 99.87 %) as well. In this assay 5 male Sprague-Dawley rats per group were treated by gavage with doses of 250, 500, and 1000 mg diphenyl

carbonate/kg bw. 1000 mg/kg bw were determined as MTD in preceding experiments. Hepatocytes were isolated 2 - 4 and 12 - 16 hours after dosing. In none of the treated groups positive results were obtained. An appropriate reference mutagen (dimethylnitrosamine, single oral application of 35 mg/kg bw in deionized water) was used as positive control and showed the expected results (General Electric Plastics, 2002).

Conclusion

Diphenyl carbonate showed no mutagenic properties in bacterial and mammalian cell gene mutation assays performed according to current guidelines. In the *in vitro* chromosome aberration assay diphenyl carbonate led to increased frequencies of structural chromosomal aberrations in V79 cells both in the absence and in the presence of metabolic activation. This positive result could not be confirmed *in vivo* by two mouse bone marrow micronucleus assays performed according to current guidelines and with evidence of target cell exposure. An *in vivo/in vitro* UDS assay on rat liver, also performed according to current guidelines with oral doses up to the MTD, gave negative results. It is concluded that the genotoxic properties observed *in vitro* are not expressed *in vivo.*

3.1.7 Carcinogenicity

No reliable data available.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

In a one-generation study following OECD TG 415 and TG 416 (2001; without treatment of F1 weanlings after the balano-preputial separation or vaginal opening had occurred; including open field observations and Functional Observation Battery). 25 male and female Wistar rats per group were given 1500, 5000, or 15 000 ppm diphenyl carbonate in the food for a period of 11 weeks and then during mating for a period of up to three weeks. Males were sacrificed after the mating period, females were further treated during pregnancy and weaning and were sacrificed together with F1 animals when 28 day-old F1 offspring was weaned. One F1 male and one F1 female per litter were necropsied after a further treatment period of about 4 weeks, when sexual maturity was reached. The calculated actual doses for parental animals were 132, 427, and 1561 mg/kg bw/day for males or 219, 711, and 2432 mg/kg bw/day for females (Bayer AG, 2003). Mortality and clinical appearance of F0 and F1 animals were unchanged throughout all dose groups. Slightly reduced mean body weights (up to 8 %) became obvious in the high dosed F0 animals. Also F1 animals of the high dose group gained less body weights. This effect became significant at weaning when pups ingested increasingly diphenyl carbonate via their own food and can therefore be regarded as primary effect. Organ weight determination and histopathology revealed diphenyl carbonate dependent changes in liver, adrenals and ovaries of F0 animals (for details see Chapter 3.1.5). Ovarian morphology was changed also in treated F1 females in a dose dependent manner throughout all dose groups (mononuclear infiltration of *corpora lutea*: n=1/5/9/11 for controls, low-, mid-, and high-dose groups, respectively; presence of granulated luteal cells: 0/2/7/8; hypertrophy of ovarian interstitial cells: 0/4/10/23), showing a similar appearance as observed in F0 females. Reproduction parameters, as insemination index, mating performance, fertility index, gestation index, duration of pregnancy, live birth index, birth weights, prenatal loss and percentages of pups born, litter size, viability and lactation index, were not affected by diphenyl carbonate. The histopathological changes observed in ovaries and adrenals therefore did not influence reproductive

performance. Also in post weaned F1 animals (1 male and 1 female per litter; sacrificed at an age of 8 weeks) sexual maturation was not affected. The NOAEL for fertility was 15000 ppm (about 1561/2432 mg/kg bw/day for males/females) in this study. The NOAEL for general toxicity in parental males was 1500 ppm (about 132 mg/kg bw/day), with the LOAEL at 5000 ppm (about 427 mg/kg bw/day) based on increased relative liver weights with hepatocellular hypertrophy, and histopathological changes in adrenals. For parental females a NOAEL for general toxicity could not be determined in this study because of histopathological changes in adrenals and ovaries in all dose groups. However, a NOAEL of 50 mg/kg bw/day was obtained for female general toxicity in a follow up 18-week repeated dose toxicity study (Bayer HealthCare, 2003; for details see Chapter 3.1.5). For F1 males the NOAEL for general toxicity was 5000 ppm, with a LOAEL at 15 000 ppm based on reduced body weight gain. A NOAEL for F1 females could not be determined as changes in the ovaries were seen down to the lowest tested dose (1500 ppm).

Developmental Toxicity

Diphenyl carbonate was tested in a rat teratogenicity study following OECD TG 414. Groups of 25 to 28 inseminated Wistar rats were treated daily by gavage with diphenyl carbonate from day 6 to 19 of gestation at doses of 0, 50, 200, and 750 mg/kg bw/day. On day 20, the animals were delivered by Cesarean section (Bayer AG, 2002b). In the highest dose group severe signs of maternal toxicity became obvious. 5 females died in this group showing convulsions, ventral posture and piloerection. Additionally, food consumption was decreased leading to body weight loss. Intrauterine development, gestation rate, postimplantation loss, number of fetuses, sex distribution and placental weight were not affected by the treatment. However, at this maternally toxic dose level, mean fetal weights were reduced by nearly 10 %, unspecific malformations (mainly dysplastic forelimb bones) and skeletal variations (wavy ribs, retarded ossification of distal phalanges of toes and vertebrae) occurred and an increased incidence of engorged placentae or placentae with necrotic borders became obvious. In the 200 mg/kg bw/day group food intake (days 6 - 12 p.c.) and body weight gain (days 6 - 7 p.c.) were significantly reduced in the first week of treatment and remained marginally reduced up to sacrifice. Additionally, a slight retarding effect on fetal skeletal ossification of toes and cervical vertebral bodies became obvious at this dose. These deviations were only statistically significant when calculated on a fetal basis and the observed values were within historical controls (except for findings at toes). The overall number and type of malformations were not increased at a dose level up to and including 200 mg/kg bw. However, because the same localisations as in the 750 mg/kg bw/day group were affected, a treatment-related effect cannot be completely excluded. The NOAEL for maternal toxicity and developmental toxicity of diphenyl carbonate in rats was therefore 50 mg/kg bw/day (LOAEL, maternal and developmental toxicity: 200 mg/kg bw/day).

Studies in Humans

No data available.

Conclusion

In repeated dose toxicity studies on rats, diphenyl carbonate led to increased organ weights and morphological alterations in adrenals and ovaries. These effects did not influence reproductive performance in a one-generation dietary study on rats (OECD TG 415/416; NOAEL for fertility: 15 000 ppm = about 1561/2432 mg/kg bw/day for males/females; highest tested dose).

In a developmental toxicity study on rats according to OECD TG 414, daily gavage administration of 750 mg diphenyl carbonate/kg bw/day to pregnant rats on gestation days 6 to 19, led to severe maternal toxicity (mortality, convulsions, piloerection, body weight loss). Fetuses of this dose

group showed reduced body weights and increased incidences of unspecific malformations (mainly dysplastic forelimb bones). The NOAEL for maternal toxicity and developmental toxicity of diphenyl carbonate in rats was 50 mg/kg bw/day. At 200 mg/kg bw/day slight maternal toxicity occurred and a retarding effect on fetal skeletal ossification of toes and cervical vertebral bodies could not be completely excluded.

3.2 Initial Assessment for Human Health

The acute dermal toxicity of diphenyl carbonate is relatively low with LD_{50} values exceeding 2000 mg/kg bw in rats and rabbits (no clinical signs noted). The acute oral LD_{50} in rats was 1500 mg/kg bw, with clonic convulsions as main clinical sign appearing at doses near to or exceeding the LD_{50} value. There are no acute inhalation studies available.

Diphenyl carbonate was not irritating to the skin and eye of rabbits (OECD TG 404, 405).

Diphenyl carbonate showed no skin sensitisation potential in a Buehler patch test on 10 guinea pigs, limited by the small number of treated animals.

Repeated oral dosing of rats with diphenyl carbonate over 11 weeks (males) or 18 weeks (females) led to increases in liver weight and to hepatocellular hypertrophy and histopathological changes in the adrenals in males at a dietary concentration of 5000 ppm (about 427 mg/kg bw/day), and in females of 1500 ppm (about 219 mg/kg bw/day). At 1500 ppm, females exhibited also morphological changes in the ovaries (increased number and mononuclear infiltration of corpora lutea, granulated luteal cells, hypertrophic ovarian interstitial cells). The NOAEL in males was 1500 ppm (about 132 mg/kg bw/day) and in females about 50 mg/kg bw/day.

Diphenyl carbonate showed no mutagenic properties in bacterial and mammalian cell gene mutation assays performed according to current guidelines. In the *in vitro* chromosome aberration assay diphenyl carbonate led to increased frequencies of structural chromosomal aberrations in V79 cells both in the absence and in the presence of metabolic activation. This positive result could not be confirmed *in vivo* by two mouse bone marrow micronucleus assays performed according to current guidelines and with evidence of target cell exposure. An *in vivo/in vitro* UDS assay on rat liver, also performed according to current guidelines with oral doses up to the MTD, gave negative results. It is concluded that the genotoxic properties observed *in vitro* are not expressed *in vivo.*

In repeated dose toxicity studies on rats, diphenyl carbonate led to increased organ weights and morphological alterations in adrenals and ovaries. These effects did not influence reproductive performance in a one-generation dietary study on rats (OECD TG 415/416; NOAEL for fertility: 15 000 ppm = about 1561/2432 mg/kg bw/day for males/females; highest tested dose).

In a developmental toxicity study on rats according to OECD TG 414, daily gavage administration of 750 mg diphenyl carbonate/kg bw/day to pregnant rats on gestation days 6 to 19, led to severe maternal toxicity (mortality, convulsions, piloerection, body weight loss). Fetuses of this dose group showed reduced body weights and increased incidences of unspecific malformations (mainly dysplastic forelimb bones). The NOAEL for maternal toxicity and developmental toxicity of diphenyl carbonate in rats was 50 mg/kg bw/day. At 200 mg/kg bw/day slight maternal toxicity occurred and a retarding effect on fetal skeletal ossification of toes and cervical vertebral bodies could not be completely excluded.

4 HAZARDS TO THE ENVIRONMENT

4.1. Aquatic Effects

Acute Toxicity Test Results

Representative tests on the acute toxicity in static systems of diphenyl carbonate are available.

The stability of diphenyl carbonate was examined under abiotic conditions in a buffered medium and is estimated to be about 40 h. It is longer in acidic or cold solution and shorter in basic or hot solution (*cf*. Chapter 2.2.3). Using a half-life value of 40 °h and a water solubility of 13 mg/l for the interpretation of aquatic data, the nominal diphenyl carbonate concentrations were converted to effective concentrations by approximation as geometric means over time. It is to be considered, that the effects observed cover both, the toxicity of diphenyl carbonate as well as the toxicity of the degradation products (especially phenol). Data on phenol toxicity were compiled and evaluated by the OECD (2004).

For fish (*Danio rerio*) a LC_0 of 3.16 mg/l and a LC_{100} of 31.6 mg/l after 96 h were obtained. The study was conducted according to Directive 92/69/EEC, C.1 (Bayer AG, 1994) and the results relate to nominal concentrations. A LC_{50} of 10.0 mg/l was calculated (geometric mean). With the assumption that the half-life of diphenyl carbonate is about 40 h and a water solubility of 13 mg/l, the final concentration of the LC_0 and LC_{100} determination is estimated to be 0.91 mg/l and 5.6 mg/l (geometric mean over time). By graphic interpolation (linear) the resulting 96 h LC_{50} is 3.9 mg/l.

A test on the acute toxicity of diphenyl carbonate to the invertebrate *Daphnia magna* was performed according to the Directive 92/69/EEC, C.2 with analytical monitoring (TOC measurement). For a test period of 48 hours an EC_0 value of 6.3 mg/l and an EC_{75} value of 18.2 mg/l were obtained (Bayer AG, 1999c). The EC_{50} value is $> 6.3 < 18.2$ mg/l, the EC_{100} is larger than 18.2 mg/l. Using the half-life of 40 h and the water solubility of 13 mg/l, the geometric mean over time is estimated to be 8.5 mg/l, 4.1 mg/l and 2.1 mg/l at the nominal test concentrations of 20 mg/l, 10 mg/l and 5 mg/l. An effective 48 h EC_{50} of 6.5 mg/l by graphic interpolation (linear) is estimated.

Concerning the algal toxicity, a test with *Desmodesmus subspicatus* in the presence of diphenyl carbonate was performed according to the Directive 92/69/EEC, C.3. In a growth test a 72 h-EC_{50} of 2.4 mg/l for the growth rate and 1.4 mg/l for the integral of biomass was determined. The corresponding 72 h-NOEC was 0.63 mg/l and the 72 h-LOEC was 1.25 mg/l (Bayer AG, 1999d). An analytical monitoring was conducted in this test (TOC measurement). However, since the effect concentrations observed were lower than the limit of quantification of the method (LOQ = 2 mg/l TOC) and the analytical method could not distinguish between diphenyl carbonate and its hydrolysis product phenol, just nominal concentrations could be given. Using the half-life of 40 h and the water solubility of 13 mg/l the nominal concentrations are converted (geometric mean over time). For the EC_{50} values the effective concentrations are calculated to 0.9 mg/l (E_rC_{50}) and 0.5 mg/l (E_bC_{50}). The corresponding effective 72 h-NOEC and LOEC for growth rate are 0.22 mg/l and 0.44 mg/l. The corresponding effective 72 h-NOEC and LOEC, obtained from biomass, are 0.11 and < 0.22 mg/l, respectively.

Table 9 Tests on acute toxicity of diphenyl carbonate to fish, *Daphnia*, and algae

Species	Test type	Parameter	Effective concentration (mg/l) (nominal concentration in brackets)	Reference	IUCLID
Danio rerio	Static	96 h-LC_0 96 h-LC_{100} 96 h-LC_{50}	0.91 (3.16) 5.6 (31.5) 3.9 (10.0)	Bayer AG, 1994*	4.1
Daphnia magna	Static	48 h-EC_0 48 h-EC_{75} 48 h-EC_{100} 48 h-EC_{50}	2.1 (6.3) 8.5 (18.2) > 8.5 (>18.2) 6.5 (13.9)	Bayer AG, 1999c*	4.2
Desmodesmus subspicatus	Static	Biomass: 72 h-EC_{50} NOEC LOEC Growth rate 72 h-EC_{50} NOEC LOEC	 0.5 (1.4) 0.11 (0.31) < 0.22 (0.63) 0.9 (2.4) 0.22 (0.63) 0.44 (1.25)	Bayer AG, 1999d*	4.3

(n): nominal concentration

*Key study for the endpoint

Chronic Toxicity Test Results

No tests on the chronic toxicity of diphenyl carbonate are available.

Determination of $PNEC_{aqua}$

Since acute test results for diphenyl carbonate for three trophic levels and no long-term results (NOEC) for fish or *Daphnia* are available, an assessment factor of 1000 was applied for the derivation of the $PNEC_{aqua}$ according to the EU Technical Guidance Document. The lowest effect concentration was found for the algae species *Desmodesmus subspicatus*, 72 h-EC_{50} = 0.9 mg/l effective concentration (growth rate) (Bayer AG, 1999d), therefore resulting in a

$PNEC_{aqua}$ = 0.9 µg/l.

Toxicity to Microorganisms

A test with activated sludge with duration of 3 hours was performed by a method comparable to OECD TG 209. An EC_{50} value of 4510 mg/l was observed (Bayer AG, 2000e).

A cell multiplication inhibition test according Bringmann and Kuehn to *Pseudomonas putida* was carried out. During a test of 16 h at a concentration of 280 mg/l no effects were observed (Bayer AG, 1979b).

Microbial toxicity of diphenyl carbonate is listed in Table 10.

Table 10 Tests on acute toxicity of diphenyl carbonate to microorganisms (IUCLID 4.4)

Species	Endpoint	Parameter	Effects	Reference
Activated sludge	OECD TG 209	3 h-EC_{50}	4510 mg/l (n)	Bayer AG, 2000e*
Pseudomonas putida	Cell multiplication	16 h-EC_0	> 280 mg/l (n)	Bayer AG, 1979b*

(n): nominal concentration

*Key study for the endpoint

4.2. Terrestrial Effects

No data available.

4.3. Other Environmental Effects

No data available.

4.4. Initial Assessment for the Environment

Diphenyl carbonate is a white solid (flakes) with a melting point of 78.8 °C, and a boiling point of 302 °C. The density of the solid is 1.272 g/cm^3 at 14 °C. The vapour pressure is 0.014 Pa at 20 °C. The log K_{ow} is 3.21 - 3.28. The solubility of the substance in water is ca. 13 mg/l at 20 °C. The flash point is 168 °C.

Diphenyl carbonate hydrolyses under environmental conditions forming phenol and carbon dioxide. A study on the abiotic degradation of diphenyl carbonate in water predicted that the test substance has a $t_{1/2}$ of 39.9 h at pH 7 and 25 °C.

