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SIDS Initial Assessment Report

For

SIAM 17

Arona, 11-14th November 2003

- 1. Chemical Name:** Benzene, 1-chloro-2-(chloromethyl)-
- 2. CAS Number:** 611-19-8
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 - Process used
The industry consortium collected new data, prepared the updated IUCLID and drafted versions of the SIAR and SIAP.
- 6. Sponsorship History**
- How was the chemical or category brought into the SIDS Program?
This substance is sponsored by Japan under the ICCA Initiative and is submitted for first discussion at SIAM 17.
- 7. Review Process Prior to the SIAM:** Japanese government peer-reviewed the documents, audited selected studies.

- 8. Quality check process:** Japanese government peer-review committee performed spot checks on randomly selected endpoints and compared original studies with data in the SIDS dossier.
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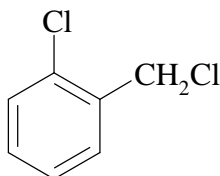
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1 IDENTITY

1.1 Identification of the Substance

CAS Number: 611-19-8
IUPAC Name: 1-Chloro-2-(chloromethyl)benzene
Molecular Formula: C₇H₆Cl₂
Structural Formula:



Molecular Weight: 161.03
Synonyms: *o*-Chlorobenzyl chloride (OCBC)
Benzene, 1-chloro-2-(chloromethyl)-
alpha, 2-Dichlorotoluene
alpha, *o*-Dichlorotoluene
1-Chloro-2-(chloromethyl)benzene
2-Chlorobenzyl chloride
o, alpha-Dichlorotoluene
Toluene, *o*, alpha-dichloro-
alpha, 2-Dichlorotoluol
alpha-2-dichlorotolueno

1.2 Purity/Impurities/Additives

Purity

> 99 %

Impurities

2-Chlorobenzaldehyde	0.01 %
alpha, 4-Dichlorotoluene	0.2 %
1-Chloro-2-(dichloromethyl)benzene	0.06 %

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Protocols (Reference) or comments
Physical state	Liquid	
Melting point	-17°C	Unknown (CRC Handbook 2nd ed.)
Boiling point	217°C (1013 hPa)	Unknown (CRC Handbook 2nd ed.)
Relative density	1.274	Density: 1.2743 g/cm ³ at 20°C (Hammond, 1949)
Vapour pressure	0.2 hPa (25°C)	Calculated (MPVPWIN V1.40, 2003)
Water solubility	100 mg/l (25°C)	OECD TG 105 (CERI, 1999a)
Partition coefficient n-octanol/water (log value)	3.32	OECD TG 107 (CERI, 1999b)
Henry's law constant	157 Pa m ³ /mol (25°C)	Calculated (HENRYWIN ver.3.10, 2003)

1-Chloro-2-(chloromethyl)benzene (*o*-Chlorobenzyl chloride; OCBC) is a clear and colorless liquid with a pungent odor.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Production Volumes

Annual production of *o*-chlorobenzyl chloride (OCBC) in Germany, Japan and Belgium is summarized in Table 2-1 (Ihara Chem. Ind., 2003; Clariant GmbH, 2003a, Tessenderlo Chemie N. V., 2003). In these countries, only one company, which has one production site, currently operates the production of OCBC. The total production volume was about 1,000 tonnes per year for last five years. Although the chemical may be produced in China, no data is available for the country's production quantity.

Table 2-1. Annual production of OCBC.

Year	Production volume (tonnes)		
	Germany	Japan	Belgium
1999	140	156	0
2000	700	390	0
2001	350	431	653
2002	180	330	552
2003	No data available	149	No data available

OCBC is produced by chlorination of *o*-chlorotoluene in a closed system (Ihara Chem. Ind., 2003; Clariant GmbH, 2003a; Tessenderlo Chemie N. V., 2003).

Use Pattern

OCBC is used only as intermediates for the production of agrochemicals (Ihara Chem. Ind., 2003; Clariant GmbH, 2003a; Tessenderlo Chemie N. V., 2003). The agrochemicals manufactured from OCBC are only two herbicides in OECD countries. All of the OCBC produced are used for the production of these herbicides.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

There is no process that generates the waste water in the production of OCBC. The waste residue is incinerated. The off-gas of the reaction is incinerated or treated on active carbon. Therefore there is no release of OCBC to the environment from its manufacturing plants (Ihara Chem. Ind., 2003; Clariant GmbH, 2003a; Tessenderlo Chemie N.V., 2003).

In the sponsor country, there is only one user site, which is located near the production site. At this site, only one agrochemical is manufactured from OCBC in a closed system. Because OCBC is reacted away in the process, there is no release of OCBC to the environment from the production site of the agrochemical (Ihara Chem. Ind., 2003).

The use of agrochemicals manufactured from OCBC might be the source of environmental exposure of OCBC. This exposure scenario is not expected in the sponsor country, however, because no contamination of OCBC is detected in the final product (detection limit 0.002%) and OCBC is not detected as degradation products of agrochemicals in soil (Ihara Chem. Ind., 2003; Ikeda et al., 1986; FMC, 2003).

2.2.2 Photodegradation

The half-life of OCBC by the reaction with OH radical in air was calculated to be 103 hr (the length of the day; 12hr/day) with the values of 1.5×10^6 molecule/cm³ and 1.2454×10^{-12} cm³/molecule/sec for the OH radical concentration and the reaction rate constant with radical, respectively (AOPWIN ver.1.90, 2003).

2.2.3 Stability in Water

Stability of OCBC in water was examined according to OECD TG 111. OCBC was hydrolyzed to *o*-chlorobenzyl alcohol at 25°C with half-lives of 34.9, 33.1 and 36.4 hours at pH 4.0, 7.0 and 9.0, respectively (CERI, 1999a, 1998).

