Hexabromocyclododecane and hexachlorocyclohexane: how lessons learnt have led to improved regulation.

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Running header: Learning lessons from hexachlorocyclohexane

Abstract

The use of chemicals by society has many benefits but contamination of the environment is an unintended consequence. One example is the organochlorine compound hexachlorocyclohexane. During the 1980s, when hexachlorocyclohexane was banned in many countries, the brominated flame retardant, hexabromocyclododecane, found increasing use. The persistent, bioaccumulative and toxic characteristics of hexabromocyclododecane are, 30 years later, likely to warrant global action on production and use under the Stockholm Convention on POPs. Historical lessons have taught us that we need to control the use of chemicals and programmes are in place worldwide in an attempt to do so.

1.0. Introduction

Over the years, the growth of the chemical industry and the manufacture and use of a number of chemical substances have resulted in global contamination of the environment with some chemical substances. In particular, those classified as persistent organic pollutants (POPs) have attracted attention due to a growing body of scientific evidence of their PBT properties and the potential for long-range environmental transport (UNEP, 2009). Among POPs are the synthetic organohalogens, hexachlorocyclohexane (HCH) and hexabromocyclododecane (HBCD). The manufacture and use of HCH began much earlier than that of HBCD (Breivik *et al.,* 1999; Alaee *et al*., 2003). For several years, the environmental fate and toxicological effects of HCH were extensively studied and known before the manufacture and use of HBCD (ATSDR, 2005; EC, 2008).

With the molecular formula $C_6H_6Cl_6$, HCH is an organochlorine first synthesized in 1825 by photochlorination of benzene, and was then known as benzene hexachloride (BHC) (CEC, 2006). Technical HCH is a mixture of five isomers: α (alpha)-HCH (55-80%), β (beta)-HCH (5-14%), γ (gamma)-HCH (8-15%), δ (delta)-HCH (2-16%) and ε (epsilon)-HCH (3-5%) (Vijgen *et al*., 2011). The proportion of the different isomers in technical products varied due to differences in production processes. The most environmentally significant isomers are the α, β and γ isomers. The insecticidal property of HCH virtually exhibited by the γ isomer was discovered in 1942. The γ-HCH was then named lindane after Van Linden, the discoverer of the α and γ isomers (CEC, 2006). With the exception of γ-HCH, the other isomers of HCH became residues of the production process. Technical HCH was used in the control of insect pests until the late 1970s when it was replaced by lindane (≥99% γ-HCH) (Breivik *et al*., 1999). The production of 1 tonne of lindane generated approximately 6-10 tonnes of α- and

β-HCH and as a result of the waste isomers generated, the production and regulation of lindane was a global problem for many years (IHPA, 2006).

Lindane and technical HCH have been used in the treatment of fruits, food crops, ornamental plants, seeds, forestry products, soil, livestock and pets to eradicate pests such as insects, ticks and mites (Li, 1999). The insecticide has also been used as a pharmaceutical formulation in shampoo, lotions or creams for treatment of head lice and scabies (mite infection) in humans (WHO, 1991). It is estimated that from 1950 to 2000, about 600,000 tonnes of lindane was used globally; on an annual basis this was about 12,000 tonnes per annum over a period of 50 years. The estimated use in agriculture in Europe, Asia, Africa and Oceania were 287,160, 73,200, 63,570, 28,540 and 1,030 tonnes, respectively (IHPA, 2006). Breivik *et al*. (1999) reported that 382,000 tonnes of technical HCH and 81,000 tonnes of lindane were used in Europe from 1970 to 1996. In addition, they observed an estimated cumulative usage of 259,000 tonnes of α-HCH, 135,000 tonnes of γ-HCH and 20,000 tonnes of β-HCH.

Release of HCH to the environment involves several pathways: emissions from manufacturing sites; volatilization to the atmosphere during application in agriculture; atmospheric deposition; leaching in soil and release from stockpiles of disposed residual HCH isomers (UNEP, 2006). Exposure of biota (including humans) to HCH is mainly through intake of contaminated food and water. In addition, human exposure to lindane may be by direct contact during its application for pharmaceutical and agricultural purposes (CEC, 2006; UNEP, 2006). Because of the adverse effects of lindane on the environment and human health, by 2006, the use of lindane had been banned in 52 countries, and restricted in 33 countries (CEC, 2006). The proposal to list lindane and α- and β-HCH on Annex A

(elimination) of Stockholm Convention on POPs was made by Mexico in 2005 and 2006, respectively (Vijgen *et al*., 2011). In 2009, they were finally listed on Annex A of Stockholm Convention on POPs. This implied a global ban on the production and use of lindane, and α- and β-HCH. However, a specific exemption (5 years limit effective 2009) allows the use of lindane as a human health pharmaceutical for the control of head lice and scabies as second line treatment (UNEP, 2009).

