

Hexachlorobenzene as a Possible Major Contributor to the Dioxin Activity of Human Milk

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A dioxinlike compound is a compound that binds to the aryl hydrocarbon (Ah) receptor, results in dioxinlike effects, and bioaccumulates. These are the three factors for including dioxinlike chemicals in the toxic equivalency factor (TEF) concept. Risk assessment of dioxinlike compounds is based on using these TEFs. Hexachlorobenzene (HCB) has all three features and should therefore be included in this TEF concept. Relative potency values express the potency of a specific compound in comparison to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most potent dioxinlike compound, with a relative potency value of 1. For the estimation of the total dioxin activity in an environmental biological sample, the TEF value of a compound is multiplied by the concentration in the specific matrix. This results in a certain amount of toxic equivalents (TEQs) for this compound. The summation of all TEQs in a certain mixture gives the total dioxin activity of this mixture. HCB binds to the Ah receptor about 10,000 times less than TCDD. HCB is also about 10,000 times less potent than TCDD based on *in vitro* cytochrome P4501A induction and porphyrin accumulation. Using a relative potency value of 0.0001, HCB could add 10–60% to the total TEQ in human milk samples in most countries. In a few countries such as Spain, Slovakia, and the Czech Republic, HCB levels in human milk expressed as TEQ could contribute up to a factor of six to the total TEQ in comparison to the contribution of polychlorinated dioxins, dibenzofurans, and biphenyls together, i.e., up to a daily intake of about 1 ng TEQ/kg for a breast-fed infant. The HCB levels in human milk in these countries are about the same as in India. Biochemical, immunological, and neurological alterations have been observed in infants fed breast milk in countries with relatively low TEQ levels in human milk. Based on the above information, it is clear that HCB should be classified as a dioxinlike compound, that more studies are needed to reduce the uncertainty in the estimation of a relative potency value for HCB, and that epidemiological studies should be undertaken in infants fed breast milk in countries with high HCB exposure levels. Furthermore, measurements of HCB levels in human and environmental samples in conjunction with other dioxinlike compounds is a prerequisite to estimate the total dioxin activity in these samples. *Key words:* breast milk, hexachlorobenzene, TEQ, toxic equivalents. *Environ Health Perspect* 106:683–688 (1998). [Online 9 October 1998]

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Hexachlorobenzene (HCB) was used as a fungicide for crops such as wheat, barley, oats, and rye (1). In the mid-1970s, most countries discontinued the application of HCB as a fungicide. In Tunisia, however, HCB was still used in 1986 (2). HCB is also generated as a by-product during the production of carbon tetrachloride, trichloroethylene, tetrachloroethylene, and various pesticides, such as pentachloronitrobenzene, chlorothalonil, dacthal, pentachlorophenol, atrazine, simazine, propazine, and maleic hydrazide (1,3–5). Furthermore, HCB is released into the environment by waste incineration (1). Table 1 presents data on the estimated production volume and release in the environment of hexachlorobenzene in the last few decades in various countries. The release of HCB from all municipal incinerators in the United States was estimated by the EPA to be between 57

and 454 kg/year as documented in 1986 (1). In the United States, the annual production of hexachlorobenzene as a by-product was estimated to be 4.1×10^6 kg as published in 1986 (3). It was estimated that about 77% of this amount was produced during the manufacture of carbon tetrachloride, trichloroethylene, and tetrachloroethylene. No recent data are available on the production volume of hexachlorobenzene either on production as a by-product or waste incineration.

The goals of this paper are to inform scientists and regulators who work in the field of dioxinlike compounds that hexachlorobenzene should be classified as a dioxinlike compound, stimulate discussion on the impact of this classification, and encourage further research based on human and environmental exposure levels to hexachlorobenzene.