2.2.4 Transport between Environmental Compartments

Taking the following physico-chemical properties of OCBC into consideration, it is suggested that OCBC released into the environment is distributed into all the environmental compartments; air, water, soil and sediment. The index values of this chemical are water solubility as 100 mg/l (measured; CERI, 1999a), vapour pressure as 0.2 hPa (calculated; CERI, 2003), Partition Coefficient (LogP_{OW}) as 3.32 (measured; CERI, 1999b), Henry's law constant as 157 Pa m³/mol (calculated; CERI, 2003) and soil adsorption coefficient (K_{OC}) as 856 (calculated; CERI, 2003). This adsorption coefficient indicates a moderate potential of the substance for adsorption to soil and sediment.

The distribution of OCBC released into a particular compartment was estimated with a fugacity-based model, Mackay level III (CERI, 2003). The input parameters of half-life are 103hr (estimated), 33hr (measured), 240,000hr (default) and 720,000hr (default) in air, water, soil and sediment, respectively. The results are shown in Table 2-2. The model predicted that OCBC released into water is distributed into the water (73.5 %), the air (12.2%), the sediment (7.7%) and the soil (6.6%) compartments while OCBC released into air is distributed mainly into the air (64.1%) and the soil (34.6%) compartments. Almost all of the substance (99.8%) released into soil, on the other hand, was predicted to remain in its original compartment.

Table 2-2. Estimation of environmental distribution of OCBC with a generic Fugacity model, Mackay level III.

Compartment	Release		
	100% to air	100% to water	100% to soil
Air	64.1%	12.2%	0.2%
Water	1.1%	73.5%	0.0%
Soil	34.6%	6.6%	99.8%
Sediment	0.1%	7.7%	0.0%

2.2.5 Biodegradation

Biodegradation of OCBC by an activated sludge in 28 days was tested according to OECD TG 301C. The determination by the BOD and TOC methods showed 0% degradation of OCBC. The analysis by HPLC, however, indicated that all the substance was transformed, generating *o*-chlorobenzyl alcohol (92%), *o*-chlorobenzaldehyde (2%) and *o*-chlorobenzoic acid (3%) (CERI, 1998). The test without the activated sludge also indicated that OCBC was completely converted to *o*-chlorobenzyl alcohol without further transformation. Based on these observations, it is concluded that OCBC is hydrolyzed in water via an abiotic process to generate *o*-chlorobenzyl alcohol, which is then slowly biotransformed by oxidation to *o*-chlorobenzoic acid via *o*-chlorobenzaldehyde. Therefore OCBC and its hydrolysis products are not readily biodegradable.

An inherent biodegradability test was conducted according to OECD TG 302B (Wellens H., 1990). A mixture containing OCBC, mineral nutrients and an industrial activated sludge was agitated with aeration. This test was adapted to the volatility of a test substance by using a respirometric method to determine the biodegradation instead of DOC measurement. Thus the result was not influenced by volatilisation if any. The test showed 99% degradation of OCBC after 9 days. First 6 days were adaptation period (less than 10% degradation) and 90% degradation of OCBC was observed in the last 3 days. Thus, OCBC is inherently biodegradable with adapted industrial sludge.

2.2.6 Bioaccumulation

Bioconcentration factor for OCBC was calculated to be 71.85 (BCFWIN v 2.14) with a measured log K_{OW} of 3.32, indicating that accumulation of the substance in aquatic organisms is unlikely.

2.2.7 Other Information on Environmental Fate

No other information on environmental fate is available.

2.3 Human Exposure

2.3.1 Occupational Exposure

There is no Occupational Exposure Limit (OEL) for OCBC in Japan, Germany and Belgium. In each country, only one company, which has one production site, currently produces OCBC. And, the number of workers engaged in manufacturing and processing of OCBC is limited to less than twenty in each country (Ihara Chem. Ind., 2003; Clariant GmbH, 2003a; Tessenderlo Chemie N.V., 2003). Furthermore, in Japan and Germany, the number of operation days at the site is also limited (Japan; approx. 2-6weeks/year in 1999-2003, Germany; approx. 3-24 weeks/year) (Ihara Chem. Ind., 2003; Clariant GmbH, 2003a). The production of OCBC is carried out in a closed system. However, there are some possibilities that the workers are exposed to OCBC via the dermal or inhalation route in the processes such as putting stabilizer and raw material into a reaction tank, sampling and preparation for GC-FID analysis, filling a drum with OCBC produced, and handling residuals/wastes from the plant.

Occupational exposure monitoring was conducted at the production site in Japan. The results are summarized in Table 2-3 (Ihara Chem. Ind., 2003). These monitoring data revealed that the OCBC concentrations in the air of various workplace atmospheres ranged from 0.008 ppm to 0.017 ppm. Practically, the production of OCBC is operated in a closed system and workers are obliged to use personal protection equipments such as mask, safety glasses and gloves during operation. Thus, the actual levels of exposure to the chemical via the dermal or inhalation routes are expected to be minimal.

At the user site in the sponsor country, OCBC is used as the intermediate for the production of the agrochemical in a closed system and treated in a way similar to that at the production site. Putting OCBC into a reaction tank is the only process that might cause occupational exposure at the user site because OCBC is reacted away in the production of the agrochemical and no contamination of OCBC is detected in the final product (detection limit 0.002%). This process is just like a reverse process of filling drum with OCBC at the production site. Thus the OCBC concentrations in the air of workplace atmospheres at the user site are anticipated to be at the same level or less at the production site. Furthermore, workers at the user site are also obliged to use personal protection equipments such as mask, safety glasses and gloves during operation. Based on these facts, occupational exposure situation at the user site is equal or less compared to the situation at the production site in the sponsor country. Therefore the occupational exposure to OCBC is also considered to be negligible in the sponsor country (Ihara Chem. Ind., 2003).