A halogenated cyclic alkane, similar in structure to HCH (Fig. 1), HBCD has a molecular formula of $C_{12}H_{18}Br_6$, and is an additive brominated flame retardant (BFR) produced by bromination of 1,5,9-cyclododecatriene (Heeb *et al*., 2005). As a flame retardant, it is incorporated into a wide range of consumer products to resist ignition of combustion and prevent or reduce flammability, particularly in materials that are susceptible to combustion (BSEF, 2009). Law *et al.* (2005) described 16 possible stereoisomers of HBCD comprising 6 pairs of enantiomers and 4 mesoforms. However, technical HBCD is a mixture of 3 diastereomers: α-HBCD (10-13%), β-HBCD (1-12%) and γ-HBCD (75-89%) (Covaci *et al*., 2006). Like HCH, the complex stereochemistry of HBCD and the differential environmental behaviour and fate of its isomers have made chemical analysis and regulation of HBCD difficult (Law *et al*., 2005; Janak *et al*., 2005). The production of HBCD for use as a BFR in polystyrene materials commenced in the 1980s, though the chemical had been available on the market since the 1960s (EC, 2008). HCH had been in use for at least, 2 decades before the global introduction of HBCD. HBCD is mainly used in expanded polystyrene (EPS), extruded polystyrene (XPS) and backcoating of textiles for upholstered furniture, upholstery seating in transportation vehicles, draperies, wall coverings, mattress ticking and interior textiles such as car cushions and roller blinds (Swedish Chemicals Agency, 2008).

Polystyrenes are principally used for thermal insulation boards in construction and building industries (Darnerud, 2003). In Europe in particular, HBCD is also used in high impact polystyrene (HIPS) for electrical and electronic equipment such as audio-visual equipment cabinets, wire and cable distribution boxes and refrigerator lining (ECHA, 2009). Deng *et al*. (2009) observed that the estimated total market demand for HBCD in 2001 globally was over 16,700 tonnes, with 2,800 tonnes from USA, 9,500 tonnes from Europe, 3,900 tonnes from Asia and 500 tonnes from the rest of the world. In 2002 and 2003, the global demands were 21,447 and 21,951 tonnes, respectively (UNEP, 2010b). The increasing global demand for HBCD has resulted in an annual production of almost twice that historically reached for HCH.

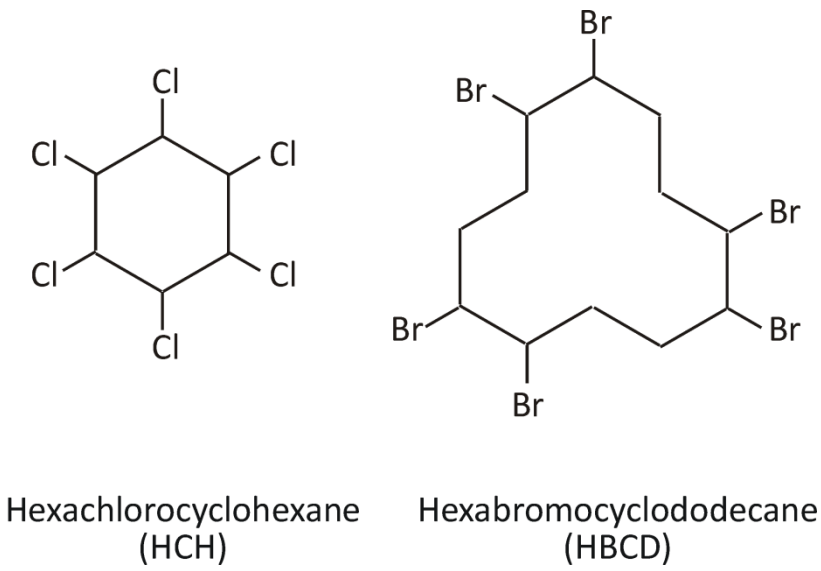


Figure 1. The structures of the two halogenated cyclic alkanes, HCH and HBCD

Release of HBCD to the environment may arise from emissions and discharge of HBCD from manufacturing sites (Covaci *et* al., 2006), and the use and disposal of its products (Wu *et al*., 2011). HBCD is an additive flame retardant; it is not chemically bound to the material it

protects unlike reactive flame retardants. Therefore, it is predisposed to high leaching and release to the environment from its products in use or after disposal (USEPA, 2010). Evidence of the distribution of HBCD in environmental media such as air, soil, sediments, surface water and sewage sludge, and biota (including humans) have been reported (ECHA, 2008; Environment Canada, 2011). Because of its volatility, atmospheric transport is also an important pathway for transport of HBCD within the environment (de Wit *et al*., 2010). In the European Union, due to the PBT properties of HBCD, HBCD has been identified as a substance of very high concern (SVHC) within the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) framework (ECHA, 2008). In the USA, HBCD is also considered to be of high concern based on its PBT properties, high toxicity to aquatic organisms and occurrence in remote regions of the world (UNEP, 2010a).

