ASSESSING THE CARCINOGENICITY OF TOTAL PCBs USING TOXICITY EQUIVALENTS (TEQ)

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Introduction

PCBs are carcinogens in animals and are considered probable or possible human carcinogens.[1,2] However, few agencies have conducted formal carcinogenic risk assessments for PCBs, perhaps because PCB carcinogenicity is complicated by the variability in the composition of commercial mixtures generally used in laboratory studies, thus resulting in different potencies,[1,2] and additional uncertainties associated with the composition of weathered environmental mixtures.

There is suggestive evidence indicating that some adverse effects of PCB mixtures are attributed to a selected number of congeners which share a common mechanism with polychlorinated dibenzodioxins (PCDDs) and/or polychlorinated dibenzofurans (PCDFs). These dioxin-like PCBs were shown to interact with a nuclear receptor (aryl hydrocarbon (Ah) receptor) and induce a pleiotropic response that include many of the features reported for PCDD/F.[2] The toxicity of these congeners is generally assessed by estimating their potency relative to 2,3,7,8-tetrachlorodibenzo-*p*-dioxins (TCDD) using Toxicity Equivalent Factors (TEF). Although their concentration in commercial and environmental PCB mixtures may be quite variable on a mass basis, dioxin-like PCBs have been associated with most of the critical effects reported for PCBs. For this reason, the use of dioxin-toxicity equivalents (TEQ) represents a practical and attractive regulatory tool for the assessment of potential health risks of widely different PCB mixtures. Despite uncertainties and limitations associated with the use of TEQ, there is a substantial amount of information supporting this approach.[2] In the present analysis, we provide additional evidence supporting the use of TEQ for the carcinogenic assessment of PCB mixtures.

Approach and Methods

As a first step, results from the bioassays reported by Mayes *et al.*[3] were contrasted against available information in order to determine possible associations between the incidence of liver neoplasia and administered TEQ in female Sprague-Dawley rats. Thereafter, a dose response analysis was conducted on the combined liver cancer data for all Aroclor formulations (1016, 1242, 1254 and 1260) using dioxin equivalents based on the TEF scheme for human and mammals proposed by World Health organization (WHO)[4]. The experimental exposure data in terms of TEQ is shown in Table 1. Concentrations of dioxin-like PCBs in the original Aroclor formulation were converted to dioxin equivalents by using TEFs. TEFs for each dioxin-like PCB were then summed to generate a TEQ for each dose of Aroclor (n=12). TEQ's were log transformed to normalize the data prior to Benchmark dose (BMD) analysis (USEPA BMD software version 1.3.2). A BMD response model was also run on the liver tumourigenesis data of rats / Aroclor 1254 (Mayes *et al*.[3]) which was expected to be the most potent of all the Aroclor, using the USEPA BMD software.

Table 1. Incidence of Hepatocellular Adenomas and/or Carcinomas and Corresponding Doses Expressed as TEQ in Female Sprague-Dawley Rats Exposed to Aroclor Mixtures through the Diet for 2 Years (US EPA[1], Mayes *et al*.[3])

Aroclor	Administered dose (ppm)	TEQ (ng/kg/day)	No. of animals at termination	No. of animals with tumors
Control	0	0	85	1
1016	50	0.30	48	1
	100	0.60	45	7
	200	1.20	50	6
1242	50	21.8	49	11
	100	44.5	45	15
1254	25	66.6	45	19
	50	138.0	49	28
	100	290.4	49	28
1260	25	10.1	49	10
	50	20.2	45	11
	100	41.8	50	24

Results and Discussion

The relative potencies of the various Aroclor mixtures evaluated by Mayes *et al*.[3] (1254 > 1242 ≈ 1260 > 1016) as assessed either with the upper-bound slope factors or LED_{10} reported by U.S. EPA[1] or with the $BMDL_{10}$ derived by SDB (see accompanying abstract[5]), is correlated with their TEQ content (and thus with administered TEQ in the diet) and with total TEQ measured in the liver, but not with their degree of chlorination (Figure 1) nor with total liver PCBs (results not shown).

