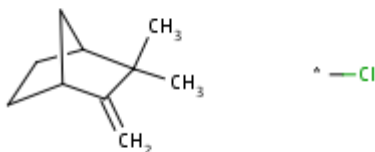


TOXAPHENE	
CAS No.: 8001-35-2 Synonyms: <ul style="list-style-type: none">- Camphechlor- Chlorinated camphene- PCC- Polychlorocamphene	
Chemical structure	
 <p style="text-align: center;">Chemical formulae¹</p>	
Properties	
<p>Toxaphene is an amber, waxy solid with a mild terpene odour consisting of a complex mixture of polychlorinated terpenes with a melting range of 65 - 90°C (table 1). It is also known as camphechlor, chlorocamphene, polychlorocamphene, and chlorinated camphene (EFSA, 2005).</p>	
Table 1: Properties of toxaphene (EFSA, 2005)	
Solubility in water	0.63 mg/L at 25°C.
Melting point	65 - 90°C
Henry's law constant	1.05 Pa-m ³ /mol at 25°C
log K _{oc}	
log K _{ow}	4.82 to 6.4
Vapour pressure	4x10 ⁻⁵ Pa at 20°C to 4.4x10 ⁻³ Pa at 20-25°C
Contamination source	
<p>Toxaphene is a complex mixture of chlorinated hydrocarbons produced by the chlorination of camphene. Toxaphene was widely used from the late 1940s as an insecticide on crops and to control parasites on livestock (IARC, 2001).</p> <p>Camphechlor is a non-systemic insecticide with some acaricidal action and was used on crops and animals. The primary crops on which camphechlor were used was cotton, cereal grains, fruits, nuts, oil seeds, and vegetables. It was also used as piscicide in freshwater lakes. Use on livestock was primarily for the control of ticks and mites. Camphechlor has been the most heavily applied insecticide in the U.S. and in many parts of the world and replaced DDT as a major insecticide in the early 1970s (EFSA, 2005). Its production was banned in the European Union for all uses in 1984. The use of camphechlor is now phased out in most of the world.</p> <p>Camphechlor belongs to those persistent organic pollutants (POPs), which were initially chosen for elimination by the Stockholm Convention on POPs in May 2001 (EFSA, 2005).</p> <p>Technical camphechlor mixtures show a complex composition, with at least 202 different compounds identified. Due to its persistence and chemical properties it has found a widespread distribution. Environmental biotransformation and accumulation in the aquatic environment has led to relatively high levels of certain camphechlor congeners in fish, marine mammals and sea birds</p>	

¹<http://chem.sis.nlm.nih.gov/chemidplus/jsp/common/ChemInfo.jsp?calledFrom=lite&type=formulas>

while other congeners rapidly degrade (EFSA, 2005).

Occupational exposure to toxaphene has occurred during its production and application. Human exposure to toxaphene is still possible owing to its persistence in the environment and its consequent continuing occurrence in fish, milk and other foodstuffs. In those countries in which its use has been banned, dietary intake has probably decreased in recent years (IARC, 2001).

Analytical method

Currently, high resolution gas chromatography with electron capture detection (GC/ECD) or preferably high resolution gas chromatography coupled to mass spectrometry (GC/MS) in the electron impact (EI) or negative ion chemical ionization (NICI) mode are the analytical methods of choice for the analysis of toxaphene. The latter offers the advantage of being both more selective and sensitive (EFSA, 2005).

Toxicity

General toxicological effects

Camphechlor is readily absorbed from the gastrointestinal tract and distributed to the lipid portion of the organism. It passes the placenta and transfer to milk has been shown in animals and humans.

Fatal poisonings associated with neurotoxic symptoms (convulsions, tremor, salivation, vomiting and breathing difficulties) in humans, especially in small children, have been reported. Particularly occupational exposure via skin or inhalation may give rise to high dose exposure (EFSA, 2005).

The oral LD₅₀s, which have been obtained in rats, mice and hamster, are 60 to 300 mg/kg bw (ATSDR, 1994). Camphechlor seems to be somewhat more toxic in dogs, dependent on the vehicle used. In corn oil the LD₅₀ was 15 mg/kg bw in dogs (Lackey, 1949). Very little is known about the toxicity of different camphechlor components. The LD₅₀ is not only dependent on the number of chlorines but also on their position on the ring structure.

The harmful effects of toxaphene are injures the kidneys and liver, damages the immune system, harms the adrenal gland, causes changes in the development of unborn children, may cause cancer, damages the lungs and damages the nervous system (EPA, 2011).