HBCD is among new POPs being considered for global elimination. It was nominated by Norway in 2008 for listing in the annexes of Stockholm Convention on POPs. It has met criteria for inclusion in Annex D of the Convention based on the screening criteria of PBT properties and the potential for long-range environmental transport, and completed the Annex E assessment (UNEP, 2010a). The Persistent Organic Pollutants Review Committee (POPRC), a subsidiary body of Stockholm Convention mandated to assess a given proposal by a Party for listing of a chemical as a POP in Annex(es) A, B (restriction) and/or C (unintentional production), at its sixth meeting held from 11-15 October 2010 in Geneva, Switzerland, considered and adopted the risk profile of HBCD. It was concluded that HBCD should proceed to Annex F (management evaluation). At its seventh meeting held from 10 - 14 October 2011 in Geneva, the Committee considered a draft risk management plan for possible control measures and socio-economic considerations and recommended that HBCD

should be listed in Annex A as a control measure. However, the recommendation is yet to be adopted by the Convention (UNEP, 2011).

This paper will comparatively review the PBT properties and the potential for long-range environmental transport of HCH and HBCD, and evaluate where the consequences of using HBCD could have been foreseen as a result the early warnings from HCH.

2.0. Persistence

Characteristically, HCH and HBCD are persistent and resistant to degradation. Though degradation by microorganisms may result in the slow removal of HCH from water, photolysis and hydrolysis are not considered to be significant pathways for degradation of HCH isomers (CEC, 2006; Addison *et al*., 2009; Hu *et al*., 2010). Once released to the environment, HCH partitions into the air, water, sediments and soil, and accumulates in biota. Technical HCH is no longer used as an insecticide in most parts of the world, but its isomers are still reported to occur in surface waters, sediments, soil and biota in countries where it has long been banned because of its persistence in the environment (Zhao *et al*., 2009; Hu *et al*., 2010; Vijgen *et al*., 2011). Among banned organochlorines, Brun *et al.* (2008) reported α- and γ-HCH among the most frequently detected chemical substances in wet-precipitation across Atlantic Canada.

Chen *et al*. (1984) reported half-lives of 91 hours (3.79 days), 152 hours (6.33 days) and 104 hours (4.33 days) for α-HCH, β-HCH and γ-HCH, respectively, in the air. Hydrolytic half-lives of 0.8 year (292 days) (pH 8.0, 20^0C) and 26 years (pH 7.8, 5^0C) were estimated for α-HCH by Ngabe *et al*. (1993). In addition, Harner *et al*. (1999) estimated a half-life of 63 years for α-

HCH in the Arctic Ocean. In natural freshwaters such as rivers and lakes, the estimated half-lives for γ-HCH/lindane range from 3 to 300 days (Mackay *et al*., 1997). In seawater (pH 8.0, 20^0C), a half-life of 1.1 years is estimated while 110 years is estimated in the Arctic Ocean (pH 8.0, 0^0C) for lindane (UNEP, 2006). In soils, half-lives of 55 days (Singh *et al*., 1991) and 161 days (Doelman *et al*., 1990) for α-HCH, 100 and 184 days for β-HCH (Singh *et al*., 1991), and 88 to 1146 days (aerobic conditions) and 12 to 174 days (anaerobic conditions) for γ-HCH (Slooff and Matthijsen, 1988; IPCS, 1991), have been reported. Information on degradation half-lives of HCH in sediments is limited. However, in aquatic sediments, half-lives of 90 days (WWFC, 1999), and 0.9, 12.6 and 1.26 years for α-, β- and γ-HCH, respectively, in the Arctic (Helm *et al*., 2002) have been estimated. In environmental media, β-HCH does not undergo degradation easily. Compared to other HCH isomers, it is detected most commonly in environmental media due to its lower water solubility (higher k_{ow}) and greater chemical stability (Bhatt *et al*., 2009). HCH persists in biota. Data on the occurrence of HCH in biota are usually in the form of concentrations rather than biological half-lives, although in humans, an estimated half-life of 7 to 10 years for β-HCH, which is the predominant isomer in mammals, has been reported (Zou and Matsumura, 2003).

HBCD also has the propensity for persistence. Like HCH, half-lives in air and water greater than the regulatory thresholds of >2 and >60 days (UNEP, 2001), respectively, have been reported (Table 1). However, there appears to be a lack of experimental data on the degradation half-life of HBCD in both freshwater and marine water. The range of values (60-130 days) stated in Table 1 for HBCD are rather estimates derived from models. In studies on the biodegradation of HBCD in aquatic sediments, half-lives of 210, 130 and 190 days (aerobic) and 210, 80 and 125 days (anaerobic) for α-, β- and γ-HBCD, respectively, have

been reported. However, using temperature of 12^{o}C as benchmark, the half-life of HBCD in sediments is estimated to be 125-191 days (EC, 2008). Compared to β- and γ-HBCD, α-HBCD is resistant to reductive dehalogenation under anaerobic condition in sediments (EC, 2008). Data on degradation half-lives of HBCD in soils are limited. Davis *et al*. (2005) determined half-lives of 63 and 6.9 days in aerobic and anaerobic soils, respectively, for HBCD. However, in the study, degradation products were not reported, and only the fate of γ-HBCD was determined. On the basis of empirical data primarily, the half-life of HBCD in soil is ≥182 days (Environment Canada, 2011).

