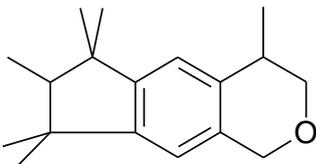


SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1222-05-5
Chemical Name	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta- γ -2-benzopyran (HHCB)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

HHCB is a viscous liquid with a melting point between -10 and 0°C and a boiling point of 325 °C. The vapour pressure is 0.0727 Pa at 25 °C. HHCB has a measured water solubility of 1.75 mg/l at 25°C. The log Kow as determined by the slow stirring method was 5.3.

Human Health

There are no toxicokinetic data available of HHCB after oral or inhalation exposure. After intravenous administration numerous HHCB metabolites were found in rat and pig urine samples. In an *in vitro* absorption study using 1% HHCB in 96 % alcohol with human epidermal membranes 5.2% of the applied dose was absorbed over 24 hours.

HHCB was also found in human milk samples from women in several European countries, which were not intentionally exposed, at levels up to 1316 µg/kg fat and in adipose tissue at levels ranging from 12 – 189 µg/kg fat.

The oral LD₅₀ for rats, as well as the dermal LD₅₀ for rabbits were > 3000 mg/kg bw. The dermal LD₅₀ for (female) rats was > 6500 mg/kg bw. Data for acute inhalation toxicity were not available.

HHCB was not corrosive, not irritating and not sensitizing to the skin, as determined from irritation and sensitisation studies in animals and humans. No data on respiratory tract irritation were available. In relevant studies, HHCB was considered to be a minimal eye irritant in rabbits. There were some indications from animal studies (rabbits and guinea pigs) that HHCB could be a photo-irritant. Human and *in vitro* studies showed no photo-irritating effects.

In a 90-day oral study in accordance with OECD Guideline 408 with 15 animals/sex/dose (concentrations via diet were 5, 15, 50 or 150 mg/kg bw/day), there were no mortalities or adverse clinical signs. Body weight and food consumption of treated groups were similar to those observed in the control group. No changes in ophthalmologic evaluation were observed and no significant histopathological findings at any dose were observed. Haematology and blood chemistry differences from controls were all small, often not proportional to dose. These findings were not accompanied by any adverse histopathology or other related findings, led to the conclusion that they were not adverse effects. A NOAEL of 150 mg/kg bw/day, the highest dose tested, for HHCB in rats was concluded.

HHCB was a non-genotoxic substance as evidenced by a wide array of *in vitro* tests and in an *in vivo* mouse micronucleus test. *In vitro*, HHCB was negative in gene mutation tests with bacteria with and without metabolic activation, in a chromosomal aberration assay with CHO-K1 cells with and without metabolic activation, in SCE and micronucleus tests with human cells with and without metabolic activation, and in an UDS test with primary rat hepatocytes. HHCB also did not induce significant chromosome aberrations in the *in vivo* micronucleus test.

There were no carcinogenicity test data available.

No standard multiple generation studies were available. In the 13-week oral repeated dose toxicity study, administration of doses of 0, 5, 15, 50 and 150 mg/kg bw/day via the diet had no effects on the reproductive organs of male or female rats. Furthermore, no effect on reproduction performance was found in a peri/postnatal study.

In an oral peri/postnatal toxicity study groups of 28 pregnant female rats were exposed once daily by gavage to doses of 0, 2, 6 and 20 mg/kg bw/day from day 14 of pregnancy through weaning on day 21 post partum (exposure of only the F₁-generation to HHCB *in utero* during the perinatal phase or through any transfer in the milk of the lactating dams). No toxicity in dams or their F1 and F2 offspring was seen at up to the highest dose. A NOAEL of 20 mg HHCB /kg bw/day (the highest dose tested) was established.

In an oral developmental study HHCB was administered by gavage in corn oil to groups of 25 female rats at doses of 50, 150 and 500 mg/kg bw/day on day 7 through 17 of pregnancy. Signs of maternal toxicity were observed at 150 mg/kg bw/day and higher. There was an increased incidence of skeletal malformations and decreased ossification in foetuses at the highest dose of 500 mg/kg bw/day. The NOAEL for maternal toxicity was 50 mg/kg bw/day and for developmental toxicity the NOAEL was 150 mg/kg bw/day. From the peri/postnatal toxicity study described above a NOAEL of 20 mg/kg bw/day (the highest dose tested) was established. HHCB had a very weak estrogenic potency *in vitro*, but such effects were not seen *in vivo* in a uterotrophic assay in non-ovariectomized mice but otherwise similar to OECD TG 440 up to 40 mg/kg bw (300 ppm in the diet of mice for 2 weeks).

HHCB does not present a concern for reproductive/developmental toxicity based on the information available.

HHCB does not present a hazard for human health due to its low hazard profile. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

HHCB is considered hydrolytically stable, because the molecule does not contain any functional groups that would react with water. Under atmospheric conditions direct photolysis by sunlight and gas phase reaction with OH radicals are considered to be the major degradation routes for HHCB. Based on the measured rate constant of $2.6 \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ sec}^{-1}$ and assuming a daylight period of 12h and OH radical concentration of $1.5 \times 10^6 \text{ OH-radicals/cm}^3$, the atmospheric half-life is 3.7 hours. The half-life for degradation by UV radiation in lake water was circa 109 hours in a laboratory set-up comparable to mid-summer clear sky sunlight conditions at 50°N. HHCB was not readily biodegradable in an OECD TG 301B test. In a primary biodegradation process HHCB was rapidly transformed to a series of more polar metabolites, with HHCB-lactone and hydroxycarboxylic acid as likely intermediates. In a river water die-away study with 10 mg activated sludge to simulate surface water conditions at the point of discharge, the disappearance of ¹⁴C-labeled parent material and the formation of metabolites was determined. The overall half life was 100 hours and the biological degradation (primary) was over 60% in 28 days. In a sludge die-away study a half-life of 10 to 15 hours was observed, with 70% present as metabolite after 28 days. Mesocosm studies on spiked soil and sediment indicate that HHCB disappeared almost completely within

one year. Residues in soil, expressed as the sum of HHCb and AHTN (CAS. 1506-02-1), in fields with regular sludge application were well below 1% of the estimated applied amount within a few years after the last sludge application.