According to a Mackay Level I calculation the favourite target compartment of the substance is water with 72.2 % (soil 11°%, sediment 11°% and air 6°%). Henry's law constants of 8.59 Pa × m^3 mol^{-1} (calculated according to the Bond method) and of 0.23 Pa × m^3 mol^{-1} respectively (derived from water solubility and vapour pressure) indicate that the compound has a slight to moderate potential for volatilization from surface waters. These results should only be considered of theoretical interest since the calculation programs are adequate for substances which show stability in water. The calculated half-life of diphenyl carbonate in air due to indirect photodegradation is $t_{1/2}$ = 4.0 days. Due to the low absorption in the UV-B range, no direct photodegradation is expected.

Diphenyl carbonate is not readily biodegradable but biodegraded by adapted microorganisms. After 28 days 37 % of the test substance had been degraded in a closed bottle test (Directive 92/69/EEC, C.4-E). With adapted domestic sewage, more than 99 % of the test substance had been degraded after 20 days in another closed bottle test (OECD TG 301 D).

According to the bioconcentration factor BCF = 66.9, calculated from the octanol-water partition coefficient the substance has a low potential to bioaccumulate in aquatic organisms. With a calculated K_{oc} value of 3926, diphenyl carbonate could be regarded as a substance with high geoaccumulation properties. However, due to hydrolysis, geoaccumulation is not expected.

For fish (*Danio rerio)* the acute toxicity (LC_{50}, 96 h) of diphenyl carbonate (Directive 92/69/EEC, C.1) was 3.9 mg/l (effective concentration; nominal concentration: 10.0 mg/l). The acute toxicity (EC_{50}, 48 h) of diphenyl carbonate to the invertebrate *Daphnia magna* (Directive 92/69/EEC, C.2) was 6.5 mg/l (effective; nominal: 14.2 mg/l;). Concerning the algal toxicity (Directive 92/69/EEC, C.3), for *Desmodesmus subspicatus* a 72 h-E_rC_{50} of 0.9 mg/l (effective; nominal: 2.4 mg/l) for the growth rate and a 72 h-E_bC_{50} of 0.5 mg/l (effective; nominal: 1.4 mg/l) for the integral of biomass were determined. The corresponding 72 h-NOEC obtained from growth rate and biomass were 0.22 mg/l and 0.11 mg/l, respectively (effective; nominal 0.63 mg/l and 0.31 mg/l, respectively). The corresponding 72 h-LOEC obtained from growth rate and biomass were 0.44 mg/l and 0.22 mg/l, respectively (effective; nominal 1.25 mg/l and 0.63 mg/l, respectively).

Based on the lowest effect concentration observed for the algae a Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 1000. Using the effective 72 h-E_rC_{50} of 0.9 mg/l (growth rate) found for the algae species *Desmodesmus subspicatus* a $PNEC_{aqua}$ = 0.9 µg/l was determined.

5 RECOMMENDATIONS

Human Health:

The chemical is currently of low priority for further work because of its low hazard profile.

Environment:

The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by one producer which accounts for approximately 4 % to 20 % of global production and relating to the use pattern in several OECD countries), exposure to the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor.

6 REFERENCES

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I U C L I D

Data Set

Existing Chemical	:	ID: 102-09-0
CAS No.	:	102-09-0
EINECS Name	:	diphenyl carbonate
EC No.	:	203-005-8
TSCA Name	:	Carbonic acid, diphenyl ester
Molecular Formula	:	C13H10O3

Producer related part

Company	:	Bayer AG
Creation date	:	30.07.1992

Substance related part

Company	:	Bayer AG
Creation date	:	30.07.1992
Status	:	
Memo	:	AKTUELL ICCA
Printing date	:	14.07.2005
Revision date	:	20.05.1994
Date of last update	:	14.07.2005
Number of pages	:	69
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 : diphenyl carbonate
Smiles Code : C1=CC=CC(OC(=O)OC2=CC=CC=C2)=C1
Molecular formula : C13H10O3
Molecular weight : 214,22 g/mol
Petrol class :

Remark : The Smiles Code can also be written as: c1cccc (OC (=O) Oc2cccc2) c1
01.06.2004

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : organic
Physical status : solid
Purity : >= 99.5 % w/w
Colour : white
Odour : weak

Remark : substance is usually marketed in the form of flakes
Flag : Critical study for SIDS endpoint
13.07.2005 (1) (2)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

CARBONIC ACID, DIPHENYL ESTER

Flag : Critical study for SIDS endpoint

DIPHENYL CARBONATE

Flag : Critical study for SIDS endpoint

DPC

Flag : Critical study for SIDS endpoint
12.03.2004

PHENYL CARBONATE

12.03.2004

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No : 108-95-2
EC-No : 203-632-7
EINECS-Name : phenol
Molecular formula : C6H5OH
Value : <= .2 % w/w

Flag : Critical study for SIDS endpoint
25.05.2004 (1)

Purity : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name : ashes
Molecular formula :
Value : <= .02 g/kg

Flag : Critical study for SIDS endpoint
25.05.2004 (1)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : - tonnes in 2002

Result : In 2002, the world wide production capacity of diphenyl carbonate is estimated to be 254,000 metric tonnes (Western Europe 141,000, Japan 61,000, Far East (excl. Japan) 52,000) by about 10 producers
Flag : Critical study for SIDS endpoint
14.07.2005 (3)

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits :
Symbols : Xn, , ,
Nota : , ,
R-Phrases : (22) Harmful if swallowed
S-Phrases :

Flag : Critical study for SIDS endpoint
15.03.2004

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC

Class of danger : harmful
R-Phrases : (22) Harmful if swallowed
Specific limits :

Flag : Critical study for SIDS endpoint
15.03.2004

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Use in closed system

Remark : Diphenyl carbonate is listed in the Danish, Finnish, Norwegian, and Swedish Product Registers as product with industrial applications.
For Denmark, four industrial preparations with a consumption of 0.0 tonnes/a are listed in 2001. No consumer application is registered. In 2002, five industrial products with a content of diphenyl carbonate of 0-2 % and a quantity of < 1 tonnes/a are registered.
Diphenyl carbonate is used in closed systems.

Flag : Critical study for SIDS endpoint
23.09.2004 (4)

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

Flag : Critical study for SIDS endpoint
08.06.2004 (5)

Type of use : use
Category : Intermediates

Flag : Critical study for SIDS endpoint
12.07.2005 (5) (6)

Type of use : use
Category :

Remark : In Buysch (2002) several direct uses are reported: All of the main simple carbonates - DMC [dimethyl carbonate], DEC [diethyl carbonate], EC [ethylen carbonate], PC [propylen carbonate] and even DPC [diphenyl carbonate] in the molten state - are excellent solvents for a variety of substances such as cellulose ethers and esters [26], [454-456], pharmaceutical and cosmetic preparations [458-465], natural and synthetic resins and polymers [5], and salts.
This information is not consistent with the literature cited (see below). Only one of the references covers diphenyl carbonate (Lewis 1997), and it is assumed that diphenyl carbonate is not used as a solvent.

Compilation of results of literature review:
Diphenyl carbonate use as solvent for cellulose ethers and esters
- Ref. 26 Shaikh + Sivaram 1996: Only some dialkyl carbonates are mentioned as solvents
- Ref. 454 Hawley 1987 Hawley 13th edition (= Lewis 1997) cites use as a solvent in a general context, without focussing on cellulose ethers and esters and without quoting any reference.

- Ref. 455 Kirk-Othmer (4th ed.) 1993 The only use of diphenyl carbonate mentioned (p. 94) is the preparation of polycarbonate resins by transesterification
- Ref. 456 Lenga (Sigma-Aldrich data sheets) Does not contain any information on use of diphenyl carbonate!

Diphenyl carbonate use as solvent for pharmaceutical and cosmetic preparations
- Ref. 458 Manufacturing Chemist 1992 Only use of propylen carbonate is mentioned. Reference does not contain any information on use of diphenyl carbonate!
- Ref. 459 Soap Perfumery and Cosmetics (2 references) 1992 and 1998 Both references cannot be obtained (presumably advertisemant page - citation not correct)
- Ref. 460 Bresciani 1993 (US patent) Describes a method to produce acrylic acid polymers/copolymers to use as polymeric thickening agent for cosmetics. During the synthesis of the thickener (only) dialkyl carbonates are used. Diphenyl carbonate is not mentioned (e.g. column 6)
- Ref. 461 Lang et al. 1992 GBF monogr. The isolation and inhibition of luciferase is described. Luciferase is used as an analytical tool in medical laboratories. No reference to diphenyl carbonate found.
- Ref. 462 Lang et al. 1992 Enzyme Microb. Tech. The isolation and inhibition of luciferase is described. No reference to diphenyl carbonate found (the only organic carbonate mentioned is diethyl carbonate).
- Ref. 463 Terrell et al. 1993 Inhibition of yeast by dimethyldicarbonate (a cold sterilant) was examined! No reference to diphenyl carbonate found (or other carbonates mentioned in Buysch 2002)
- Ref. 464 Bialer et al. 1994 Application of a specific organic carbonate as a prodrug! No reference to diphenyl carbonate found
- Ref. 465 Samara et al. 1995 Pharmakokinetic analysis of 2 prodrugs which have been synthesized using diethylcarbonate! No reference to diphenyl carbonate found
- Additional ref. INCI and Inventory of fragrance ingredients (perfume and aromatic raw materials) INCI and the Inventory of fragrances are the most relevant sources for cosmetic ingredients in Europe. They do not mention diphenyl carbonate. Thus, diphenyl carbonate is not used in cosmetics produced in the EU
- Additional ref. WHO (2003) The International Pharmacopoeia 5th ed. Diphenyl carbonate is not mentioned in the index!

Diphenyl carbonate use as solvent for natural and synthetic resins and polymers
- Ref. 5Jefferson Chem. Comp. Techn. Bulletin 1960 Presumably company brochure, cannot be obtained

Diphenyl carbonate use as solvent for salts
No citation At room temperature diphenyl carbonate is a solid compound. Application of diphenylcarbonate as a solvent is not known to experts.

Flag : Critical study for SIDS endpoint
18.06.2004 (7) (8) (9) (10) (5) (11) (12) (13) (14) (15) (16) (17) (18)

Type of use : use
Category :

Remark : Diphenyl carbonate is reportedly used as a solvent for nitrocellulose (Merck Index, 2001). No reference for this information was presented by the authors of the Merck Index, and the reliability of this statement remains therefore unclear. Other authors (Kirk-Othmer, 2003; Shaikh and Sivaram, 1996) report the use of diethyl carbonate and higher dialkyl carbonates, but not of diphenyl carbonate as solvents for (nitro)cellulose ethers and esters.

Flag : Critical study for SIDS endpoint

12.07.2005 (6) (19) (20)

Type of use : use
Category : Intermediates

Result : Diphenyl carbonate is a chemical intermediate. It is mainly used for the synthesis of thermoplastic aromatic polycarbonates through transesterification of bisphenols. Beside this it is an intermediate for the production of aliphatic polycarbonates and of carbonates. Lower-mass aliphatic mono-isocyanates, especially methyl isocyanate, which is further used in the synthesis of crop protection agents, are produced by treating diphenyl carbonate with aliphatic amines, followed by cleavage of the obtained phenyl urethane

13.07.2005 (21)

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : other: TLV in Belgium for respirable fine dust
Limit value : 3 mg/m3

Remark : In Belgium there is no exposure limit value designated for diphenyl carbonate.
Flag : Critical study for SIDS endpoint
08.06.2004 (3)

Remark : no occupational exposure limits established
15.03.2004

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 1 (weakly water polluting)

Remark : Kenn-Nummer 1227
15.03.2004

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation :
Substance listed : no
No. in Seveso directive :

1.8.5 AIR POLLUTION

Classified by : other: no classification
Labelled by :
Number :
Class of danger :

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

Type : degradation product in water
CAS-No : 108-95-2
EC-No : 203-632-7
EINECS-Name : phenol
IUCLID Chapter : 3.1.2

Flag : Critical study for SIDS endpoint
01.06.2004 (22)

Type : degradation product
CAS-No : 124-38-9
EC-No : 204-696-9
EINECS-Name : carbon dioxide
IUCLID Chapter : 3.1.2

Flag : Critical study for SIDS endpoint
25.05.2004 (22)

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 : 08.10.2003

Flag : Critical study for SIDS endpoint
12.03.2004

Type of search : Internal and External
Chapters covered : 2
Date of search : 08.10.2003

Flag : Critical study for SIDS endpoint
12.03.2004

Type of search : Internal and External
Chapters covered : 3, 4
Date of search : 08.10.2003

Flag : Critical study for SIDS endpoint
12.03.2004

Type of search : Internal and External
Chapters covered : 5
Date of search : 22.01.2004

Remark : Human health: CAS-No. search in external and internal data bases, e.g. Biosys, Embase, Toxline, Scisearch
Flag : Critical study for SIDS endpoint
12.03.2004

1.13 REVIEWS

Memo : EU Risk Assessment "Phenol" - not yet published

23.11.2000

Memo : BUA Report No. 209 "Phenol", VCH, 1997

23.11.2000

2.1 MELTING POINT

Value : 78.8 °C
Sublimation :
Method :
Year : 2002
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Remark : A similar melting point is reported by Lewis and in the Bayer MaterialScience MSDS
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data, weight of evidence
Flag : Critical study for SIDS endpoint
25.05.2004 (23)

Value : 70 - 88 °C
Sublimation :
Method :
Year : 2003
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Remark : Beilstein reports several melting points in the range of 70 to 88 °C.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
26.05.2004 (24)

Value : 80 - 81 °C
Sublimation :
Method :
Year : 2001
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
26.05.2004 (19)

Value : 83 °C
Sublimation :
Method :
Year : 1992
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Remark : Another melting point of 88° is reported.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
26.05.2004 (25)

Value : 78 °C
Sublimation :
Method :
Year : 1993
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
03.06.2004 (14)

2.2 BOILING POINT

Value : 302 °C at 1013 hPa
Decomposition :
Method :
Year : 2002
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Remark : A similar boiling point is reported by Lewis and in the Bayer MaterialScience MSDS
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data, weight of evidence
Flag : Critical study for SIDS endpoint
12.07.2005 (23)

Value : 302 °C at 1013 hPa
Decomposition :
Method :
Year :
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Result : Beilstein's reports several boiling point values:

Pressure (hPa)	Boiling point (°C)
1013	302
1014	309
31	190
20	167-168

Reliability : (2) valid with restrictions
Data from handbook or collection of data
12.07.2005 (24)

Value : 306 °C at 1013 hPa
Decomposition :
Method :
Year : 1992
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Remark : Another boiling point of 168° at 20 hPa is reported.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
12.07.2005 (25)

Value : 302 °C at 1013 hPa
Decomposition :
Method :
Year : 1993
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
12.07.2005 (14)

Value : 302 - 306 °C at 1013 hPa
Decomposition :
Method :
Year : 2001
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Remark : Another boiling point of 168° at 20 hPa is reported.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
12.07.2005 (19)

2.3 DENSITY

Type : density
Value : g/cm³ at °C
Method :
Year : 2003
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Result : 1.272 g/cm³ at 14 °C (solid)
1.1032 g/cm³ at 100 °C (liquid)
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
12.07.2005 (24)

Type : relative density
Value : at °C
Method :
Year : 2003
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Result : 1.1215 at 87 °C
1.0997 at 111 °C
1.069 at 145 °C
Reliability : (2) valid with restrictions
Data from handbook or collection of data
12.07.2005 (24)

Type : relative density
Value : 1.1215 at 87 °C
Method :
Year : 1992
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
12.07.2005 (25)

Type : relative density
Value : 1.1215 at 87 °C
Method :
Year : 1993
GLP :
Test substance : other TS: Diphenyl carbonate, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
12.07.2005 (14)

Type : bulk density
Value : ca. 550 kg/m3 at °C
Method :
Year :
GLP :
Test substance : other TS: Diphenyl carbonate

Reliability : (4) not assignable
Manufacturer data without proof
12.07.2005 (2)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : .00014 hPa at 20 °C
Decomposition :
Method : Directive 92/69/EEC, A.4
Year : 1998
GLP : no
Test substance : other TS: Diphenyl carbonate, purity is not specified

Method : The vapour pressure of diphenyl carbonate was determined according to a dynamic method (Official Journal of the European Communities L 338A (1992), A4. 1.6.) for a range of temperatures between 161 °C and 312 °C.
- Measuring apparatus consists of a boiling vessel with an attached cooler, an equipment for measuring the temperature and equipment for adjusting (including vacuum pump) and measuring the pressure
- The vapour pressure is determined by measuring the boiling point of the substance at different pressures. A constant temperature at constant pressure indicates that the boiling point has been reached at the respective pressure
- The results were correlated according to Antoine equation. The following equation was obtained:
log (P)= 7.303457-2044.046/(T+163.156) where P is given in hPa and T in °C.
- The vapour pressure at temperatures of 20, 40 and 60 °C was calculated

Result : .00014 hPa at 20 °C
.0017 hPa at 40 °C
.014 hPa at 60 °C

The vapour pressure at temperatures of 20, 40 and 60 °C was calculated. The vapour pressure of diphenyl carbonate was determined according to a dynamic method (Official Journal of the European Communities L 338A (1992)) for a range of temperatures between 161 °C and 312 °C. The results were correlated according to Antoine equation. The following equation was obtained:
log (P)= 7.303457-2044.046/(T+163.156) where P is given in hPa and T in °C.

