Use of a Toxic Equivalency Quotient Approach Based on 2,3,7,8-TCDD To Evaluate Potential Carcinogenic Risks of PCBs

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I. Introduction

In its Work Plan for the Human Health Risk Assessment of the Lower Housatonic River (Weston, 2000), EPA has proposed to evaluate the potential carcinogenic risks of PCBs using the Toxic Equivalency Quotient (TEQ) methodology for “dioxin-like” congeners, combined with a cancer slope factor (CSF) for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The TEQ approach was developed as a screening tool to evaluate dioxins and furans because there were a number of congeners for which specific toxicity data were lacking. Because TCDD had been studied extensively and shown to be carcinogenic in laboratory animals, a scheme was devised to relate the toxicity of all other dioxin/furan congeners to the cancer potency of TCDD. In this way, a single CSF could be used for screening level risk assessment of these compounds. More recently, this methodology has been expanded to include certain PCB congeners because of observed “dioxin-like” properties of those congeners.

Under this approach, the concentrations of the “dioxin-like” PCB congeners within a PCB mixture are converted to TEQs of TCDD using Toxic Equivalency Factors (TEFs). Such TEFs have been developed for 12 PCB congeners based on a variety of endpoints demonstrated in in vitro and in vivo animal studies, most of which are non-cancer endpoints (WHO, 1997; Ahlborg et al., 1994). 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 estimate the risks of those congeners. The remaining, non-dioxin-like PCB congeners are then evaluated using the specific CSF developed for PCBs and the total risks are derived as the sum of risks of the dioxin-like and non-dioxin-like congeners.

For a number of reasons that are further discussed in this paper, this approach is not scientifically defensible and results in a substantial overestimate of the potential cancer risks associated with PCBs. First, the TEF/TEQ approach substantially overpredicts the cancer potency of PCB mixtures when compared to cancer potencies determined experimentally in studies of laboratory rodents in which these mixtures were administered. Second, the approach is based on a number of assumptions that are unproven, uncertain, and likely incorrect. Third, because of the use of both the PCB and TCDD CSFs for different components of the PCB mixtures, the TEF/TEQ approach double-counts the potency of the dioxin-like PCBs in those mixtures. Fourth, this approach unnecessarily requires application of a highly uncertain and controversial CSF for TCDD. Finally, the TEFs are not borne out by the most direct evidence concerning PCB carcinogenicity in humans – the large number of human epidemiological and clinical studies performed to investigate this issue over the past quarter-century.
These issues are further discussed below. Note that this paper does not address the separate questions of whether EPA has sufficient site-specific PCB congener data for the Housatonic River to provide reliable estimates of the congener concentrations in the river and its floodplain, or of how EPA would relate congener-based TEQ concentrations to Aroclor or total PCB concentrations. Those questions can be addressed at a later time if appropriate. However, this paper shows that, regardless of the sufficiency of the congener data, use of the TEF/TEQ approach does not provide a scientifically supportable basis for assessing the carcinogenic risks of PCBs.

II. Inconsistency with Empirical Bioassay Data

If the TEF/TEQ approach used for dioxin-like PCBs were truly predictive of the carcinogenic potency of PCBs (even in laboratory animals), then the cancer potencies predicted through that approach for various PCB Aroclor mixtures should be consistent with the potencies actually exhibited for those mixtures in bioassays. In fact, however, the cancer potencies predicted using the TEF/TEQ approach are substantially greater than the potencies that have been determined empirically in animal bioassays. This can be demonstrated by calculating hypothetical CSFs for several Aroclors using the TEF/TEQ approach and then comparing those TEQ-based CSFs to the empirically based CSFs derived for the same Aroclors in actual rodent bioassays.

To make this comparison, it is first necessary to calculate TEQ-based CSFs for several PCB Aroclor mixtures. This can be done through the following four steps:

♦ Step 1 – identify the fraction of each “dioxin-like” congener in each PCB mixture. The fractions of “dioxin-like” congeners in PCB mixtures have been determined with a variety of high-resolution gas chromatographic analytical methods, and are reported in Frame et al. (1996), Frame (1997), and Schultz et al. (1989).1

♦ Step 2 – multiply the fraction of each “dioxin-like” congener in the PCB mixture by its respective TEF, as developed by the World Health Organization (WHO) (van den Berg et al., 1998) to calculate the fractional TEQ of the PCB mixture attributable to each congener.

♦ Step 3 – sum the fractional TEQs across “dioxin-like” congeners to yield the total TEQ of the PCB mixture relative to pure TCDD.

