AN EMPIRICAL EVALUATION OF THE POTENCY OF DIOXIN TOXIC EQUIVALENTS (TEQs) IN SEVERAL PCB MIXTURES

Russell E. Keenan[1], Jane M. Hamblen[1], Jay B. Silkworth[2], Michael N. Gray[1], Patrick O. Gwinn[1], and Stephen B. Hamilton[3]

1 AMEC Earth & Environmental, 15 Franklin Street, Portland, Maine 04101
2 General Electric Global Research Center, Niskayuna, New York
3 General Electric Co., 3135 Easton Turnpike, Fairfield, Connecticut

Introduction

The U.S. Environmental Protection Agency (EPA) has evaluated polychlorinated biphenyl (PCB) cancer risks using conservative animal models and PCB-specific data for over 20 years. In 1996, EPA thoroughly reviewed both the animal and human data, and developed a range of cancer slope factors (CSFs) for use in PCB risk assessments[1]. The upper bound of this range was set at 2 $(mg/kg\text{-}day)^{-1}$, a value lower than that previously used by the agency. In its 1996 reassessment, EPA's approach characterized the potency of the entire PCB mixture. According to EPA, "These mixtures contain overlapping groups of congeners that, together, span the range of congeners most often found in environmental mixtures"[2]. Such PCB mixtures include both so-called dioxin-like and non-dioxin-like compounds.

In April 1991, EPA launched a scientific reassessment of the potential health risks posed by exposure to dioxins and dioxin-like compounds. In 2000, EPA released its latest revision of the draft Dioxin Reassessment [3, 4] for scientific peer review and public comment, including a review by the U.S. EPA Science Advisory Board (SAB)[5]. Work on this Dioxin Reassessment is continuing. The Dioxin Reassessment uses a toxic equivalency method to relate the toxicity of the designated dioxin-like chemicals to the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), believed to be the most potent dioxin compound. Originally, the theory of toxic equivalency (TEQ) was developed for screening risks from dioxins and furans in combustion sources and incinerator emissions. The TEQ approach assigns TCDD a toxic equivalency factor (TEF) of 1, and each dioxin-like chemical a relative TEF less than or equal to 1. When the TEQ approach is applied to PCBs, the concentrations of the dioxin-like PCB congeners within a PCB mixture are converted to toxic equivalents (TEQs) of TCDD using various TEFs. Twelve of the 209 PCB congeners have been assigned dioxin-like toxicity, primarily based on their structural similarity to dioxins, their ability to induce activity in certain enzymes and their ability to bind to the aromatic hydrocarbon receptors in animal cells. The TEFs for these 12 PCB congeners are based on a variety of endpoints demonstrated in *in vitro* assays and *in vivo* animal studies, most of which are non-cancer endpoints [6]. Once the TEQs have been calculated for the various dioxin-like congeners, they are summed to determine a total TEQ concentration, and the CSF for TCDD is then applied to quantify the potential risks associated with estimated exposures to those congeners.

To evaluate the application of the TEQ methodology in estimating the cancer potency of PCB mixtures, we tested the approach empirically using the results from 2-year cancer bioassays involving four PCB mixtures of known composition that were fed to Sprague-Dawley (SD) rats and from a 2-year cancer bioassay of SD rats that had been fed TCDD. The effective CSFs in SD rats were determined for the TEQ components of each PCB mixture and compared to that of TCDD. A basic precept of the TEQ method is that a given dose of TEQs has equal biological

potency irrespective of the chemical mixture from whence it came. Thus, each CSF determined in this way should be equivalent to that of TCDD, if the tenet is correct.

Materials and Methods

Data Source. A comprehensive chronic toxicity and oncogenicity feeding study of four PCB mixtures was performed [7], and the findings associated with the carcinogenicity segment of the study have been published [8]. This study was conducted on male and female Sprague-Dawley (SD) rats using four PCB mixtures with varying degrees of chlorination (Aroclors 1016, 1242, 1254, and 1260). In each group, the animals received feed containing PCBs for 7 days/week for 24 months. Two or three dose rates plus controls were employed for each PCB mixture tested.

For each PCB mixture, the concentrations of twelve coplanar dioxin-like PCB congeners within a given PCB mixture were converted to TCDD TEQs using the TEF scheme adopted for the draft Dioxin Reassessment [6]. Once the TEQs were calculated for the various dioxin-like congeners, they were summed to determine a total TEQ concentration for each PCB mixture. These TEQ concentrations were then used in the dose-response assessment using the EPA benchmark dose model along with the survival-adjusted Battelle [7] animal bioassay data [8]. Only data for the female rats were included since the male rats showed no statistical elevation in tumor incidence except for those exposed to Aroclor 1260, but even in this instance only at the 100-ppm dose level. For 2,3,7,8-TCDD, the two-year rodent bioassay of Kociba et al. [9], with the Pathology Working Group[10] reevaluation of liver pathology and corresponding tumor incidence data, was used in the dose-response assessment. Because 2,3,7,8-TCDD has a TEQ value of 1, the doses of TCDD were modeled directly as TEQ in the dose-response model.