Table 2-3. Concentration of OCBC in the air of workplace atmosphere

Work Process	Working time	Mean Conc. (ppm)
Putting stabilizer in a tank	10 sec./3days	ND (<0.013)
Putting raw material in a tank	10 sec./day	ND (<0.017)
Sampling and preparation for GC-FID analysis	20 min./day	0.0153
Filling a drum	6.5 hrs./day	0.008
	3 min./drum	
Treatment of waste oil (residual)	5 min./day	ND (<0.013)

ND: not detected

2.3.2 Consumer Exposure

The use of OCBC is limited to intermediates for producing agrochemicals. The agrochemicals manufactured from OCBC are only two herbicides in OECD countries. In the sponsor country, only one herbicide is produced and used. No contamination of OCBC is detected in this herbicide by GC

analysis (detection limit 0.002%). Therefore, consumer exposure is considered negligible in the sponsor country (Ihara Chem. Ind., 2003; Clariant GmbH, 2003a; Tessenderlo Chemie N. V., 2003).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

There are no data available for toxicokinetics, metabolism, and distribution of *o*-chlorobenzyl chloride (OCBC).

3.1.2 Acute Toxicity

Available data for acute toxicity of OCBC are summarized in Table 3-1.

Table 3-1. Summary of acute toxicity studies.

Species, strain	Route	Type	Value	Reference
Rat, Wistar	Inhalation (aerosol)	LC ₅₀	M & F: 2.8 mg/l 4hour	Clariant GmbH, 1987
Rat, Wistar	Inhalation (vapour)	LC ₅₀	M & F: > 1.14 mg/l 60min	Occidental Chem. Corp., 1990a
Rat, SD	Dermal	LD ₅₀	M & F: > 2,000 mg/kg bw	Ihara Chem. Ind., 1993b
Rabbit, N.Z.White	Dermal	LD ₅₀	M: 1,700 mg/kg bw F: 2,200 mg/kg bw	Monsanto Co., 1992
Rat, SD	Oral	LD ₅₀	M: 951 mg/kg bw F: 783 mg/kg bw	MHLW Japan, 1999a
Rat, SD	Oral	LD ₅₀	M: 690 mg/kg bw F: 533 mg/kg bw	Ihara Chem. Ind., 1993a
Rat, SD	Oral	LD ₅₀	M: 880 mg/kg bw F: 350 mg/kg bw	Monsanto Co., 1992
Rat, SD	Oral	LD ₅₀	M & F: 430 mg/kg bw	Occidental Chem. Corp., 1990a

Studies in Animals

Inhalation

There are two reliable studies on acute inhalation toxicity.

A study on acute inhalation toxicity in rats was carried out under OECD TG 403 in compliance with GLP (Clariant GmbH, 1987). Rats (5 animals/sex/group) were exposed (mouth/nose only) continuously for 4 hours to OCBC aerosol at concentrations of 0.587, 1.548, 1.648, 2.716, 5.268 and 5.723 mg/l, and observed for 14 days. Death occurred at 1.548 mg/l and higher. The LC₅₀ value was estimated to be 2.8 mg/l in both sexes. Clinical signs observed were gasping respiration, respiratory sounds, uncoordinated, ataxic and stilted gait, cyanosis, stupor, squatting posture, prone position, flanks pinched in, nose and lid margin red-encrusted, corneal opacity, and narrow palpebra fissure.

The other study on acute inhalation toxicity in rats was conducted by the method basically equivalent to OECD TG 403 in compliance with GLP (Occidental Chem. Corp., 1990a). Rats (10 animals/sex/group) were exposed systemically for 1 hour to OCBC vapour at a concentration of 1.140 mg/l and observed for 14 days. No animal death occurred during the observation period, indicating that the LC_{50} value is over 1.140 mg/l. Clinical signs as described above were also observed in the OCBC-treated animals. All the rats recovered to normal in 5 days after the exposure. There was no macroscopic and histopathological change observed in the animals.

Dermal

There are two reliable studies on acute dermal toxicity. Both studies were conducted under national guideline in compliance with GLP.

In a study, OCBC was applied to shaven skin of rats (5 animals/sex) at a dose of 2,000 mg/kg bw by semi-occlusive dressing for 24 hours and the animals were observed for 14 days (Ihara Chem. Ind., 1993b). No death occurred during the observation period, indicating that the LD_{50} value is over 2,000 mg/kg bw in both sexes. Clinical signs observed were clear ocular discharge, reddened extremities, urogenital staining, soft stool and hypoactivity. The signs disappeared by day 3 or earlier. The substance also induced irritation to skin, consisting of erythema, edema, desquamation, eschar and exfoliation.

In the other study, OCBC was applied to clipped skin of rabbits (15 animals/sex/group) at doses of 1,000, 2,000, and 4,000 mg/kg bw by occlusive dressing and the animals were observed for 14 days (Monsanto Co., 1992). The LD_{50} values were estimated to be 1,700 and 2,200 mg/kg bw in male and female rabbits, respectively. Clinical signs observed were reduction of food consumption, ataxia, tremors, hypopnea, hypothermia, nasal discharge, unthrifty coats and urinary/fecal staining. In addition, severe dermal lesion at the application site was also noted.

Oral

There are four reliable studies on acute oral toxicity in rats. LD_{50} values in these studies were determined on the basis of 14-day observation.

