Differential Toxicity and Environmental Fates of Hexachlorocyclohexane Isomers

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The differential environmental fates and toxicities of the various hexachlorocyclohexane (HCH) isomers including lindane and isomers in the technical mixture will be the focus of this review. HCHs are one of the most widely used and most readily detected organochlorine pesticides in environmental samples. The relatively high volatility of HCH has led to global transport, even into formerly pristine locations such as the Arctic. Certain HCHs cause central nervous system, reproductive, and endocrine damage. Because γ-HCH is rapidly metabolized, the β-HCH isomer is consistently found in higher concentrations in human fat, blood, and breast milk. In contrast, α- and γ-HCH are the most prevalent isomers in soil, water, and air samples. The ratio of the α- to γ-isomers can be used to track global transport of HCHs. A new area of HCH research focuses on the selective degradation of the two α-HCH enantiomers in various environmental matrices. These HCH issues and recommendations for future HCH research are presented in this review.

Introduction

Hexachlorocyclohexane (HCH) is a name used collectively for the eight isomers of 1,2,3,4,5,6-hexachlorocyclohexane. At one time, HCH was called benzene hexachloride (BHC), clearly a misnomer. The eight isomers differ in their axial−equatorial substitution pattern around the ring. These eight isomers are denoted by Greek letters (α, β, γ, δ, ϵ, η, and θ). Their structures are shown in Figure 1; note that α-HCH can exist in two enantiomeric forms. The manufacture of HCH involves the photochlorination of benzene. Subsequent treatment with methanol or acetic acid followed by fractional recrystallization will concentrate the γ-HCH isomer to 99.9% (*1*). The γ-isomer (CAS Registry No. 58-89-9), also known as lindane, is the isomer with the highest pesticidal activity; however, technical mixtures of all isomers (CAS Registry No. 608-73-1) have been widely used as commercial pesticides. These commercial mixtures typically contain 60−70% α, 5−12% β, 10−12% γ, 6−10% δ, and 3−4% ϵ (*2*). HCH was first synthesized in 1825 by Michael Faraday, but the pesticidal properties were not identified until 1942 (*3*). γ-HCH is used as an insecticide on fruits and vegetables, rice paddies, Christmas trees, and animals and as a seed treatment. Medicinally, γ-HCH has been applied topically to people for the treatment of lice and scabies. The various formulations of lindane and technical HCH have many trade names, including Agrocide, Ben-Hex, Gammexane, Kwell, Quellada, Lindatox, and Tri-6. The National Toxicology Program chemical repository has the complete listing of names (*4*).

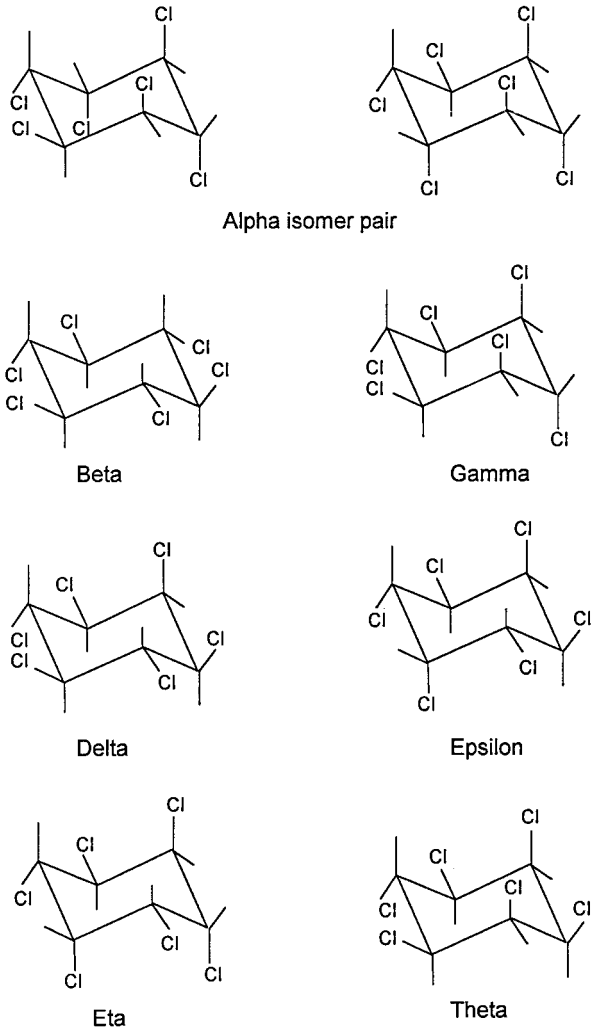

FIGURE 1. Structures of HCH isomers, including the two α-enantiomers. The axial and equatorial positions of the chlorine atoms are as follows: α, aaaaee; β, eeeeee; γ, aaaeee; δ, aeeeee; ϵ, aeeaee; η, aaeaee; and θ, aeaeee.

Environmental chemists and toxicologists both study the HCH isomers; however, the varied isomer toxicity and different environmental fates are often not considered outside of each respective field. The focus of this review is on this interdisciplinary gap, and the goal of this review is to provide an integrated summary of both the toxicities and the

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TABLE 1. Selected Physical Properties of HCH Isomers

property	α	β	γ	δ	ε
melting point (°C)[a]	159−160	309−310	112−113	138−139	219−220
vapor pressure[b]	$(1.6 \pm 0.9) \times 10^{-2}$	$(4.2 \pm 0.3) \times 10^{-5}$	$(5.3 \pm 1.4) \times 10^{-3}$	2.1×10^{-3}	
log K_{ow}[c]	3.9 ± 0.2	3.9 ± 0.1	3.7 ± 0.5	4.1 ± 0.02	
BCF in human fat[d]	20 ± 8	527 ± 140	19 ± 9	8.5	
BCF in aquatic animals[e]	2.6 ± 0.5	2.9 ± 0.3	2.5 ± 0.4		

[a] From ref *3*. [b] In Pa, at 20 or 25 °C; averaged from ref *143*. ± values are standard errors. [c] Averaged from ref *143*. [d] Bioconcentration factor; from ref *144*. [e] Bioconcentration factors from various aquatic species; averaged from ref *143*.

environmental fates of the individual HCH isomers, with a particular focus on their differential behavior. Because over 10 000 papers have been published about the HCHs, this review is selective, and we have used only those papers giving information on all (or most) of the HCH isomers.

Production, Use, and Properties

The global production and usage of HCH is difficult to quantify because of poor record keeping in some countries and because of proprietary restrictions in others. Recently, Voldner and Li (*5*) estimated that the cumulative, global technical HCH and lindane usage was 550 000 and 720 000 metric tons (t), respectively. More recently total global consumption of technical HCH has been estimated as high as 6 000 000 tons (*6*). Barrie and co-workers (*7*) estimated that HCH production between 1945 and 1992 was 1 400 000 t, with about 400 000 t of that contributed by U.S. producers. On an isomer basis, Strand and Hov (*8*) estimated that the world consumption between 1960 and 1989 was 403 900 and 146 700 t for the α- and γ-isomers, respectively. The highest consumption of α-HCH was between 0° and 30° N latitude, while the highest consumption of γ-HCH was between 30° and 60° N (*8*).