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
Flag : Critical study for SIDS endpoint
12.07.2005 (26) (27)

Value	:	.0002 - .00053 hPa at 25 °C
Decomposition	:	
Method	:	other (calculated): EPIWIN MPBPWIN v1.41
Year	:	2005
GLP	:	no
Test substance	:	
Remark	:	Lower value is experimental data base (no reference reported), higher value is calculated by the modified Grain Method
Reliability	:	(2) valid with restrictions

13.07.2005 (28)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	3.21 at 25 °C
pH value	:	7.4
Method	:	other (measured): Microemulsion electrokinetic chromatography
Year	:	2003
GLP	:	no data
Test substance	:	other TS: Diphenyl carbonate, Aldrich-Chemie
Method	:	- Microemulsion electrokinetic chromatography was used as an alternative to the shake-flask method using migration indices for estimation of log Kow. - Capillary electrophoresis was performed on a Beckman instrument. UV detection was performed at 214 nm. - The capillary chamber temperature was set to 25 °C. - Microemulsions containing 1.44-2.88 % sodium dodecyl sulfate, 6.49 % 1-butanol, and 0.82 % n-heptane were a good model of octanol-water partitioning for neutral solutes in the pH range of 1.4 - 7.4. -The relationship between migration index (Mi) and log Kow is: log Kow = 0.549 Mi - 1.17. -The correlation obtained between MI and log Kow was uneffected by pH and, thus, indicating partitioning are independent of pH. -The MEEKC method used does not require the tested solutes to be stable and pure, thus, MEEKC is well suited to study the partitioning of unstable compounds like carbonate esters
Remark	:	Not stable in water due to hydrolysis, see Chapter 3.1.2.
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles
Flag	:	Critical study for SIDS endpoint

29.01.2004 (29)

Partition coefficient	:	octanol-water
Log pow	:	3.28 at 25 °C
pH value	:	
Method	:	other (measured)
Year	:	1989
GLP	:	
Test substance	:	other TS: Diphenyl carbonate, purity is not specified
Remark	:	Not stable in water due to hydrolysis, see Chapter 3.1.2. In the reference (Sangster, 1989) a compilation of log Kow values obtained from literature search is presented and the data evaluated. The basis of the literature search was the Pomona College log Kow database, created by Hansch and Leo. According Table 20 (page 1226) the log Kow was determined via a direct method (shake flask or generator column; no further information). The log Kow value recommended for diphenyl carbonate is 3.28.

Result	:	The source of the value of log Kow for diphenyl carbonate was given in the literature as unpublished data collected by Dr. Hansch and Dr. Leo responsible for the Database of log Kow of the Pomona College Medical Chemistry Project.
Reliability	:	(2) valid with restrictions Data from handbook or collection of data
Flag	:	Critical study for SIDS endpoint

13.07.2005 (30)

Partition coefficient	:	octanol-water
Log pow	:	3.21 at 25 °C
pH value	:	
Method	:	other (calculated): EPIWIN KOWWIN v1.67
Year	:	2005
GLP	:	no
Test substance	:	
Remark	:	Not stable in water due to hydrolysis, see Chapter 3.1.2.
Reliability	:	(2) valid with restrictions Accepted calculation method

13.07.2005 (28)

Partition coefficient	:	octanol-water
Log pow	:	3.28 at °C
pH value	:	
Method	:	other (measured): Polarographic method
Year	:	1972
GLP	:	no
Test substance	:	other TS: Diphenyl carbonate, purity is not specified
Remark	:	Not stable in water due to hydrolysis, see Chapter 3.1.2. Hansch, Leo, and Hoekman cite Butkiewicz K (1972) Elektroanalytical Chemistry 39, 407 and 419.
Reliability	:	(2) valid with restrictions Data from peer-reviewed handbook or collection of data

13.07.2005 (31)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	ca. 13 mg/l at 20 °C
pH value	:	7.1
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	no
Deg. product	:	yes
Method	:	Directive 92/69/EEC, A.6
Year	:	2000
GLP	:	yes
Test substance	:	other TS: Diphenyl carbonate, purity = 99.98%
Remark	:	It is concluded that due to the fact that the substance hydrolyses in water, the determination of the water solubility with this method is not appropriate. The stability of the concentrations despite degradation of the test substance due to hydrolysis can be explained by the fact, that additional test substance is dissolved from the undissolved substance (see

Chapter 3.1.2)

Result : Test substance hydrolyses in water generating phenol and carbon dioxide.
The measured concentrations of the test substance in water and the corresponding pH-values were:
F1: 12.9 mg/l, pH=7.2
F2: 13.0 mg/l, pH=7.1
F3: 13.3 mg/l, pH=7.0

Test condition : Three flasks (F1, F2 and F3) were filled with solutions of diphenyl carbonate in the concentrations: 499, 510 and 505 mg/l respectively.
Flasks were agitated according to the following procedure:

F1: 24 h at 30 °C and 24 h at 20 °C
F2: 48 h at 30 °C and 24 h at 20 °C
F3: 72 h at 30 °C and 24 h at 20 °C

Reliability : (2) valid with restrictions
Reliable with restrictions

Flag : Critical study for SIDS endpoint

13.07.2005 (32)

Solubility in : Water
Value : 13.9 - 67 mg/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : slightly soluble (0.1-100 mg/L)
Stable :
Deg. product :
Method : other: (calculated) EPIWIN WSKOW v1.41
Year : 2005
GLP : no
Test substance :

Remark : Not stable in water due to hydrolysis, see Chapter 3.1.2.

Result : Water solubility estimate from log Kow 3.28 (melting point 83 °C): 46.65 mg/l
(equation used: log water solubility (mol/l) = 0.693 - 0.96 log Kow - 0.0092 (Tm-25) - 0.00314 MW (Tm: 25))
Water solubility estimate from log Kow 3.28 (no-melting point equation used): 58.37 mg/l
Water solubility estimate from log Kow 3.21 (no-melting point equation used): 66.99 mg/l
Water solubility estimate from fragments: 13.853 mg/l

Reliability : (2) valid with restrictions
Accepted calculation method

13.07.2005 (28)

Remark : Test substance soluble in:
hot alcohol, benzene, ether, glacial acetic acid.

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

01.06.2004 (19)

Remark : Test substance soluble in:
acetone, hot alcohol, benzene, carbon tetrachloride, ether, glacial acetic acid and other organic solvents.

Reliability : (4) not assignable

Data from non peer-reviewed handbook or collection of data
03.06.2004 (14)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : 168 °C
Type : closed cup

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
18.01.2004 (23)

2.8 AUTO FLAMMABILITY

Value : ca. 620 °C at
Method : other: DIN 51794
Year : 2003
GLP : no data
Test substance : other TS: Diphenyl carbonate, purity is not specified

Reliability : (4) not assignable
Manufacturer data without proof
Flag : Critical study for SIDS endpoint
26.05.2004 (2)

2.9 FLAMMABILITY

16.02.2004

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm³
Rate constant	:	.0000000000040219 cm³/(molecule*sec)
Degradation	:	50 % after 4 day(s)
Deg. product	:	
Method	:	other (calculated): with SRC-AOPWIN v. 1.91 (2000)
Year	:	2003
GLP	:	
Test substance	:	other TS: Diphenyl carbonate
Remark	:	In deviation from the U.S. EPA AOPWIN (calculation program) the calculated half-life is based on a mean OH radical concentration of 5E+05 OH radicals/cm3 as a 24 h average.
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

13.07.2004 (33)

Type	:	air
Light source	:	Sun light
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: Diphenyl carbonate, purity 99 %, sublimed three times
Remark	:	Expert judgement from the spectra given in the study of Hoyle et al., 1995.
Result	:	Due to the low absorption in the UV-B range, no direct photodegradation of diphenyl carbonate is expected
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint

15.06.2004 (34)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	= 61.8 hour(s) at 25 °C
t1/2 pH7	:	= 39.9 hour(s) at 25 °C
t1/2 pH9	:	= .2 hour(s) at 50 °C
Deg. product	:	yes
Method	:	Directive 92/69/EEC, C.7
Year	:	2001
GLP	:	yes
Test substance	:	other TS: Diphenyl carbonate, purity = 99.98 %
Deg. products	:	108-95-2 phenol 124-38-9 204-696-9 carbon dioxide
Result	:	- At pH 9 and 50 °C a fast degradation was observed. Within

about 40 minutes the concentration of diphenyl carbonate decreased to less than 7 %. During this time just 4 analytical determinations were possible. Assuming a pseudo-first order reaction the half-life value of 0.15 hours was calculated.
- At pH 7 and pH 4 degradation was observed at 30 and 50 °C. According to the Arrhenius equation the half-life time and the rate constant (first order reaction) at 25 °C was calculated.
- The test substance is degradable at pH 9, pH 7, and pH 4.

Test condition : - Test solutions were analysed by HPLC
- Initial concentration of diphenyl carbonate in test solution was about 10 mg/l
- Determinations were performed at 50 °C and at 30 °C for pH 4, 7, and 9

Reliability : (1) valid without restriction
GLP guideline study

Flag : Critical study for SIDS endpoint

26.05.2004 (35)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
t1/2 pH : 73.5 hour(s) at 23 °C
Deg. product : yes
Method : other:
Year : 2000
GLP : no
Test substance : other TS: Diphenyl carbonate, purity is not specified
Deg. products : 108-95-2 203-632-7 phenol
124-38-9 204-696-9 carbon dioxide

Method : - A saturated solution of diphenyl carbonate in water was stirred at room temperature (23 °C) for 48 h.
- The separation of phases proceeded by centrifugation 2 times each time 10 minutes at 23 °C and 5000 U/min.
- Regularly, the concentration of diphenyl carbonate was determined by HPLC.
- The initial concentration was 14.9 mg/l.

Remark : Diphenylcarbonat hydrolyses in water forming phenol and CO2

Result :

t (h)	C (mg/l)	Ct/C0 (%)
0	14.9	100
15.8	12.9	86.6
86.5	6.3	42.3
94.7	5.7	38.3
137.8	4	26.8
159.8	3.3	22.1
183.9	2.3	15.4
255.9	1.4	9.4

t1/2= 73,5 h

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

Flag : Critical study for SIDS endpoint

03.06.2004 (22)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

Type of measurement	:	background concentration
Media	:	other: acetonitrile eluates from polycarbonate products like dishes
Concentration	:	
Method	:	
Result	:	Diphenyl carbonate was not detectable in eluates from 12 out of 14 polycarbonate products. In two products (dishes, cups) diphenyl carbonate concentrations of 225 ± 6.8 mg/kg and 79 ± 4.6mg/kg were measured after elution with acetonitrile
Reliability	:	(4) not assignable Original reference not translated
Flag	:	Critical study for SIDS endpoint

13.07.2005 (36)

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	:	other:QSAR Estimation Method: PCKOCWIN v.1.66 (2000)
Year	:	2003
Remark	:	The calculated value reflects the properties of the undissociated molecule without taking into account the sensitivity of diphenyl carbonate towards hydrolysis.
Result	:	Koc =3926
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

13.07.2004 (33)

Type	:	volatility
Media	:	water - air
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: QSAR Estimation Method: HENRYWIN v. 3.10 (2000)
Year	:	2003
Remark	:	The calculated value reflects the properties of the undissociated molecule without taking into account the sensitivity of diphenyl carbonate towards hydrolysis.
Result	:	8.59 Paxm3/mol (Bond method) Results at 25°C
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

13.07.2004 (33)

Type	:	volatility
Media	:	water - air
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: Calculation from the ratio of the vapour pressure to the water solubility
Year	:	2003
Method	:	Chemical data used in the calculation: Water solubility: 13 mg/l Vapour pressure: 0.014 Pa Values at 20 °C
Remark	:	The calculated value reflects the properties of the undissociated molecule without taking into account the sensitivity of diphenyl carbonate towards hydrolysis.
Result	:	0.23 Paxm3/mol Result at 20 °C
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

13.07.2004 (33)

3.3.2 DISTRIBUTION

Media	:	air - biota - sediment(s) - soil - water
Method	:	Calculation according Mackay, Level I
Year	:	2003
Method	:	Chemical data used in the calculation: - Temperature (°C) = 20 - Molar Mass (g/mol) = 214.22 - Vapour Pressure (Pa) = 0.014 - Water Solubility (mg/l) = 13 - log Kow = 3.28 - Melting point = 78.8°C

Phase properties and composition of the compartments:

	Volumina (m3)	Density (kg/m3)	Organic Carbon (%)
Air:	6.0 E+09	1.206	
Water:	7.0 E+06	1000	
Soil:	4.5 E+04	1500	2
Sediment:	2.1 E+04	1300	5
Susp. Sed.:	3.5 E+01	1500	16.7
Aerosol:	1.2 E-01	1500	
Aquatic Biota:	7.0 E+00	1000	5*

*lipid content

Calculation was performed according to the model described in the first publication of Mackay (1991). Phase properties and composition of the compartments were modified as suggested by the Federal Environmental Agency (UBA, Germany).

Remark	:	These results should be only considered of theoretical interest since the Mackay Fugacity Model is just adequate for substances which show

stability in water (see Chapter 3.1.2).

Result : Based on the model calculations (Mackay level I, v. 2.11) the target compartment of the environmental distribution of diphenyl carbonate (Cas No. 102-09-0) is the hydrosphere.
Water: 72.18 %
Air: 5.86 %
Sediment: 11.0 %
Soil: 10.88 %
Susp. Sed.: 0.0706 %
Aerosol: 0.0129 %
Aquatic Biota: 0.0069 %

Reliability : (2) valid with restrictions
Accepted calculation method

Flag : Critical study for SIDS endpoint

13.07.2005 (33)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : 3.3 mg/l related to Test substance
related to
Contact time : 28 day(s)
Degradation : 37 (±) % after 28 day(s)
Result : other: not readily biodegradable
Deg. product : not measured
Method : Directive 92/69/EEC, C.4-E
Year : 2000
GLP : yes
Test substance : other TS: Diphenyl carbonate, purity = 99.98 %

Result : The amount of oxygen taken up by the test substance is expressed as a percentage of ThOD.

Test condition : - The solution of the test chemical in mineral medium is inoculated with microorganisms from a mixed population and kept in closed bottles in the dark at constant temperature of 20 +/- 1°C
- Further, an inoculum blanc and a toxicity test, containing both the test substance at a concentration of 3.3 mg/l and the reference substance at a concentration of 2.9 mg/l were carried out under the same conditions
- Degradation is followed by analysis of dissolved oxygen over a 28-day period
- As reference substance sodium benzoate at a concentration of 2.9 mg/l releted to the reference substance was used
- Measurements of oxygen consumption were carried out after 0, 7, 13, 21 and 28 days
- Degradation of the reference substance has reached the level for ready biodegradability by 13 days. In the toxicity test, containing both the test substance and the reference substance, more than 25 % (based on ThOD) occurred in 13 days. The quality criteria for 14 days are already fulfilled in 13 days. Since the duration of the test is 28 days, there is no influence on the result of the test

Reliability : (1) valid without restriction
GLP guideline study

Flag : Critical study for SIDS endpoint

19.02.2004 (37)

Type	:	aerobic
Inoculum	:	predominantly domestic sewage, adapted
Concentration	:	2.4 mg/l related to COD (Chemical Oxygen Demand) related to
Contact time	:	
Degradation	:	> 99 (±) % after 20 day(s)
Result	:	other: biodegradable
Kinetic of testsubst.	:	5 day(s) ca. 40 % 10 day(s) ca. 97 % 20 day(s) > 99 % % %
Deg. product	:	not measured
Method	:	other: Closed Bottle Test, comparable to OECD TG 301 D
Year	:	1979
GLP	:	no
Test substance	:	other TS: Diphenyl carbonate, purity = 99.9 %
Remark	:	- Related to BOD - pH 7.4
Reliability	:	(2) valid with restrictions Guideline study without detailed documentation
Flag	:	Critical study for SIDS endpoint

14.06.2004 (38)

Type	:	aerobic
Inoculum	:	activated sludge, adapted
Concentration	:	833 mg/l related to related to
Contact time	:	
Degradation	:	100 (±) % after 2.7 day(s)
Result	:	other: primary degradation
Deg. product	:	
Method	:	other: description under Test Conditions
Year	:	1989
GLP	:	no
Test substance	:	other TS: Diphenyl carbonate, purity is not specified
Result	:	Enriched mixed cultures and the isolated strain Acinetobacter calcoaceticus showed good growth in the presence of Diphenyl carbonate. - Degradation/hydrolysis was complete after 65 h
Test condition	:	- For enrichment 500 ml Erlenmeyer flasks containing 100 ml liquid mineral medium (M9) were used. - Phenyl-2-octyl carbonate served as sole carbon and energy source and was supplied directly to the medium at 0.1 % (w/v). - Activated sludges from a waste water treatment plant were used as inoculum. - The cultures were incubated by shaking at 30 °C. - For isolation serial dilutions were plated on Difco nutrient agar and incubated at 30 °C. -Test substance was added to the enriched mixed culture at a concentration of 50 mg to 60 ml M9 mineral medium (test concentration = 833 mg/l).
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint

02.07.2004 (39)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF	:	66.9
Elimination	:	
Method	:	other: QSAR Estimation Method: BCFWIN v. 2.15 (2000)
Year	:	2003
GLP	:	
Test substance	:	other TS: Diphenyl carbonate, purity is not specified
Remark	:	Calculation of BCF unsuitable for diphenyl carbonate. The calculated theoretical value reflects the undissociated molecule without influence of water.
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

13.07.2004 (33)

3.8 ADDITIONAL REMARKS

Memo	:	EU Directive on plastic materials and articles intended to come into contact with foodstuffs
Result	:	The use of diphenyl carbonate is restricted to a maximum limit of migration of 0.05 mg/kg of food
Reliability	:	(2) valid with restrictions Reliable source
Flag	:	Critical study for SIDS endpoint

13.07.2005 (40)

Memo	:	EU on safety of monomers and additives for food contact materials
Result	:	In 2003, the European Scientific Committee on Food (SCF) evaluated the use of diphenyl carbonate in polycarbonate for food contact materials. Migration of diphenyl carbonate was determined in 3 % acetic acid, 10 % ethanol and HB 307. Diphenyl carbonate hydrolyses in aqueous food simulants into phenol and carbon dioxide. Migration of diphenyl carbonate was not detectable at levels of approximately 0.05 mg/kg food simulant (6 dm2/kg). Phenol was detected in 3 % acetic acid (0.16 mg/kg) and in 10 % ethanol (0.2 mg/kg) after a contact period of 2 h at 100 °C. Most likely the polycarbonate is hydrolysed at the high temperature conditions. Based on the results from the required tests on physical chemical properties, as well as on the migration and mutagenicity data, the Scientific Committee on Food classified diphenyl carbonate in "List 3", i.e. substances for which an ADI or TDI could not be established, but where the present use could be accepted due to a very low migration. The use was, therefore, restricted to a maximum limit of migration of 0.05 mg/kg of food
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint

13.07.2005 (41)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	3.16
LC100	:	31.6
Geom. Mean	:	10 calculated
Effective LC50	:	3.9 calculated
Limit test	:	
Analytical monitoring	:	no
Method	:	Directive 92/69/EEC, C.1
Year	:	1994
GLP	:	no
Test substance	:	other TS: Diphenyl carbonate, purity is not specified
Remark	:	The toxicity of the hydrolysis product phenol might have influenced the testing. Accepted new scientific name for Brachydanio rerio: Danio rerio.
Result	:	At a test substance concentration of 31.6 mg/l already 9 fish were dead after a period of 48 h. At a nominal concentration of 10 mg/l 2 fishes died after a period of 96 h. Due to the hydrolyses of diphenyl carbonate in the presence of water, forming phenol and carbon dioxide, the effective concentrations of diphenyl carbonate are estimated for each test concentration. With the assumption that the half-life of diphenyl carbonate is about 40 hours under abiotic conditions in a buffered medium, and a water solubility of 13 mg/l, the geometric mean over time (inclusive 24 hours of stirring before the test) is 5.6 mg/l, 2.9 mg/l and 0.91 mg/l at the nominal test concentrations of 31.6 mg/l, 10 mg/l and 3.16 mg/l. By graphic interpolation (linear) the resulting effective 96 h LC50 is 3.9 mg/l
Test condition	:	- The test was conducted in 300mmx135mmx200mm aquaria with 5 l test medium - Recipients were constantly aerated with air - 10 fishes were used at each concentration. Length: 2.5-3.5 cm - Fish were submitted to a regime of 16 h light / 8 h dark - The following nominal concentrations were tested: 3.16, 10.0, 31.6 mg/l - The necessary amount of test substance was first dissolved in water and stirrer with a magnetic stirrer during 24 h. The suspension was filtered in order to remove the undissolved particles - The test temperature was 21.3+/-0.45 °C; the pH-value was 7.9+/-0.2, the oxygen concentration varied between 8.4 and 9.7 mg/l during the tests
Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions
Flag	:	Critical study for SIDS endpoint

13.07.2005 (42)

Type	:	other: Estimation
Species	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	7.3
Method	:	other: (calculated) EPIWIN ECOSAR (v0.99h)
Year	:	2005
GLP	:	no
Test substance	:	
Remark	:	This estimate is generally consistant with the available experimental data
Reliability	:	(2) valid with restrictions

Accepted calculation method
13.07.2005 (28)

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	72 hour(s)
Unit	:	mg/l
LC0	:	200
Limit test	:	
Analytical monitoring	:	no
Method	:	other: DIN-Standard 38412 Part 15 (Fish, Acute toxicity test)
Year	:	1979
GLP	:	no
Test substance	:	other TS: Diphenyl carbonate, purity = 99.9 %
Method	:	Method of the German Standards Institution, Berlin, Germany
Result	:	At a nominal concentration of 500 mg/l both fish were dead after 20 h
Test condition	:	- The test was conducted with 2 fish for each concentration - 2 tests were carried out: A 20 h test at a concentration of 500 mg/l and a 72 h test at a concentration of 200 mg/l
Reliability	:	(4) not assignable Documentation insufficient for assessment

13.07.2005 (43)

Type	:	
Species	:	Cyprinus carpio (Fish, fresh water)
Exposure period	:	5 day(s)
Unit	:	
NE	:	122 - 215
Limit test	:	
Analytical monitoring	:	no
Method	:	other: not specified
Year	:	1963
GLP	:	no
Test substance	:	other TS: Diphenyl carbonate, purity is not specified
Method	:	- A method for forced-feeding was developed according to which the carps were immobilized in a nose-up position by a specially constructed device employing foam rubber jaw and activated by compressed air. - The chemicals to be tested were placed in one or two gelatin capsules by means of an eyedropper or draw glass funnel. - The basic objective of the force-feeding program was to discover compounds that were lethal at low doses of 30 mg or less of compounds per kg of body weight. - The test fish were removed from 8.3 °C (47 °F) water, forced fed, tagged and placed in 18.3 °C (65 °F) running water for observation. - Fish that had been forced-fed with one chemical were often held with fish that contained other chemicals. The mixing method was considered suitable since interesting chemicals were retested on isolated fish. -If a fish acted or looked other than normal it was considered to be sick. If no movement occured it was recorded as dead.
Remark	:	Dissection showed that gelatin capsules held disintegrated in the fishes at 18.3 °C (65 °F) for approximately 1 h.
Result	:	The effect concentration (NE= No effect) is given in mg/kg body weight.
Reliability	:	(4) not assignable Documentation insufficient for assessment

13.07.2005 (44)

Type	:	static
Species	:	Salmo gairdneri (Fish, estuary, fresh water)
Exposure period	:	24 hour(s)
Unit	:	mg/l

NOEC	:	< 5
LOEC	:	<= 5
Limit test	:	
Analytical monitoring	:	no
Method	:	other: see Test conditions
Year	:	1957
GLP	:	no
Test substance	:	other TS: Diphenyl carbonate, purity is not specified
Remark	:	The time necessary to produce death or obvious distress of the fish was determined and the results presented are an average response for each species.
Result	:	Effects were observed at 5 hours test duration
Test condition	:	- Length of fish was about 10 cm - 2 specimens were used - The test animals were placed in a 10 l glass jar containing 5 l of water - The jar was aerated (at near oxygen saturation) and a constant temperature (+/- 1 °F) was maintained - Just one concentration was tested (5 mg/l)
Reliability	:	(4) not assignable Documentation insufficient for assessment

13.07.2005 (45)

Type	:	static
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	24 hour(s)
Unit	:	mg/l
NOEC	:	< 5
LOEC	:	<= 5
Limit test	:	
Analytical monitoring	:	no
Method	:	other: see Test conditions
Year	:	1957
GLP	:	no
Test substance	:	other TS: Diphenyl carbonate, purity is not specified
Remark	:	The time necessary to produce death or obvious distress of the fish was determined and the results presented are an average response for each species. In this case only illness of the test species was observed.
Result	:	Results refers to nominal concentration being the endpoint distress. Effects were observed at 15 minutes test duration.
Test condition	:	- Length of fish was about 10 cm - 2 specimens were used - The test animals were placed in a 10 l glass jar containing 5 l of water - The jar was aerated (at near oxygen saturation) and a constant temperature (+/- 1 °F) was maintained - Just one concentration was tested (5 mg/l)
Reliability	:	(4) not assignable Documentation insufficient for assessment

13.07.2005 (45)

Type	:	static
Species	:	Petromyzon marinus
Exposure period	:	24 hour(s)
Unit	:	mg/l
LC0	:	5
Limit test	:	
Analytical monitoring	:	no
Method	:	other: see Test conditions
Year	:	1957
GLP	:	no
Test substance	:	other TS: Diphenyl carbonate, purity is not specified

Remark	:	The time necessary to produce death or obvious distress of the fish was determined and the results presented are an average response for each species.
Result	:	Result refers to nominal concentration being the endpoint death.
Test condition	:	- Larval lamprey varied from 8 to 13 cm. - 2 specimens were used. - The test animals were placed in a 10 l glass jar containing 5 l of water. - The jar was aerated (at near oxygen saturation) and a constant temperature (+/- 1 °F) was maintained. - Just one concentration was tested (5 mg/l). - Total duration of the test was 24 h.
Reliability	:	(4) not assignable Documentation insufficient for assessment

13.07.2005 (45)

Type	:	static
Species	:	other: see Remark
Exposure period	:	24 hour(s)
Unit	:	mg/l
Limit test	:	
Analytical monitoring	:	no
Method	:	other: see Test conditions
Year	:	1969
GLP	:	no
Test substance	:	other TS: Diphenyl carbonate, purity is not specified
Method	:	The relative toxicity of diphenyl carbonate lethal to species of freshwater fish is reported. The test criteria is the exposure time at which loss-of-equilibrium and death occurred.
Remark	:	Following species were tested: Ptychocheilus oregonensis (nothern squawfish), Oncorhynchus tshawytscha (chinook salmon) and Oncorhynchus kisutch (coho salmon).
Result	:	The effect abbreviated with E is for loss-of-equilibrium time, and D for death time. Under E and D a range of hours is given. The lower limit of a range indicates the time that the last observation was made before loss-of-equilibrium or death. The upper limit indicates the time that loss-of-equilibrium or death was noted. Test concentration: 10 mg/l Squawfish: E = 1-2 h; D = 7.5 - 13 h Chinook salmon: E = 1-2 h; D = 2 - 4 h Coho salmon: E = 1-2 h; D = 2 - 4 h
Test condition	:	- Length of the fish was about 5 to 10 cm - One fish of each species was tested - The test animals were placed in a 9.5 l plastic aquaria containing 4 l of water - The water was obtained from Rochat Creek - The pH was 7.2, the alkalinity was 7 ppm and the hardness was about 0-17 ppm - The aquarium was aerated - The temperature was taken several times during the test. The highest temperature of 50°F in the 24-hour test period is given - One concentration was tested (10 mg/l) - The elapsed times in hours in which an obvious change in the pathological status of fish were noted
Reliability	:	(4) not assignable Documentation insufficient for assessment

13.07.2005 (46)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC0	:	6.3
EC100	:	> 18.2
Analytical monitoring	:	no
Method	:	other: Directive 92/69/EEC C.2 "Acute toxicity for Daphnia"
Year	:	1999
GLP	:	yes
Test substance	:	other TS: Diphenyl carbonate, purity = 99.98 %
Remark	:	At the highest test concentration (20 mg/l) 75 % of the daphnids showed immobility after 48 h.
Result	:	EC50 = > 6.3 < 18.2 mg/l At the effective concentration of 6.3 mg/l (nominal concentration of 5 mg/l), related to the TOC single results at 0 and 48 h, no adverse effect was observed. At the effective concentration of 18.2 mg/l (nominal concentration of 20 mg/l), related to the TOC single results at 0 and 48 h, an immobilization of 75 % of the daphnids was observed. The TOC single results: Conc. 0 hours 48 hours control < 2 mg/l 3 mg/l 5.0 mg/l (nominal) 5 mg/l 4 mg/l 10 mg/l (nominal) 8 mg/l 5 mg/l 20 mg/l (nominal) 15 mg/l 11 mg/l Due to the hydrolyses of diphenyl carbonate in the presence of water, forming phenol and carbon dioxide, the effective concentrations of diphenyl carbonate are estimated for each test concentration. With the assumption that the half-life of diphenyl carbonate is about 40 hours under abiotic conditions in a buffered medium, and a water solubility of 13 mg/l, the geometric mean over time is 8.5 mg/l, 4.1 mg/l and 2.1 mg/l at the nominal test concentrations of 20 mg/l, 10 mg/l and 5 mg/l. By graphic interpolation (linear) the resulting effective 96 h EC50 is 6.5 mg/l.
Test condition	:	The test was carried out under the following conditions: - Test organism: Daphnia magna Straus - 10 daphnids (max age 24 h) were used per concentration in 20 ml test medium, 2 replicates - Stock solution was prepared dissolving in water an amount of test substance approximately 5 times higher (60 mg/l) than the corresponding water solubilty. This mixture was then stirred with a magnetic stirrer during 24 h. The suspension was finally filtered in order to remove the undissolved particles - The following nominal concentrations were tested: 5, 10 and 20 mg/l - Hardness of dilution water= 15.1 °dH - Test temperature = 21 °C, pH= 8.1, oxygen concentration was between 4.0 and 7.1 mg/l - Analytical monitoring: total organic carbon (TOC) The results are listed below: Conc. 0 hours 48 hours control < 2 mg/l 3 mg/l 5.0 mg/l (nominal) 5 mg/l 4 mg/l 10 mg/l (nominal) 8 mg/l 5 mg/l 20 mg/l (nominal) 15 mg/l 11 mg/l
Reliability	:	(2) valid with restrictions GLP guideline study with acceptable restrictions
Flag	:	Critical study for SIDS endpoint

13.07.2005 (47)

Type	:	other: Estimate
Species	:	Daphnia sp. (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	13.5 calculated
Method	:	other: (calculated) EPIWIN ECOSAR (v0.99h)
Year	:	2005
GLP	:	no
Test substance	:	
Remark	:	This estimate is generally consistant with the available experimental data
Reliability	:	(2) valid with restrictions Accepted calculation method

13.07.2005 (28)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	.63
LOEC	:	1.25
EC50	:	2.4
Limit test	:	
Analytical monitoring	:	no
Method	:	Directive 92/69/EEC, C.3
Year	:	1999
GLP	:	yes
Test substance	:	other TS: Diphenyl carbonate, purity = 99.98 %
Remark	:	Toxicity of the hydrolysis product phenol might have influenced the testing. Accepted new scientific name for Scenedesmus subspicatus: Desmodesmus subspicatus.
Result	:	Concerning the analytical monitoring it was observed that for nominal concentrations equal or lower than 2.5 mg/l the corresponding measured values were below the limit of quantification (LOQ = 2 mg/l TOC). For a nominal concentration of 5 mg/l no decrease of the concentration was observed after 72 h. Since the measured effect concentrations found (EC10 and EC50) were lower than LOQ, following results refer to nominal concentrations. Results were given for 10, 50 and 90 % growth inhibition. After 72 h the following effect concentrations were observed: - Biomass EbC10= 0.64 mg/l EbC50= 1.4 mg/l Eb90= 3.2 mg/l - Growth rate ErC10= 1.0 mg/l ErC50= 2.4 mg/l Er90= 5.8 mg/l Due to the hydrolyses of diphenyl carbonate in the presence of water, forming phenol and carbon dioxide, the effective concentrations of diphenyl carbonate are estimated for each test concentration. With the assumption that the half-life of diphenyl carbonate is about 40 hours under abiotic conditions in a buffered medium, and a water solubility of 13 mg/l, the geometric mean over time (inclusive 24 hours of stirring before the test) is 1.77 mg/l, 0.88 mg/l, 0.44 mg/l and 0.22 mg/l at the nominal test concentrations of 5 mg/l, 2.5 mg/l, 1.25 mg/l and 0.63 mg/l. The resulting effective ErC50 (72h) is 0.9 mg/l and 0.5 mg/l for the EbC50 (72h). The corresponding 72h-NOEC, obtained from growth rate, is 0.22 mg/l and the

72h-LOEC is 0.44 mg/l.
The corresponding 72h-NOEC, obtained from biomass, is <0.22 mg/l and the 72h-LOEC is <0.22 mg/l.