A study was conducted under OECD TG 401 in compliance with GLP (MHLW Japan, 1999a). OCBC diluted in 0.1% Tween80 was administered by gavage to rats (5 animals/sex/group) at doses of 350, 500, 700, 1,000 and 1,400 mg/kg bw. Animal death occurred at the doses of 500 mg/kg bw and higher. The LD_{50} values were estimated to be 951 and 783 mg/kg bw in male and female rats, respectively. Clinical signs observed were salivation, lacrimation, flushing, decrease in locomotor activity, loose stool and abnormal gait. Autopsy and histopathological examination of dead animals showed erosion/ulceration of the glandular stomach and submucosal edema of the forestomach. Autopsy of surviving animals revealed thickening of the forestomach wall, erosion/ulceration of forestomach and adhesion of the organs in the abdominal cavity. Histopathological examination of the surviving animals also showed ulceration, squamous epithelium hyperplasia, inflammatory cellular infiltration and granulation tissue in the forestomach, and peritonitis in the serous membrane.

The other studies in rats were conducted under national guideline or the method equivalent to OECD TG 401. The LD_{50} values determined by the studies were as follows: 690 (male) and 533 mg/kg bw (female) (Ihara Chem. Ind., 1993a); 880 (male) and 350 mg/kg bw (female) (Monsanto Co., 1992); 430 mg/kg bw (male/female) (Occidental Chem. Corp., 1990a). In these studies, clinical signs quite similar to those observed in the MHLW study were observed. Abnormalities indicative of irritation to gastrointestinal tract as described above were also noted in the OCBC-treated animals.

Conclusion

The inhalation LC₅₀ value in male and female rats was 2.8 mg/l. The dermal LD₅₀ values were 1,700 mg/kg bw (male) and 2,200 mg/kg bw (female) in rabbits and higher than 2,000 mg/kg bw in rats of both sexes. The oral LD₅₀ values in rats were in the range of 350 and 951 mg/kg bw. OCBC primarily caused irritation-related histological damage to a tissue where the substance was administered; lung by inhalation, skin by dermal application and stomach by oral administration.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Four reliable studies were available for skin irritation of OCBC. Two studies were conducted under OECD TG 404 (Ihara Chem. Ind., 1992; Clariant GmbH, 1985a) and the other two studies under the method equivalent to the OECD TG (Monsanto Co., 1992; Occidental Chem. Corp., 1990a). All the studies were performed in compliance with GLP.

In the study by Ihara Chem. Ind., 0.5 ml of OCBC was applied to skin of rabbits for 3 min, 60 min or 4 hours by semi-occlusive covering (Ihara Chem. Ind., 1992). Very slight to well-defined erythema was observed in all application sites. This reaction disappeared within 7 or 10 days. Very slight to slight edema was observed only in the 4-hour application sites from 24 to 48 hours after application. No necrosis was observed in any application sites. Based on these observations, OCBC was considered to have a mild dermal irritation potential on the rabbit skin.

In the other studies, OCBC was applied to skin of rabbits for 4 hours (Clariant GmbH, 1985a; Monsanto Co., 1992; Occidental Chem. Corp., 1990a) and also for 24 hours (Monsanto Co., 1992). The 4-hour application caused mild/moderate irritation to the rabbit skin with erythema and edema. No necrosis was observed, however. The 24-hour application, on the other hand, exhibited severer irritation accompanied with blanching of the skin in addition to moderate to severe edema. The primary irritation index for the 24-hour application was 3.9.

Eye Irritation

Studies in Animals

There are three reliable studies on eye irritation of OCBC.

The study by Clariant GmbH (Clariant GmbH, 1985b) was well conducted under OECD TG 405 in compliance with GLP. OCBC (0.1 ml) was applied to eyes of three rabbits and the eyes were rinsed 24 hours later. The animals were observed for 14 days after the application. All animals applied this substance showed a positive response with mild/moderate irritation to conjunctivae, iris and cornea. All the symptoms observed disappeared completely within the observation period, concluding that OCBC is mildly irritating to the eyes of rabbits.

In the other studies, 0.1 ml of OCBC was applied to eyes of rabbits with or without rinsing thereafter, and the animals were then observed for 21 days (Monsanto Co., 1992; Occidental Chem. Corp., 1990a). In either case, OCBC exhibited mild to moderate ocular irritation, which was reversible in the observation period.

Respiratory Tract Irritation

Studies in Animals

There are two reliable studies on respiratory irritation of OCBC in mice.

Male and female mice were exposed continuously for 30 minutes to OCBC vapour at concentrations of 11.9, 24.2, 82.3 and 179.5 mg/m³ (Vijayaraghavan et al., 1993). Respiratory rates were determined with body plethysmography. Inspiratory and expiratory airflow, and tidal volume were also measured. The potency for sensory irritation defined as the airborne concentration that caused 50 % decrease in the respiratory rate (RD₅₀) was 85 and 69 mg/m³ for male and female mice, respectively.

In the other study, male mice were exposed continuously for 10 min to OCBC vapour at least 4 doses (concentrations unknown) (Dudek et al., 1992). Sensory irritation was determined with body plethysmography. The RD₅₀ value in this study was 32.9 mg/m³.

Conclusion

OCBC is irritating but not corrosive to the skin of rabbits. OCBC is also irritating to the eyes of rabbits. Respiratory irritation was further noted for OCBC with the RD₅₀ value of 32.9 mg/m³ for male mice.

3.1.4 Sensitisation

Studies in Animals

Skin

No reliable study on skin sensitisation of OCBC has been reported while there is one study report with low reliability (Landsteiner and Jacobs, 1936). The study was conducted in guinea pigs, suggesting that eight out of thirteen animals tested gave a positive response to OCBC. However, this study was considered invalid because the criteria for positive/negative response were not defined in the report.

Respiratory Tract

There is no study available for respiratory tract sensitisation of OCBC in animals.