Estimation of Dioxin Activity of Mixtures of Dioxinlike Compounds

A dioxinlike compound is a compound that binds to the aryl hydrocarbon (Ah) receptor, results in dioxinlike effects, and bioaccumulates. These are the three factors for inclusion of dioxinlike chemicals in the toxic equivalency factor (TEF) scheme (6,7). Risk assessment of dioxinlike compounds is based on using these TEFs. TEFs are consensus values based on the available data on relative potency values on a specific compound and are protective in nature. Relative potency values express the potency of a specific compound in comparison to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most potent dioxinlike compound, with a relative potency value of 1. For the estimation of the total dioxin activity in a certain matrix, the TEF value of a compound is multiplied by the concentration in the specific matrix. This results in a certain amount of toxic equivalents (TEQs) for this compound based on the dioxin effect of the chemical. The summation of all TEQs in a certain mixture gives the total dioxin activity of this mixture.

Is HCB a Dioxinlike Compound?

For HCB to be classified as a dioxinlike compound, it should bind to the Ah receptor, result in dioxinlike effects, and bioaccumulate. HCB has an affinity for the Ah receptor 10,000 times less than TCDD (8). This is in the same range as the mono-*ortho*-substituted polychlorinated biphenyls (PCBs) 2,3,3',4,4'-pentachlorobiphenyl (PCB 105), 2,3',4,4',5-pentachlorobiphenyl (PCB 118), and 2,3,3',4,4',5-hexachlorobiphenyl (PCB 156) (9).

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Table 1. Data on the production and release of hexachlorobenzene in the environment

Location	Production (kg)	Production (kg TEQ) ^a	Reference
Global production 1978–1981	1 × 10 ⁷	1000	(66)
U.S. production in 1973	3 × 10 ⁵	30	(32)
U.S. production as a by-product ^b	4.1 × 10 ⁶	413	(3)
Spain (one company)	1.5 × 10 ⁵	15	(32)
Germany (for the production of the rubber auxiliary PCTC, discontinued in 1993)	1.5 × 10 ⁶	150	(1)
Germany as a by-product in 1980	>5 × 10 ⁶	>500	(66)

^aUsing a relative potency of 0.0001.

^bAbout 77% of this is produced during the manufacture of carbon tetrachloride, trichloroethylene, and tetrachloroethylene.

Exposure to HCB results in dioxinlike effects such as induction of hepatic cytochrome P4501A1 (CYP1A1) and P4501A2 (CYP1A2) activities, hepatic porphyrin accumulation and excretion, alterations in thyroid hormone levels and metabolism, alterations in retinoid levels, liver damage, reduction in reproduction, splenomegaly, increase in mortality, neurological alterations, teratologic effects, and immunotoxic effects (8,10–21). Some of these effects cannot be classified as unique for TCDD-like compounds, such as porphyrin accumulation and a decrease in circulating thyroid hormone levels, because it has been shown that multiple mechanisms are involved in these responses (22–25). HCB is a mixed-type inducer, having also the properties of phenobarbital-like effects such as induction of hepatic cytochrome P4502B (CYP2B) activity (15,20). This property, in addition to the dioxinlike property of PCBs, may be responsible for a higher efficacy in hepatic porphyrin accumulation after exposure to mono-*ortho*-substituted PCBs in mice (26). For the decrease in circulating thyroid hormone levels, it has been shown that multiple mechanisms are involved after exposure to HCB, one existing of an increase in the metabolism of thyroxin by glucuronidation and one of binding of a metabolite of HCB (pentachlorophenol) to the transport protein of thyroxin (transthyretin) (27). HCB is a rodent carcinogen, with the liver, thyroid, adrenals, and parathyroid gland as major target organs (28–31). The no-observed-effect-level (NOEL) was estimated to be 0.38 mg/kg/day for neoplastic liver nodules and adrenal pheochromocytomas in female rats in a two-generation study (1,30). The NOEL for parathyroid adenomas in male rats in the same study design was estimated to be 0.29 mg/kg/day (1,30). The range of NOELs for both biochemical and toxicological effects ranged from 0.05 to 0.07 mg HCB/kg/day (1). The range of lowest observed effect levels (LOELs) for biochemical and toxicological effects in pigs,

monkeys, rats, mice, dogs, and mink divided over 12 studies ranged from 0.1 to 0.7 mg/kg/day (1). These tight ranges in various species for both NOELs and LOELs indicate that the effects by HCB are receptor mediated.