Table 1. A comparison of the persistence of HCH and HBCD in environmental media.

Criterion	Regulatory threshold (UNEP, 2001)	HCH	HBCD
Half-life in air	>2 days	3.7 to 6.33 (Chen *et al*., 1984)	0.4 to 5.2 (Marvin *et al., 2011)*
Half-life in water	>60 days	3 to 300 days (Mackay *et al*., 1997)	60 to 130 days (Marvin *et al*., 2011)
Half-life in aquatic sediments	>180 days	90 days (WWFC, 1999) 0.9 to 12.6 years (Helm *et al.*, 2002)	125-191 days (EC, 2008)
Half-life in soil	>180 days	<180-1146 (IPCS, 1991)	6.9 to 63 days (Davis *et al*., 2005) ≥182 days (Environment Canada, 2011)
Half-life in biota (days/years)	none	7 to 10 years (humans) (Zou and Matsumura, 2003)	23 to 219 days (humans) (Schecter *et al*., 2012) 1 to 17 days (mice) (Schecter *et al.*, 2012) 53 to 136 days (fish) (Janak *et al.*, 2005)

When released to the environment, HBCD isomers will adsorb onto solid particles of sediments and soil (Janak *et al*., 2005). Though there is a predominance (>90%) of γ-HCBD in the environment compared to α- and β-HBCD, α-HBCD often has the highest prevalence in biota, followed by β-HBCD (Birnbaum and Staskal, 2004). This has been attributed to bioisomerization of the diastereomers and differences in the metabolizing capacity of organisms, particularly fish (Law *et al*., 2004; Janak et al*.,* 2005). Half-lives of 136 and 53 days for α- and β-HBCD, respectively, in *Oncorhynchus mykiss* (rainbow trout) have been reported (Janak *et al*., 2005).

The abundance of HBCD in environmental media in remote locations such as the Arctic without demonstrable existing sources of exposure, and its trophic transfer in food webs provide evidence of persistence of HBCD. Concentrations of HBCD measured in dated sediment core samples indicate widespread occurrence and also provide evidence of the persistence of HBCD in the environment (UNEP, 2007a). Generally, HCH is more persistent in environmental media than HBCD (Table 1), however isomers of both HCH and, HBCD exhibit differences in their persistence in environmental media.

3.0. Bioaccumulation

Octanol-water partition coefficient (K_{OW}) and bioconcentration factor (BCF) are used to assess the potential for a chemical to bioaccumulate. Log K_{ow} values of 3.8, 3.78 and 3.72 for α-, β- and γ-HCH, respectively (ATSDR, 2005), indicate a potential for bioaccumulation. A wide range of BCFs for HCH have been reported in several studies. Oliver and Niimi (1985) reported BCF of 1100 – 2800 in fish. In invertebrates, BCFs ranging from 60 – 2,750 have

been estimated (UNEP, 2007b). Due to its lipophilicity, HCH accumulates in food chains. It has been reported to accumulate rapidly in invertebrates, fish, birds and mammals (CEC, 2006). In biota, particularly mammals, the variations observed in the isomeric composition of HCH may be due to differences in sources and time of exposure, isomeric uptake, metabolism and adiposity of species (Willett *et al*., 1998). Generally, β-HCH being the most persistent and bioaccumulative isomer, may exhibit highest prevalence among HCH isomers detected in mammalian tissues (Solomon and Weiss, 2002; Liu and Macdonald, 2005). This is attributable to the greater resistance to metabolism and the much longer half-life of β-HCH than other HCH isomers in adipose tissues of mammals (Liu and Macdonald, 2005). Zou and Matsumura (2003) reported the accumulation of β-HCH in the adipose and breast tissues of humans.

HBCD also has the potential for bioaccumulation like HCH. However, the log K_{OW} values of HBCD are higher than those of HCH. For technical HBCD, α-HBCD, β-HBCD and γ-HBCD, the estimated log K_{ow} values are 5.62, 5.07, 5.12 and 5.47, respectively (ECHA, 2008). HBCD has low water solubility of 66 µg/l (Swedish Chemicals Agency, 2008). Because of its hydrophobicity and lipophilicity, it exhibits partitioning into adipose tissues in biota, followed by accumulation, characteristic of many POPs (de Wit. 2002; Law *et al*., 2003). The accumulation of HBCD in different organisms such as invertebrates, fish, birds and mammals (including humans), and its biomagnification in food chains have been reported (Tomy *et al.,* 2004; Law *et al*., 2006; Covaci *et al* ., 2006). BCFs of 18,100 in *Pimephales promelas* (fathead minnows) (Veith *et al*., 1979) and 19,200 in *O. mykiss* (Drottar *et al*., 2001) have been measured. Stereoisomer-specific bioaccumulation has been observed in HBCD. Like HCH, HBCD seems to undergo stereoselective processes such as biotransformation and