♦ Step 4 – multiply the total TEQ of the PCB mixture by a CSF for TCDD to derive the CSF for the total TEQ of the mixture. As discussed below (Section V), EPA does not currently list a CSF for TCDD on either its Integrated Risk Information System (IRIS)

1 For purposes of this analysis, the fractions of dioxin-like congeners in PCB mixtures are computed as the mean of the data from Frame et al. (1996) and Frame (1997). It should be noted that the data from Schultz et al. (1989) would not significantly alter the results presented herein.
or its Health Effects Assessment Summary Tables (HEAST), and a wide range of CSFs have been proposed. However, for purposes of this analysis, we have used the most recent draft TCDD CSF of 1,000,000 (mg/kg-day)^{-1} proposed in EPA's draft final Dioxin Reassessment document (EPA, 2000), although that CSF has not been adopted by EPA and we do not accept the validity of that CSF.\(^2\)

Note that use of this four-step procedure produces CSFs only for the dioxin-like congeners in the mixtures. Under the approach proposed by EPA, the remaining congeners in the mixture are then evaluated using a CSF developed for PCBs and the two sets of risks are added to produce an overall carcinogenic risk – a procedure which, as shown in Section IV below, results in double counting the potency of the dioxin-like congeners.

Using the four-step procedure discussed above, the following TEQ-based CSFs have been derived for the dioxin-like congeners in three PCB Aroclors:

<table>
<thead>
<tr>
<th>Aroclor</th>
<th>TEQ-Based CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aroclor 1242</td>
<td>4.7 (mg/kg-day)^{-1}</td>
</tr>
<tr>
<td>Aroclor 1254</td>
<td>42.5 (mg/kg-day)^{-1}</td>
</tr>
<tr>
<td>Aroclor 1260</td>
<td>6.5 (mg/kg-day)^{-1}</td>
</tr>
</tbody>
</table>

For comparison, CSFs have been derived for all combined PCB congeners present in these Aroclors based on actual rodent bioassays. For example, in its 1996 reassessment of the cancer dose-response information for PCBs, EPA (1996a) reported the upper-bound CSFs derived based on the results of the Brunner et al. (1996) rodent feeding study, which included parallel experiments for several PCB Aroclors and which EPA itself stated “provides the most comprehensive information for empirical modeling” (EPA, 1996a, p. 32). The results of that study were also later published by Mayes et al. (1998). Based on these bioassay results, the CSFs derived for the Aroclors listed above are as follows (see EPA, 1996a, p. 34):

<table>
<thead>
<tr>
<th>Aroclor</th>
<th>Aroclor-Based CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aroclor 1242</td>
<td>0.4 (mg/kg-day)^{-1}</td>
</tr>
<tr>
<td>Aroclor 1254</td>
<td>1.5 (mg/kg-day)^{-1}</td>
</tr>
<tr>
<td>Aroclor 1260</td>
<td>0.5 (mg/kg-day)^{-1}</td>
</tr>
</tbody>
</table>

Comparison of the hypothetical TEQ-based CSFs with the empirically derived Aroclor-based CSFs clearly demonstrates that the TEF/TEQ approach substantially overstates the carcinogenic potential of the dioxin-like congeners in the PCB mixtures (even in rodents) – by factors ranging from at least 12 to 28 times. This comparison is illustrated

\(^2\) As discussed below, we have also, for illustrative purposes, calculated TEQ-based CSFs using EPA's prior provisional TCDD CSF of 156,000 (mg/kg-day)^{-1}, which was previously listed on HEAST, although we do not accept the validity of that CSF either (as noted in note 3 below).
in Figure 1. Moreover, the TEQ-based CSFs are also substantially higher than EPA’s current CSFs for PCBs, which take into account both the dioxin-like and non-dioxin-like congeners and which range from 0.04 (mg/kg-day)^{-1} to the most conservative upper bound of 2 (mg/kg-day)^{-1}, depending on the exposure pathway and the congener mix (EPA, 1996a).

Figure 1

Comparison of TEQ-based CSFs to Aroclor-Specific CSFs

- Aroclor-specific CSF (EPA, 1996a, based on Brunner et al., 1996)
- TEQ-based CSF (based on Frame et al., 1996, and Frame, 1997)

If EPA’s prior provisional CSF for TCDD of 156,000 (mg/kg-day)^{-1}, previously listed on HEAST, is used in the calculation of TEQ-based CSFs, the resulting TEQ-based CSFs for the dioxin-like congeners in the mixtures are: 0.73 (mg/kg-day)^{-1} for Aroclor 1242, 6.6 (mg/kg-day)^{-1} for Aroclor 1254, and 1.0 (mg/kg-day)^{-1} for Aroclor 1260. These TEQ-based CSFs are still 2 to 4 times higher than the empirically derived CSFs for these mixtures based on the rodent bioassay reported by Brunner et al. (1996) and Mayes et al. (1998).
Again, it should be emphasized that these TEQ-based CSFs are based only on the
dioxin-like congeners in the mixtures, whereas the empirically derived Aroclor-based
CSFs are based on all PCBs in the mixtures. Under EPA’s proposed approach of
evaluating the non-dioxin-like congeners using a CSF for PCBs and then summing the
risks, the resulting effective CSFs used for the overall PCB mixtures would be even
higher than the TEQ-based CSFs calculated using the four-step procedure described
above. This further demonstrates the overprediction in the TEF/TEQ approach.

