Does the Available Toxicological Evidence Warrant Identification of Hexachlorobenzene as a "Dioxin-Like" Chemical?

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Introduction

Toxic equivalency factors (TEFs) were originally developed as an interim approach for assessing the risks associated with exposure to complex mixtures of polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) in the environment. The adoption of TEFs was generally viewed as an interim science policy measure in the absence of sufficient bioassay information on the 209 congeners other than of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) (USEPA, 1989). Using the limited available toxicological data and structure-activity relationships among the different PCDD and PCDF congeners, the significance of environmental levels and exposure was expressed as an equivalent amount of 2,3,7,8-TCDD.

Over the past ten years, several refinements to the TEF scheme have been proposed for assessing PCDD and PCDF congeners (USEPA, 1989), and most recently by the World Health Organization (WHO, 1997). Within the past five years, the use of TEFs has been expanded to include the coplanar polychlorinated biphenyls (PCBs) on the basis of experimental evidence suggesting that these compounds have similar structural features to PCDDs and possess "dioxin-like" activity (Ahlborg et al., 1994; Safe et al., 1994). According to WHO (1997), other chemicals that may possess dioxin-like activity include polycyclic aromatic compounds such as 2- and 3- ring polycyclic hydrocarbons, polychlorinated naphthalenes and other heterocyclic compounds.

As part of the latest proposed refinement to the TEF scheme, it has been suggested that the health risks associated with exposure to hexachlorobenzene (HCB) could be assessed using the TEF scheme (van Birgelen, 1997). It has been claimed that HCB should be

included in the TEF scheme because it binds to the Ah-receptor, elicits "dioxin-like effects, and has been shown to bioaccumulate. In this paper, we address the question of whether the available toxicological evidence warrants identification of HCB as a "dioxin-like" chemical and incorporation into the proposed new TEF scheme.

Does HCB Meet WHO's Definition as a "Dioxin-Like" Chemical?

HCB does not satisfy the four criteria defined by WHO (1997) for determining whether a chemical might possess dioxin-like activity. Each of these criteria, as they apply to HCB, is discussed below.

Structural Similarity to 2,3,7,8-TCDD - As shown in Figure 1, HCB is a monocyclic (single-ringed) compound with full chlorine substitution, whereas 2,3,7,8-TCDD is a coplanar, polycyclic compound with chlorine substitution at four locations. As such, HCB lacks the conformation required for dioxin-like toxicity (McKinney and Singh, 1981).

Figure 1. Chemical Structure of HCB and 2,3,7,8-TCDD

Hexachlorobenzene 2,3,7,8-TCDD

Binding to the Ah Receptor - The available evidence supporting HCB binding to the Ah-receptor has been described as equivocal and at best a very weak competitor (Hahn, 1989). HCB affinity for the Ah-receptor is approximately 10,000-fold lower than that of 2,3,7,8-TCDD (Schneider et al., 1995). The binding affinity of HCB is less than that of the other 2,3,7,8-substituted PCDD and PCDF congeners, and much less than that observed for naturally occurring aromatic compounds such as polycyclic aromatic hydrocarbons and indole carbazoles (Kleman and Gustafsson, 1996).

Dioxin-Like Toxicological Response - HCB can induce several biochemical responses that can also be induced by TCDD, including CYPIA1/IA2 induction, thyroid hormone alterations, hepatic retinol depletion, porphyrin accumulation, hepatic hypertrophy, and

immunotoxicity (IPCS, 1997). However, the mechanism by which HCB elicits these responses appears to be different from that associated with 2,3,7,8-TCDD. Oxidative metabolites of HCB (e.g., pentachlorophenol and tetrachlorohydroquinone) have been implicated in the manifestation of hepatic porphyria and other toxic effects (Rietjens et al., 1995; Schielen et al., 1995; van Ommen et al., 1989). Conversely, the apparent toxicity of 2,3,7,8-TCDD is generally attributed to the interaction of the parent compound with the Ah receptor.

Persistence - In humans, the half-life of HCB has been estimated to be approximately 215 days (Freeman et al., 1989), which is less than a tenth of the 7.5 year half-life reported for 2,3,7,8-TCDD (WHO, 1997).

Is Sufficient Toxicological Information Available to Characterize HCB Toxicity?

The toxicity of HCB has been extensively studied in humans and animals, and the dose-response relationships for various toxic effects have been well characterized. The current human health and ecological toxicity factors for HCB have been derived without prejudice to the mechanism of action by which the adverse effects are produced. For ecological risk assessment, the available ecotoxicological data are based on subchronic and chronic studies of the dose-related effects of HCB on survival, growth, reproduction and development in ten species of mammals and five species of birds. A summary of the key toxicological values for HCB and 2,3,7,8-TCDD used for risk assessment are summarized in Table 1.

Table 1. Human Health and Ecological Endpoints for HCB and 2,3,7,8-TCDD

Endpoint	Toxicity Factor	HCB	2,3,7,8-TCDD
Human Health	USEPA Cancer Slope Factor	Based on liver tumors in female rats (Eturk, 1986)	Based on liver tumors in female rats (Kociba et al, 1986)
	USEPA Oral Reference Dose	Based on liver effects in rats (Arnold et al., 1985)	Not available
Ecological	Mammal Toxicity Reference Values	Based on survival and reproductive effects in mink (Bleavins et al., 1984)	Based on reproductive effects in rats (Murray et al., 1979)
	Fish Toxicity	Based on survival in	Based on survival in

	Reference Values	several aquatic species (USEPA, 1988)	rainbow trout and northern pike (USEPA, 1993)
	Bird Toxicity Reference Values	Based on survival and reproductive effects in several species of birds (Vos et al., 1971)	Based on survival, reproductive and developmental effects in several species of birds (Nosek et al., 1992)

Conclusions

The TEF approach was developed specifically to address the potential risks posed by related chemicals with similar structural features that might elicit a response or toxic effect by similar mechanisms of action. HCB is a well-studied chemical for which current risk assessment methods are superior to the TEF approach. As such, there would be appear to be no discernible benefit in adding HCB to the proposed new TEF scheme.

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