Estimates of the amount of technical HCH used in China and southern Asia in the late 1970s were about 60 000 t annually (*7*). In the years 1980 and 1990, global usage of technical HCH was estimated to be 40 000 and 29 000 t, respectively (*9*). Annual technical HCH use in India alone in 1990 was estimated to be 28 400 t/yr or approximately 98% of the worldwide use at that time. In the United States, lindane use decreased from 270 to 110 t/yr between 1980 and 1990 (*9*). Because of the environmental and biological persistence of HCHs, their use has been regulated. Canada and the United States banned technical HCH mixtures in 1971 and 1978, respectively (*7, 10*). China banned technical HCH in 1983, and the former Soviet Union banned it in 1990 (*6*). However, as of 1992, neither technical HCH nor lindane was banned in several countries; these include India, Sudan, and Columbia. In fact, lindane's use is not completely banned in North America or in most of Europe (*5*). For example, lindane is still used in Canada and the United States as a seed dressing and as a human medicinal.

The physical and chemical properties of the HCH isomers are quite different from one another as illustrated in Table 1. For example, β-HCH has a much lower vapor pressure and a much higher melting point and bioconcentration factor in human fat (BCF) as compared to the α-isomer. These properties are largely dictated by the axial and equatorial positions of the chlorine atoms on each molecule. As shown in Figure 1, all of the chlorines on β-HCH are in the equatorial positions, which seems to confer the greatest physical and metabolic stability to this isomer. This stability is reflected in the environmental and biological persistence of this isomer. For instance, the BCF in human fat of β-HCH is nearly 30 times higher than that of γ-HCH (Table 1). The γ-isomer has three chlorines in axial positions creating two ways that HCl can be eliminated by anti-periplanar dehydrohalogenation, generating pentachlorocyclohex-1-ene (PCCH) metabolites (*11*).

Laboratory studies have indicated that the γ-isomer can be isomerized to the α-form by UV radiation although this has not been proven in an environmental setting (*12*). In general, isomers of HCH are stable to light, high temperatures, hot water, and acid; however, they are dechlorinated by alkali (*13*). At pH 8 and 5 °C, hydrolytic half-lives of α- and γ-HCH were 26 and 42 yr, respectively (*14*). Differential accumulation and environmental persistence of the various HCH isomers will be discussed throughout this review. Compared to other organochlorines (such as DDT), HCH isomers are generally more water soluble and volatile, which explains why HCHs are now detected in all environmental compartments including water, sediments, air, and animals.

Toxicity

The toxicological effects of the various isomers of HCH have been previously reviewed (*1, 3*); therefore, this section is only a brief summary in order to provide relevancy for our concern about environmental and human residues of HCH. While the toxicological mechanisms of action remain largely unknown, HCHs primarily affect the central nervous system (CNS). In insects, γ-HCH stimulates the CNS and causes rapid, violent convulsions that are generally followed by death or recovery within 24 h (*3*). Hypotheses suggest that convulsions are mediated by the inhibition of γ-aminobutyric acid (GABA) neurotransmission or stimulation related to neurotransmitter release (*15*). A relationship has been established between HCH toxicity and interaction with the GABA receptor. For example, γ-HCH competitively inhibited binding to the GABA receptor in rat cerebellar neuronal cultures (*16*). In contrast to γ-HCH, the α-, β-, and δ-HCH isomers are considered CNS depressants. Furthermore, in competitive binding studies, α- and δ-HCH were 15−30 times less potent in inhibiting binding to the GABA receptor than the convulsant γ-isomer, and β-HCH was inactive (*16*).

Other physiological systems affected by HCH isomers include renal and liver function, hematology, and biochemical homeostasis. For example, dietary intake of β- or γ-HCH resulted in glucosuria in rats without altering their blood glucose levels, indicating a renal tubular effect (*17*). Furthermore, histological studies of renal tubules indicated more severe degenerative changes in the β-HCH treated rats as compared to control rats (*17*). Dietary β- or γ-HCH treatment of variously aged rats also resulted in liver toxicity including liver enlargement and liver fatty metamorphosis (*18*). Both male and female rats receiving 250 mg/kg β-HCH had significantly lower red blood cell counts, white blood cell counts, hemoglobin concentrations, and packed cell volumes as compared to controls (*19*). Packed cell volume decrease and increased serum alkaline phosphatase and alanine aminotransferase, indicating hepatocyte damage, were reported in rabbits dosed with γ-HCH (*20*). Biochemical effects include increased cytochrome P450 concentrations (*3, 19, 21*) and decreased glutathione reductase, glutathione-*S*-transferase, and glucose-6-phosphate dehydrogenase activities (*22*).

Reproductive effects of β-HCH in rats include atrophy of the testes characterized by reduced seminiferous tubule size and decreased interstitial cell-associated spermatogenic arrest (*19*). Dermal application of technical HCH to rats caused a decrease in serum testosterone levels, epididymal sperm counts, sperm motility, increased abnormal sperm, and altered activities of testicular enzymes (*23*). Female rats treated with γ-HCH showed significantly reduced ovulation rates (*24*). HCH can also be a developmental toxin; γ-HCH exposure to gestational day 10 rat concepti resulted in dose- and time-dependent increases in mortality and decreases in growth parameters. Furthermore, γ-HCH leads to complete degeneration of pre-implantation mouse embryos (*25*).

Recently environmental estrogens have become the focus of intense scientific debate (*26*−*30*). Other organochlorines such as *o,p′*-DDT and certain hydroxylated PCBs have estrogenic characteristics and have been implicated in the etiology of various tumors. Several studies have implicated β-HCH as an environmental estrogen. For example, 50 mg/kg of β-HCH administered in the diet of juvenile female rats for 5 days caused significantly increased uterine weights (*31*). Likewise, uterine dry weight and the height of uterine epithelial cells (hypertrophy) increased as compared to untreated controls in mice whose ovaries were removed and then treated with 100 μg/g body weight β-HCH for 3 days. However, β-HCH caused uterine dry weight increases to only approximately 50% of the response in animals treated with 5 ng/g body weight 17β-estradiol for 3 days (*32*).

Vitellogenesis, which is the production of an egg yolk precursor protein, occurs in mature female fish during breeding season. Vitellogenesis can be artificially induced in juvenile female or male fish upon exposure to estrogens (*33, 34*). Wester and Canton (*35*) reported induction of vitellogenesis in male medaka fish upon exposure to waterborne 0.1−1 mg/L β-HCH. Development of testis-ova (hermaphroditism) was also reported in males (*35*). Similar results were found with guppies *(Poecilia reticulata*) (*36*). In contrast to these studies, B6C3F1 mice fed up to 300 mg β-HCH/kg diet did not show estrogen-like immunotoxic responses such as thymic atrophy and anovulation. However, cell-mediated immunity was suppressed by β-HCH (*37*). The mechanism of the estrogenic action of β-HCH has been investigated in vitro using human breast cancer cells. β-HCH (at 10 μM) caused redistribution of the estrogen receptor, induction of the cytosolic progesterone receptor (*38*), dose-dependent cell proliferation, and increased pS2 mRNA (*39*). On the other hand, no significant displacement of [^{3}H]-estradiol at up to 40 000 times higher concentrations of β-HCH has been reported (*38, 39*). These studies indicate that β-HCH produces estrogen-like effects through nonclassical estrogen-dependent mechanisms of action (*39*).