Biochemical and cellular effects of camphechlor include i.a. phenobarbital like induction of drug metabolising enzymes in the liver, inhibition of ATPases in the liver, kidney and brain, and blocking of GABA gated chloride channels in the nervous system (Brüschweiler *et al.*, 2004).

Neurotoxicity has been reported in fish, birds and mammals. Other toxic effects occur in the liver, thyroid and immune system (EFSA, 2005).

Carcinogenicity

One case-control study of non-Hodgkin lymphoma and one of leukaemia not otherwise specified in the same populations showed no significant increase in risk associated with exposure to toxaphene (IARC, 2001).

Toxaphene has been tested for carcinogenicity by oral administration in one study in mice and one study in rats. It increased the incidence of hepatocellular adenomas and carcinomas combined in male and female mice. In rats, it produced thyroid follicular-cell adenomas and carcinomas in both males and females and pituitary adenomas in females (IARC, 2001).

Toxaphene is lipid-soluble and accumulates in animals. It is metabolized by dechlorination and excreted into the bile. Toxaphene is a well-known microsomal enzyme inducer that increases phase I and II drug metabolizing enzymes, consistent with a phenobarbital-like effect. It also increases the size of the thyroid gland and thyroid-stimulating hormone concentrations (IARC, 2001).

There is *inadequate evidence* in humans for the carcinogenicity of toxaphene (IARC, 2001).

There is *sufficient evidence* in experimental animals for the carcinogenicity of toxaphene. Toxaphene is *possibly carcinogenic to humans (Group 2B)* (IARC, 2001).

In the European Union, toxaphene was classified as Carc. Cat.3; R40 according to Dir 67/548/EEC and as Carc.2 H351 according to CLP Regulation (EC) No. 1272/2008.

Genotoxicity

Camphechlor was mutagenic in some *Salmonella* strains (TA98 and TA100, but not in TA1535 or TA1537) and is a weak inducer of sister chromatid exchanges *in vitro*. It induced micronuclei in the only assay for this end-point performed in mammalian cells. Other *in vitro* tests of mutagenicity have been negative. A dominant lethal study in mice was negative and DNA adducts were not found in the livers of mice exposed to camphechlor using ³²Ppost- labelling (Anonymous, 1997, Goodman *et al.*, 2000, Hedli *et al.*, 1998). It also inhibited gap-junctional intercellular communication in cultured mammalian cells (IARC, 2001).

An increased frequency of chromosomal aberrations was observed in the lymphocytes of workers exposed to toxaphene in one study.

Reproductive toxicity

No reproductive or developmental effects were seen in three multigeneration studies in rats (IARC, 2001).

Camphechlor was administered to mice and rats on days 7 -16 of gestation by oral intubation at levels of 15 - 35 mg/kg body weight per day (Chernoff & Carver, 1976). The highest dose produced marked maternal mortality in rats and mice and an increase in encephaloceles among offspring of mice. Fetal mortality was slightly increased in mice at all dose levels. Small decreases in fetal body weight and in the number of sternal and caudal ossification centres were observed in rats, mostly in the 25 mg/kg dosage group (Chernoff & Carver, 1976).

Endocrine effects

Camphechlor may cause endocrine effects (Mohammed *et al.*, 1985). Camphechlor accumulates in the adrenal cortex/zona fasciculata in mice and was found to inhibit ACTH stimulated corticosterone synthesis *in vitro*. *In vitro* camphechlor was weakly anti estrogenic possibly via orphan receptor ERR α -1 binding and suppression of aromatase (Arcaro *et al.*, 2000, Chen *et al.*, 2001). In rats receiving 100 mg camphechlor/kg bw/day for three days and then 75 mg/kg bw/day for another 25 days showed a time dependent increase in thyroid stimulating hormone (TSH) in the blood was observed (Waritz *et al.*, 1996).

Establishment of Health Based Reference Values

Health Canada established in 1995 a TDI of 200 ng/kg bw/day based on the NOAEL value (0.2 mg/kg/day) found for liver toxicity in a 13-week study in dogs, using an uncertainty factor of 1000. In a review, Brüsweiler *et al.* (2004) derived a TDI of 100 ng/kg bw/day based on the NOAEL for immunotoxicity in a 33 weeks study in macaque using an uncertainty factor of 1000 because humans are exposed to a different mixture of camphechlor through food than the technical mixture used in experiment (EFSA, 2005).

Occurrence in food

The data available on human dietary exposure indicate that the highest exposure to camphechlor can be expected from intake of fish with high lipid content (EFSA, 2005).