Test condition : The test was performed under the following conditions:
- Test organism: Scenedesmus subspicatus Chodat
- Static
- Algal inoculum 10000 cells/ml initial cell density
- 300 ml Erlenmeyer flasks
- Temperature = 23 +/- 2 °C
- Lighting 120 µE/m2s
- Analytical monitoring: The highest tested concentration in presence and absence of algae and a control were determined (TOC) directly at the beginning of the test and 72 h after the start of the incubation
- Stock solution was prepared dissolving the amount of test substance in water, stirring the mixture during 24 h with a magnetic stirrer and finally filtering the suspension in order to remove the undissolved particles
- The following initial nominal concentrations were tested: 0.63, 1.25, 2.5 and 5.0 mg/l
- The biomass was determined at 0, 24, 48 and 72 h
- The pH-value was determined after 0 and 72 h. At 0 h pH ranged from 7.8 to 8.2 and after 72 h the following pH was observed: Control= 10.3; 0.63 mg/l= 10.3, 1.25 mg/l= 9.1, 2.5 mg/l= 7.7 and 5 mg/l= 7.3

Reliability : (2) valid with restrictions
GLP guideline study with acceptable restrictions

Flag : Critical study for SIDS endpoint

13.07.2005 (48)

Species : other algae: Not specified
Endpoint :
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : .61 calculated
Method : other: (calculated) EPIWIN ECOSAR (v0.99h)
Year : 2005
GLP : no
Test substance :

Remark : This estimate is lower (by the factor of 4) than the available experimental data, but it is generally consistant with the available experimental data

Reliability : (2) valid with restrictions
Accepted calculation method

13.07.2005 (28)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species : activated sludge, domestic
Exposure period : 3 hour(s)
Unit : mg/l
EC50 : 4510
Analytical monitoring : no
Method : other: Directive EG L 133, part C corresponds to OECD 209
Year : 2000
GLP : yes
Test substance : other TS: Diphenyl carbonate, purity = 99.98 %

Result : The EC50 was obtained with Probit Analysis whereby all concentrations were weighted equal.

Test condition : - The following concentrations were tested: 1000, 1800, 3200, 5600 and 10000 mg/l

- The system was aerated and stirred during 3 h at 20 +/- 2 °C
- Concentration of the activated sludge was 320 mg/l
- Oxygen consumption was recorded over a period of 6 minutes

Reliability : (1) valid without restriction
GLP guideline study
Flag : Critical study for SIDS endpoint
04.06.2004 (49)

Type : aquatic
Species : Pseudomonas putida (Bacteria)
Exposure period : 16 hour(s)
Unit : mg/l
EC0 : > 280
Analytical monitoring : no
Method : other: Cell multiplication inhibition test according to Bringmann and Kuehn (1977)
Year : 1979
GLP : no
Test substance : other TS: Diphenyl carbonate, purity = 99.9 %

Reliability : (4) not assignable
Documentation insufficient for assessment
Flag : Critical study for SIDS endpoint
02.07.2004 (50) (51)

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

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	> 2500 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	
Vehicle	:	other: DMSO
Doses	:	100, 250, 500, 1000, 2500 mg/kg bw
Method	:	other: no detailed information available
Year	:	1963
GLP	:	no
Test substance	:	other TS: no data on purity
Remark	:	No. of Animals: 10/dose post dose observation period: no data
Reliability	:	(2) valid with restrictions Limited documentation

03.05.2004 (52)

Type	:	LD50
Value	:	> 2500 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	male/female
Number of animals	:	
Vehicle	:	other: water and Cremophor EL
Doses	:	
Method	:	other: no detailed information available
Year	:	1967
GLP	:	no
Test substance	:	other TS: no data on purity
Remark	:	No. of Animals: 15/sex/dose dose levels: 500, 1000 and 2500 mg/kg (male) 1000 and 2500 mg/kg (female) volume administered: no data concentration administered: 500 mg/kg: 5 % 1000 mg/kg: 10 % 2500 mg/kg: 25 % post dose observation period: 7 days
Result	:	500 mg/kg (male): no deaths, no clinical symptoms 1000 mg/kg (male): no deaths, 15/15 with clinical symptoms 2500 mg/kg (male): 1/15 died, 15/15 with clinical symptoms 1000 mg/kg (female): no deaths, 15/15 with clinical symptoms 2500 mg/kg (female): no deaths, 15/15 with clinical symptoms Clinical symptoms became obvious 1 hour after dosing and vanished 48 hours after dosing: bad condition and convulsions.
Reliability	:	(2) valid with restrictions Limited documentation
Flag	:	Critical study for SIDS endpoint

04.02.2004 (53)

Type	:	LD50
Value	:	1500 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	
Vehicle	:	other: corn oil
Doses	:	
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1990
GLP	:	yes
Test substance	:	other TS: composition/purity: 99.95 % DPC, 0.05 % phenol
Remark	:	dose levels: 0.75, 1.5 and 3 g/kg No. of Animals: 5/sex/dose volume administered: no data post dose observation period: 14 days value: The LD50 of the TS has been determined to be 1500 mg/kg bw based upon the observed 50 % mortality at this dose. The method of Litchfield and Wilcoxon could not be employed due to a limitation in this procedure that requires at least two response values that are not 0 or 100 %.
Result	:	dose group - 3.00 g/kg: body weight: nine of the animals died by 4 h of the study and the one animals that died by day 1 lost weight clinical observations: the one animal that survived until day 1 showed signs of clonic convulsions mortality: all animals died by the end of day 1 necropsy: no unusual lesions were noted in any of the animals dose group - 1.50 g/kg: body weights: the five surviving animals of this dose level gained weight; the three animals that died at day 1 exhibited a slight decrease in weight from their initial day 0 weight clinical observations: the five surviving animals and three of the animals that died experienced clonic convulsions mortality: two out of the ten animals (1m/1f) died by 4 h and 3 died (1m/2f) by day 1 of the study. Five animals survived the 14 day observation period necropsy: no unusual lesions were noted in any of the animals dose group - 0.75 g/kg: body weights: all of the ten surviving animals had an increase in body weight clinical observations: none of the surviving animals exhibited any clinical signs during the 14 day observation period mortality: all animals survived at this dose level necropsy: no unusual lesions were noted in any of the animals
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

03.05.2004 (54)

Type	:	LD50
Value	:	> 1000 mg/kg bw
Species	:	mouse
Strain	:	
Sex	:	male
Number of animals	:	
Vehicle	:	other: water and Cremophor EL
Doses	:	
Method	:	
Year	:	1967
GLP	:	no
Test substance	:	other TS: purity not given

Remark : No. of animals per dose: 15
doses tested - deaths - animals with clinical signs:
250 mg/kg bw - 0 - 0
500 - 0 - 15
1000 - 0 - 15
At 500 mg/kg bw and above all animals displayed signs of toxicity but no deaths occurred.
post dose observation period: 7 days
Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
03.05.2004 (53)

Type : LD50
Value : > 1000 mg/kg bw
Species : rabbit
Strain :
Sex :
Number of animals :
Vehicle : other: water and Cremophor EL
Doses :
Method :
Year : 1967
GLP : no
Test substance : other TS: purity not given

Remark : No. of animals per dose: 3
doses tested - deaths - animals with clinical signs:
500 - 0 - 0
1000 - 0 - 3
post dose observation period: 7 days
Reliability : (2) valid with restrictions
Limited documentation
04.02.2004 (53)

Type : LD50
Value : > 1000 mg/kg bw
Species : dog
Strain :
Sex :
Number of animals :
Vehicle : other: water and Cremophor EL
Doses :
Method :
Year : 1967
GLP : no
Test substance : other TS: purity not given

Remark : No. of animals per dose: 2 or 1
doses tested - deaths - animals with clinical signs - No.:
250 mg/kg bw - 0 - 0 - 2
500 - 0 - 0 - 1
1000 - 0 - 1 - 1
At 1000 mg/kg bw the dog displayed signs of toxicity but no death occurred.
post dose observation period: 7 days
Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
03.05.2004 (53)

Type	:	LD50
Value	:	> 1000 mg/kg bw
Species	:	guinea pig
Strain	:	
Sex	:	female
Number of animals	:	
Vehicle	:	other: water and Cremophor EL
Doses	:	
Method	:	
Year	:	1967
GLP	:	no
Test substance	:	other TS: purity not given
Remark	:	No. of animals per dose: 5 doses tested - deaths - animals with clinical signs: 500 - 0 - 5 1000 - 0 - 5 At 500 mg/kg bw and above all animals displayed signs of toxicity but no deaths occurred. post dose observation period: 7 days
Reliability	:	(2) valid with restrictions Limited documentation

03.05.2004 (53)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	6
Vehicle	:	water
Doses	:	2000 mg/kg bw
Method	:	other: OECD Guide-Line 402, modified according to the acute toxic class method
Year	:	1999
GLP	:	yes
Test substance	:	other TS: diphenylcarbonate (approx. 100 %)
Remark	:	Deviation from GLP: No analytical investigations on stability and homogeneity were perfomed. Deviation from OECD 402: the number of animals and the procedure of dose finding was done according to OECD guideline 423 (Acute Oral Toxicity - Acute Toxic Class Method) due to animal welfare reasons.
Result	:	no local effects and no clinical signs of toxicity were observed; body weight and body weight gain of male and female rats were not affected by treatment; no mortality; at sacrifice no gross pathological findings
Test condition	:	No. of animals: 3/sex Starting dose: 2000 mg/kg bw No further doses tested. For a better contact to the skin, the test substance was moistened with water, applied to the prepared skin area and fixed with non-irritant skin plaster (occlusive conditions) for 24 hours.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

25.01.2005 (55)

Type	:	LD50
Value	:	> 500 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	5
Vehicle	:	
Doses	:	500 mg/kg bw
Method	:	other
Year	:	1967
GLP	:	no
Test substance	:	other TS: purity not given
Test condition	:	preparation of dose: 10% emulsion (vehicle: no data) Application of emulsion on shaved skin of backs. Licking was prevented by a collar. Observation period: 7 days TS was not removed during this period. No signs of intoxication
Reliability	:	(2) valid with restrictions Limited documentation

03.05.2004 (53)

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	other: rabbit (New Zealand White)
Strain	:	
Sex	:	male/female
Number of animals	:	10
Vehicle	:	water
Doses	:	2000 mg/kg bw
Method	:	OECD Guide-line 402 "Acute dermal Toxicity"
Year	:	1990
GLP	:	yes
Test substance	:	other TS: composition/purity: 99.95 % DPC, 0.05 % phenol (moistened with water)
Remark	:	No. of animals: 5/sex The TS was introduced under gauze patches two single layers thick and applied directly to the skin of the body surface (approximately 10%) of each of the ten animals for 24 hours. The patches were secured in place by wrapping the entire trunk of the animal with an impervious bandaging. Animals were observed immediately following dosing and at three times during the first two hours after application. Animals were observed twice daily for 14 days for clinical manifestations and mortality.
Result	:	A limit test was performed at a dose level of 2 g/kg bw. There were no overt signs of toxicity noted in any test animal during the observation period and no animal died. Skin reactions were graded 30-60 min after bandage removal. The skin showed no signs of erythema or edema. No unusual lesions were noted at necropsy.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

25.01.2005 (56)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LD50

Value	:	= 200 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	
Year	:	1963
GLP	:	no
Test substance	:	no data
Remark	:	No. of animals per dose: 10 (presumably males) vehicle: DMSO observation period: 7 days tested doses: 0.005g, 0.01g, 0.025g,0.05g, 0.1g, 0.25g, 0.5g, 1g/kg bw
Reliability	:	(2) valid with restrictions Limited documentation

21.10.2003 (52)

Type	:	LD50
Value	:	= 1005 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	
Vehicle	:	other: water and Cremophor EL
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	
Year	:	1967
GLP	:	no
Test substance	:	other TS: purity not given
Remark	:	No. of animals per dose: 15 tested doses - dead animals - animals with clinical signs: 100 mg/kg bw - 0 - 0 250 - 0 - 15 500 - 0 - 15 750 - 5 - 15 1000 - 7 - 15 1500 - 10 - 15 2000 - 14 - 15 2500 - 15 - 15 clinical symptoms: convulsions and bad condition starting 10-20 min up to 3 days after dosing. Deaths occurred in the first 24 hours after dosing.
Reliability	:	(2) valid with restrictions Limited documentation

23.06.2003 (53)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	24 hour(s)
Number of animals	:	1

Vehicle	:	
PDII	:	
Result	:	slightly irritating
Classification	:	
Method	:	other: see remarks
Year	:	1963
GLP	:	no
Test substance	:	no data
Test condition	:	The solid moistened with water (left ear) or oil (right ear) was applied to the external ear on a gauze patch. The gauze patch was fixed with a tape during the exposure period (24 h). Immediately after patch removal very slight erythema and edema was observed at both ears. At the right ear these signs of irritation lasted for 24 h and were disappeared after 48 hours. Post dose observation period: 7 days No information on amount of applied TS given.
Reliability	:	(3) invalid Significant methodological deficiences

11.05.2004 (52)

Species	:	rabbit
Concentration	:	100 %
Exposure	:	
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	other: undiluted
PDII	:	0
Result	:	not irritating
Classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1990
GLP	:	yes
Test substance	:	other TS: TS 99.95%, Phenol 0.05%
Remark	:	The TS was applied in a single dose semiocclusively to the skin of six rabbits. An adjacent area of untreated skin on each animal served as control. Animals were observed for signs of erythema and edema 30-60 minutes, and 24, 48, and 72 hours after the 4 hour exposure period. After patch removal no signs of erythema or edema were observed at any time during the observation period. The primary irritation index was 0.0/8.0. Exposure: 0.5 grams applied to one intact skin site per animal Sex: female
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

24.05.2004 (57)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	not irritating
Classification	:	
Method	:	other: see remarks
Year	:	1963
GLP	:	no

Test substance	:	no data
Remark	:	The solid was placed in the conjunctival sac. After 1 h the eye was washed out with water. No irritation of the conjunctivae and no corneal lesions were observed.
Reliability	:	(2) valid with restrictions Limited documentation

21.10.2003 (52)

Species	:	rabbit
Concentration	:	100 %
Dose	:	100 other: mg
Exposure time	:	24 hour(s)
Comment	:	other: see remarks
Number of animals	:	6
Vehicle	:	
Result	:	not irritating
Classification	:	
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1990
GLP	:	yes
Test substance	:	other TS: TS 99.95%, Phenol 0.05%
Remark	:	No. of animals: 6 Sex: female Dose: 0.1 grams administered to each test eye The left eye of each animal was treated with the test substance. The right eye remained untreated, and thus served as a control The eyes of the test animals were not washed out for 24 hours following instillation. Eyes were examined at 1, 24, 48, and 72 hours after treatment using the Draize scale. Fluorescein staining was used during each examination, excluding the 1 hour examination.
Result	:	Slight swelling (Grade 1) of conjunctivae was evident in the treated eyes of the test animals at 1 hour (5/6 animals). No signs of irritation were evident at the 24, 48, or 72 hour observation points, therefore the study was not continued. (Maximum Draize Score = 2.0/110)
Reliability	:	(1) valid without restriction Guideline study
Flag	:	Critical study for SIDS endpoint

25.01.2005 (58)

5.3 SENSITIZATION

Type	:	Buehler Test
Species	:	guinea pig
Number of animals	:	30
Vehicle	:	petrolatum
Result	:	not sensitizing
Classification	:	
Method	:	other: (Buehler, E.V. 1965. Delayed contact hypersensitivity in the Guinea Pig. Arch. Dermat. 91:171-175.)
Year	:	1990
GLP	:	yes
Test substance	:	other TS: Commercial, purity: TS 99.95%, Phenol 0.05%
Remark	:	No. of animals: 10/group Sex: female Administration: 75% DPC in petrolatum This method utilizes an occlusive, topical patch technique applied for six hours at Induction and Challenge. In an initial range-finding study with 12.5

to 75% DCP, suspended in petrolatum USP, all of the tested concentrations were not irritating. Therefore, as maximum non-irritating concentration 75% was used for the main study.
In the Main Study (Induction Phase) the test article or positive control article was administered to the respective group of animals by occlusive patch, once per week for three weeks in an attempt to boost the sensitization potential of the animal to the allergen. Two weeks after completion of this Induction Phase, an unused skin site on the animals was challenged with the respective test article or control articles and evaluated for dermal reactions 24 and 48 hours later. Reactions were compared to a negative control group of animals that received the same concentration of test article only at the Challenge Phase. On completion of the Challenge Phase all animals were sacrificed without necropsy. No dermal reactions were observed in any of the animals subjected to the TS (0/10). The positive control, 0.1% Dinitrochlorobenzene, exhibited positive reactions in 7 of 10 animals at the 24 hour reading, indicating that it is a strong sensitizer. In conclusion, the TS when used at a 75% concentration in Petrolatum would be considered a non-sensitizer according to the study design.
Deviations from current guideline:
- only 10 animals in treatment group

Reliability : (2) valid with restrictions
In deviation of the current OECD TG 406, only 10 (instead of 20) animals were used in the treatment group. According to the current guideline, 20 animals are needed to confirm a negative test result.