Conclusion

There is no reliable data available for sensitisation of OCBC although one study suggested skin sensitisation of OCBC in guinea pigs.

3.1.5 Repeated Dose Toxicity

Studies in Animals

There are two reliable studies on repeated dose toxicity in rats; one inhalation and one oral study. The studies were conducted under OECD TG in compliance with GLP.

Inhalation

The repeated dose inhalation toxicity study in rats was conducted under OECD TG 412 (Occidental Chem. Corp., 1990b). Rats (5 animals/sex/group) were exposed systemically to OCBC vapour for 4 consecutive weeks (6 hr/day, 5 days/week (Monday to Friday)) at concentrations of 0.01, 0.03 and 0.10 mg/l. No death occurred in any groups. Various toxicological findings were observed in male and female rats at 0.1 mg/l. Clinical signs indicative of irritation to respiratory tract were observed

during the exposure period. These included eyes shut/half-shut, adoption of a prone/hunched posture, rubbing of the chin on the mesh floor of the exposure chamber with licking of the inside of the mouth, red ears, agitated grooming and short periods of head shaking. Rales were noted in one male rat, during the latter half of Week 4. Body weight gain, food consumption and water consumption were reduced during the exposure period. Increases in packed cell volume, hemoglobin and red cell count, and a decrease in urinary volume were also observed. The ratio of myeloid and erythroid cells was increased. Gross autopsy revealed enlarged tracheobronchial lymph nodes and elevated lung weights. Histopathological examination showed damage to the nasal mucosa, trachea and bronchi (epithelial degeneration and hyperplasia of the nasal mucosa and the bronchiolar epithelium, squamous metaplasia of the bronchiolar epithelium), which was consistent with the irritating property of the OCBC vapour. Lymphoid hyperplasia was further observed in the tracheobronchial lymph nodes of some of the rats. There was no treatment-related change in male and female rats exposed at 0.01 and 0.03 mg/l. Based on these observations, NOAEL for inhalation repeated dose toxicity was considered to be 0.03 mg/l in both sexes.

Dermal

There is no study available for repeated dose dermal toxicity of OCBC in animals.

Oral

The repeated dose oral toxicity study in rats was conducted under OECD TG 422 (combined repeat dose and reproductive/developmental toxicity screening test) (MHLW, Japan, 1999b). Rats (12 animals/sex/group) were given OCBC by gavage at doses of 2, 10 and 50 mg/kg bw/day. Male rats were dosed from 14 days before mating to the day before scheduled sacrifice through the mating period (total 45 days). Female rats were dosed from 14 days before mating to 4 days after delivery through the mating and gestation periods (total 41-48 days). Suppression of body weight gain and a decrease in food consumption were observed in the early period of administration in male and female rats at 50 mg/kg bw/day. Increases in the relative and absolute liver weights were also observed in females at this dose. At scheduled sacrifice, thickening of the forestomach wall was observed in males at 10 mg/kg bw/day and both sexes at 50 mg/kg bw/day. Histopathological examination revealed squamous epithelium hyperplasia, erosion and ulceration in the forestomach in males at 10 mg/kg bw/day and both sexes at 50 mg/kg bw/day. The changes observed in the forestomach were considered due to the irritating property of OCBC. In addition, increases in the numbers of hyaline droplets in the proximal tubular epithelium, eosinophilic bodies, granular casts and basophilic tubules were observed in the kidneys of males at 50 mg/kg bw/day. There was no effect on hematological and clinical examinations and organ weights in male rats in the OCBC-treated groups. Based on these observations, the NOAEL for oral repeated dose toxicity was considered to be 2 mg/kg/day in male rats and 10 mg/kg/day in female rats.

Conclusion

In the inhalation toxicity study, clinical signs indicative of irritation to the respiratory tract were observed. The NOAEL for inhalation repeated dose toxicity was determined to be 0.03 mg/l in rats of both sexes. In the oral toxicity study, thickening of the forestomach wall, and squamous epithelium hyperplasia, erosion and ulceration in the forestomach were observed in male rats at 10 and 50 mg/kg bw/day and in female rats at 50 mg/kg bw/day. The NOAEL for oral repeated dose toxicity was considered to be 2 mg/kg/day in male rats and 10 mg/kg/day in female rats.

3.1.6 Mutagenicity

Available mutagenicity data of OCBC are summarized in Table 3-2.

In vivo Studies

There is one reliable study available for *in vivo* mutagenicity of OCBC.

A micronucleus assay in male and female rats was conducted under OECD TG 474 in compliance with GLP (Clariant GmbH, 2003b). A preliminary experiment showed that no death occurred at doses of 400 and 500 mg/kg bw while death (one out of three males and two out of three females) was observed 600 mg/kg bw. Thus OCBC was orally administered twice at an interval of 24 hours to the animals at 50, 150 and 500 mg/kg bw. In the dose group of 500 mg/kg bw, one out of ten animals died and the following clinical signs were observed 2 to 6 hours after the second treatment; diarrhea, stilted gait and cowering posture. All the animals were sacrificed 24 hours after the second treatment and subjected to the erythrocyte micronucleus test. No statistically significant increase in the micronucleated polychromatic erythrocyte frequencies was observed in any dose groups, indicating that OCBC is not clastogenic *in vivo*.

In vitro Studies

Bacterial mutation tests:

There are two reliable studies on bacterial mutation.

A study was conducted under OECD TG 471 in compliance with GLP (MHLW, Japan, 1999c). Effect of OCBC on reverse mutation was examined in four *Salmonella typhimurium* strains, TA98, TA100, TA1535 and TA1537, and in an *Escherichia coli* strain, WP2 *uvrA*, at concentrations up to 0.5 mg/plate with or without exogenous metabolic activation system. A marginal but dose-related increase was observed in TA100 without metabolic activation. In the presence of metabolic activation system, however, TA100 did not show any positive response. The other strains showed negative response regardless of metabolic activation. Based on these results, OCBC was considered a weak mutagen in the absence of metabolic activation but the mutagenicity was diminished or negated in the presence of the activation system.