A level III fugacity model with equal and continuous distribution to air, water and soil compartment suggest that HHCb will distribute in air <<1%, water, 2%, soil, 34% and sediment 64%. The measured Henry's Law Constant is 36.9 Pa.m³/mol at 25°C. The calculated log K_{oc}, based on log K_{ow} is 4.39 and is within the range of the measured log K_{oc} values (3.6 to 4.9 in various matrices). The measured bioconcentration factor of HHCb determined according to OECD TG 305E in bluegill sunfish was 1584 and in zebra fish 624. The half-life for elimination was less than 2 days.

Acute aquatic toxicity data are available:

Taxon	Test species	Endpoint	Result mg/L	Guideline	M/N**
Fish	<i>Lepomis macrochirus</i> Bluegill sunfish	96h-LC ₅₀ (mortality)	1.36	OECD TG 204	M
Invert	<i>Daphnia magna</i>	72h-EC ₅₀ * (immobility)	0.88	OECD TG 202- part 2	M
Algae	<i>Pseudokirchneriella subcapitata</i>	72h-EC ₅₀ (growth rate biomass)	0.854 0.723	OECD TG 201	M
Invert	<i>Acartia tonsa</i> [marine]	48h-LC ₅₀ (mortality)	0.47	draft ISO/DIS 14669	N
Invert	<i>Nitocra spinipes</i> [marine]	48h-LC ₅₀ (mortality)	1.9	draft ISO/DIS 14669	N

* Derived from OECD TG 202-part 2 test (see below)

**N: nominal; M: measured

The following chronic toxicity test results have been determined for aquatic species:

Taxon	Test species	Endpoint	Result mg/L	Guideline	M/N*
Alga	<i>Pseudokirchneriella subcapitata</i>	72h-NOEC (growth rate)	0.201	OECD TG 201	M
Invert	<i>Daphnia magna</i>	21d-NOEC (reproduction)	0.111	OECD TG 202-part 2	M
Invert	<i>Acartia tonsa</i> [marine]	6d-EC10 (larval development ratio)	0.044	OECD draft TG (life cycle test) (2004)	M
Fish	<i>Lepomis macrochirus</i> Bluegill sunfish	21d-NOEC (respiration, equilibrium)	0.093	OECD TG 204	M
Fish	<i>Pimephales promelas</i> Fathead minnow	32d-NOEC (survival, growth, development)	0.068	OECD TG 210	M

*N: nominal; M: measured

Toxicity tests were carried out with three species of sediment organisms according to or in line with OECD TG 218. The 28-day NOEC for the midge larvae *Chironomus riparius* was 200 mg/kg dwt (development), for the amphipod *Hyalella azteca* 7.1 mg/kg dwt (growth) and for the aquatic oligochaete worm *Lumbriculus variegatus* 16.2 mg/kg dwt (growth) at an organic carbon content of 2%. Toxicity tests were also carried out with soil organisms. The 8-week NOEC (reproduction) for the earthworm *Eisenia foetida* according to OECD TG 207 and the 4-week NOEC (reproduction) for springtail *Folsomia Candida* were both 45 mg/kg according to ISO/CD 11267.

HHCB may present a hazard for the environment (acute aquatic toxicity values <1 mg/L and not readily biodegradable). Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

The entire production of HHCB is at one plant in Europe, with a production volume in 2000 between 1000 and 5000 ton/y. Use volumes are according to RIFM (Research Institute of Fragrance Materials) and IFRA (International Fragrance Association) based on regional surveys carried out between 1993 and 2006. For the countries belonging to EU-15 plus the two associated countries Norway and Switzerland, the use volumes declined from 2400 ton per year in 1992, 1427 ton per year in 2000 to 1307 ton per year in 2004.

HHCB is used as an ingredient in fragrance oils (fragrance oils is also referred to in literature as fragrance compounds, fragrances, fragrance composition, perfume oil or perfume compositions). HHCB is the largest volume product of the fragrance materials known collectively as polycyclic musks. Fragrance oils are complex mixtures, prepared by blending (compounding) many fragrance ingredients in varying concentrations. Most of these ingredients are liquids, in which HHCB is dissolved. Applications of the fragrance oils are mainly in consumer products such as perfumes, cosmetics, soaps, shampoos, detergents, fabric conditioners, household cleaning products and air fresheners. Blending of the fragrance oil with other ingredients to make the final consumer product is often referred to as a formulation.

Environmental release of HHCB may occur during production, during compounding, during formulation and during/after use by consumers. It is assumed that the total use volume is discharged to the sewer.

Occupational exposure is possible during production, during compounding, during formulation and during cleaning by professional cleaners. Dermal and inhalation occupational exposure to pure HHCB and dermal exposure to mixtures containing HHCB are relevant. Compounding fragrance oils and formulating consumer products involve a high level of automation, intensive ventilation and a high working accuracy required to prevent any cross contamination. Professional cleaners may be exposed to HHCB while using cleaning products and dermal exposure may occur each time hands are submersed in the diluted cleaning solution.

Consumer exposure may occur following dermal and inhalation exposure of which the dermal exposure is the highest.