bioisomerization in the environment, resulting in relative enrichment of different stereoisomers (Law *et al*., 2005; Janak *et al*., 2005; Heeb *et al*., 2008).This has been observed in the preferential accumulation of α-HBCD in relation to the much dominant γ-HBCD in the technical HBCD mixture (Janak *et al*., 2005). Differences in the water solubility of HBCD stereoisomers (48.8, 14.7 and 2.1 µg/l for α-, β- and γ-HBCD, respectively) may also be responsible for differences in the metabolism and bioaccumulation of the stereoisomers (Hunziker *et al*., 2004). The regulatory criteria for bioaccumulation assessment based on K_{ow} and BCF include United Nations Environment Programme (UNEP) (Stockholm Convention on POPs), log K_{ow}≥5 and BCF≥5000; European Union (REACH), BCFs ≥2000 (bioaccumulative) and ≥5000 (very bioaccumulative); United States (Toxic Substances Control Act), BCFs of 1000-5000 (bioaccumulative) and ≥5000 (very bioaccumulative), and Environment Canada (Canadian Environment Protection Act), log K_{ow}≥5 and BCF≥5000 (Arnot and Gobas, 2006). On the basis of these criteria, HBCD is much more bioaccumulative than HCH.

4.0. Toxicity

Reported adverse effects of HCH (Table 2) in laboratory animals and humans include carcinogenicity, genotoxicity, neurotoxicity, developmental toxicity, endocrine disruption, reproductive disorders, haematological alterations and immunosuppression (ATSDR, 2005; UNEP, 2006). Mathur *et al*. (2002) reported β-HCH levels to be significantly higher in breast cancer patients, 31-50 years of age in relation to non-cancer patients. β-HCH is a risk factor for the progression of breast cancer cells to advanced state of malignancy (Zou and Matsumura, 2003). Studies by Khan *et al*. (2010) indicated a positive significant association between sperm count and the level of α- and β-HCH in infertile human males as a result of Y

chromosome microdeletions by the HCH isomers. HCH is mutagenic, and can cause spermatogenic failure in humans. Neurological effects such as seizures, convulsion and coma in humans, and immunosuppression and suppressed antibody responses in laboratory animals arising from exposure to lindane have been observed (WHO/Europe, 2003). Prenatal exposure to β-HCH has been associated with alteration in thyroid hormone levels and possible adverse brain development in humans (Alvarez-Pedrerol *et al*., 2008). Studies on rats and rabbits have indicated reproductive disorders such as reduced ovulation, reduction in the number of testicular spermatids and epididymal sperms, degeneration of seminiferous tubules and disruption of spermatogenesis as a result of exposure to lindane. Haematological changes such as leukocytosis, granulocytosis, eosinophilia, thrombocytopenia and leukopenia have also been observed in humans following chronic exposure to lindane (UNEP, 2006). Acute exposure to lindane in humans may cause adverse effects ranging from skin irritation to dizziness, diarrhoea, vomiting, headache nausea convulsion and death (CEC, 2006).

The ecotoxicity of HCH has been extensively studied. Lindane is toxic to aquatic organisms. Schafer *et al*. (1994) reported lindane's inhibiton of growth in the freshwater algae, *Chlamydomonas reinhardi* and *Scenedesmus subspicatus* at 72h EC_{50} of 4.0 mg/l and 72h EC_{50} of 3.2 mg/l, respectively.The LC_{50} (median lethal concentration) for aquatic invertebrates and fish ranges from 10-520 µg/l and 1.7-131 µg/l, respectively (UNEP, 2006). Studies on the chronic toxicity of lindane showed reduction in the growth of freshwater fish larvae at a NOAEC (no observed adverse effect concentration) of 2.9 µg/l, and decline in reproduction in aquatic invertebrates at NOAEC of 54 µg/l (UNEP, 2006). In aquatic birds

and mammals generally, chronic exposure to lindane has resulted in reduced rate of growth and survival, decrease in body weight and egg production and endocrine disruption as important endpoints (CEC, 2006). In the terrestrial environment, Pereira *et al*. (2010) reported on the phytotoxicity of HCH in relation to the germination and growth responses of different plant species.