Flag : Critical study for SIDS endpoint

25.01.2005 (59)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	oral feed
Exposure period	:	13 weeks
Frequency of treatm.	:	continuous
Post exposure period	:	none
Doses	:	5.000, 10.000, and 15.000 ppm
Control group	:	yes, concurrent no treatment
Method	:	other: pilot study for a one-generation study
Year	:	2001
GLP	:	yes
Test substance	:	other TS: purity 99.98%

Remark : Orientating analytical investigations on homogeneity in this pilot study revealed that DPC could not be homogeneously distributed in the diet, and the stability of the mixtures was not granted. There is, therefore, uncertainty about the actually administered doses of the test substance, as these were calculated from the daily food consumption under the (wrong) assumption of an homogenous distribution of the test substance in the food. In the main study (Bayer AG, 2003) 1% peanut oil was added to the food/test substance mixture, ensuring a good homogeneity.
Pilot Study with limited number of evaluated endpoints

Result : TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: none
- Clinical signs: no TS-dependent effects
- Body weight gain: at temination high dosed males (-8%) and females (-5%) exhibited slightly lower body weight compared to control
- Food consumption: not significantly influenced by TS

- Organ weights: significantly increased relative liver weights in 15.000 ppm males (+22%) and females from 5.000 ppm onwards (+11%, +7%, +16%); relative kidney weights were significantly enhanced in 15.000 ppm males (+27%); uterus weights were dose-independently lower in treated females than in the wide spreading control means
- Gross pathology: no signifcant findings

Test condition : ANIMALS
- Age: about 6 weeks
- Weight at study initiation:
males: 134-163 g; females: 111-131 g
- Number of animals: 5/sex/group
ADMINISTRATION / EXPOSURE
- Duration of test/exposure: 13 w
- Type of exposure: oral feeding
- Post exposure period: none
- Vehicle: food, fresh diets were prepared weekly
- Concentration in vehicle: no data
- Doses: 5.000, 10.000, 15.000 ppm
- Control: basal diet
- mean daily compound consumption: low dose: 401 (m) or 545 (f) mg/kg bw/d; mid dose: 825 (m) or 1288 (f) mg/kg bw/d; high dose: 1325 (m) or 1877 (f) mg/kg bw/d
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: at least weekly
- Mortality: twice daily
- Body weight: weekly
- Food consumption: weekly
- Water consumption: no data
- Ophthalmoscopic examination: no data
- Haematology: no data
- Biochemistry: no data
- Urinalysis: no data
- gross pathology: yes
ORGANS EXAMINED AT NECROPSY:
- gross pathology: adrenals, liver, spleen, pituitary, vagina, uterus/cervix, ovaries, oviducts, seminal vesicles, prostate, brain, mammary glands with skin, epididymes, thyroids/parathyroids, urethra with preputium, coagulating glands, gross lesions and physical identifiers
- organ weights: brain, adrenals, liver, spleen, kidney, testes, epididymis, seminal vesicles/coagulating vesicles, prostate, ovaries/oviducts, uterus
- Histopathology: no
STATISTICAL METHODS:
Dunnet-Test with variance analysis for body and organ weights; Kruskal-Wallis-Test with a Steel-Test for food consumption data

Reliability : (2) valid with restrictions
Limited documentation; pilot study: no determination of haematology, biochemistry, urinanalysis, histopathology; defined limits of analytics could not be met;

Flag : Critical study for SIDS endpoint

25.01.2005 (60)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	oral feed
Exposure period	:	about 18 weeks
Frequency of treatm.	:	continuous
Post exposure period	:	no
Doses	:	1.500, 5.000, and 15.000 ppm
Control group	:	yes, concurrent no treatment
Method	:	

Year	:	2002
GLP	:	yes
Test substance	:	other TS: purity 99.98%
Method	:	One-generation study following OECD TG 416 (2001) without treatment of F1 weanlings after developmental milestones had occurred (balano-preputial separation or vaginal opening at an age of about 8 weeks). The conduct of this study includes also recommendations of OECD TG 415 (adopted 1983) and 407 (open field observation and Functional Observation Battery).
Remark	:	Rationale for dose selection: based on a subchronic feeding pilot study (Bayer AG (2002a). Diphenylcarbonate (DPC) Subchronic study in Wistar rats (Pilot study for a one-generation study with administration in the diet). Eiben R. Report No. AT00045. Oct 22, 2002)
Result	:	NOAEL parental males: 1500 ppm (about 132 mg/kg bw/day) LOAEL parental males: 5000 ppm (about 427 mg/kg/day), based on increased relative liver weights with hepatocellular hypertrophy LOAEL parental females: 1500 ppm (about 219 mg/kg bw/day), based on increased relative and absolute adrenal weights with histopathological changes in the zona fasciculata, and morphological changes in the ovaries. ACTUAL DOSE (mean) RECEIVED BY DOSE LEVEL BY SEX: - low dose: 132 (m) or 219 (f) mg/kg bw/day; mid dose: 427 (m) or 710 (f) mg/kg bw/day; high dose: 1561 (m) or 2432 (f) mg/kg bw/day TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: - Mortality and time to death: none - Clinical signs: no TS-dependent effects - Food consumption: not significantly influenced by TS - Body weight gain: F0 males of 15000 ppm group showed significantly lower (about -7%) body weights compared to controls nearly throughout the total study; 15000 ppm females exhibited sporadically significantly lower body weights, which reached -8% during lactation - Functional Observation Battery: no indication of neurotoxic potential - Organ weights: significantly increased relative liver weights in 5000 and 15.000 ppm males (+10.1, +13.5%) and 15000 ppm females (+12%); significantly increased absolute (+11.5, +13.5, +17.3%) and relative (+9.5%, +14.3%, +19%) adrenal weights in females; significantly increased ovarian weights (absolute: +22.8%, +16.3%; relative: +27.1%, +22.9%) from 5000 ppm onwards. - spermatological investigations: no significant findings - estrus cycle staging in F0 females: no TS-related findings - Gross pathology: no significant findings - Histopathology: LIVER: Hepatocellular hypertrophy was found in males of the mid and high dose group (0, 0, 4, 6) and in females of the high dose group (0, 0, 0, 2) in low frequency and severity score. The incidence of Kupffer cell foci was slightly increased in females of the high dose group (6, 5, 5, 10). ADRENAL GLANDS: In mid and high dosed males the frequency of mixed-size vacuolation of zona fasciculata and partly also glomerulosa cells was slightly and the severity moderately increased (incidence: 18, 21, 25, 25; grade 2: 5, 6, 13, 9; grade 3: 0, 0, 5, 15). In females microvesicular vacuolation (0, 17, 23, 24) and hypertrophy (0, 17, 23, 25) of the zona fasciculata cells were found in high incidences in all dose groups. The severity score increased dose-dependently.OVARIES: The number of corpora lutea (severity score grade 2) increased slightly from 1500 ppm onwards (8, 12, 17, 16). The total number of corpora lutea per group was also slightly elevated (365, 391, 443, 428). At 1500 ppm and above, large corpora lutea exhibited an infiltration of predominantly mononuclear cells (0, 21, 24, 21). In addition, many of these corpora lutea contained granulated luteal cells (0, 20, 18, 9). Hypertrophic ovarian interstitial cells increased (0, 16, 24, 24) with severity score increasing in a dose dependent manner.

Test condition : ANIMALS
- Number of animals: 25/sex/group
- Age: about 6 w
- Weight at study initiation:
males: 111-151 g; females: 96-132 g
ADMINISTRATION / EXPOSURE
- Duration of test/exposure: Animals were exposed during the premating period of about 11 weeks, and during the mating period of up to 3 weeks. Males were sacrificed after the mating period. Females were further exposed during pregnancy and lactation, and were sacrificed when F1 offspring was weaned (after 4 weeks). At the same time most F1 animals were sacrificed, except of one F1 male and one F1 female per litter, which were sacrificed after a further treatment period of about 4 weeks, when developmental milestones had occurred (balano-preputial separation or vaginal opening).
- Type of exposure: oral feeding in a diet containing 1% peanut oil
- Vehicle: food, fresh diets were prepared weekly
- Doses: 1.500, 5.000, 15.000 ppm
- Control: basal diet
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: at least weekly
- Mortality: twice daily
- Body weight: weekly
- Food consumption: weekly
- Water consumption: not determined
- Ophthalmoscopic examination: not determined
- Haematology: not determined
- Biochemistry: not determined
- Urinalysis: not determined
- spermatology: yes (control and 15000 ppm group) spermatozoa motility and viability, spermatozoa morphology, quantitative determination of spermatozoa in epididymis, quantitative determination of homogenization resistant spermatid heads in the testis)
- functional observation battery (neurotoxicity screening: sensory reactivity to stimuli of different types): yes
- developmental milestones and investigations in post weaned F1 rats: yes
ORGANS EXAMINED AT NECROPSY:
- gross pathology: adrenals, liver, kidney, spleen, pituitary, vagina, uterus/cervix, ovaries, oviducts, seminal vesicles with coagulation glands, prostate, brain, trachea, larynx and esophagus, mammary glands with skin, epididymides, thyroids/parathyroids, urethra with preputium, coagulating glands
- organ weights: brain, pituitary gland (fixed), liver, kidneys, adrenals, spleen, thyroid (one fixed organ), uterus, seminal vesicles with coagulation glands, prostate, epididymis (only left organ), testes and ovaries
- Histopathology F0 (control and 15000 ppm group): adrenals, liver, kidney spleen, pituitary, vagina, uterus/cervix, ovaries, oviducts, seminal vesicles with coagulation glands, prostate, brain, mammary glands with skin, testes, epididymides, thyroids/parathyroids,
- Histopathology F1 weanlings: ovaries
STATISTICAL METHODS:
Dunnett-Test with variance analysis for body and organ weights; Kruskal-Wallis-Test with a Steel-Test for food consumption data

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
25.01.2005 (61)

Type : Sub-chronic
Species : rat
Sex : female
Strain : Wistar
Route of admin. : gavage

Exposure period	:	18 weeks
Frequency of treatm.	:	once daily
Post exposure period	:	none
Doses	:	2, 10, 50, and 200 mg/kg bw/day
Control group	:	yes, concurrent vehicle
Method	:	other: see Test Condition
Year	:	2003
GLP	:	yes
Test substance	:	other TS: purity 99.98%
Remark	:	Study was performed to clarify results of a previous study (one-generation reproduction feeding study, Bayer Report No. AT00196, Jan 13, 2003), where morphological changes were found in adrenals and ovaries of females of all dose groups, and to establish a NOAEL.
Result	:	NOAEL: 50 mg/kg bw/day for female rats LOAEL: 200 mg/kg bw/day, based on histopathological changes in the ovaries and adrenals (zona fasciculata) TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: - Mortality: no compound-related deaths (due to misapplication throughout all groups animals died: 1 in vehicle control, 1 in 10 mg/kg bw/day group, 2 in 50 mg/kg bw/day group, 2 in 200 mg/kg bw/day group. One rat in the 200 mg/kg bw/day group had to be killed in moribund condition.) - Clinical signs: no TS-dependent effects - Body weight gain: not affected by TS - Food consumption: not affected by TS - clinical chemical parameters: no TS-related effects - Organ weights: not affected by TS - Gross pathology: no signifcant findings - Histopathology: at 200 mg/kg bw/day ovaries of 4 animals exhibited interstitial glands (control and lower doses 0) characterized by slight hypertrophy and pale cytoplasm (grade 2); no TS-related effects on number of corpora lutea (both ovaries; 287, 200, 276, 234, 247); in 3 high dosed females adrenal glands showed hypertrophy of Zona fasciculata cells with microvesicular vacuolation.
Test condition	:	Lower DPC doses were given to females over the same time as in the one-generation study to establish a NOAEL for this gender. Because of instability of DPC below 1500 ppm in food, DPC was administered by gavage. This study was not conducted in accordance with a special guideline. ANIMALS - Number of animals: 10/group - Age: about 5-6 w - Weight at study initiation: 140-180 g ADMINISTRATION / EXPOSURE - Vehicle for 0, 10, and 200 mg/kg dose: 0.5% Tween 20 in demin. water - Vehicle for 2 and 50 mg/kg dose: < 0.5% Tween 20 in demin. water depending on dilution factor - Adimistration volume: 5 ml/kg bw - Doses: 2, 10, 50, and 200 mg/kg bw/day - Control: concurrent vehicle CLINICAL OBSERVATIONS AND FREQUENCY: - Clinical signs: at least weekly - Mortality: twice daily (once on weekends and public holidays) - Body weight: weekly - Food consumption: weekly - Water consumption: not determined - clinical chemical investigations: blood parameters at sacrifice (cholesterol, glucose, urea, creatinine, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and the electrolytes Na, K, Ca, Cl) - Haematology: not determined - Urinalysis: not determined

ORGANS EXAMINED AT NECROPSY:
- gross pathology: adrenals, liver, spleen, pituitary, vagina, uterus/cervix, ovaries, oviducts, brain, heart, thymus, tattooed auricles, kidneys, lungs, and gross lesions
- organ weights: brain, liver, kidneys, adrenals, spleen, ovaries with oviducts, and uterus
- Histopathology:
liver, adrenals, ovaries, oviducts, uterus, and vagina
STATISTICAL METHODS:
Dunnett-Test with variance analysis for body and organ weights; adjusted welch test

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
25.01.2005 (62)

Type :
Species : rat
Sex : male
Strain : Wistar
Route of admin. : gavage
Exposure period : 10 w
Frequency of treatm. : once daily, 5 doses/week
Post exposure period : 24 h
Doses : 85, 165, 415, 550, 660, 830, 1000 mg/kg bw/day
Control group : yes, concurrent vehicle
NOAEL : >= 830 mg/kg bw
Method : other
Year : 1967
GLP : no
Test substance : other TS: purity not given

Result : 85-830 mg/kg bw/day: no clinical signs, weight gain, haematology and gross necropsy normal;
1000 mg/kg bw: elevated absolute (18%) and relative (15%) liver weights; other investigated parameters normal
Test condition : No. of animals: 15 males/dose and control
TS: aqueous emulsion in Cremophor EL
OBSERVATIONS:
clinical signs: daily
body weight: weekly
haematology: after last TS application in 5 animals/group
organ weight (abs. and rel.): liver, spleen, kidney, adrenals, thyroid, testes, lung
macroscopic examinations: liver, spleen, kidney, adrenals, thyroid, testes, lung
STATISTICS:
Wilcoxons rank sum test; $p<0.05$ for significance
Test substance : TS was tested for acute toxicity in the beginning, in the middle and at the end of the study and showed throughout simiar toxicity
Reliability : (2) valid with restrictions
Only limited observation parameters.
Purity of test substance not given
Flag : Critical study for SIDS endpoint
04.05.2004 (53)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Salmonella typhimurium reverse mutation assay
System of testing : S. typhimurium TA 1535, TA 1537, TA 98, TA 100
Test concentration : see test condition

Cycotoxic concentr.	:	> 330 µg/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 471
Year	:	1989
GLP	:	yes
Test substance	:	other TS: purity: 99.9 %
Remark	:	Appropriate reference mutagens (sodium azid, 4-NOPD, 2-AA) were used as positive controls and showed the expected results.
Result	:	A distinct reduction in the number of revertants occurred in all strains (except TA 1537) at 1000 µg/plate without S9 mix. With S9 mix no cytotoxicity became obvious.
Test condition	:	Metabolic activation system: S9 liver microsomal fraction of male Wistar rats which received a single i.p. injection of 500 mg/kg bw Aroclor 1254. TS concentrations tested: exp. I without S9 mix: 1; 3.3; 10; 33.3; 100 and 333.3 ug/plate; with S9 mix: 10; 33.3; 100; 333.3; 1000 and 5000 ug/plate; exp. II without S9 mix: 3.3; 10; 33.3; 100; 333.3 and 1000 ug/plate; with S9 mix: 10; 33.3; 100; 333.3; 1000 and 5000 ug/plate; TS dissolved in DMSO. Precipitation in the overlay agar at 333.3 ug/plate and higher concentration
Reliability	:	(1) valid without restriction Guideline study. Limitation: only 4 strains tested.
Flag	:	Critical study for SIDS endpoint

25.01.2005 (63)

Type	:	Salmonella typhimurium reverse mutation assay
System of testing	:	S. typhimurium TA 1535, TA 1537, TA 98, TA 100 and E. coli strain (WP2)
Test concentration	:	0, 0.015, 0.05, 0.15, 0.5, 1.5, and 5 mg/plate
Cycotoxic concentr.	:	> 500 µg/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: EPA 40 CFR 798.5100 "Bacterial Reverse Mutation Test"
Year	:	1990
GLP	:	yes
Test substance	:	other TS: (purity assumed to be > 99%)
Remark	:	In the assay without metabolic activation, DPC was toxic to all four Salmonella strains at the dose levels of 0.15 mg/plate and higher. At 0.05 mg/plate, slight toxicity was seen in strains TA 98 and TA 1537. E. coli showed no toxicity at any dose. No bacterial strain demonstrated any mutagenicity in conjunction with DPC. All test plate counts remained within acceptable historical background parameters. With metabolic activation, DPC was assayed at the same concentrations. Extreme toxicity was seen in all four Salmonella typhimurium strains at 5 mg/plate. In addition, TA1535 and TA1537 also showed increased toxicity to the test chemical at 1.5 mg/plate. Slight toxicity was also observed at 1.5 and 0.5 mg/plate in the Salmonella strains. E. coli was not affected by the test chemical at any dose level. As with the non-activated assay, no mutagenicity was observed at any dose level. Appropriate reference mutagens (sodium azid, 9-aminoacridine, 2-AA, ENNG, 2-NF) were used as positive controls and showed the expected results.
Test condition	:	Metabolic activation system: S9 liver microsomal fraction of male Sprague Dawley rats which received a single i.p. injection of Aroclor 1254. TS dissolved in DMSO. TS concentrations tested: Because of strong cytotoxicity at >= 500 µg/plate in a non-activation range-finding study, the conc. were limited to 150 µg/plate. exp. I and II without S9-mix: 0.5 - 150 µg/plate exp. I and II with S9-mix: 15 - 5000 µg/plate