The other bacterial mutation assay was performed under the scientifically acceptable method in compliance with GLP (Clariant GmbH, 1983) up to higher dose levels than the MHLW study. In this study, OCBC did not show any mutagenic activity in any tester strains regardless of metabolic activation.

Chromosome aberration test:

There is one reliable study on *in vitro* chromosome aberration in Chinese hamster lung (CHL/IU) cells.

The study was conducted under OECD TG 473 in compliance with GLP (MHLW, Japan, 1999d). The CHL/IU cells were continuously treated with OCBC for 24 or 48 hours at concentrations of 0.0013, 0.0025, 0.0050, 0.010 and 0.020 mg/ml without metabolic activation. A significant increase in polyploidy (3.38%) was observed at 0.010 mg/ml for 24 hours continuous treatment, at which concentration cytotoxicity was observed. In another assay, the CHL/IU cells were shortly (6 hours) treated with OCBC in the presence or absence of an exogenous metabolic activation system at concentrations of 0.013, 0.025, 0.050, 0.10 and 0.20 mg/ml. A significant increase in structural chromosomal aberrations (frequency: 13.0%) was observed only in the top concentration culture. These clastogenic and aneugenic activities were observed only at the highest concentration, which showed cytotoxicity, and next lower concentration of OCBC did not induce any chromosomal aberrations.

Table 3-2 Available genetic toxicity data

	Type	System of testing	Conc./Dose	Result		Reference
				-S9	+S9	
<i>In vitro</i>	Ames test	<i>Salmonella typhimurium</i> TA100, TA1535, TA98, TA1537, <i>Escherichia coli</i> WP2 <i>uvrA</i>	0.0156 – 0.5 mg/plate	+/-	-	MHLW, Japan, 1999c
			0.09 – 0.24 mg/plate	+/-	-	
				(TA100)	(TA100)	
	chromosomal aberration test	<i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538, <i>Escherichia coli</i> WP2 <i>uvrA</i>	0.0008 – 1.5 mg/plate	-	-	Clariant GmbH, 1983
		Chinese hamster lung (CHL/IU) cells	0.0013 – 0.02 mg/ml	+ ^{a)}	ND	MHLW, Japan, 1999d
<i>In vivo</i>	Micronucleus assay	SD Rat	0.013 – 0.2 mg/ml	-	+ ^{a)}	
					(0.1)	
<i>In vivo</i>	Micronucleus assay	SD Rat	50, 150, 500 ^{b)} mg/kg bw	-	ND	Clariant GmbH, 2003b

+: positive, +/-: equivocal, -: negative, ND: no data

a): positive at the concentration showed cytotoxicity.

b): In the dose group of 500 mg/kg bw, one out of ten animals died.

Conclusion

One bacterial mutation study revealed that OCBC was negative with or without exogenous metabolic activation. Another bacterial mutation study, on the other hand, showed weakly positive response without metabolic activation but negative with metabolic activation. An *in vitro* chromosome aberration test using CHL/IU cells was positive in the presence or absence of an exogenous metabolic activation system only at the cytotoxic concentrations. The micronucleus assay using male and female rats was negative tested up to the maximum tolerated dose. Based on the weight of evidence, OCBC is not anticipated to be genotoxic *in vivo*.

3.1.7 Carcinogenicity

There are no data available for carcinogenicity of OCBC.

3.1.8 Toxicity for Reproduction

Studies in Animals

There is one reliable study on reproductive/developmental toxicity of OCBC. This study was conducted as a combined repeat dose and reproductive/developmental toxicity screening test under OECD TG 422 in compliance with GLP (MHLW, Japan, 1999b). OCBC was administered by gavage to rats (12 animals/sex/group) at doses of 0 (vehicle control, 0.1% Tween80 solution), 2, 10 and 50 mg/kg bw/day. Males were dosed from 14 days before mating to the day before scheduled sacrifice through the mating period (total 45 days). Females were dosed from 14 days before mating to 4 days after delivery through the mating and gestation periods (total 41-48 days). OCBC showed no effect on the following parental reproductive parameters; mating index, fertility index, numbers of corpora lutea and implantations, implantation index, delivery index, gestation index, gestation length, and parturition and maternal behavior. In examination of neonates, there was no effect of OCBC on the numbers of total offspring and live offspring, sex ratio, live birth index, viability index, or body weight. No compound-related abnormality was also found in external features, clinical signs, or autopsy findings of offspring. Based on these observations, the NOAEL for reproductive/developmental toxicity was considered to be 50 mg/kg bw/day in rats.

Conclusion

There was no effect of OCBC observed on any reproductive and developmental parameters in rats up to 50 mg/kg bw/day. Thus the NOAEL for reproductive/developmental toxicity was considered to be 50 mg/kg bw/day in rats.

3.2 Initial Assessment for Human Health

No data are available for toxicokinetics, metabolism and distribution of OCBC.

The acute inhalation LC₅₀ value in male and female rats was 2.8 mg/l. The acute dermal LD₅₀ values were 1,700 (male) and 2,200 mg/kg bw (female) in rabbits and higher than 2,000 mg/kg bw in rats of both sexes. The oral LD₅₀ values in rats were in the range of 350 and 951 mg/kg bw. OCBC primarily caused irritation-related histological damage to a tissue where the substance was administered; lung by inhalation, skin by dermal application and stomach by oral administration.