TCDD has been shown to cause tumors at multiple sites in rats, mice, and hamsters (32). HCB has also been shown to be a tumor promotor in rats, with the liver as a target organ (33). In humans, an excess in soft-tissue sarcoma and thyroid neoplasms was observed in males exposed to HCB in ambient air in the Flix cohort in Spain (34). This cohort was rather small and the excess in tumors were based on three and two cases for soft-tissue sarcoma and thyroid neoplasms, respectively. TCDD has been classified as a human carcinogen by the International Agency for Research on Cancer (32).

The bioaccumulation of HCB can be found in the long half-life in various species (ranging from weeks to years), the high log octanol/water partition coefficient (5.5), and the biomagnification of HCB in various studies in natural aquatic ecosystems (1). For example, the (whole body) half-life of HCB in male Wistar rats has been reported to be 20 days (35). In male Sprague-Dawley rats and male white rabbits, the half-life was calculated to be 24 days and 32 days, respectively (36). For TCDD, the half-life in rats has been reported to range from 12 to 31 days (37). In rhesus monkeys, the half-life for HCB has been estimated to be 2.5–3 years (38). The half-life of TCDD in adipose tissue of rhesus monkeys was about a year (39). No data on the half-life of HCB in humans are available. The half-life of TCDD in humans has been reported to range from 5 to 11 years (40–42).

Metabolites found in rats after exposure to HCB include pentachlorophenol, tetrachloro-1,4-hydroquinone, and diverse tetra- and trichlorophenols (43). Another major pathway is the conjugation of HCB with glutathione (43). This conjugate is further metabolized by cleavage of the glycine and

glutamate residues in order to be converted into pentachlorophenyl-*N*-acetyl-L-cysteine. A portion of the mercapturate is eliminated unchanged via the urine (44,45). Another portion is further metabolized by cleavage of the C-S bond to produce pentachlorobenzethiol (PCBT), pentachlorothioanisole, tetrachloro-1,4-benzenedithiol, tetrachlorobenzethiol, pentachlorobenzene, and other minor metabolites (46). Accidental human exposure to HCB resulted in detectable metabolites of HCB in the urine. Pentachlorophenol and a sulfur derivative were the major detectable metabolites. The sulfur derivative yielded PCBT after hydrolysis (45). PCBT concentrations in the urine correlated strongly with serum HCB concentrations, especially in males (45). These results indicate that the metabolism of HCB in humans resembles that of HCB in rodents.

In summary, HCB can be classified as a dioxinlike compound similar to mono-*ortho*-substituted PCBs.

Which Studies Can Be Used to Determine a Relative Potency Value?

The World Health Organization (WHO) uses a tiered approach for estimating TEF values, giving long-term *in vivo* studies the preference over short-term *in vivo* studies, which have a priority over *in vitro* studies or structure-activity considerations (7,47). Unfortunately, no *in vivo* studies designed for estimating a TEF value are available. The porphyrinogenic potency of HCB was estimated to be 1,400 times less than TCDD based on the concentration of the compounds in the liver in a 45-week gavage study with TCDD in female CD-COBS rats and in a 112-day diet study with HCB in female rats of the inbred Agus strain (48,49). However, it is not appropriate to compare the effect of HCB and TCDD in two different experimental designs (7,47). In addition, it can be expected that the porphyrinogenic effect of HCB is caused by multiple mechanisms, making it difficult to use this end point for the estimation of a TEF value. The available *in vitro* data were derived from a study of HCB and TCDD in chicken hepatocytes (50). The median effective concentrations (EC₅₀s) for HCB and TCDD in this system were determined for ethoxyresorufin *O*-deethylase (EROD) activity and accumulation of uroporphyrin. The uroporphyrin accumulation in this specific system was not dependent on the rate-limiting enzyme δ -aminolevulinic acid synthetase, suggesting that only an Ah receptor-mediated mechanism was involved. Based on the EC₅₀s of these two end points, the relative potency for HCB was

estimated to range from 0.00006 to 0.0002 (Table 2). In another study in which HCB was compared to TCDD, binding to the Ah receptor was reported to be 10,000 times less than TCDD (8). From all these data together, it can be estimated that HCB has a relative potency value of 0.0001 (Table 2).