Hepatocellular carcinomas occurred in CF1, B6C3F1, and yellow (YS/UY)F-1 mice exposed to 4.7−52 mg of lindane kg^{-1} day^{-1} via the diet for 80−104 weeks (*1*). In mice, the α-HCH isomer is considered the most tumorgenic, whereas rats seem to be unsusceptible to tumorgenic effects of lindane or technical HCH (*3*). Schroter and co-workers (*40*) found significant tumor promotion in *N*-nitrosomorpholine-treated rats exposed to 2−3 mg/kg α-, β-, or γ-HCH in their diet. No reported studies conclusively indicate that any HCH isomers are human carcinogens. The EPA has classified α-HCH and technical HCH as class B2 carcinogens (probable human carcinogen), γ-HCH as B2/C, β-HCH as C (possible human carcinogen), and δ-HCH as D (not classified) (*1*). The IARC on the other hand, considers α-, β-, and γ-HCH as group 3 (cannot be classified as to human carcinogenicity) (*1*). The EPA oral cancer potency factors (higher number implies a more potent carcinogen) for γ-, α-, and β-, and technical HCH are 1.3, 6.3, 1.8, and 1.8 mg kg^{-1} day^{-1}, respectively (see ref *1* and references therein). These values are based on the incidence of hepatic nodules and hepatocellular carcinomas in male mice administered HCH isomers in their diet. For comparison, benzo[*a*]pyrene, a class B2 probable human carcinogen, has a cancer potency factor of 7.3 mg kg^{-1} day^{-1}(*41*) while the organochlorines DDT and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin have potency factors of 0.34 and 156 000 mg kg^{-1} day^{-1}, respectively (*42*).

Toxicological reports of the effects of HCH in humans are largely limited to accidental poisonings and occupational exposures. Lindane poisoning causes tremors, ataxia, convulsions, and stimulated respiration (*43*). In severe cases, violent convulsions and death can occur (*43*). Symptoms reported in the exposed workers at a lindane manufacturing plant included parasthesia of the face and extremities, headache, and giddiness. A few of these workers showed symptoms of malaise, vomiting, tremors, confusion, loss of sleep, and impaired memory (*44*). In 60 male workers from a different lindane factory, no significant neurologic or electrocardiogram differences from controls were found, although there were some differences in clinical chemical blood tests (*45*). A series of human HCH exposure case studies, including many children, are presented in ref *3*.

To summarize, at very high doses γ-HCH causes CNS damage resulting in convulsions and possible death. However, in lower doses this isomer is quickly metabolized. Some renal, liver, and reproductive problems have been reported in γ-HCH-dosed laboratory animals. γ-HCH has the lowest oral cancer potency factor as compared to the other isomers. In comparison, fewer toxicological studies have been conducted with α-HCH, but this isomer resulted in the highest incidence of hepatic nodules and hepatocellular carcinomas in male mice orally exposed. The β-isomer may currently be the most toxicologically significant HCH due to the recent reports of its estrogenic effects in mammalian cells, laboratory mammals, and fish. β-HCH is highly persistent in mammalian tissues (see next section), and more research is expected with respect to the estrogenicity of β-HCH. In contrast to what is known about the toxicity of HCHs to laboratory animals, very limited wildlife toxicity data exist, and there are no well-established biomarkers of effect for the HCHs. Because of this lack of ecotoxicological data, risk assessments of global or even local HCH contamination must largely be based on results from laboratory studies.

Human HCH Residue Concentrations and Exposure Routes

The lipophilic nature of HCH is evident from several human and animal organochlorine pesticide monitoring programs. The β-isomer is generally considered the most persistent and metabolically inactive, with a BCF of 2.9 in various aquatic species and 527 in human fat (see Table 1). For example, in workers involved in the production of lindane, concentrations of β-HCH (46 mg/kg lipid) were 8 and 15 times the concentrations of α- and γ-HCH, respectively (*46*). Likewise, average lipid β-HCH concentrations in 20 Pakistani citizens (average, 2.4 mg/kg; range, 0.14−21 mg/kg) were 8 and 80 times higher than α- and γ-HCH (*47*). In contrast, two studies of HCH residues in Indians indicated higher concentrations of α- and γ-HCH. In 1978, 50 Indian males had average α-, β-, and γ-HCH concentrations of 0.9, 0.4, and 1 mg/kg (*48*), while lower averages were observed (0.3, 0.2, and 0.09 mg/kg, respectively) for 15 individuals sampled from Delhi in 1988−1989 (*49*). One explanation for the relatively elevated α- and γ-HCH levels in these individuals is that they were potentially receiving a high daily dose of technical HCH, which was still being used in India at that time.

Occupational exposure studies have often used men as test subjects; however, a report comparing male and female adipose β-HCH concentrations indicated that females had

TABLE 2. Serum HCH Concentrations (ppm) Mean and Range in Control and Occupationally Exposed Workers (from ref *44*)

group[a]	α-HCH	β-HCH	γ-HCH	δ-HCH
control (14)	0.022	0.029	0.0007	0
	0−0.26	0−0.1	0−0.01	
maintenance (19)	0.022*	0.097*	0.023*	0.0021
	0.004−0.1	0.022−0.2	0−0.32	0−0.04
nonhandlers (26)	0.041*	0.21*	0.016*	0.0017
	0.004−0.16	0.065−0.5	0−0.04	0−0.022
handlers (19)	0.1*	0.41*	0.057*	0.041*
	0.024−0.18	0.16−0.72	0.01−0.17	0−0.16

[a] Number of samples in parentheses. [a] (*) indicates $P < 0.01$ as compared to control by the Mann−Whitney test.

statistically significant higher concentrations (*50*). In the United States, the National Human Monitoring Program encompassing the National Human Adipose Tissue Survey was designed to monitor toxic compounds in the general population (*2*). β-HCH was included in this monitoring program and database. Estimates of population residue levels for the entire United States, census regions, and demographic groups were calculated based on data collected from 1970 to 1983. This analysis estimated a 1983 human adipose concentration of 0.14 ppm β-HCH for the entire United States (*2*). While the southern U.S. census region had a higher median concentration, the levels did not differ by sex or by race in this analysis. Consistent with the banning of technical HCH in the United States, the average β-HCH concentration decreased from 0.45 ppm in 1970 to 0.16 ppm in 1981 (*2*).

Serum concentrations of HCH isomers have also been used to monitor HCH exposure in humans. Sixty-four employees from a pesticide manufacturing plant in India were divided with respect to their potential job-related HCH exposure, and serum concentrations of α-, β-, γ-, and δ-HCH of each group were monitored. The results are shown in Table 2. The employees who were most closely associated with the pesticide (handlers) were significantly contaminated as compared to controls. The β-isomer made up 60 to nearly 100 percent of the total HCHs in most exposed workers' serum (*44*). Similar results were found in another cohort of lindane production workers where serum concentrations for the α-, β-, and γ-isomers were 70, 190, and 37 μg/L (*46*). The higher concentrations of β-HCH in these studies is consistent with a recent study of 40 former workers from a lindane plant, which concluded that the median half-life of β-HCH in the blood is 7.2 years (*51*). In contrast, the half-life of γ-HCH was only about 1 day (*52*).