Mean concentration of toxaphene (sum) measured for commercially Atlantic salmon fillets on the Norwegian market in 2007 range <5.7–16.9 ng/g ww (n =27) (Berntssen *et al.*, 2011).

Concentration of toxaphene of 2.3 ng/g lipid measured in a Belgian pooled sample collected in 2006 during the fourth World Health Organization Human biomonitoring campaigns is low (Colles *et al.*, 2008).

Dietary exposure assessment

Based on fish consumption data and most recent concentrations of total camphechlor in European fishery products an average daily intake between 0.2 and 1.2 μ g was estimated for Norway, Germany, Ireland, and The Netherlands based on an average fish consumption between 9 and 60 g/day, and the average camphechlor concentration in fish was 20 μ g/kg. Converted to body weight (60 kg), these intake figures range approximately from 3.5 to 20 ng/kg bw. Similar results were obtained for Netherlands by RIVM (2001) by using levels of the three indicator congeners CHB 26, 50 and 62 from a German database on fish and assuming that the sum of CHB 26, 50 and 62 amounts to 25 – 50 % of total camphechlor. However, for high fish consumers from Norway (184 g/day) the estimated daily average intake of camphechlor was 3.7 μ g or 62 ng/kg bw, respectively (EFSA, 2005). Brüsweiler *et al.* (2004) estimated the daily intake of 25 ng total camphechlor/kg

bw by linking camphechlor concentrations of medium contaminated fish samples from Europe and Canada, milk and meat samples from Finland and food samples of plant origin from the United States with a typical European diet according to the Global Environmental Monitoring System (GEMS/Food) by WHO. More than 65% of this intake was attributed to fish. However, it has to be stated that these estimations are tainted with significant uncertainties, particularly in food of plant origin, due to the lack of representative and recent occurrence data in food as well as the imprecision of estimating total camphechlor concentrations. For example, camphechlor contamination of fish was calculated from the sum of CHB 26, 50 and 62 by multiplying by 4.

Although tainted with a lot of uncertainties, most intake estimations indicate an average daily camphechlor intake for adults in the range of 1 - 25 ng/kg bw. For high fish consumers, intake values up to 62 ng total camphechlor/kg bw/day were estimated. The limited data available from Europe suggest an average daily intake of persistent camphechlor congeners between 25 and 70 ng/kg bw for nursing infants (EFSA, 2005).

Risk characterization

Human dietary exposure is mainly from fatty fish, which is estimated to be between 1 and 25 ng/kg bw/day. High fish consumers may have intakes of about 60 ng/kg bw/day, which is still considered to remain without health effects, based on a NOAEL of 100 µg/kg bw for immunotoxicity, the most sensitive endpoint, from a 33 week study in macaque (EFSA, 2005).

Table 2: Dietary exposure and % TDI for toxaphene

Source data exposure	Dietary exposure (ng/kg bw/day)	%TDI (100 ng/kg bw/day) (Brüschweiler et al., 2004)
Europa (EFSA, 2005).	3.5	3.5
Europa (EFSA, 2005).	20	20
Netherlands (RIVM, 2001)	3.7	3.7
Netherlands (RIVM, 2001)	62	62
Brüschweiler <i>et al.</i> (2004)	25	25
Nursing infants (EFSA, 2005).	25 - 70	25 - 70

Legislation

Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC which will repeal the four Council Directives

Recommendations

The CONTAM Panel of EFSA made the following recommendations (EFSA, 2005):

- In the future more attention should be given to the congeners CHB 40, 41, 42 and 44 which have also been found in food, especially in fish samples, and since animal experiments show that CHB 42 is one of the most toxic congeners.
- CHB 32 should be included as an indicator for a recent contamination, because this compound is a major constituent in technical camphechlor mixtures, but readily, degrades in the environment
- Proficiency tests performed on environmental and food samples reveal large discrepancies in the performance of laboratories, indicating scope for improvement of the analytical methods
- Availability of certified reference materials for relevant matrices, such as fish oil or fish meal would be an important tool for laboratories to check and optimise their analytical methodologies. Because such certified reference materials are presently unavailable, it is recommended such materials are prepared and made available to analytical laboratories.
- The organization of further proficiency tests is essential to verify the applied analytical methodologies and to demonstrate that they are appropriate for a reliable determination of camphechlor levels at the trace levels expected in feed, food and human samples.
- Oral toxicity studies of camphechlor especially in farmed fish should be performed.
- Most of the monitoring data from Member States are reported to the EU Commission only as compliant or non-compliant. For future risk assessments it would be valuable if the actual levels measured were available.

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