This estimated relative potency is only based on *in vitro* experiments and therefore does not include differences in pharmacokinetic behavior between TCDD and HCB. For compounds with a considerably shorter half-life than TCDD, a marked decrease in relative potency occurs immediately after *in vivo* administration; in repeat-dose experiments, these compounds will reach steady-state levels fairly quickly, whereas TCDD will still accumulate. TCDD will thus appear more potent over time in comparison to these compounds. This has been shown for 2,3,7,8-tetrachlorodibenzofuran, 3,3',4,4'-tetrachlorobiphenyl, and 3,3',4,4'-tetrachloroazobenzene (7,51,52).

However, the available studies in the literature on the half-life of HCB and TCDD in rodents and nonhuman primates report similar half-lives for both compounds (see above). This indicates that there is little difference in pharmacokinetic behavior between HCB and TCDD. Until robust *in vivo* data are available, a relative potency value for HCB of 0.0001 based on *in vitro* experiments is probably a reasonable basis to estimate the dioxin activity of HCB in mixtures of dioxinlike compounds.

Exposure to HCB

In the general population. HCB is detected in fatty food items, especially those of animal origin, such as dairy products, meats, and fish, but also in peanut products (1). In many countries, the HCB concentration in food declined from the mid-1970s to the mid-1990s (1); however, in some countries, this trend has not been observed. In the most recent survey, conducted during 1990–1991, mean HCB levels in the United States were less than 1 ppb for all products (1). In food surveys from countries such as Spain, Morocco, Mexico, India, and the United Kingdom, higher concentrations of HCB have been found (1). HCB concentrations in potatoes in the United Kingdom are quite high (3 ppb), with the majority of HCB on the peel of the potatoes (6 ppb) (53). These concentrations are similar to those in fish in the United Kingdom, i.e., 6 ppb HCB (1).

The daily intake of HCB by adults is estimated to range from 0.0004 to 0.0030 μg HCB/kg body weight in various countries,

based on HCB levels in air, water, and food (1). This intake is mainly from the diet. Using a relative potency value of 0.0001 for HCB, this equals 0.04–0.3 pg TEQ/kg/day . For comparison, the daily intake for polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and PCBs in the United States was estimated to range from 1.2 to 3.6 pg TEQ/kg/day (54). In an extensive food survey in the Netherlands, the average daily intake from PCDDs, PCDFs, and PCBs was 135 pg TEQ/day (55). Using a body weight of 60 kg, this would equal 2.3 pg TEQ/kg/day .

In breast-fed infants. The daily intake by infants via breast milk ranges from <0.018 to 5.1 $\mu\text{g/kg}$ body weight in various countries (1). Using a relative potency value of 0.0001 for HCB, this equals <1.8–510 pg TEQ/kg/day . The concentration of HCB in breast milk samples covers a wide range, with the highest concentration in samples from Spain, the Czech Republic, Slovakia, and India (Table 3). In the mid-1970s, similar concentrations of HCB in breast milk were reported in Austria and France (Table 3). Lipid-adjusted HCB levels range from 0.007 to 5 mg/kg human milk. Using a relative potency value of 0.0001, these HCB values range from 0.7 to 500 ng TEQ/kg lipid . For comparison, the concentration of PCDDs, PCDFs, and PCBs together range from about 10 to 45 ng TEQ/kg lipid (Table 3). This indicates that in most countries with lower HCB levels in human milk the contribution of HCB to the total TEQ can add an additional 10–60% to the total TEQ (Canada, Denmark, Faroe Islands, Germany, Japan, Kazakhstan, the Netherlands, and the United States). However, of most concern are the high levels of HCB in human milk in the Czech Republic, Slovakia, and Spain, which are up to six times the dioxin activity in human milk in comparison to the contribution of PCDDs, PCDFs, and PCBs together expressed as TEQ. For a breast-fed infant consuming 150 ml milk/kg body weight/day, this could be as high as 1 ng TEQ/kg/day . The HCB levels in human milk in these countries are about the same as in India.

