Dioxin-like and Non-dioxin-like Toxic Effects of Polychlorinated Biphenyls (PCBs): Implications for Risk Assessment

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Abstract

Polychlorinated biphenyls (PCBs) are persistent, bioaccumulative and toxic contaminants in the environment. Individual PCB congeners exhibit different physico-chemical properties and biological activities which result in different environmental distributions and toxicity profiles. The variable composition of PCB residues in environmental matrices and their different mechanisms of toxicity, complicate the development of scientifically based regulations for the risk assessment. Various approaches for the assessment of risks of PCBs have been critically examined. Recent developments in the toxic equivalency factor (TEF) approach for the assessment of toxic effects due to dioxin-like PCBs have been examined. PCB exposure studies which describe non-dioxin-like toxic effects, particularly neuro-behavioral effects and their effective doses in animals were also considered. A comparative assessment of effective doses for dioxin-like and non-dioxin-like effects by PCBs was made to evaluate the relative significance of non-*ortho* and *ortho*-substituted PCBs in risk assessment. Using mink as an example, relative merits and implications of using TEF and total PCB approaches for assessing the potential for toxic effects in wildlife was examined.

Introduction

Polychlorinated biphenyls (PCBs) are members of the group of halogenated aromatic hydrocarbons (HAHs), and consist of 209 isomers and congeners with different numbers and positions of chlorine atoms substituted on the biphenyl moiety.[1] Although 209 congeners of PCBs are theoretically possible, only about 130 individual congeners have been identified in commercial PCB mixtures at concentrations $\geq$0.05%. Individual PCB congeners exhibit different physico-chemical properties which result in different profiles for environmental distribution and toxicity. The differences in the composition of PCB residues in environmental matrices has implications for quantification and hazard evaluation, particularly when considering the differences in the biological activity, both qualitatively and quantitatively, among isomers as well as congeners. Due to the differences in metabolism and/or biodegradation rates of individual congeners, the compositions of the original commercial technical mixtures are different from the compositions of the mixtures which humans or wildlife are exposed. Only a few studies have investigated the effects of environmentally altered mixtures of PCBs. Health risks due to PCB exposure in humans or wildlife has been assessed based on either total PCB concentrations or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin equivalents (TEQs) using toxic equivalency factors (TEF). The U.S. Environmental Protection Agency (EPA) has adopted the TEF approach as an interim procedure for the calculation of risks of planar PCBs.[2, 3] The concept of TEF was developed in the early

1980s for assessing the risks of polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) in waste incinerators.[4, 5] The TEF model for PCBs presupposes a common mechanism of toxic action and additivity for the toxic effects of the individual congeners in the mixture and that PCBs act through the same mechanism of action as PCDDs/PCDFs. Further, the approach assumes that the dioxin-like effects of PCBs are the critical effects on animals. The critical effects are those that occur at the least concentration and would result in the least allowable total concentration of PCB mixtures.

Here we describe, compare and contrast several approaches to assessing the potential risks of PCBs to which wildlife might be exposed. Specifically, the concept of a critical toxicant will be developed based on the determination of mechanisms of actions that are likely to cause biological effects at the lowest concentrations of PCBs. This was done by comparing reference doses (RfDs) or toxicity reference values (TRV) for various toxic endpoints. A second level of assessment undertaken was to determine the effects of various environmental fate processes on outcomes of risk assessment based on total PCBs. Recent developments in the TEF approach for the assessment of dioxin-like effects of PCBs are also examined. Laboratory PCB-exposure studies for neuro-behavioral effects and their effective doses in animals were compiled. A comparative assessment of effective doses for dioxin-like and non-dioxin-like PCBs has been made to evaluate their significance in risk assessment process. Using mink as an example, the relative merits and implications of using the TEQ- and total PCB- approaches for assessing the potential for toxic effects in wildlife was examined.