As these comparisons illustrate, use of the TEF/TEQ approach to calculate carcinogenic
risks of PCBs substantially overpredicts the carcinogenic potency of PCBs relative to
the actual potencies demonstrated in laboratory bioassays. As will be discussed below
(Section VI), this approach even more substantially overpredicts cancer risks to
humans.

III. Unsupported Assumptions

The TEF/TEQ approach is based on a number of assumptions that are not well
supported by the scientific evidence and may well not be true. These include the
following: (1) that all of the congeners for which TEFs are assigned are carcinogenic
and that this carcinogenicity can be predicted based on noncarcinogenic endpoints; (2)
that the dose-response curve for the individual “dioxin-like” PCB congeners is parallel to
the dose-response curve for TCDD; (3) that the toxic effects of all those PCB congeners
in a mixture is additive; and (4) that there is no inter-species variability in sensitivities to
these compounds and specifically that the potency of TCDD and “dioxin-like” PCBs in
human cells is equivalent to that in animal cells. As discussed below, none of these
assumptions has been established and evidence exists to indicate that they are likely
incorrect. Reliance on these simplifying assumptions may account for the
overprediction of cancer potency discussed above.

Predicting Carcinogenicity of Individual Congeners Based on Noncancer Endpoints

Since the TEF/TEQ approach is designed to estimate the carcinogenic risks of the
dioxin-like PCB congeners, an underlying assumption of the method is that all these
congeners are carcinogenic agents and that the TEFs will accurately predict that
carcinogenicity. In fact, however, the TEFs are based on a number of different
endpoints, most of which are not related to carcinogenic activity.

The basis for expanding the TEF/TEQ approach to include PCBs was that scientists
found that the 12 coplanar PCB congeners exhibited some structural and toxicokinetic
similarities to TCDD. Safe (1990) hypothesized that responses to such compounds are
mediated through binding with a common receptor protein, the aryl hydrocarbon
receptor (AhR), and involve the induction of various cytochrome P-450 enzymes,
including aryl hydrocarbon hydroxylase (AHH) and 7-ethoxyresorufin-o-deethylase
(EROD). Using the TEFs to predict carcinogenicity thus assumes that if a compound
has the ability to induce these enzymes, it also has the ability to result in a carcinogenic
response.
This assumption has not been supported by evidence. For most of the 12 PCB congeners for which TEFs have been assigned, there are limited or no carcinogenicity data available. In fact, an indicator of carcinogenic activity (either cancer induction or promotion) is the basis for the TEFs for only three of those 12 PCB congeners. The majority of TEFs are based on enzyme induction studies and body and organ weight effects (WHO, 1997). For example, the TEF assigned for PCB congener 169 is based on EROD induction and thymic atrophy, and the TEF assigned for PCB congener 77 is based on EROD induction and hepatic retinol decreases. Thus, the appropriateness of the TEF approach rests upon the questionable scientific validity of extrapolating from endpoints such as body/organ weight changes and enzyme induction to tumorigenesis. Correlation between these endpoints and carcinogenic activity has not been established.

Shape of the Dose-Response Curve

Since the TEFs are used to equate the toxicity of PCB congeners to that of TCDD (at any dose or concentration), the approach also necessarily assumes that the dose-response curves for those congeners are parallel to that for TCDD. In order for TEFs to remain constant over the range of the doses or concentrations in the dose-response curve, both the shape of the dose-response curve and the maximum response must be the same for the PCB congeners and for TCDD. However, non-parallel dose-response curves for TCDD and dioxin-like PCB congeners have been reported.

Kennedy et al. (1996) investigated the dose-response relationships for several PCB congeners in avian hepatocyte cultures. Comparison of curves for the PCB congeners and TCDD indicated considerable differences in shape and maximum response. Specifically, the TEFs relating the toxicity of the PCB congeners to that of TCDD were as much as an order of magnitude higher at the effective concentration that caused a 50 percent response (EC50) than at the effective concentration that caused a 10 percent response (EC10). These results indicate that the dose-response curves are not parallel and that the TEFs derived based on the EC50 are not predictive of the toxicity at lower dose levels.