Occupational exposures and accidental poisonings are not the only ways humans are exposed to HCHs. Several studies report HCH intake from food. For example, of 460 cow milk samples collected in Leon, Spain, in 1987−1988, 75, 37, and 96% had detectable levels of α-, β-, and γ-isomers, respectively (*53*). Three of the milk samples exceeded the 1986 European Economic Community maximum residue limit of 0.1 mg/kg of α-HCH (*53*). A 1996 study by Urieta and co-workers (*54*) calculated that the dietary intakes of α-, β-, and γ-HCH were 0.1, 0.1, and 2.9 μg/day, respectively. The study was based on a market basket food survey carried out in Basque Country, Spain, between 1988 and 1990. Total diet samples were analyzed for contaminants between 1990 and 1991. The high intake of lindane was attributed to bread contamination by a local bakery. Bread, cereals, milk, and dairy products were the food groups that contributed the most to the Spanish acceptable daily intake (ADI) (*54*). In the United States, the Food and Drug Administration (FDA) monitors pesticide residues in food. In a total diet study in 1991, the FDA found lindane residues in 22 of the 936 (2% occurrence) items tested (*55*). The α- and γ-HCH intake for three age/sex groups were calculated. α-HCH intakes for 6−11-month-old infants and 60−65-year-old women were 0.0002 μg (kg of body weight)$^{-1}$ day^{-1} while intakes were twice that for 14−16-year-old males. The highest intake was for the γ-HCH isomer in the 14−16-year-old males (0.0008 μg (kg of body weight)$^{-1}$ day^{-1}) (*55*). The U.S. intake of γ-HCH was 10^4 times less than the United Nations' Food and Agriculture Organization/World Health Organization ADI of 8 μg (kg of body weight)$^{-1}$ day^{-1}.

Infants and children often are the most sensitive to toxic insults, and therefore many studies have investigated potential maternal transfer of pesticides to their young. A potential route of HCH transfer from mother to young is via breast milk, and several studies have addressed this issue in Germany (*56*), Denmark (*57*), Japan (*58*), Sweden (*59*), Finland (*60*), Canada (*61*), Italy (*62*), southern India (*63*), Kenya (*64*), and Hong Kong (*65*). For example, concentrations of β-HCH in Hong Kong mothers' milk ranged from 3 to 27 μg/g of lipid (mean 16), and α- and γ-HCH concentrations varied from 0.04 to 2.6 and <0.01 and 0.21 μg/g of lipid, respectively (*65*). While the 1985 β-HCH concentrations in milk in Hong Kong were lower than those from 1976, these concentrations were still the highest reported in the literature. No conclusive reason was offered for the high breast milk concentrations in Hong Kong. For comparison, in southern India, where technical HCH is still used, α-, β-, γ-, and δ-HCH were analyzed in breast milk, and the highest total HCH concentration was 10 μg/g of lipid in women from the Nattarasankottai region (*63*) (see Figure 2; note the logarithmic scale). As shown in Figure 2, the β-isomer is the most prevalent, and there were detectable, though minimal, concentrations of δ-HCH reported. Total HCH residues were higher than those of PCBs and total DDT in these women (*63*), and with the continued use of HCH in India, the authors speculated that HCH residues would continue to rise in Indian citizens. Because the health effects of pesticides to infants are largely unknown but the nutritional and immunological benefits of breast milk are widely established, breast feeding is generally not discouraged based on HCH concentrations in milk.

Several studies have been conducted that try to link human HCH concentrations with disease etiology. Four studies compared HCH concentrations in control and cancer patients from the United States, Canada, Finland, and Germany (*30*, *66*−*68*). There were no correlations between breast cancer (*30*), either estrogen receptor positive or negative status (*67*) or bone marrow cancers (*68*), and HCH tissue concentrations. In contrast Mussalo-Rauhamaa and co-workers (*66*) found that after adjusting for age and parity by stepwise logistic regression, β-HCH was a significant risk factor of breast cancer in Finnish patients. More studies, both mechanistic and epidemologic, are necessary to confirm the relationship between human cancers and HCHs.

Animal HCH Residue Concentrations

Like humans, wildlife can also accumulate HCHs. Several species have been used as sentinels to monitor contamination

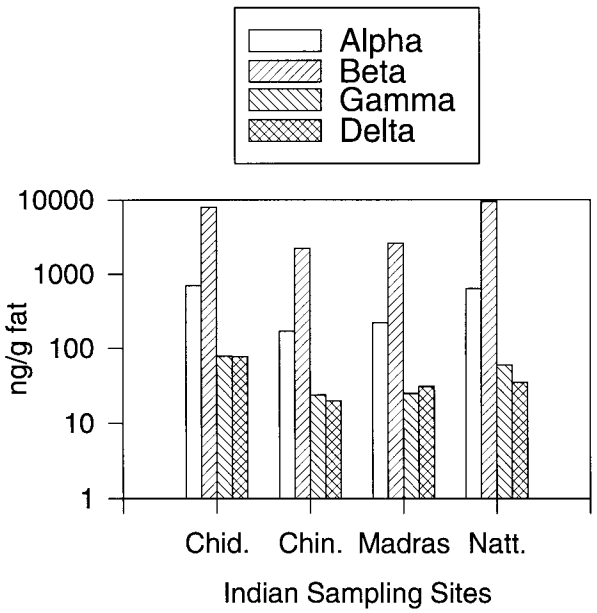

FIGURE 2. Concentrations (ng/g fat basis) of HCH isomers in human breast milk from women from the Chidambaram (Chid., $n = 11$), Chinnoor Parangipettai (Chin., $n = 5$), Madras ($n = 6$), and Nattarasankottai (Natt., $n = 3$) regions of southern India (*63*). These regions represent semi-urban, fishing village, industrial city, and rural farming areas, respectively. Note the logarithmic scale.

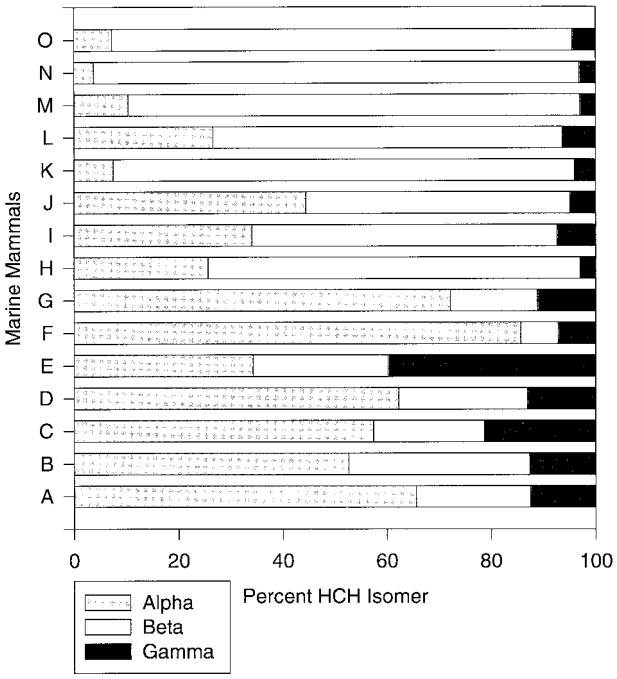

FIGURE 3. Percent composition of HCH isomers in marine mammal blubber. Bars represent the following species and their respective sampling location: A, bowhead whale; B, Beluga whale from North Pacific−Arctic waters; C, pilot whale; D, common dolphin from North Atlantic; E, harbor porpoise from Danish Norwegian waters; F, harbor seal from the North Atlantic; G, harp seal from Greenland Sea; H, northern fur seal from North Pacific−Arctic waters; I, neonatal fur seal from Alaskan waters; J, Baird's beaked whale; K, melon-headed whale from Japanese waters; L, Dall's porpoise from Bering Sea and North Pacific; M, Pacific white-sided dolphin from North Pacific; N, striped dolphin; O, Fraser's dolphin from Japanese waters. Data replotted from refs *77*, A−D and F; ref *82*, E; ref *83*, G; ref *78*, I; and ref *80*, J−O.