Reliability	:	(1) valid without restriction Guideline study
Flag	:	Critical study for SIDS endpoint
25.01.2005		(64)
Type	:	other: In vitro gene mutation assay in mammalian cells
System of testing	:	Chinese hamster V79/HPRT cells
Test concentration	:	Without S9 mix: 1, 3, 10, 30, 60, 100, 120, and 150 ug/mL With S9 mix: 30, 100, 300, 600, 1000, and 2000 ug/mL
Cycotoxic concentr.	:	> 100 µg/ml
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: OECD Guideline 476 (1984) "In Vitro Mammalian Cell Gene Mutation Test"
Year	:	1996
GLP	:	yes
Test substance	:	other TS: purity > 99%
Remark	:	Appropriate reference mutagens (EMS at 0.6 mg/ml, DMBA at 3.85 µg/ml) were used as positive controls and showed the expected results.
Result	:	Relevant toxic effects occurred at concentrations of 60 ug/mL and above without and at 600 ug/mL and above with metabolic activation. Visible precipitation of the test article occurred at the two highest concentrations with and without metabolic activation. The cloning efficiency of the cells was reduced at the maximal concentrations tested without S9 mix. No substantial increase in the number of mutant colonies occurred at any of the evaluated concentrations neither in the presence nor absence of metabolic activation. There was no indication of a dose dependent increase in the number of colonies even below the threshold of biological relevance. The number of mutant colonies in any of the TS groups with or without metabolic activation remained well within the range of historical negative controls.
Test condition	:	Metabolic activation system: S9 liver microsomal fraction of male Wistar rats which received a single i.p. injection of 500 mg/kg bw Aroclor 1254. TS dissolved in DMSO. Final DMSO concentration in the medium did not exceed 1 %
Reliability	:	(1) valid without restriction Guideline study
Flag	:	Critical study for SIDS endpoint
25.01.2005		(65)
Type	:	other: In vitro chromosome aberration assay
System of testing	:	Chinese hamster V79 cells
Test concentration	:	Without S9 mix: 3, 5, 10, 30, 50, 70, and 100 ug/mL. With S9 mix: 10, 30, 50, 100, 300, and 500 ug/mL
Cycotoxic concentr.	:	> 50 µg/ml
Metabolic activation	:	with and without
Result	:	positive
Method	:	other: OECD Guideline 473 (1984) "In Vitro Mammalian Cytogenetic
Year	:	1996
GLP	:	yes
Test substance	:	other TS: purity > 99%
Remark	:	Appropriate reference mutagens (EMS at 0.6 mg/ml, CPA at 0.71 µg/ml) were used as positive controls and showed the expected results (up to 24.5% and 20% aberrant cells, respectively).
Result	:	Precipitation of the TS in the culture medium was observed at concentrations of 300 ug/mL and above. In the absence of S9 mix, the mitotic indices were reduced after treatment with the highest evaluated concentration at each preparation interval, whereas in the presence of S9 mix no reduction was observed. In the absence of metabolic activation 30 and 50 ug/mL and in the presence of metabolic activation 100, 300, and

500 ug/mL of the test article induced a statistically significant aberration frequency. The laboratory's historical negative control range of aberrant cells is 0-4% and the observed aberration frequencies after treatment with the TS are:

	Exp.I	Exp.II
solvent (-S9)	0.0 %	2.0 %
5 µg/ml (-S9)	0.5 %	1.0 %
30 µg/ml (-S9)	9.5 %	9.5 %
50 µg/ml (-S9)	7.5 %	-
70 µg/ml (-S9)	-	4.5 %
solvent (+S9)	2.0 %	0.0 %
50 µg/ml (+S9)	0.0 %	-
100 µg/ml (+S9)	-	7.5 %
300 µg/ml (+S9)	17.0 %	13.0 %
500 µg/ml (+S9)	15.5 %	21.5 %

Test condition : Metabolic activation system: S9 liver microsomal fraction of male Wistar rats which received a single i.p. injection of 500 mg/kg bw Aroclor 1254. TS was dissolved in DMSO (not to exceed 1% final DMSO concentration in nutrient medium).
The chromosomes were prepared 18 and 28 hours after start of treatment with TS. The treatment interval was 4 hours with metabolic activation and 18 and 28 hours without metabolic activation. In each experimental group, two parallel cultures were set up. Per culture 100 metaphases were scored for structural chromosome aberrations

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint

25.01.2005 (66)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : mouse
Sex : male
Strain : other: Hsd/Win: NMRI
Route of admin. : i.p.
Exposure period : twice
Doses : 0, 75, 150 and 300 mg/kg bw, 2 applications separated by 24 hours
Result : negative
Method : other: OECD Guide-line 474 (1997)
Year : 1999
GLP : yes
Test substance : other TS: purity: 99.98 %

Remark : An appropriate reference mutagen (cyclophosphamide, single i.p. application of 20 mg/kg bw) was used as positive control and showed the expected results (23.4 MNPCE/ 2000 PCEs). Also vehicle controls showed expected results.

Result : Symptoms of toxicity (apathy, roughened fur, loss of weight, spasm, twitching, difficulty in breathing, slitted eyes and closed eyes) after administration of >= 2x75 mg/kg; no substance-induced mortalities; the ratio between polychromatic and normochromatic erythrocytes was reduced in the highest dose group by > 30%, indicating cytotoxic effects in the bone marrow; no indication of a TS dependent clastogenic effect at any TS dose.
Micronucleated PCEs/2000 PCEs (MNPCE in %)
(mean values of 5 animals in each group):
vehicle control: 3.6 (0.18%)
2 x 75 mg/kg: 2.6 (0.13%)

2 x 150 mg/kg: 2.8 (0.14%)
2 x 300 mg/kg: 5.6 (0.28%)
No statistically significant increase.
The highest dose group with the mean of 0.28% MNPCE includes one animal with an exceptional high number of 16 MNPCE. Since this value is clearly different from the other findings in this group (1-5 MNPCE), it is interpreted as outlier. Without this outlier the MNPCE-value for this group would be 3.0 (0.15%).

Test condition : No. of animals/dose: 5
TS was suspended in 0.5% aqueous Cremophor emulsion. CP was dissolved in deionized water.
administered volume: 10 mg/kg bw
24 hours after the last dose the animals were sacrificed.
Dose selection:
Pilot test with 3 male and 3 female rats treated with two i.p. doses of 500 mg/kg bw, separated by 24 hours. All animals showed clinical signs and 1 male and 1 female died. Therefore, 300 mg/kg bw was chosen as MTD for both sexes and this dose was used in the main study with males only.
No. of cells scored for micronuclei: 2000 PCEs/animal
PCE/NCE-ratio determined for 2000 PCEs/animal
Statistics:
Wilcoxon's non-parametric rank sum test; p<0.001 for significance

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint

25.01.2005 (67)

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : other: Hsd/Win: NMRI
Route of admin. : i.p.
Exposure period : once
Doses : 0, 30, 100 and 300 mg/kg bw (24 hour preparation interval) and 0, 300 mg/kg bw (48 hour preparation interval)
Result : ambiguous
Method : other: OECD Guideline 474 (1997) "Mammalian Erythrocyte Micronucleus Test"
Year : 1998
GLP : yes
Test substance : other TS: purity: > 99%

Remark : The mean value of the highest micronucleus frequency (0.19%) was well within the range of the laboratory's historical negative control range (0.03-0.26%).
An appropriate reference mutagen (cyclophosphamide, single i.p. application of 40 mg/kg bw) was used as positive control and showed the expected results (2.20% corresponding to 44 micronucleated PCEs/2000 PCEs).

Result : Symptoms of toxicity were present in the pilot experiments at doses of >= 250 mg/kg bw, however, not recorded in the main experiments; no substance-induced mortalities in the main experiment; the ratio between polychromatic and normochromatic erythrocytes was reduced in the highest dose group (48 h preparation interval) by > 40%, indicating cytotoxic effects in the bone marrow;
Micronucleated PCEs (in %):
vehicle control: 0.065 (range 0-2)
30 mg/kg (24 h): 0.030 (range 0-2)
100 mg/kg (24 h): 0.060 (range 0-3)
300 mg/kg (24 h): 0.190 (range 0-15)
300 mg/kg (48h): 0.190 (range 0-10)
Statistical significance ($p < 0.05$) at 300 mg/kg (24 and 48 h). However, in

		each of the highest dose groups one animal showed an exceptional high number of 15 (24h) or 10 (48h) MNPCE. Since these values are clearly different from the other findings in this groups (0-6, 24h; 0-7, 48h), they are interpreted as outliers. In conclusion, the results were considered as to be equivocal.
Test condition	:	No. of animals: 5/sex/dose TS was fomulated in corn oil, CP in deionized water. Administration volume: 10 ml/kg bw. 24 and 48 hours after single dosing the bone marrow cells were collected for micronuclei analysis. Dose selection: Several pilot tests were performed with i.p. administration in doses of 250 to 500 mg/kg bw with 2 male and 2 female rats each. In sum, i.p. administration of >= 400 mg/kg bw DPC led to death of females. Throughout all doses males and females showed clinical signs (apathy, eyelid closure). Some females showed temporary tremors. 300 mg/kg bw was chosen as MTD for both sexes. No. of cells scored for micronuclei: 2000 PCEs/animal PCE/NCE-ratio determined for 2000 PCEs/animal Statistics: non-parametric Mann-Whitney test; $p < 0.05$ for significance
Reliability	:	(1) valid without restriction Guideline study
Flag	:	Critical study for SIDS endpoint

04.02.2004 (68)

Type	:	Unscheduled DNA synthesis
Species	:	rat
Sex	:	male
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	
Doses	:	0, 250, 500, 1000 mg/kg bw
Result	:	negative
Method	:	OECD Guide-line 486
Year	:	2001
GLP	:	yes
Test substance	:	other TS: purity: 99.87 %
Remark	:	An appropriate reference mutagen (dimethylnitrosamine, single oral application of 35 mg/kg bw in deionized water) was used as positive control and showed the expected results (+22.4 NG after 2-4 hours treatment and +19.2 NG after 12-16 hours treatment). Also vehicle controls showed expected results (-3.2 NG and -3.1 NG).
Result	:	Clinical signs: at 1000 mg/kg bw all animals showed ataxia and tremors. Average net grains: -2.0/-2.7 NG at 250 mg/kg bw (2-4/12-16 h) -1.8/-3.0 NG at 500 mg/kg bw -2.8/-1.4 NG at 1000 mg/kg bw
Test condition	:	No. of treated animals/group: 5 No. of rats/group used for hepatocyte cultures: 3 treatment intervals: 2-4 hours and 12-16 hours vehicle for TS: 0.5 % carboxymethylcellulose in water postive control substance: 35 mg/kg bw DMN administration volume: 20 ml/kg bw (DMN: 10 ml/kg bw) No. of hepatocytes scored/animal: 150 Criteria for positive result: A dose-related increase with at least one dose significantly elevated (at least 5 grains) above the negative control. Criteria for dose selection: Pilot gavage study with 1, 10, 100, 1000, 1500, and 2000 mg/kg bw. At 1500 and 2000 mg/kg bw 2/5 animals died within two days of dose administration. At 1000 mg/kg bw the two treated animals were lethargic

and showed tremors. 1000 mg/kg bw was determined as MTD

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
04.05.2004 (69)

5.7 CARCINOGENICITY

Species	:	mouse
Sex	:	male/female
Strain	:	other: (C57BL/6 X C3H/Anf)F1
Route of admin.	:	other: gavage for first 3 weeks of the study followed by oral feeding
Exposure period	:	18 months
Frequency of treatm.	:	daily/continuous
Post exposure period	:	
Doses	:	100 mg/kg bw/day (260 ppm)
Result	:	negative
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1967
GLP	:	no
Test substance	:	other TS: no data on purity
Remark	:	Carcinogenicity study with 130 chemicals. Limited documentation.
Result	:	Mortality: no treatment related differences; tumor incidences not affected by TS (only limited information) CLINICAL SIGNS: not reported NECROPSY FINDINGS: no significant findings as compared to untreated and vehicle controls. Administration of 11 of the test compounds induced a significantly elevated incidence of tumors, and the administration of the positive control substances also resulted in the expected increases in tumor incidence.
Test condition	:	Animals: specific pathogen free mice. Females of the C57BL/6 strain were mated with C3H/Anf males to obtain the F1 hybrid (C57BL/6 X C3H/Anf)F1. No. of animals: 18/sex per group; 4 untreated control groups, and vehicle control (gelatin); 7 positive controls (urethane, ethylene imine, amitrole, aramite, dihydrosafrole, isosafrole, safrole). Administration of the test substance began when the mice were 7 days of age. The same absolute amount of each compound was given each day until the mice were 4 weeks old; the dose was not readjusted according to weight gain during this period. After the mice were weaned at 4 weeks of age, the chemicals were mixed directly with the diet, which was provided ad libitum; no vehicle was used. The concentration in the diet was calculated according to the weight and food consumption of the 4-week-old mice so that they would receive approximately the maximal tolerated dose, The same concentration was maintained throughout the observation period of approximately 18 months. Vehicle used for stomach tubing: 0.5% gelatin The maximum tolerated dose (MTD) was given. The MTD was determined in a preliminary acute toxicity study (data not shown). The postmortem procedure included an external examination and a thorough examination of thoracic and abdominal cavities, with histologic examination of major organs and of all grossly visible lesions. STATISTICAL ANALYSES: The individual positive controls and experimental groups were compared with the grouped five negative controls, and the relative risk for four tumor groupings (hepatomas, pulmonary tumors, lymphomas, and total mice with tumors) was calculated for each experimental group. Additionally, the relative risk was calculated, lumping together the 7 positive controls.
Reliability	:	(2) valid with restrictions

Limited documentation

25.01.2005 (70) (71)

Species	:	mouse
Sex	:	male/female
Strain	:	other: (C57BL/6 X AKR)F1
Route of admin.	:	other: gavage for first 3 weeks of the study followed by oral feeding
Exposure period	:	18 months
Frequency of treatm.	:	daily/continuous
Post exposure period	:	
Doses	:	100 mg/kg bw (260 ppm)
Result	:	negative
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1967
GLP	:	no
Test substance	:	other TS: no data on purity
Remark	:	Carcinogenicity study with 130 chemicals. Limited documentation.
Result	:	Mortality: no treatment related differences; tumor incidences not affected by TS (only limited information) NECROPSY FINDINGS: no significant findings as compared to untreated and vehicle controls CLINICAL SIGNS: not reported. Administration of 11 of the test compounds induced a significantly elevated incidence of tumors, and the administration of the positive control substances also resulted in the expected increases in tumor incidence.
Test condition	:	Animals: specific pathogen free mice. Females of the C57BL/6 strain were mated with C3H/AKR males to obtain the F1 hybrid (C57BL/6 X C3H/Anf)F1. No. of animals: 18/sex per group; 4 untreated control groups, and vehicle control (gelatin); 7 positive controls (urethane, ethylene imine, amitrole, aramite, dihydrosafrole, isosafrole, safrole). Administration of the test substance began when the mice were 7 days of age. The same absolute amount of each compound was given each day until the mice were 4 weeks old; the dose was not readjusted according to weight gain during this period. After the mice were weaned at 4 weeks of age, the chemicals were mixed directly with the diet, which was provided ad libitum; no vehicle was used. The concentration in the diet was calculated according to the weight and food consumption of the 4-week-old mice so that they would receive approximately the maximal tolerated dose. The same concentration was maintained throughout the observation period of approximately 18 months. Vehicle used for stomach tubing: 0.5% gelatin The maximal tolerated dose (MTD) was given. The MTD was determined in a preliminary acute toxicity study (data not shown). The postmortem procedure included an external examination and a thorough examination of thoracic and abdominal cavities, with histologic examination of major organs and of all grossly visible lesions. STATISTICAL ANALYSES: The individual positive controls and experimental groups were compared with the grouped five negative controls, and the relative risk for four tumor groupings (hepatomas, pulmonary tumors, lymphomas, and total mice with tumors) was calculated for each experimental group. Additionally, the relative risk was calculated, lumping together the 7 positive controls.
Reliability	:	(2) valid with restrictions Limited documentation

25.01.2005 (70) (71)

Species	:	mouse
Sex	:	male/female

Strain	:	other: (C57BL/6 X C3H/Anf)F1
Route of admin.	:	s.c.
Exposure period	:	1 day
Frequency of treatm.	:	single injection on day 28 of age
Post exposure period	:	18 months
Doses	:	1000 mg/kg bw
Result	:	
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1966
GLP	:	no
Test substance	:	other TS: no data on purity
Remark	:	Carcinogenicity study with 130 chemicals. Limited documentation.
Result	:	Mortality: no treatment related differences; tumor incidences not affected by TS (only limited information)
Test condition	:	No. of animals: 18 mice/sex (dose group), 24 mice/sex (control group) Administration of TS: single s.c. injection on day 28 of age Vehicle: DMSO Application volume: 0.05 ml of suspension was injected in nape of neck MTD was determined in a preliminary acute toxicity study
Reliability	:	(3) invalid Unsuitable test system.