OCBC is irritating but not corrosive to the skin of rabbits. OCBC is also irritating to the eyes of rabbits. Respiratory irritation was noted for OCBC with the RD₅₀ value of 32.9 mg/m³ for male mice.

There are no reliable data available for sensitisation of OCBC.

In the inhalation repeated dose toxicity study, rats were exposed to OCBC vapour for 6 hours a day for 4 weeks (5 days/week) at concentrations of 0, 0.01, 0.03 and 0.10 mg/l. At 0.10 mg/l, signs indicative of irritation to the respiratory tract such as enlarged tracheobronchial lymph nodes, elevated lung weights, damage to the nasal mucosa, tracheas and bronchi, and lymphoid hyperplasia in the tracheobronchial lymph nodes were observed. There was no treatment-related change in rats exposed at 0.01 and 0.03 mg/l. The NOAEL for inhalation repeated dose toxicity was determined to be 0.03 mg/l in rats of both sexes.

In the oral repeated dose toxicity study performed as a combined repeat dose and reproductive/developmental toxicity screening test, OCBC was administered by gavage to rats at doses of 0, 2, 10 and 50 mg/kg bw/day. The administration periods were 45 days for males and 41-48 days for females including all the periods between pre-mating and post-delivery. Thickening of the forestomach wall, and squamous epithelium hyperplasia, erosion and ulceration in the forestomach were observed in males at 10 and 50 mg/kg bw/day and in females at 50 mg/kg bw/day. Histological changes in kidney, such as increases in the numbers of hyaline droplets in the proximal tubular epithelium, eosinophilic bodies, granular casts and basophilic tubules, were also observed in males at 50 mg/kg bw. The NOAEL for oral repeated dose toxicity was considered to be 2 mg/kg bw/day in male rats and 10 mg/kg bw in female rats.

One bacterial mutation study revealed that OCBC was negative with or without exogenous metabolic activation. Another bacterial mutation study, on the other hand, showed weakly positive response without metabolic activation but negative with metabolic activation. An *in vitro* chromosome aberration test using CHL/IU cells was positive in the presence or absence of an exogenous metabolic activation system only at the cytotoxic concentrations. The micronucleus assay using male and female rats was negative tested up to the maximum tolerated dose. Base on the weight of evidence, OCBC is considered non-genotoxic *in vivo*.

There are no data available for carcinogenicity of OCBC.

As for the reproductive/developmental toxicity, no effect of OCBC on any reproductive and developmental parameters was observed in the above-mentioned combined repeat dose toxicity

study in rats at doses up to 50 mg/kg bw/day. Thus the NOAEL for reproductive/developmental toxicity was considered to be 50 mg/kg bw/day in rats.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The aquatic toxicity of *o*-chlorobenzyl chloride (OCBC) is summarized in Table 4. In each study, OCBC in the test solutions was measured except for two studies (Clariant GmbH, 1988, Dupont Chem., 1992). All the studies except one study (Dupont chem., 1992) were conducted under OECD test guidelines in compliance with GLP. However, these studies were considered reliable with restrictions because solvents and/or dispersants were used in the studies.

Acute Toxicity Test Results

Algae

There is one study with fresh water algae, *Selenastrum capricornutum*, which was conducted in a static system according to OECD TG 201 in compliance with GLP (EA, Japan, 1999a). The 72-hr EC₅₀ obtained on the basis of biomass and growth rate were 0.78 and 1.2 mg/l, respectively.

Invertebrates

One acute toxicity study with *Daphnia magna* has been reported (EA, Japan, 1999b). This study was conducted in a flow-through system according to OECD TG 202 in compliance with GLP. The 48-hr EC₅₀ based on immobilization was 0.38 mg/l.

Fish

There are three studies available on acute toxicity to fish. These studies except one study (Dupont chem., 1992) were conducted according to OECD TG 203 in compliance with GLP.

One study was conducted with *Oryzias latipes* in a flow-through system and showed that the 96-hr LC₅₀ was 0.27 mg/l (EA, Japan, 1999d).

The other studies were conducted with *Danio rerio* (Clariant GmbH, 1988) and with *Pimephales promelas* (Dupont Chem., 1992) in a static system and showed that the 96-hr LC₅₀ were 0.5-0.71 mg/l (nominal) and 0.71-0.96 mg/l (nominal), respectively.

Chronic Toxicity Test Results

Algae

A study with fresh water algae, *Selenastrum capricornutum*, was performed in a static system according to OECD TG 201 in compliance with GLP (EA, Japan, 1999a). The 72-hr NOEC based on the biomass and growth rate were 0.045 and 0.18 mg/l, respectively.

Invertebrates

The effect of 21-day exposure on reproduction of *Daphnia magna* was investigated as a chronic study, which was conducted in a semi-static system according to OECD TG 211. This study was well controlled under GLP regulation (EA, Japan, 1999c). The 21-day NOEC in this study was 0.020 mg/l.

Toxicity to Microorganisms

No toxicity data on aquatic microorganisms are available.

Table 4. Summary of toxicity test results to aquatic organisms.