and temporal trends of HCHs. For example, significant declines in β- and γ-HCH in eggs of seabirds from around the Barents Sea reflect the decreasing use of HCHs (*69*). Six species of bird eggs at four different sites around northern Norway were collected and, with only one exception, eggs from all species and sites had lower β-HCH concentrations in 1993 as compared to the results from 1983. The 1993 β-HCH concentrations in eggs ranged from 0.95 ng/g wet weight for eider to 16 ng/g for razorbill, whereas concentrations of γ-HCH were only nondetectable to 1.8 ng/g in gannet (*69*). A similarly low concentration of lindane (1.9 ng/g) was reported in shag eggs from an island in the central Irish Sea (*11*).

Fish are also used as sentinel species for HCH contamination. Fish caged in the Italian River Po upstream and downstream of the Lambro River confluence differentially accumulated α- and γ-HCH. These results indicated that the drainage area of the Lambro was a point source for HCH contamination in the Po River (*70*). Ramesh and co-workers (*71*) conducted a survey of organochlorine contamination in wildlife from an agricultural watershed in southern India. HCH concentrations in fish and crabs ranged from 0.48 to 150 ng/g wet weight. In birds, HCH concentrations varied between 8.1 and 4000 ng/g, and in turtles and lizards, it ranged from 5.5 to 170 ng/g. The authors concluded that the HCH concentrations in birds varied according to feeding habits with inland piscivores and scavengers > coastal piscivores > insectivores > omnivores > granivores (*71*). The β-isomer was most prevalent in birds and sediment feeders such as crabs and turtle; however, in fish, the α-isomer predominated (*71*). Arctic char from an Alpine lake and Peru fish oil from the South Pacific also had severalfold higher concentrations of α-HCH as compared to β-HCH (*72*). Alternatively, Lee and co-workers (*73*) found higher percentages of β-HCH as compared to α- or γ-isomers in surface and deep sea fish collected from Suruga Bay, Japan. Furthermore, the surface fish had higher percent β-HCH compositions as compared to the deep sea organisms. Relatively high concentrations of α-HCH are indicative of either (a) relatively recent technical HCH use (rather than lindane alone) or (b) in an otherwise pristine environment, atmospheric transport and deposition. In contrast, β-HCH concentrations such as in the Japanese fish could indicate technical HCH contamination at some earlier time because the α- and γ-HCH isomers can be more readily metabolized and would not be detected.

Global HCH transport is also evident in residues found in marine mammals and Arctic species. For example, total HCH in adipose tissue of polar bears from Canada was 490 ppb (range 300−900) (*74*) and from 40 to 190 ppb lipid weight in blubber of harp seals collected in Russian waters (*75*). In a survey of 11 species of adult male odontoceti cetaceans, Prudente and co-workers (*76*) found higher HCH blubber concentrations in animals inhabiting cold and temperate waters compared to those from tropical waters, indicating HCH transport to northern sinks. In all of the species in this survey except the Baird's beaked whale from Chiba, Japan, the β-HCH isomer was predominant (*76*). Isomer analysis of marine mammals from the North Pacific, North Atlantic, and Danish−Norwegian waters revealed that the β-isomer did not necessarily predominate (see Figure 3). α-HCH was most prevalent in bowhead (A), beluga (B), and pilot whale (C), common dolphin (D), and harbor seal blubber (F) from the North Pacific/Arctic and from the North Atlantic (G) (*77*). In contrast, the β-HCH blubber concentration was highest in fur seals (H) (*77*−*79*) and in animals collected in the North Pacific (I, L, M) and near Japan (J, K, N, O) (*80*) (see Figure 3). Differences have also been reported in blubber concentrations of γ-HCH. For example, harbor seals and harbor porpoises collected in the same area of the North Sea had 12 and 480 ppb γ-HCH, respectively (*81*). The γ-isomer also predominates in harbor porpoise blubber from Danish−

Norwegian waters (E in Figure 3) (*82*). Given that all these marine mammal species probably have similar metabolic capabilities, blubber HCH profiles should be similar among these species, and the β-HCH isomer should predominate as it does in human fat samples. However, even among seal species, there were significant differences in α- and β-HCH compositions (see row F vs rows H and I in Figure 3). Similar variability is seen comparing various whale, dolphin, and porpoise species in Figure 3. Contamination of these oceanic species is indicative of global distribution of technical HCH, but the differential isomer concentrations in these marine animals is curious. Isomer differences could indicate different sources of contamination, different times since exposure, or different mechanisms of uptake, metabolism, or storage by the various species. Clearly, further research is necessary within and among species to understand the differential isomer tissue concentrations.

Several studies have addressed organ specificity in HCH isomer accumulation using seals (*78, 83*) and male striped dolphins (*84*). In a neonatal fur seal, β-HCH constituted 59−62% of the HCH in the blubber, liver, and lung, while α-HCH was only 28−34%. In the brain, however, the α-HCH was 91% of the total HCHs (*78*). Similar results were reported in male striped dolphins, where β-HCH was 84 and 94% in the muscle and kidney, but α-HCH constituted 75, 73, and 83% of the HCHs in the cerebrum, cerebellum, and medulla oblongata (*84*). In contrast, α-HCH was the predominant HCH isomer in both harp seal blubber and brain tissue making up 71 and 60% of total tissue HCHs, respectively (*83*). Preferential accumulation of certain isomers by various tissue systems could have significant toxicological implications. For instance, high concentrations of α-HCH in marine mammal brains indicate that this compound can cross the blood/brain barrier. α-HCH accumulation in rat brain white matter has also been documented; however, no functional consequences of this accumulation were detected in rats (*85*). More research is necessary to determine if organ-specific accumulation of HCH isomers occurs in humans and whether any tissue specific toxic effects result.

In both human and wildlife samples, the variable percentages of HCH isomer contributions can be indicative of the source and formulation of HCH contamination. For example, residues in some Indians indicated recent exposure to technical HCH while contamination in Arctic wildlife shows global transport of HCHs. While isomer-specific residue concentrations do provide evidence for HCH transport and fate, there are still no clear correlations between isomer tissue concentrations and toxicological effect.