25.01.2005 (70)

Species	:	mouse
Sex	:	male/female
Strain	:	other: (C57BL/6 X AKR)F1
Route of admin.	:	s.c.
Exposure period	:	1 day
Frequency of treatm.	:	single injection on day 28 of age
Post exposure period	:	18 months
Doses	:	1000 mg/kg bw
Result	:	negative
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1966
GLP	:	no
Test substance	:	other TS: no data on purity
Remark	:	Carcinogenicity study with 130 chemicals. Limited documentation.
Result	:	Mortality: no treatment related differences; tumor incidences not affected by TS (only limited information)
Test condition	:	No. of animals: 18 mice/sex (dose group), 24 mice/sex (control group) Administration of TS: single s.c. injection on day 28 of age Vehicle: DMSO Application volume: 0.05 ml of suspension was injected in nape of neck MTD was determined in a preliminary acute toxicity study
Reliability	:	(3) invalid Unsuitable test system.

25.01.2005 (70)

5.8.1 TOXICITY TO FERTILITY

Type	:	One generation study
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	oral feed
Exposure period	:	about 18 weeks (see test condition)

Frequency of treatm.	:	continuous
Premating exposure period		
Male	:	11 weeks
Female	:	11 weeks
Duration of test	:	see test condition
No. of generation studies	:	
Doses	:	1.500, 5.000, and 15.000 ppm
Control group	:	yes, concurrent no treatment
Method	:	
Year	:	2002
GLP	:	yes
Test substance	:	other TS: purity 99.98%

Method : One-generation study following OECD TG 416 (2001) without treatment of F1 weanlings after developmental milestones had occurred (balano-preputial separation or vaginal opening at an age of about 8 weeks). The conduct of this study includes also recommendations of OECD TG 415 (adopted 1983) and 407 (only open field observations and Functional Observation Battery).

Remark : Rationale for dose selection:
based on a subchronic feeding pilot study (Bayer AG, 2002a. Diphenylcarbonate (DPC) Subchronic study in Wistar rats (Pilot study for a one-generation study with administration in the diet). Eiben R. Report No. AT00045. Oct 22, 2002)
See also chapter 5.4 (repeated dose toxicity).

Result : NOAEL parental males: 1500 ppm (about 132 mg/kg bw/day)
LOAEL parental females: 1500 ppm (about 219 mg/kg bw/day), based on increased relative and absolute adrenal weights with histopathological changes in the zona fasciculata, and morphological changes in the ovaries.
NOAEL fertility: 15000 ppm (about 1561/2432 mg/kg bw/day for males/females)
NOAEL F1 males: 5000 ppm
LOAEL F1 females: 1500 ppm, based on histopathological changes in ovaries.
ACTUAL DOSE (mean) RECEIVED BY DOSE LEVEL BY SEX:
- low dose: 132 (m) or 219 (f) mg/kg bw/day; mid dose: 427 (m) or 710 (f) mg/kg bw/day; high dose: 1561 (m) or 2432 (f) mg/kg bw/day
TOXIC RESPONSE/EFFECTS IN F0 BY DOSE LEVEL:
- Mortality and time to death: none
- Clinical signs: no TS-dependent effects
- Food consumption: not significantly influenced by TS
- Body weight gain of F0: slightly reduced mean body weights (up to 8%) became obvious in high dosed animals
- Functional Observation Battery: no indication of neurotoxic potential
- spermatological investigations: no significant findings
- estrus cycle staging in F0 females: no TS-related findings
- Organ weights of F0: increased absolute and relative adrenal weights in females of all dose groups; increased relative liver weights in 5000 and 15.000 ppm males and 15000 ppm females; increased ovarian weights from 5000 ppm onwards
- Gross pathology of F0: no significant findings
- Histopathology of F0 (for details see chapter 5.5):
OVARIES: Number of corpora lutea slightly elevated in all dose groups; large corpora lutea exhibited an infiltration of predominantly mononuclear cells and contained granulated luteal cells. Number of hypertrophic ovarian interstitial cells increased with severity score increasing in a dose dependent manner.
LIVER: Hepatocellular hypertrophy was found in low frequency and severity score predominantly in males.
ADRENAL GLANDS: In mid and high dosed males the frequency of mixed-size vacuolation of Zona fasciculata and partly also glomerulosa cells was

slightly and the severity moderately increased. In females microvesicular vacuolation and hypertrophy of Zona fasciculata cells were found in high incidences in all dose groups. The severity score increased dose-dependently.
PARAMETERS OF REPRODUCTION IN F0:
- fertility index (91.7%, 100%, 91.7%, 100%)
- gestation index (95.5%, 100%, 100%, 100%)
- duration of gestation (21.9, 22.29, 22.70, 22.33 days)
- mating performance not affected by TS
OFFSPRING TOXICITY F1:
- total number of pups (228, 249, 204, 220)
- mean litter size (10.71, 9.72, 8.73, 9.91)
- sex ratio (% males: 49.31, 53.41, 45.66, 52.67)
- live birth index (98.74%, 97.47%, 93.12%, 99.04%)
- mean pup weight in g (m: 5.71, 5.97, 5.94, 5.79; f: 5.48, 5.57, 5.65, 5.39)
- viability index day 4 (98.68%, 86.67%, 85.51%, 94.17%)
- clinical signs: no TS-dependent effects
- malformations: none
- gross pathology at weaning: no TS-dependent effects
- body weights at weaning: in 15000 ppm pups reduced by 11-12% (this is most likely directly induced by compound consumption rather than a reprotoxic effect)
- organ weights at weaning: at 15000 ppm reduced absolute spleen weights in both sexes (ca. -20%; relative weights not affected) and reduced absolute (-29%) and relative (-16%) thymus weights in females
- histopathology F1 at weaning: at 1500 ppm and above in ovaries large corpora lutea exhibited an infiltration of predominantly mononuclear cells (1/5/9/11); many of corpora lutea contained granulated luteal cells (0/2/7/8); hypertrophy of ovarian interstitial cells (0/4/10/23) with severity score increasing in a dose dependent manner
- developmental milestones in F1 weanlings:
no treatment effect on sexual maturation

Test condition : ANIMALS
- Number of animals F0: 25/sex/group
- number of viable pups F1: 196-244/group
- Age: about 6 w
- Weight at study initiation:
males: 111-151 g; females: 96-132 g
ADMINISTRATION / EXPOSURE
- Duration of test/exposure: Animals were exposed during the premating period of about 11 weeks, and during the mating period of up to 3 weeks. Males were sacrificed after the mating period. Females were further exposed during pregnancy and lactation, and were sacrificed when F1 offspring was weaned (after 4 weeks). At the same time most F1 animals were sacrificed, except of one F1 male and one F1 female per litter, which were sacrificed after a further treatment period of about 4 weeks, when developmental milestones had occurred (balano-preputial separation or vaginal opening).
- Type of exposure: oral feeding in a diet containing 1% peanut oil
- Post exposure period: none
- Vehicle: food, fresh diets were prepared weekly
- Concentration in vehicle: no data
- Doses: 1.500, 5.000, 15.000 ppm
- Control: basal diet
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: at least weekly
- Mortality: twice daily
- Body weight: weekly
- Food consumption: weekly
- Water consumption: no data
- Ophthalmoscopic examination: no data
- Haematology: no data

- Biochemistry: no data
- Urinalysis: no data
- Reproduction parameters: estrus cycle staging, insemination rate, duration of pregnancy, data on pups
- functional observation battery : yes
- developmental milestones and investigations in post weaned F1 rats: age and body weight at which balano-preputial separation and vaginal opening occurred
- Functional Observation Battery: yes

ORGANS EXAMINED AT NECROPSY:
- gross pathology F0/F1: organs as given in OECD TG 416
- organ weights F0: as given in OECD TG 416
- organ weights F1: brain, spleen, thymus, testes, epididymides, uterus were determined for the first male and female living F1 weanling of each litter
- spermatology: yes (control and 15000 ppm group) spermatozoa motility and viability, spermatozoa morphology, quantitative determination of spermatozoa in epididymis, quantitative determination of homogenization resistant spermatid heads in the testis
- Histopathology F0 (control and 15000 ppm group): adrenals, liver, kidney spleen, pituitary, vagina, uterus/cervix, ovaries, oviducts, seminal vesicles with coagulation glands, prostate, brain, mammary glands with skin, testes, epididymides, thyroids/parathyroids,
- Histopathology F1 weanlings: ovaries
- determination of offspring toxicity according to OECD TG 416

STATISTICAL METHODS:
Dunnet-Test with variance analysis for body and organ weights; Kruskal-Wallis-Test with a Steel-Test for food consumption data

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
25.01.2005 (61)

Type : other: supplementary 18 week study with females only
Species : rat
Sex : female
Strain : Wistar
Route of admin. : gavage
Exposure period : 18 weeks
Frequency of treatm. : once daily
Premating exposure period
Male :
Female :
Duration of test :
No. of generation studies :
Doses : 2, 10, 50, and 200 mg/kg bw/day
Control group : yes, concurrent vehicle
Method : other
Year : 2003
GLP : yes
Test substance : other TS: purity 99.98%

Method : RATIONALE FOR STUDY DESIGN AND DOSE SELECTION:
Study was initiated as a supplementary study to a one-generation reproduction feeding study (0, 1500, 5000, 15000 ppm; Eiben and Hartmann, Bayer Report No. AT00196, Jan 13, 2003), where morphological changes were found in adrenals and ovaries of females of all dose groups. Here, lower DPC doses were given to females over the same time as in the one-generation study to establish a NOAEL for this gender. Because of instability of DPC below 1500 ppm in food, DPC was administered by gavage. This study was not conducted in accordance with a special guideline.

Remark	:	Detailed description of the study see chapter 5.4.
Result	:	NOAEL: 50 mg/kg bw/day for female rats - Histopathology: at 200 mg/kg bw/day ovaries of 4 animals exhibited interstitial glands (control and lower doses 0) characterized by slight hypertrophy and pale cytoplasm (grade 2); no TS-related effects on number of corpora lutea (both ovaries; 287, 200, 276, 234, 247); in 3 high dosed females adrenal glands showed hypertrophy of Zona fasciculata cells with microvesicular vacuolation.
Test condition	:	No. of animals: 10/group
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

04.05.2004 (62)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	day 6 - 19 of gestation
Frequency of treatm.	:	once daily
Duration of test	:	sacrifice on day 20 of gestation
Doses	:	0, 50, 200, and 750 mg/kg bw
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	>= 50 mg/kg bw
NOAEL teratogen.	:	>= 50 mg/kg bw
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	2001
GLP	:	yes
Test substance	:	other TS: purity 99.98 %

Remark	:	The dose levels used were selected according to a preceding dose-range finding study (Study No. T0062796) in rats with dose levels of 0, 20, 125, and 750 mg/kg bw/d. For selected fetuses a peer review of fetal visceral findings was performed by Tesh Consultants International, UK.
Result	:	MATERNAL TOXICITY: Mortality: in 750 mg/kg group 5 females died (4 after 1st dose, 1 after 7th dose) Clinical signs: only in 750 mg/kg group: signs of severe toxicity after administration (convulsions and ventral posture), which disappeared within 4 hours; in surviving females such clinical signs became less severe or were not longer evident with increasing duration of treatment; piloerection; Food intake: distinctly reduced in 750 (up to 36%) and slightly reduced in 200 mg/kg group (up to 12% on days 6-12) Water consumption and urination: increased only in high dosed females Body weight development: stat. sign. reduced at 750 mg/kg throughout the entire study (mean body weight gain day 0-20 reduced by 24%); in the 200 mg/kg bw/day group stat. sign. reduced only on day 6-7 p.c. and remained marginally reduced up to sacrifice Pathological findings: in 750 mg/kg group some females showed empty of gas filled stomach, related to morbidity/mortility and regarded as unspecific finding Total number of females with implantations (vehicle control, 50, 200, 750 mg/kg bw/d): 23/22/25/21 No. of resorptions: 0/0/1/0 Total number of females with viable fetuses: 23/22/24/21 No. of corpora lutea/female: 14.3/14.3/14.9/14.7 Postimplantation loss/female: no meaningful effects (0.7/0.8/1.1/1.2) since no. of viable fetuses per litter not affected and inbetween historical control

range
placenta weight: unaffected
placenta appearance: at 750 mg/kg engorged placentae/ necrotic placental borders

FETAL TOXICITY:
No. viable: 275/249/269/253
No. dead: 0/0/2/1 (deaths did not affect the mean number of viable fetuses per litter and was comparable to the incidences in historical control, so that toxicological relevance was not assumed)
Sex ratio (% males): not affected (48.4/50.1/50.5/48.6)
Fetal weight (mean in g): 3.77/3.74/3.64/3.40 (high dose group $p<0.01$)
Fetal malformations: at 750 mg/kg bw (severe maternally toxic dose) incidence of common malformations increased on a fetal and litter basis as
- dysplastic forelimb bones: fetal incidence 5.5%, litter incidence 33.3% compared to 0% in control (in historical control groups indicences of up to 4.3/20% were seen)
- 2 cases of multiple malformations
- 3 cases of atrial septal defect of the heart within 3 litters
- 2 cases of flat and stretched kidneys
- 1 case of situs inversus
- 1 case of shortened tail with missing sacral and caudal vertebrae
Fetal external and visceral deviations: no TS-related effects
Fetal skeletal deviations including cartilaginous deviations: slightly retarded ossification in comparison to control could not be completely excluded in the 200 mg/kg group (retarded ossification of distal phalanges of toes, cervical vertebral bodies, sacral vertebral arches and wavy ribs: only stat. sign. when calculated on a fetal basis) and was evident to a more pronounced degree in the 750 mg/kg group. Fetal cartilage was not affected.
The overall number and type of malformations were not increased at a dose level up to and including 200 mg/kg bw/day.

Test condition : TEST ORGANISMS:
No. of animals/dose: 25 (50 mg/kg and 750 mg/kg group: 28) inseminated females
body weight on day 0 p.c.: 207 to 249 g
age of females on day 0 p.c.: 12-16 weeks
ADMINISTRATION/EXPOSURE:
vehicle: carboxymethylcellulose 0.5 % in deionized water
administration volume: 10 ml/kg bw
MATING PROCEDURE:
1 male/2 females per cage; if sperm was detected in the vaginal smear this day was day 0 of gestation
PARAMETERS ASSESSED DURING STUDY:
Body weight gain: on day 0 p.c. and daily from day 6-20
Food consumption: yes
Water consumption: yes (by visual estimation)
Clinical observations: appearance, behaviour, excretory products and mortality, from day 0-20 twice daily
Gross pathological examination: at time of cesarian section on day 20 p.c. or after death/premature sacrifice
Examination of uterine content: gravid uterine weight, no. of corpora lutea, no. of implantations, no. of resorptions, placenta weight
Examination of fetuses: no., weight and sex of live fetuses, external, visceral and skeletal malformations
Total numer of live fetuses examined: 275/249/269/253
STATISTICS:
Kruskal-Wallis test, analysis of variance, Dunnett's test, Chi^2 test were used

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint

26.01.2005 (72)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

28.01.2004

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

Type	:	other: in vitro estrogenic activity
Result	:	Diphenyl carbonate showed a REC10 of >3x10 EE-4 M and is therefore regarded as negative in this assay
Test condition	:	Yeast two-hybrid system, based on the ligand-dependent interaction of two proteins, a hormone receptor, ER alpha, and a coactivator, TIF2. Hormonal activity is detected by ß-galactosidase activity. The results were evaluated by relative activity, expressed as REC10 (10% relative effective concentration compared to activity of 10 EE-7 M 17-ß-estradiol).
Test substance	:	Most chemicals were of the highest grade commercially available (purity for diphenyl carbonate not given)
Reliability	:	(2) valid with restrictions In vitro System with limited significance.

11.02.2004 (73)

Type	:	other: liver function
Result	:	No alterations of liver function
Test condition	:	A single oral dose of the test substance (500 mg/kg bw emulsion) was administered to two rabbits. The following liver function tests were performed after 1 hour, 24 hours and 7 days: Bromthaleintest of Hofmann-Oettel Serum-glutaminacid-pyruvat-transaminase (SGPT) activity Serum-sorbit-dehydrogenase (SDH) activity
Reliability	:	(4) not assignable Documentation insufficient for assessment

03.02.2004 (53)

Type	:	other: renal function
Result	:	No alterations of renal function (kidney weight, urine volume)
Test condition	:	A single dose of the test substance (500 mg/kg bw) was injected s.c. to 10 male rats. 24 hours later the animals were given hourly oral doses of 5 x 50 ml tap water. Urine volume was determined after 5 and 8 hours. Body weight was determined after 5, 8, and 24 hours. 48 hours after treatment with TS the animals were sacrificed and the kidneys were weighted. The control group consisted of 10 animals.
Reliability	:	(4) not assignable Documentation insufficient for assessment

07.01.2004 (53)

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