A plot of the Mayes *et al.*[3] incidence of parenchymal liver neoplasms (hepatocellular adenomas and/or carcinomas) in female Sprague-Dawley rats for all Aroclor mixtures as a function of administered TEQ resulted in a supralinear relationship (Figure 2). However, there was a linear relationship between administered TEQ and total liver TEQ, thus indicating no evidence of saturation of hepatic uptake (data not shown). While these observations can be interpreted to suggest saturation of possible toxicokinetic processes involved in the carcinogenic response (*e.g.,* metabolic activation of specific PCB congeners, if any; intracellular mobilization and/or transport of PCBs from storage sites), they are also consistent with toxicodynamic events that reflect saturation of receptor-based mechanisms, thus supporting the possible involvement of the Ah receptor. There is also a good agreement between the dose-response derived by SDB using the Mayes *et al.*[3] data and those estimated from other studies using comparable protocols (Figure 2) and for which TEQ were either reported or could be estimated. For example, a similar dose-response for hepatocellular adenomas and/or carcinomas in female Sprague-Dawley ratsas a function of dietary 2,3,7,8-TCDD was derived with data reported by Kociba *et al*.[6] This study used species/strain of animals and a dosing schedule similar to that of Mayes *et al*.[3]$BMDL_{10}$ values of the BMD analysis were used as the point of departure to derive a toxicity reference value (TRV) using an uncertainty factor (UF) of 1350 derived using the Australian Medical Research Council protocol (see accompanying abstract[5]). No statistically significant $BMDL_{10}$ value could be derived with the

combined Aroclor mixtures when expressed as mg Aroclor/kg bw-day. However, when expressed as TEQ equivalents, most dichotomous benchmark models provided a good statistical fit of the data. The $BMDL_{10}$ predicted from these models ranged from 0.8 ng TEQ/kg bw-day to 4.8 ng TEQ/kg bw-day. A TRV range of 0.6 to 3.6 pg TEQ/kg bw-day, or 1-4 pg TEQ/kg bw-day. This range is consistent with the TRV range proposed by WHO.[7] Using a similar dose response analysis with Aroclor 1254 alone, a $BMDL_{10}$ of 7.8 ng TEQ/kg bw-day and a TRV of 5.78 pg/kg/day were obtained.

In summary, the information available indicates sufficient support for the use of the TEQ approach for the assessment of carcinogenic risks of PCB mixtures. However, additional research is required in order to fully characterize the uncertainties associated with TEFs and to evaluate the appropriateness of TEQs as surrogates for the assessment of environmental mixtures of PCBs.

References

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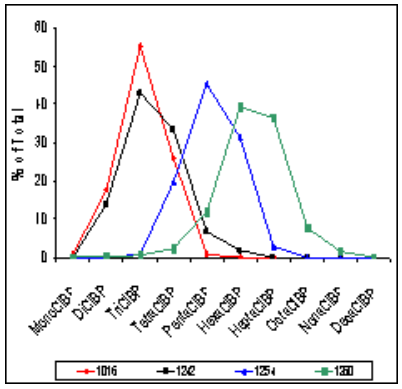
Figure 1 Correlation between potency ($1/BMDL_{10}$) and TEQ content measured in the liver of female Sprague-Dawley rats (B). (A): composition of Aroclor mixtures as reported by Mayes *et al*.[28] *Total liver TEQ correspond to the high dose of Aroclor 1242, 1254, and 1260, and mid-dose for Aroclor 1016.

A



B

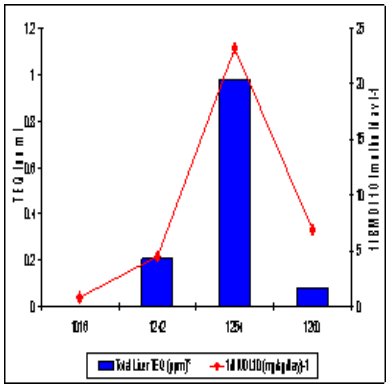


Figure 2 Percent hepatocellular adenomas and/or carcinomas in female Sprague-Dawley rats as a function of administered TEQ contained in various Aroclor mixtures (Data from Mayes *et al.*[28] are based on Aroclor 1016, 1242, 1254, and 1260).