Species	Age/Size	Stat/ Flow	Temp (°C)	Dissolved oxygen (mg/l)	Hardness (mg CaCO ₃ /l)	pH	Solvent/disper sant	Endpoint	Concentration (mg/l)	Test method	Reference
Algae											
<i>Selenastrum capricornutum</i> ^{a)}	1x10 ⁴ cells/ml (Initial cell number)	Static	23 ± 2			7.9-8.0 (begin ning) 8.0- 10.5 (end)	Polyoxyethyle nesorbitan fatty acid ester, 10 mg/l	72h EC ₅₀ 72h NOEC biomass 24-72h EC ₅₀ 24-72h NOEC growth rate	0.78 ^{c)} 0.045 ^{c)} 1.2 ^{c)} 0.18 ^{c)}	OECD 201 GLP	EA, Japan, 1999a
Invertebrates											
<i>Daphnia magna</i>	< 24 h old	Flow- through	20 ± 1	8.6-9	75	7.6-7.8	mixture of DMSO ^{b)} and polyoxyethyle nesorbitan fatty acid ester, 100 ul/l	48h EC ₅₀ immobilization	0.38 ^{c)}	OECD 202 GLP	EA, Japan, 1999b
	< 24 h old	Semi- static	20 ± 1	8.4-9.8	87-88	7.8-8.7	Polyoxyethyle nesorbitan fatty acid ester, 0.22 mg/l	21d NOEC 21d LOEC reproduction	0.020 ^{c)} 0.041 ^{c)}	OECD 211 GLP	EA, Japan, 1999c
Fish											
<i>Oryzias latipes</i>	2.2 cm 0.16 g	Flow- through	24 ± 2	8.5-9.1	45	7.1-7.4	mixture of DMSO ^{b)} and polyoxyethyle nesorbitan fatty acid ester, 100 ul/l	96 h LC ₅₀ NOEC behaviour	0.27 ^{c)} 0.18 ^{c)}	OECD 203 GLP	EA, Japan, 1999d
<i>Danio rerio</i>	2.8 cm	Static	21.0- 23.0	6.0-9.6		7.3-8.1	Tween80, 100 ul/l	96 h LC ₅₀	0.5-0.71 ^{d)}	OECD 203 GLP	Clariant GmbH, 1988
<i>Pimephales promelas</i>	2.2 cm, 0.17g	Static	22	8.3-8.4 (beginning) 2.4-7.3 (end)	72	7 (begin ning) 6.2-6.9 (end)	Acetone, 0.2%	96 h LC ₅₀	0.71-0.96 ^{d)}	Other	Dupont chem., 1992

a) now *Pseudokirchneriella subcapitata* b) dimethylsulfoxide c) Analytical monitoring was conducted. d) nominal concentration

4.2 Terrestrial Effects

No toxicity data on terrestrial organisms are available.

4.3 Other Environmental Effects

No other environmental effects data are available.

4.4 Initial Assessment for the Environment

OCBC has the water solubility of 100 mg/l at 25°C, the vapour pressure of 0.2 hPa at 25°C and the Log P_{OW} of 3.32. The K_{OC} of 856 indicates a moderate potential of the substance for adsorption to soil and sediment. The half life of OCBC by the reaction with OH radical in air was calculated to be 103 hr. Bioconcentration factor for OCBC was calculated to be 71.85, indicating that the bioaccumulation potential of the substance is low. In the biodegradation test [OECD TG 301C], OCBC is not readily biodegradable (BOD 0% after 28 days). OCBC is hydrolyzed in water via abiotic process to generate *o*-chlorobenzyl alcohol, which is then slowly biotransformed by oxidation to *o*-chlorobenzoic acid via *o*-chlorobenzaldehyde. An inherent biodegradability test [OECD TG 302B] showed that OCBC is inherently biodegradable with adapted industrial sludge.

Acute toxicity studies with algae, invertebrates including *Daphnia*, and fish have been reported. The results obtained from these studies are the 72-hr EC₅₀ of 0.78 mg/l for *Selenastrum capricornutum*, the 48-hr EC₅₀ of 0.38 mg/l for *Daphnia magna*, and the 96-hr LC₅₀ of 0.27 mg/l for *Oryzias latipes*.

A chronic toxicity test was performed to *Daphnia magna*. The 21-day NOEC for its reproduction was 0.020 mg/l (measured). The 72-hr NOEC (biomass) for the growth of *Selenastrum capricornutum* was 0.045 mg/l. No chronic toxicity data on fish are available.

Based on the stability of OCBC in water (half-life, 33.1 hours at pH7), considerable hydrolysis of OCBC to *o*-chlorobenzyl alcohol is anticipated. Thus the aquatic effect of *o*-chlorobenzyl alcohol was taken into consideration. Although no toxicity data is available for this substance, the analysis by ECOSAR (ECOWIN v0.99g) showed 96-hr LC₅₀ of 15.7-189.7 mg/l for fish and 48-hr LC₅₀ of 0.3-0.6 mg/l for *Daphnia*, suggesting that *o*-chlorobenzyl alcohol is not more toxic to aquatic organisms than OCBC. Consistent with this prediction, the 96 hr LC₅₀ values (nominal) of OCBC for fish obtained in a static system (0.5-0.71 mg/l for *Danio rerio* and 0.71-0.96 mg/l for *Pimephales promelas*) were larger than that obtained in a flow-through system (0.27 mg/l for *Oryzias latipes*).

OCBC is produced by chlorination of *o*-chlorotoluene in a closed system. There is no process that generates the waste water in the production of OCBC. The waste residue is incinerated. The off-gas of the reaction is incinerated or treated on active carbon. Therefore, there is no release of OCBC to the environment from its manufacturing plants. The use pattern of OCBC is also limited to the intermediates for the production of agrochemicals. In the sponsor country, only one agrochemical is manufactured from OCBC in a closed system. Because OCBC is reacted away in the process, there is no release of OCBC from the production site of the agrochemical. No contamination of OCBC is detected in the agrochemical (detection limit 0.002%). OCBC is not detected in soil as degradation products of agrochemicals. Based on these facts, it is considered that the impact of OCBC to the environment (aquatic and terrestrial) is negligible.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work.

The chemical possesses properties indicating a hazard for human health (repeated dose toxicity) and the environment. Based on data presented by the Sponsor country, exposure to humans and 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 Sponsor countries.

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