Risk Assessment of PCBs

Traditionally, ecological risk assessment of PCBs have involved comparison of exposure concentration in target species to a toxicity reference value (TRV; equation 1). The TRV or RfD is an estimate of daily exposure, which during an entire lifetime, is likely to be without an appreciable adverse effects. The TRV can be expressed as a mass of chemical per unit body mass per unit time (e.g., mg/kg bw/d). Alternatively, doses can be given as maximum acceptable toxicant concentrations (MATCs) or burdens in target tissue (mg) or as dietary exposures expressed as concentrations in the food (mg/kg in the diet).

$$\text{TRV} = \text{NOAEC (or LOAEC)/uncertainty or correction factor} \quad (1)$$

The TRV is estimated by dividing the no observable effect concentration (NOAEC) or the lowest observable effect concentration (LOAEC), which are usually derived from dietary exposure to animals with technical PCB mixtures such as Aroclors, by correction (safety) factors. Here we compare the two methods of risk assessments for complex mixtures of PCBs by calculating HQ values based on total concentrations of PCBs by using the neuro-behavioral effects of di-*ortho*-substituted congeners, which are the primary components of the mixture and comparing these to the HQ values derived by the use of 2,3,7,8-TCDD equivalents (TEQs) that describe the toxicity of the dioxin-like congeners.

A toxic units approach was used to quantify the hazards due to PCB exposure in wild populations based on the NOAEC estimates from laboratory dietary exposure studies. [6, 7, 8] The Hazard Quotient (HQ) is defined as the ratio of the concentration in the tissue or diet divided by the TRV (equation 2). The units for the HQ are toxic units (TU).

$$HQ = [\text{Concentration in tissue or diet}]/TRV \quad (2)$$

An HQ of greater than one (1 TU) indicates that the concentration in the diet was expected to be sufficiently great to equal the threshold concentrations to elicit a statistically significant response.

The complex nature of PCB mixtures complicates the risk evaluation for wildlife. [9] In order to evaluate risks due to PCBs, a fundamental understanding of the mechanism of action is a prerequisite. At present sufficient evidence is available that there is a common mechanism for non- and mono-*ortho* PCB congeners, involving binding to the Ah-receptor as an initial step. When applying the TEF-concept, the toxicity of these coplanar congeners relative to that of 2,3,7,8-TCDD is determined on the basis of available *in vivo* or *in vitro* data. However, it should also be understood that the TEF concept is based on a number of assumptions and has limitations. Studies have also shown that, apart from non- and mono-*ortho* PCBs, *ortho*- substituted nonplanar PCB congeners elicit neuro-toxic effects in exposed animals and in cell cultures. Although TEFs have not been derived for non-planar PCB congeners, it appears that at greater exposures these congeners may cause neuro-toxic effects in humans or wildlife through various mechanisms but do not appear to act through the Ah receptor. Therefore, for a complete evaluation of risks due to PCBs, consideration of the effects of both *ortho*- and non-*ortho* substituted congeners are needed.

Table 1. Hazard Quotients (HQ) for various measures of dietary exposures of mink (for details see Ref 1)

Metric	NOAEC	HQ
Total Weathered PCBs	72 ng/g	50
Total Technical PCBs	200 ng/g	18
TEQ	0.3 pg/g	190
Di- to Tetra-*ortho* PCBs	500 ng/g	5.9

In order to evaluate relative hazards of coplanar and non-planar PCBs, concentrations of these congener were estimated for mink (1). Details on the estimation of PCB concentrations in mink from their diet and dietary threshold values for reproductive and neurotoxic effects are described elsewhere (1). Mink was selected because of the availability of threshold doses for neurotoxic effects in this species. Based on this example using mink, it was found that the hazard quotients (HQs) (Table 1) of dioxin-like PCBs were greater than those of non-dioxin-like PCBs, indicating that the coplanar PCBs are the critical in the risk assessment of PCBs. Nevertheless, it should be noted that mink are sensitive to reproductive effects of PCBs, [10, 11] and therefore the effects due to coplanar PCBs have been critical. Further, the RfDs/TRVs derived for non-dioxin-like effects of *ortho*-PCBs in mink were based on adult exposure. Since developing organisms are more sensitive to neuro-toxic effects of *ortho*-PCBs, RfDs/TRV from developmental exposures (pre- and/or perinatal) is necessary. However, TRVs for the neuro-toxic effects of *ortho*-PCBs are not available for mink or other wildlife. Further studies are needed to derive TRVs for neuro-toxic

effects of *ortho*-PCBs in wildlife. In any case, laboratory exposure studies with rodents and other mammals and *in vitro* bioassays have indicated that the neuro-toxic effects have occurred only at relatively great exposures. Therefore, it is considered that TEQs for dioxin-like PCBs are critical in setting environmental quality criteria. In other words, establishment of threshold limits for PCBs based on dioxin-like effects would be able to protect the animals from non-dioxin-like effects.

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