Determination of Effective CSFs for TEQ Components of PCB Mixtures and of 2,3,7,8-TCDD. In this analysis, a rodent CSF was determined for the TEQ in each PCB mixture that had been administered to SD rats using the EPA benchmark dose software. We also developed a rodent CSF for TCDD using the EPA benchmark dose software. In each CSF determination, whether for the TEQ concentrations in each PCB mixture or for TCDD itself, we derived CSFs only for the SD rats in order to facilitate comparisons on an equivalent basis. In each instance, the values represent rodent CSFs, because an interspecies extrapolation to humans involving either body weight or half-life scaling assumptions were not made. Thus, a simple direct comparison of the TEQ CSFs and the CSF for TCDD was possible. If the dioxin toxic equivalency method is predictive of the potency of dioxin-like PCB congeners, then the CSFs for TEQs in each PCB mixture should be equivalent, or nearly so, to each other and to the rodent CSF for TCDD.

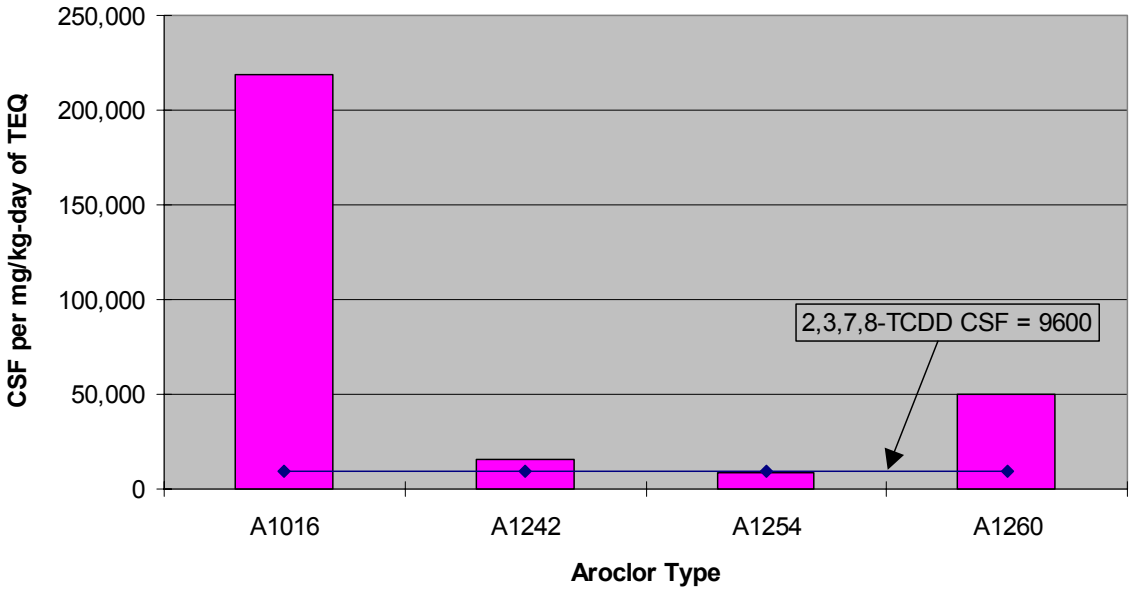
Results and Discussion

Results of the benchmark dose modeling to derive the CSF for the TEQ present in each PCB mixture as well as for TCDD are presented graphically in Figure 1. Comparison of the rodent CSFs generated for the TEQ present in each PCB mixture shows disparities that are significant and are not uniform across Aroclors [CSFs of 219,000; 16,300; 8,860; and 50,200 $(mg/kg\text{-}d)^{-1}$]. The modeled CSFs for the TEQ in PCB mixtures varied by approximately 24 fold across the mixtures tested. Moreover, these modeled CSFs did not match the 2,3,7,8-TCDD CSF of 9,600 $(mg/kg\text{-}day)^{-1}$ that was determined empirically from Kociba's animal bioassay of TCDD. These comparisons show that the TEQ component in each of the PCB mixtures, as determined through the use of the TEFs in Van den Berg et al. [6], does not have the same potency as TCDD.

The dioxin toxic equivalency hypothesis requires that any unit of TEQ is equivalent to any other unit in terms of biological potency, regardless of its origin, i.e., from dioxin-like congeners or TCDD itself, and regardless of the medium in which it exists. This is a difficult requirement to meet, since it necessitates that effects such as antagonism resulting from competition for receptor sites by other molecules in the mixtures, species differences, and differences in dose-response curves be insignificant. All of these issues have been tested experimentally and conformance of experimental results with the hypothesis has been inconsistent. Also implicit in this hypothesis is that relative potencies, largely based on initial cellular responses to these chemicals, such as enzyme induction, apply equally well to complex disease outcomes, such as tumorigenesis.

The current study reveals that the modeled CSFs for the TEQ in PCB mixtures varied by approximately 24 fold. In addition, these modeled CSFs did not match the CSF that has been determined empirically for TCDD. (Although this study based the comparisons on the use of rodent CSFs, the same points would hold true if equivalent interspecies scaling factors had been applied to each CSF to convert them to human CSFs. Thus, these observations and conclusions would not change regardless of the specific CSF selected for 2,3,7,8-TCDD.) These results demonstrate the uncertainty associated with the use of the TEQ method and suggest that it is not an accurate approach for characterizing the cancer potency of PCB mixtures.

Figure 1. Calculated Rodent CSFs for TEQ in PCB Mixtures and for 2,3,7,8-TCDD



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