HCH Residues in Plants

Several environmental matrices have been analyzed to characterize the extent of HCH contamination in the environment. Recently plants have started to be used in pesticide monitoring (*86*). HCHs have been detected in tree bark, pine needles, lichens, mosses, and mango leaves. Simonich and Hites (*87*) found that HCHs were one of the most predominant organochlorine residues in tree bark samples collected from around the world. Increasing HCH concentrations in tree bark with increasing latitude suggested the global distillation of HCHs toward polar regions (*87*). There was, however, no correlation between HCHs in bark and gross national product of the countries from which the bark was sampled (*88*). In contrast, Calamari and co-workers (*89*) found a positive correlation between α- and γ-HCH concentrations detected in mango leaves, pine needles, lichens, and mosses and economic development. In both studies, India was an outlier because, while it has a low GNP per person, significant HCH concentrations were detected in vegetation (*88, 89*). A survey of organochlorines in lichens from Ontario, Canada, collected between 1985 and 1987 found that more volatile organochlorine compounds, such as the HCHs, were present in higher concentrations at the northwestern sampling sites (*90*). The range of mean α-HCH concentrations in Ontario lichens was 0.37−5.5 ng/g dry weight, and the ratio of α- to γ-HCH ranged from 2.5 to 6.7 (*90*). Pine needles collected in Germany, Denmark, Norway, and Sweden had uniform α-HCH concentrations; however, higher γ-HCH residues were reported in German and Danish pine needles (*91*). Because studying vegetation contaminant loads is a relatively new area of environmental research, more papers are expected on this topic in coming years.

HCH Residues in Soil and Sediment

Because of their low polarity, upon release or atmospheric deposition, HCHs tend to associate with soils and sediments. Sediment HCH loads have been reported recently in Arctic lakes (*92*), along the coast of India (*93*), in the Ya-Er lake area of China (*94*), and from the Skagerrak and Kattegat areas of the North Sea (*95*). In a study of eight Arctic lakes, Muir and co-workers (*92*) found that total HCH residues from surface sediments showed neither a significant latitudinal gradient nor a correlation with lake drainage area or surface area. However, there were isomer-specific differences between lake sediments. For example, the β-isomer represented 45−65% of total HCHs in the four southern lakes. In contrast, concentrations of α-HCH were generally higher in the six Arctic lakes as compared to northwest Ontario lakes (*92*). Detection of the α- and γ-isomers at higher latitudes indicates the higher volatility of these compounds as compared to β-HCH. Total HCH concentrations in the Arctic lake sediments ranged from 0.05 to nearly 3 ng/g dry weight, which was slightly higher than sediment concentrations reported in the Skagerrak and Kattegatt regions where total HCHs were 0.02−0.7 ng/g (*95*). In 9 of 11 Swedish sampling sites, β-HCH had the highest concentration (*95*).

In contrast, α-HCH was most prevalent in both offshore and estuarine sediments from the west coast of India. As expected from the continued use of HCHs in India, sediment concentrations were higher than those in Europe, ranging from 0.85 to 7.9 ng/g total HCHs (*93*). Estuarine total HCH concentrations were three times higher than residues at offshore sites, indicating land runoff as a source of contamination. Furthermore, Indian rice paddy soil HCH concentrations have been reported up to 1100 and 190 ng/g in the wet and dry seasons, respectively. HCH in sediment from the Vellar River in southern India ranged from 2 to 27 ng/g (*96*). Similarly high total HCH concentrations were reported in sediments and soils sampled in China, even though technical HCH use has been discontinued there (*94*). β-HCH predominated in these samples, and δ-HCH residues were detectable. The persistence of HCHs in soil was indicated from samples taken from around a factory formerly belonging to the Institute of Malarial Studies in Rio de Janeiro. In 1955, approximately 340 000 kg of HCH was left at the site (*97*). Recently, samples of the top 10 cm of soil 80 m from the site still had 42, 84, 12, and 3 ng/g of α-, β-, γ-, and δ-HCH, respectively, while those 500 m away contained a factor of 10 less (*97*). Because the β-HCH isomer is the most persistent with respect to microbial degradation and has the lowest volatility, detection of β-HCH in soils or sediments is probably indicative of local technical HCH contamination. In contrast, the predominance of the more volatile α- and γ-HCH isomers in the high Arctic lakes (*92*) is probably indicative of long-range transport.

Once HCHs are in soil, they are degraded by soil-associated microbes, or they volatilize to the atmosphere. In 1966, the persistence of lindane in soil and sediment was first calculated as 2900 and 1200 h, respectively (*98*). Rapaport and Eisenreich (*99*) studied HCH residues in peat bog cores and found that the highest HCH burdens (98 $\mu g/m^2$)

TABLE 3. Atmospheric α- to γ-HCH Isomer Ratios

location	ratio	year	ref
Sea of Japan	1.01−1.02	summer 1988	107
Okhotsk Sea	1.05−1.06	summer 1988	107
Bering Sea	1.9	summer 1988	107
Chirikov Sea	2.6	summer 1988	107
Chukchi Sea	2.3	summer 1988	107
Mississaugua, N. Lake Ontario	1−17	1985	111
Stoney Creek, Lake Ontario	0.3−0.4	1985	111
Turkey Lake, central Ontario	3−10	1987−1989	114
Point Petre, N. Lake Ontario	6−20	1987−1989	114
Green Bay, WI	1.7−3.0	June 1989	112
Lake Michigan	5.2−8.4	August 1990	112
Lake Huron	4.0−7.9	Aug 1990	112
Lake Erie	2.0−9.1	Aug 1990	112
Lake Ontario	4.2−5.8	Aug 1990	112
Great Lakes (av)	6.0 ± 1.9	Aug 1990	112
Egbert, Ontario	~7	winter 1988−1989	116
Egbert, Ontario	<4	summer 1988−1989	116
Alert, Ellesmere Island	2.2; 10	May; Feb 1992	109
Chukchi Sea	9.2−10	1989−1990	106
Bering Sea	4.8−12	1989−1990	106
Gulf of Alaska	5.5−7.6	1989−1990	106
northern North Pacific	3.5−40	1989−1990	106
Southern Ocean	0.87−2.9	1989−1990	106
Bering and Chukchi Seas	4.1	Aug 1988	127
Lista, southern Norway	~1	summer 1991−1995	115
Lista, southern Norway	~3	winter 1991−1995	115
Stockholm and Aspvreten, Sweden	1.6−9.0 (4.5 av)	1983−1985	145
Ny-Alesund, Spitsbergen	10.2	summer 1984	146
Ny-Alesund, Spitsbergen	9.4	winter 1984	146
Karvatin, west Norway	4.8	summer 1984	146
Karvatin, west Norway	10.7	winter 1984	146
Jergul, north Norway	4.8	summer 1984	146
Jergul, north Norway	8.5	winter 1984	146
Birkenes, south Norway	1.8	summer 1984	146
Birkenes, south Norway	9.0	winter 1984	146
Rorvik, west Sweden	1.2−2.4	Jan−Feb 1989	147
Rorvik, west Sweden	0.4−1.0	Feb. 1990	147
Rorvik, west Sweden	0.5−0.7	May 1990	147

correlated with the lowest mean bog temperature and presumably with the lowest microbial activity. Both aerobic and anaerobic soil bacteria cultures have been established that can degrade HCHs, including the persistent β-isomer (*100, 101*). When a technical HCH mixture was applied to flooded rice fields, half-lives of 360, 620, 180, and 720 h were observed for α, β, γ, and δ, respectively (*102*). The removal rates of HCH isomers from a HCH technical mixture-treated agriculture plot were α > γ > δ ≫ β-HCH (*103*). In a 4-year study where a lindane preparation was sprayed on plots, climatic conditions largely influenced lindane disappearance rates (*104*).