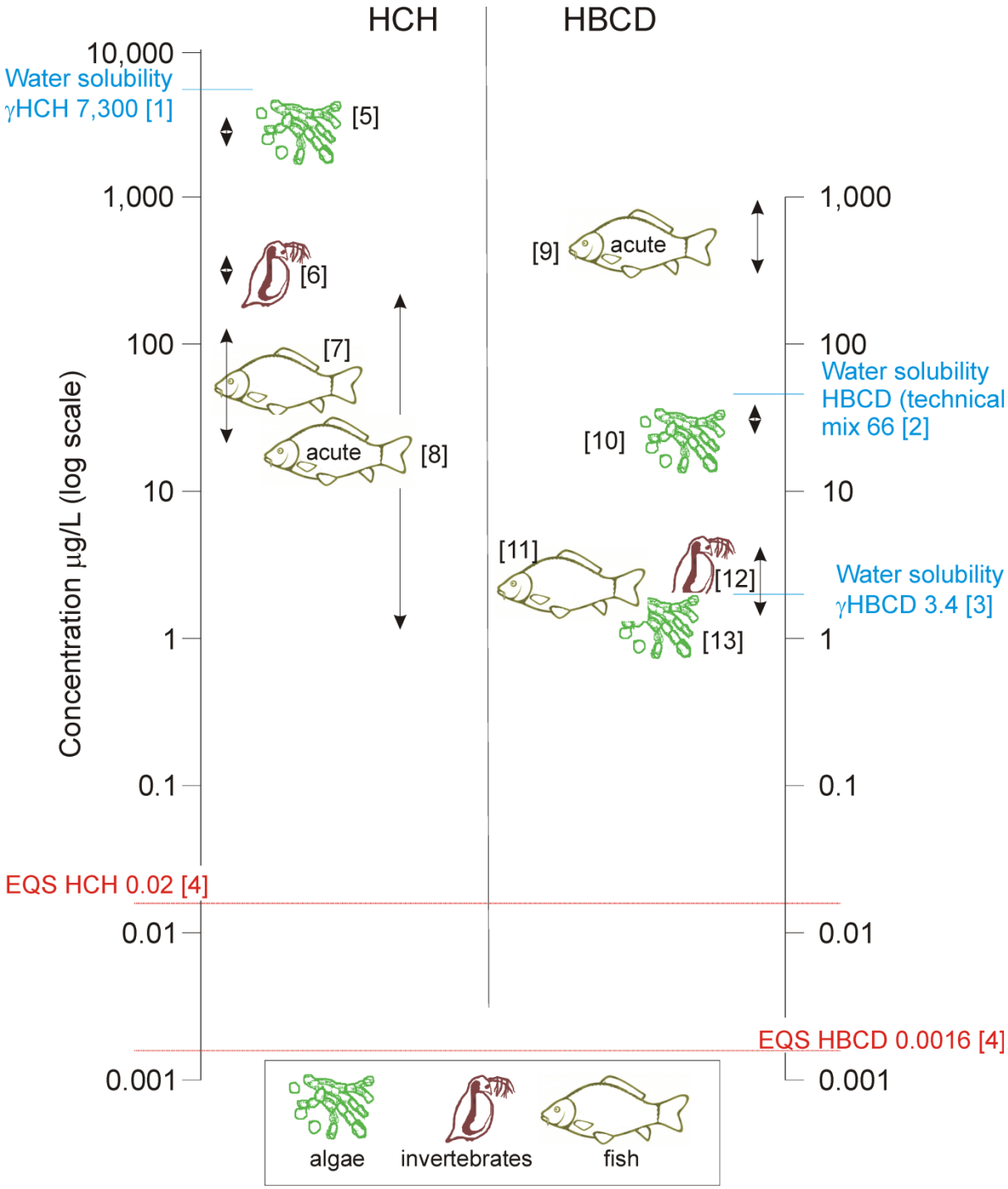
Unlike HCH, information on the relative toxicity of the different isomers of HBCD in humans and wildlife is virtually lacking. However, extrapolations of toxicological tests on technical HBCD mixture in mammals strongly indicate that HBCD has the potential to cause adverse effects in humans (Table 2). These include endocrine disruption, particularly of the thyroid-hormone system (Ibhazehiebo *et al*., 2011); neurotoxicity (learning and memory defects) (Reistad *et al*., 2006; Eriksson *et al*., 2006); reproductive disorders such as inhibition of oogenesis (Darnerud, 2003), and adverse effect on liver weight and activity (Germer *et al*., 2006). The possible role of HBCD in carcinogenicity is not known. The limited data indicate that with the exception of endocrine disruption in mammalian cell cultures, where effects occurred at concentrations of mg/l rather than µg/l, risks posed by HBCD to mammals are not greater than those of HCH.

Ecotoxicity studies (Table 2 and Figure 2) have shown that HBCD like HCH can potentially produce adverse effects in aquatic organisms, particularly algae, invertebrates, fish, birds and mammals, and terrestrial organisms at environmentally relevant concentrations (Darnerud, 2003; Birbaum and Staskal, 2004). Generally, laboratory studies on the toxicity of HBCD to aquatic organisms indicate endpoints such as inhibition of survival, growth, development and reproduction, endocrine disruption, histopathological changes, oxidative

Table 2. Comparative toxicity of HCH and HBCD. A comparison of values for ecotoxicity is shown in Figure 2.