Are Effects in the Background Population Associated with Exposure to Dioxinlike Compounds?

A change in thyroid hormone levels, immunological parameters, subtle signs of neurological dysfunctioning, a small delay in psychomotor development, and a decrease in birth weight in infants were correlated with dioxinlike compounds and nondioxinlike PCBs in breast milk in the Netherlands (56–60). Based on a relative potency value of 0.0001, HCB could add an additional 17% of the TEQ to the dioxin activity of human milk samples in the Netherlands (Table 3). This indicates that HCB very likely played a minor role in these effects. The levels of PCDDs, PCDFs, and PCBs in human milk in the Netherlands are about the same as in most countries (Table 3). In Japan, effects on immunological parameters and decreased thyroid hormone levels in infants were correlated with levels of dioxinlike compounds in human milk (61,62). HCB could add an additional 10% of the TEQ to the dioxin activity of human milk samples in Japan (Table 3). Just as in the study in the Netherlands, HCB very likely played a minor role in the observed effects. However, by including HCB in the TEF concept, HCB could considerably add to the total TEQ in some countries, leading to higher TEQ levels than in countries such as the Netherlands and Japan (Table 3).

Alterations in thyroid hormone levels are associated with exposure to dioxinlike and nondioxinlike compounds in breast-fed infants. HCB has been shown to interfere with thyroid hormone metabolism and results in immunotoxic and neurologic effects (1,13,14,16,19,27,63,64). These results strengthen that HCB could add an additional TEQ dose because the same type of effects occur in rodent models in response to other dioxinlike compounds.

What is the Concentration in Environmental Samples?

Little information is available on the concentration of HCB in environmental samples in conjunction with measurements of PCDDs,

Table 2. Relative potency estimates for hexachlorobenzene (HCB)

Effect	TCDD	HCB	Relative potency for HCB	Reference
Binding affinity to the Ah receptor (nM)	0.18	2100	0.00009	(8)
EC ₅₀ for EROD induction in chicken hepatocytes (nM)	0.014–0.020	130–150	0.00009–0.0002	(50)
EC ₅₀ for accumulation of uroporphyrin in chicken hepatocytes (nM)	0.002–0.004	25–35	0.00006–0.0002	(50)
Hepatic porphyrin accumulation in female rats	–	–	0.0007	(49)

Abbreviations: Ah, aryl hydrocarbon; EC₅₀, median effective concentration; EROD, ethoxyresorufin *O*-deethylase.

Table 3. Hexachlorobenzene (HCB) concentrations recalculated to TEQ in human milk

Country	HCB concentration (mg/kg lipid adjusted)	HCB concentration (ng TEQ/kg lipid) ^a	Concentration of PCDDs, PCDFs, and PCBs (ng TEQ/kg lipid)	Year collected	Reference
Australia	0.38 ^b	38		1973	(67)
	0.41	41			(68)
	0.1	10		1990–1991	(69)
Austria	1.2–3.7	120–370		1973	(70)
			26	1992–1993	(71)
Canada	0.026	2.6			(72)
			20	1986	(71)
Canada, Quebec, Inuits	0.136	13.6		1991	(73)
Czech Republic, Jihlava	1.64	164	28.2	1990	(74)
Czech Republic			23.2	1992–1993	(71)
Denmark	0.035	3.5	34	1993	(75)
			19.7	1992–1993	(71)
Egypt	0.29 ^b	29		1987	(76)
Faroe Islands	0.072	7.2	20	1995	(77)
Finland	0.064	6.4		1982	(78)
			20.3	1992–1993	(71)
France	0.98	98		1972–1973	(79)
Germany	1.85	185			(80)
	0.51	51		1984	(81)
	0.18	18		1991	(81)
			28.3	1992–1993	(71)
Germany (former GDR)	0.25	25		1989–1990	(82)
India; Delhi	1.28 ^{b,c}	128		1987	(83)
India; Faridabad	0.1 ^{b,c}	10		1987	(83)
Israel	0.08	8		1985	(84)
Japan	0.030	3.0	30.8	1994	(85)
Italy	0.22	22		1987	(86)
Jordan	0.29	29		1989–1990	(87)
Kazakhstan	0.078	7.8	29.2		(88,89)
Lithuania			45	1985–1986	(90)
The Netherlands	0.05	5	30	1990–1993	(91)
Norway	0.017 ^b	1.7		1991	(92)
			34	1985–1986	(90)
Poland	0.048–0.081 ^b	4.8–8.1			(93)
Slovakia	0.829	82.9	28.4	1993–1994	(74)
			23	1992–1993	(71)
Spain	1–5	100–500		1984–1987	(94)
	0.9–1.7	90–170	33.7	1990–1991	(94)
			31.6	1992–1993	(71)
Sweden	0.11	11		1978–1979	(95)
Sweden	0.04	4		1989	(96)
Thailand	0.007	0.7		1985–1987	(97)
Turkey	0.084	84		1988	(98)
United States	0.019–0.022	1.9–2.2	10	1985–1987	(97)
Russia	0.11–0.13	11–13	18–20	1993	(99)
Vietnam	0.022–0.221	2.2–22.1		1985–1987	(97)