HCH Residue Concentrations in Air and Water

Cotham and Bidleman (*105*) calculated that the annual loadings to the Arctic for α- and γ-HCH were 98 000 and 13 000 kg/yr, respectively. In a global survey, higher concentrations of HCHs were detected in the Northern Hemisphere than in the Southern Hemisphere (*106*). Air samples with concentrations as high as 10 000 pg/m^3 were observed over the Bay of Bengal and the Arabian Sea, while concentrations were also high over the South China Sea (1300 pg/m^3) and the northern North Pacific (28−1300 pg/m^3). HCH residues in the surface waters were highest (1000 pg/L on average) in latitudinal waters north of 40° N such as the Chukchi Sea, Bering Sea, Gulf of Alaska, and northern North Pacific (*106*). Likewise, on a transect from the Sea of Japan to the Bering Sea, α-HCH concentrations in surface water ranged from 810 to 1200 pg/L with a trend of increasing HCH concentrations with increasing latitude ($r^2 = 0.88$) (*107*). Total HCH residues were 3100 and 3600 pg/L for the Bering and Chukchi Seas, respectively. Interestingly, β-HCH made up 13 and 15%, respectively, of the total HCH concentration in these seawater samples (*107*). This is one of the few reports of β-HCH in seawater. γ-HCH (0.2−4.1 ng/L) and α-HCH (0.43−8.7 ng/L) made up more than 75% of the total OCs measured in snowpack samples collected in the Northwest Territories, Canada (*108*). Alert, on Ellesmere Island, Canada, is a high Arctic monitoring station where α-HCH air concentrations were 62 and 57 pg/m^3 for cold and warm periods of 1992 (*109*).

Global sources of HCH and the transfer of HCHs away from the source can be monitored based on the ratio of the α- to the γ-isomer. For example, in technical grade HCH this ratio is between 3 and 7 assuming no interconversion (*110*). However, a lindane source will show an α to γ ratio of near or less than unity. Table 3 shows the α to γ ratios reported in air samples collected around the world. Recent lindane use is suggested from samples from the Sea of Japan and the Okhotsk Sea where the ratio is close to 1 (*107*). Likewise, air from the Stoney Creek site near Lake Ontario, which is 800 m from an OC chemical plant, indicated recent lindane release (*111*). Generally, the more northern sites have a higher α to γ ratio. For example, McConnell and

co-workers (*112*) found higher α to γ ratios near the upper Great Lakes as compared to the lower lakes. This trend was also reported in Great Lakes water samples (*113*). However, Point Petre on the northern shore of Lake Ontario had ratios ranging from 6 to 20 as compared to Turkey Lake in central Ontario where these ratios were 3−10 (*114*). Seasonal variability in the ratio has also been reported (*109, 115−117*). In Egbert, Ontario, high ratios were observed in winter samples, but in the summer, local lindane use as a seed dressing or as a general pesticide caused a reduction in the α to γ ratio (*116*). Likewise, in a weekly air survey between 1991 and 1995 at Lista, Norway, high ratios (>2) occurred between October and March while low ratios occurred between April and September. These results correlated with lindane applications in Europe and air mass trajectories (*115*).

Various hypotheses have been suggested for the higher α-HCH concentrations in the Arctic air and thus in older air masses. Photochemical transformation of γ- to α-HCH during long-range transport has been suggested, but this has not been confirmed in the ambient environment (*12*). In fact, Poissant and Koprivnjak (*118*) found no increases in the α-HCH concentrations when there was a significant local source of lindane after the spring corn seeding in Quebec, Canada. This result indicated that interconversion of γ-HCH to α-HCH was slower than the lindane reaction with hydroxyl radical or that the sampling site in this study was too close to the source to allow time for interconversion.

Recently, Brubaker and Hites (*119*) determined experimental rate constants for the reaction of α- and γ-HCH with the hydroxyl radical. At 298 K, rate constants were 1.4 and 1.9×10^{-13} cm^3 s^{-1}, which corresponded to atmospheric lifetimes of 120 and 96 days for α- and γ-HCH, respectively. The experimentally derived lifetimes were longer than the 7−15 days previously predicted (*120, 121*). Long atmospheric lifetimes explain how HCHs are transported great distances and are detected at high Arctic locations. From these experimental results, α-HCH has a longer atmospheric lifetime by about 25% (*119*), and this could contribute to the higher α to γ ratios in air samples such as those reported at Point Petre (*114*), northern North Pacific (*106*), Chukchi Sea (*106*), and Bering Sea (*106*) (see Table 3). Other possible explanations for higher α to γ ratios could be differential gas exchange across air−water interfaces, washout by precipitation, or volatilization−adsorption variations between the isomers (*122*).

Fluxes of gaseous HCH isomers between atmospheric particles and soil or at air−water interfaces are related to, respectively, each isomer's vapor pressure or Henry's law constants (*H*). The *H* for a particular isomer is calculated from the ratio of its vapor pressure to its water solubility. Kucklick and co-workers (*123*) have determined *H* values for α- and γ-HCH in seawater and distilled water as a function of temperature. The slopes of a plot of log *H* (Pa m^3 mol^{-1}) versus $1/T$ (K^{-1}) for α- and γ-HCH were -2970 ± 220 and -2700 ± 280, respectively, when determined in seawater at 0.5−23 °C by the gas stripping method (*123*). These laboratory values converted to enthalpies of partition, ΔH_p, give 55 ± 4 and 53 ± 6 kJ/mol for α- and γ-HCH, respectively. These laboratory values agreed very well with those determined environmentally from surface water samples collected in the Atlantic Ocean between 50° N and 50° S (for α-HCH, $\Delta H_p = 51 \pm 11$ kJ/mol; for γ-HCH, $\Delta H_p = 59 \pm 11$ kJ/mol) (*124*). Using the relationship determined by Kucklick and co-workers, fluxes of HCH isomers in to and out of various water bodies have been calculated (*106, 112, 125−128*). In a survey of oceanic air and water during 1989−1990, the deposition of HCHs from air to water was determined (*106*). A depositional flux of −112 and −24 ng m^{-2} day^{-1} for α- and γ-HCH, respectively, was found in Lake Baikal, Russia, in 1991 (*126*). In the U.S. Great Lakes, the flux appears to depend on the season (or temperature) and the lake characteristics (volume, water column structure, etc.). McConnell and co-workers (*112*) estimated monthly fluxes for α- and γ-HCH in Lakes Michigan, Erie, Huron, and Ontario. In Lakes Michigan, Erie, and Huron, the flux for both α- and γ-HCH isomers was depositional except for the α-isomer during June−September. In contrast, Lake Ontario was almost a total sink for both the α- and γ-isomers year-round (*112*).

Two Arctic seas, the Bering and Chukchi, have been monitored routinely over several years, and recently a reversal of the air−water gas exchange was reported. Up until 1990, these seas were sinks for HCHs (*127*), but because atmospheric concentrations over these seas have decreased (91 to 23 pg/m^3), there is now a summertime reversal of flux for α-HCH and an approach to equilibrium for γ-HCH. Fluxes reported from 1993 data were 30 (range 8−56; a positive flux indicates volatilization) and −1.5 (range −16 to 5.1) ng m^{-2} day^{-1} for the α- and γ-isomers, respectively (*128*). This report implies that, while atmospheric concentrations have decreased with cutbacks in global HCH use, re-emissions from oceanic sinks may continue to augment atmospheric concentrations.