Toxicity		HCH	HBCD
Mammalian toxicity	Carcinogenicity	β-HCH 29 µg/l *in vitro* (Zou and Matsumura, 2003)	No data
	Genotoxicity	α-HCH 130 µg/l; β HCH 300 µg/l *in vitro* (Khan *et al.*, 2010)	No data
	Neurotoxicity	α-HCH at 23.4 mg/kg/day in rats (WHO Europe, 2003)	13.5 mg/kg/day in mice (Eriksson *et al.*, 2006)
	Reproductive toxicity	γ-HCH 6mg/kg/day in male rats (ATSDR, 2005)	2,500 mg/kg/day in rats (Darnerud, 2003)
	Developmental toxicity	γ-HCH 13.1 mg/kg/day in rats (ATSDR, 2005)	Has the potential (UNEP, 2010b)
	Immunotoxicity	γ-HCH 6- 25 mg/kg/day in rats (UNEP, 2006)	No data
	Endocrine disruption	β- and γ-HCH (UNEP, 2006; Alvarez-Pedrerol *et al*., 2008)	Has the potential (UNEP, 2010b)
		Technical HCH 3 to 11 mg/l *in vitro* (mammalian cells) (Tiemann, 2008)	α-HBCD 0.064 µg/l *in vitro* (mammalian cells) (Ibhazehiebo *et al.*, 2011)
Ecotoxicity	Acute toxicity	Highly toxic to freshwater fish (UNEP, 2006)	Toxic to freshwater fish embryos (Deng *et al*., 2009)
		Highly toxic to aquatic invertebrates (UNEP, 2006)	Toxic to aquatic invertebrates (ECHA, 2008)
		Moderately toxic to birds and mammals (CEC, 2006)	No data on acute toxicity to birds and mammals
		Highly toxic to algae (IPCS, 1992; Schafer *et al*.,1994)	Highly toxic to algae (Desjardins *et al*., 2005)
	Chronic toxicity	Aquatic biota (UNEP, 2006)	Aquatic biota (EC, 2008)
	Inhibition of growth and survival	In daphnids and fish (Ferrando *et al*., 1995; Gorge and Nagel, 1990)	In daphnids and fish (Drottar and Kruegar, 1998; Drottar *et al*., 2001)
	Inhibition of reproduction	In aquatic invertebrates, birds and mammals (UNEP, 2006)	In daphnids, fish, birds, mammals and earthworm (UNEP, 2010b)
	Terrestrial phytotoxicity	Technical HCH 1,250 mg/kg in soil (Pereira *et al*., 2010)	No (UNEP, 2010b)
	Endocrine disruption	Technical HCH 1 to 10 mg/l in fish (Singh and Canario, 2004)	In fish exposed to 5 µg/l (Palace *et al.*, 2010)

stress and apoptosis and mortality (Legler, 2008; Deng *et al*., 2009; Environment Canada, 2011; UNEP, 2010b). HBCD is highly toxic to algae. 72h EC_{50} (effective concentration in 50%) values based on decrease in population density in marine algae range from 9.3-12 µg/l in *Skeletonema costatum*, and 50-370 µg/l in *Thalassiosira pseudonana* (Walsh *et al*., 1987). In studies by Roberts and Swigert (1997), 72h EC_{50} >2.5 µg/l was observed in the freshwater alga, *Pseudokirchneriella subcapitata* (=*Selenastrum capricornutum*). In the cladoceran crustacean, *Daphnia magna* (water flea), a 21-day chronic exposure to HBCD indicated a NOEC (no observed effect concentration) of 3.1 µg/l and a LOEC (lowest observed effect concentration) of 5.6 µg/l based on significant reduction in growth (Drottar and Krueger, 1998). Thyroid hormone-dependent development effects in tadpoles of *Xenopus laevis* (Schriks *et al*., 2006) and significant adverse changes in the levels and patterns of circulating thyroid hormones in *Salmo salar* (Atlantic salmon) (Lower and Moore, 2007) and *O. mykiss* (Palace *et al*., 2010) exposed to HBCD have been observed. HBCD has also been reported to cause malformation and reduction of the survival of embryos of zebrafish, *Danio rerio* at 96h exposure to concentrations of 0.5 and 1.0 mg/l (Deng *et al*., 2009). In the earthworm, *Eisenia fetida*, NOEC for survival and reproduction estimated as 4190 and 128 mg HBCD/kg dry soil, respectively, have been observed following 56 days exposure (UNEP, 2010b).HBCD has also been evaluated for phytotoxicity in the terrestrial ecosystem. At NOEC>5000 mg HBCD/kg dry soil, there was no adverse effect on seedling emergence in *Zea mays* (corn), *Cucumber sativa* (cucumber), *Lycopersicon esculentum* (tomato) and *Glycine max* (soybean) (UNEP,2010b). Overall, the data on ecotoxicity for HBCD indicate a risk to the environment at lower concentrations (10 to 100 times less) than posed by HCH, which is reflected in the proposed environmental quality standards (EQS) for these compounds (Figure 2).