Abbreviations: TEQ, toxic equivalents; PCDDs, polychlorinated dibenzo-*p*-dioxins; PCDFs, polychlorinated dibenzofurans; PCBs, polychlorinated biphenyls; GDR, German Democratic Republic.

^aUsing a relative potency of 0.0001.

^bBased on lipid content of 4.2%.

^cOriginally presented on a dry weight basis, but recalculated here to a whole milk basis, using 12% as dry matter (100).

PCDFs, and PCBs. Levels of HCB in bald eagle eggs from the British Columbia coast from 1990 to 1992 ranged from 0.012 to 0.025 mg/kg wet weight (65). Assuming HCB has a relative potency of 0.0001, this could be as high as 25 ng TEQ/kg wet weight. For comparison, the concentration of PCDDs, PCDFs, and PCBs (planar and mono-*ortho*-substituted) ranged from 120 to about 320 ng TEQ/kg in bald eagle eggs from the same areas (65). This indicates that HCB can contribute considerably to the total TEQ in environmental samples.

Conclusions

Based on binding to the Ah receptor, the dioxinlike effects, and the bioaccumulation in higher trophic levels, HCB should be classified as a dioxinlike compound. The mechanism of action resembles that of mono-*ortho*-substituted PCBs, which have also phenobarbital-like properties and are included in the TEF concept. Based on the limited information available, it was estimated that HCB is about 10,000 times less potent than TCDD. Using a relative potency value of 0.0001, HCB could add

10–60% to the total TEQ in human milk samples in most countries. In a few countries such as Spain, Slovakia, and the Czech Republic, HCB levels in human milk expressed as TEQ could contribute up to a factor of 6 to the total TEQ in comparison to the contribution of PCDDs, PCDFs, and PCBs together. The HCB levels in human milk in these countries are about the same as in India. Biochemical, immunological, and neurological alterations have been observed in infants fed breast milk in countries with TEQ levels in human milk that are not very high. More studies are needed to reduce the uncertainty in the estimation of a relative potency value for HCB and epidemiological studies should be undertaken in infants fed breast milk in countries with high HCB exposure levels. Furthermore, measurements of HCB levels in human and environmental samples in conjunction with other dioxinlike compounds is a prerequisite to estimate the total dioxin activity in these samples.

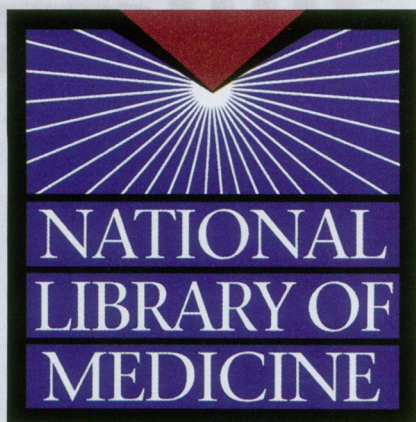
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