Because the concentrations of HCHs are so readily detectable in environmental matrices such as plants, soil, water, and air, these analyses have and will continue to be used to track the global transport and fate of HCHs. Soil sampling indicates differential rates of volatilization and microbial degradation of the various HCH isomers while paired air−water data show α-HCH-specific changes in flux and seasonal variability in flux over some water bodies. Furthermore, the ratio of the α- to γ-isomers provides a method of characterizing local lindane releases versus global transport of technical HCH residues.

Enantiomeric Ratios of α-HCH in Environmental Samples

Resolution of the chiral enantiomers of α-HCH (see Figure 1) found in the environment is now possible. The enantiomeric ratio of (+)- to (−)-α-HCH was first quantitated in North Sea water using gas chromatography with a heptakis-(3-*O*-butyryl-2,6-di-*O*-pentyl)-β-cyclodextrin stationary phase (*129*). Since this initial report, two studies have analyzed for both α-HCH enantiomers and their chiral pentachlorocyclohexene (PCCH) metabolites using different chiral stationary phases (*130, 131*). Technical HCH contains the (+)- and (−)-α-HCH enantiomers in a 1:1 racemic mixture. By monitoring the enantiomeric ratio of (+)- to (−)-α-HCH (called the ER) in environmental samples, it is possible to distinguish microbial degradation, which is mostly enantioselective, from nonenzymatic degradation.

The ER can be interpreted as a bio-indicator showing whether the α-HCH residues have encountered biota. For example, air samples collected at Resolute Bay in the summer of 1992 had an ER of 1.00 ± 0.04. However, seawater in the bay was depleted in (+)-α-HCH, resulting in an ER of 0.93 ± 0.06 (*132*). Likewise, precipitation over Lake Ontario had an ER of 1.00 ± 0.01, while the ERs for the Niagara River and Lake Ontario surface and deep water were 0.91 ± 0.02 and 0.85 ± 0.02, respectively (*133*). In laboratory studies, a North Sea microbial community degraded the (+)-α-HCH and the corresponding β-PCCH faster than their respective enantiomers (*134*). This effect was confirmed environmentally when ERs in 14 samples from the Baltic Sea and in seven samples from the North Sea averaged 0.85 ± 0.03 and 0.87 ± 0.05, respectively (*135*). Preferential (+)-α-HCH microbial degradation was also reported in Amituk Lake, Cornwallis Island (ER 0.77 ± 0.004) (*136*), the Canada Basin, and the Greenland Sea (*137*).

The (+)-enantiomer was also more quickly degraded under anaerobic conditions in sewage sludge (*11*). However, the opposite degradation pattern was found in Bering and

TABLE 4. Enantiomeric Ratios [ER = (+)-α-HCH/(−)-α-HCH] in Selected Species and Tissues

species	tissue	location	ER	ref
blue mussel		North Sea	0.7−1.04	140
common eider duck	liver	North Sea	>1.43	140
flounder	liver	North Sea	0.76−0.98	140
roe deer	liver	Germany	0.03−0.4	139
sheep	brain	Germany	1.4−3.8	148
neonatal fur seal	blubber	Alaska	1.88	78
	liver	Alaska	1.66	78
	lung	Alaska	1.55	78
	brain	Alaska	30	78
female fur seal	milk	Alaska	1.58	78
harp seal	blubber	Greenland Sea	1.08−2.45	78, 83
	brain	Greenland Sea	≫1	83
harbor seal	blubber	Baltic Sea	1.95−2.4	141
	blubber	North Sea	1.41−2.32	141
	blubber	Iceland	1.0−1.37	141
grey seal	blubber	Baltic Sea	1.61−2.12	141
	blubber	North Sea	1.02−1.87	141
	blubber	Iceland	1.0−1.50	141
hooded seal	blubber	North Sea	0.75	141
harbor porpoise	blubber	Baltic Sea	1.36−2.47	141
	blubber	North Sea	1.7−3.86	141
	blubber	Iceland	1.90−3.88	141
white beaked dolphin	blubber	North Sea	1.08−1.48	141
Dall's porpoise	blubber	N. Pacific Bering Sea	1.6−2.1	80
Baird's beaked whale	blubber	Japan	2.1−2.8	80
Pacific white-sided dolphin	blubber	North Pacific	2.2−2.8	80
Fraser's dolphin	blubber	Japan	1.6−1.8	80

Chukchi Seas surface water (*137*) and in muck soil samples collected from farms in British Columbia (*138*). The selective enrichment of either (+)- or (−)-α-HCH has been observed in different animal species and even in tissues within the same animal as shown in Table 4. For example, preferential metabolism of (+)-α-HCH was indicated in roe deer livers (*139*), blue mussels, and flounder livers (*140*). However, in most marine mammals regardless of tissue, selective degradation of (−)-α-HCH was apparent (*78, 80, 141*). In the neonatal fur seal not only did (+)-α-HCH predominate in the tissues, it was particularly concentrated in the brain as compared to the blubber, liver, and lung (*78*). In harp seal brain tissue, (+)-α-HCH was the only enantiomer detected. However, in this study (*83*) the total α-HCH concentrations were not higher in the brain tissue as compared to blubber as in ref *78*. The reasons for enantiomeric enrichment differences in environmental and biological samples are largely unclear and need further research. Several hypotheses have been suggested including the following: both enantiomers are being decomposed but at different rates, certain microbial populations or enzymes are highly selective to one isomer, or there exist certain enantiomeric active transport processes that create enantiomeric excesses in certain tissues (*142*).

Future Research Directions

We hope that this review has highlighted the differential toxicity and persistence of HCH in humans, wildlife, plants, soil, water, and the atmosphere. While much is known, there are still certain issues that we feel are incompletely understood or need further investigation.

While β-HCH makes up only a small percentage of the technical mixture and technical HCH is banned in many countries, this isomer is readily detected in human samples. Some studies suggest that β-HCH can act as an environmental estrogen (*32, 35*); however, the mechanism of action and toxic consequences in humans is unclear.

Plants have recently been successfully used to monitor environmental contamination around the world. Continued monitoring of this matrix is expected to provide useful results in tracking the global movements of HCHs and identifying sources and sinks of HCH isomers.

The composition of HCH isomers in wildlife tissues is variable. For example, in evolutionarily related marine mammals (Figure 3), some species have higher concentrations of β-HCH while others have more α-HCH in their blubber. Possible explanations for differential tissue concentrations include different sources of contamination; different times since exposure; and differences in uptake, metabolism, or storage by various species. However, the true reason or reasons for this variability between wildlife species is still unknown. In addition, the toxicological implications to species that have higher tissue concentrations of one HCH isomer as compared to another warrant further study.

A global model of paired environmental fates and toxicities of HCHs would be very helpful. However, because there are so few ecotoxicological data available and because there are no good biomarkers of HCH toxic effects, this model may be difficult to implement at this time.

Recent changes in α-HCH fluxes from deposition to volatilization from the world's seas are expected to increase as atmospheric concentrations continue to decrease. Measurements of paired air−water α- and γ-HCH concentrations will be needed to verify this trend.

The different enantiomeric ratios for α-HCH in different seas, species, and tissues within species are curious. Future research should elucidate whether different microbial populations or enzymes selectively degrade certain enantiomers or whether certain species or tissues selectively accumulate one enantiomer but not the other. Furthermore, studies are needed to determine differential toxicity of the two α-HCH enantiomers.

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