[1] Stenzel and Markley 1997; [2] HSDB, 2009; [3] UNEP, 2010b; [4] EC, 2012; [5] Schafer et al., 1994; [6] Ferrando et al., 1995; [7] George and Nagel, 1990; [8] UNEP, 2006; [9] Deng et al., 2009; [10] Desjardins et al., 2005; [11] Drottar et al., 2001; [12] Drottar and Krueger 1998; [13] Roberts and Swigert, 1997.

Figure 2 Graphical representation of the toxicity of HCH and HBCD in relation to their reported solubility and proposed (annual average) EQS.

5.0. Long-range Environmental Transport

There is evidence of long-range environmental transport of HCH dating several decades. Several studies have reported the transport of HCH over long distances in the environment by air and ocean currents (Shen *et al*., 2005; Li and Macdonald, 2005; Brun *et al*., 2008). It is estimated that 12-30% of lindane used in agriculture volatilizes and becomes air-borne for long-range transport (USEPA, 2006). In the atmosphere, HCH condenses and deposits on oceans and freshwaters, and tends to accumulate in colder climates, particularly the Arctic where it is trapped by low evaporation rates (CEC, 2006). Far from important pollution sources, the Arctic is a recipient of HCH emitted from other parts of the world. In the Arctic, HCH has been detected in environmental media such as air (Li and Bidleman, 2003a) and water (Li and Macdonald, 2005), and biota (Willett *et al*., 1998; Hoekstra *et al*., 2002).

HBCD has the potential for long-range environmental transport and trans-boundary threat like HCH. Arnot *et al*. (2009) observed that HBCD portioning behaviour in the atmosphere is such that at higher temperatures (15-35^{0}C) there is gaseous deposition while at lower temperatures (-35-5^{o}C) its association with particles will enhance the rate of dry deposition. Studies have indicated the occurrence of HBCD in water and sediments and biota such as fish, birds and mammals in remote regions of the world (for example, the Arctic) considered to be far from point sources of emission as a result of atmospheric deposition (Law *et al* ., 2006; de Wit *et al* .,2010; Letcher *et al*.,2010). Pollution of the Arctic with POPs such as HCH and HBCD is of great concern because people living in the Arctic are at high health risks due to their consumption of wildlife such as fish, birds and mammals with considerable quantities of these chemicals (CEC, 2006; UNEP, 2010b). It is concerns about the impacts of chemicals that has led to action by regulatory bodies worldwide.

6.0. Lessons Learnt: Regulation and Control

It is apparent that the use of, and subsequent release of these two chemicals to the environment, has resulted in widespread contamination and significant concerns about the consequences of exposure of wildlife and humans. Although they are different chemicals, the two halogenated chemicals which have been discussed in this work are examples of compounds which, because of their toxicity and similar physico-chemical characteristics. Experience of chemicals in the environment has led to an approach to prioritise them based on such characteristics, and for regulators to focus on their PBT properties and the amount of chemicals that are in use, because impact is related to the concentration of a chemical. Perhaps the real lesson that society has learnt from the experience of using these, and similar chemicals, is that their release to the environment was in retrospect unwanted and unwise, and that tighter controls are required to prevent this occurring in future.

Regulators are now using such properties and usage patterns to prioritise chemicals for which control measures on use, or approval for use, are based. In the United Sates, the USEPA HPV Challenge Programme (USEPA, 2007), aims to make available health and environmental effects data for “chemicals produced or imported in the United States in quantities of 1 million pounds or more per year”. Within Europe the Registration, Evaluation, Authorisation and Restriction of Chemical substances (REACH) system (EC, 2006), came into force in 2007 and those who manufacture or import chemicals are obliged to register information about them in a central database. The REACH regulations also allow for identification of the most hazardous chemicals and for their substitution with alternatives. From a world wide perspective, it is also important that countries showing strong economic growth are also involved in controlling chemicals. As well as being a

signatory to the Stockholm Convention, China has newly enacted regulation, described as "China REACH" (Lau et al, 2012), which is aimed at ensuring the relevant authorities are notified about new chemical substances so that risks they pose can be effectively managed. There is, therefore, evidence that regulatory bodies worldwide are taking action to manage the use of chemicals, and the benefits of sound chemical management are of international concern (UNEP, 2012).

7.0. Conclusions

It is important for society to take stock of, and learn from past experiences in order to better protect the environment and prevent or reduce adverse consequences. The PBT properties and the long-range environmental transport exhibited by both HCH and HBCD have been affirmed by international treaties including the Stockholm Convention on POPs. It is apparent that our understanding of the fate and behaviour of chemicals has led to a number of frameworks where information can be utilised in future to minimise the risks that using chemicals can pose. There are increasing regulatory controls at both national and regional levels and that highlighting the benefits of managing chemicals is being undertaken at an international level.

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