Similar findings were reported by Safe (1990), who evaluated the relative dose response for various dioxin, furan, and PCB congeners in terms of the potencies associated with different endpoints and different species. The relative potencies varied by more than an order of magnitude depending on the endpoints considered. For example, when comparing the relative potency of TCDD to that of 3,3',4,4',5-pentaCB at the EC50 levels in rats, Safe reported that TCDD was 66 times more potent for body weight loss, 8 times more potent for thymic atrophy, and 125 times more potent for AHH induction. Thus, it appears that, at least for certain PCB congeners, the dose response curves are not parallel to that for TCDD.
The Toxic Additivity of PCB Congener Mixtures

The TEF/TEQ approach also assumes that the toxicity of all individual PCB congeners in a mixture is additive. This assumption is unproven and likely incorrect.

Knowledge of the mechanisms by which AhR-active chemicals cause effects suggests that the PCB congeners' toxicities represented by TEFs should not be additive. The AhR binds with a variety of molecules. Whether the AhR binds with a chemical, and the strength of this binding, is a function of the shape of the chemical molecule. A chemical that binds weakly to the AhR may be replaced by a "competitor" chemical that forms a stronger bond with that receptor so that the binding is competitive rather than additive.

The fact that a chemical binds with the AhR does not indicate that it will cause an adverse effect. In fact, chemicals that bind with the AhR can have a beneficial effect (e.g., triggering a normal physiological response like enzyme induction), an adverse effect (e.g., triggering chloracne), or no effect. The adverse effects caused by chemicals that bind with the AhR can range from minor (e.g., inhibiting the production of certain cells useful in fighting infection) to major (e.g., causing reproductive disorders). A chemical that binds to the AhR and causes any effect is called an "agonist." A chemical that binds but has no effect (or inhibits a "normal" event) is called an "antagonist." The term "antagonist" results from the fact that chemicals that bind with a receptor with no adverse effect compete with agonists for sites on receptors – while an agonist occupies the site, an agonist does not occupy it and cause its effect. Moreover, even agonists can have antagonistic properties. For example, if an agonist that produces either a normal physiological effect or a minor adverse effect competes for a receptor and blocks it from another agonist that causes a more serious adverse effect, substantial harm has been avoided (Newsted et al., 1995; Walker et al., 1996).

Agonists that have antagonistic properties are sometimes called "partial" or "weak" agonists.

This understanding of the AhR mechanism substantially weakens the primary assumption of the TEF/TEQ approach that the potencies of individual agonists can be summed to predict the potency of a mixture of agonists in the body. Where antagonists are present in concentrations higher than the concentration of agonists, it is difficult for agonists to bind to receptors. Moreover, partial agonists or incomplete agonists compete with complete agonists for receptor binding sites. Thus, whenever a human body contains a mixture of complete agonists, partial agonists, and antagonists, the total impact on the body cannot possibly be predicted by the sum of the various agonist concentrations.

Empirical data indicate that PCB Aroclors have some such antagonistic properties. For example, Safe (1990) reported that Aroclor 1254 acts as a competitive antagonist to TCDD. Starr (1997) also reported that "PCBs and some PCDFs antagonize AhR-mediated responses including fetal cleft palate, hydronephrosis, immunotoxicity, embryotoxicity and induction of CYP1A1-dependent activities." Thus, additivity does not appear to be demonstrated across congeners and endpoints in animal studies, and the
applicability of this assumption to human dose response is even less certain. In these circumstances, it is unwarranted to assume that the toxicity of PCB mixtures can be predicted by summing the TEQs for the individual congeners.

**Inter-species Variability**

In addition to assuming that all “dioxin-like” PCB congeners are able to induce cytochrome P-450 enzymes, the TEF/TEQ approach assumes that the level of enzyme induction seen in animal studies is equivalent to the level of induction that occurs in exposed humans, and that thus the responses observed in the animal studies are predictive of human responses. As a result, the approach makes no adjustment for variability in species’ sensitivities. Several studies, however, demonstrate the fallacy in this approach.

To begin with, the rodent bioassays reveal considerable differences in response to PCB exposure even among genders and strains of the same species (EPA, 1996a, Table 3-1). For example, based on the Brunner et al. (1996) study, EPA (1996a) reported substantially lower ED_{10} values (and thus higher CSFs) for female Sprague-Dawley rats than for males of that strain for all the Aroclors tested. Similarly, EPA (1996a) reported considerably different ED_{10} values and CSFs for female Fisher rats exposed to Aroclor 1254 (upper-bound CSF of 0.2 (mg/kg-day)^{-1}) than for female Sprague-Dawley rats exposed to the same Aroclor (upper-bound CSF of 1.5 (mg/kg-day)^{-1}). The fact that carcinogenic responses are not even consistent among genders and strains of the same species makes it highly uncertain that these responses can be used to reliably predict human carcinogenic responses.

Moreover, a recent study by Zeiger et al. (2000) (Appendix A) demonstrates that there are substantial differences between human and rat cells in sensitivities to the enzyme induction of “dioxin-like” compounds. Zeiger et al. (2000) compared the concentrations of TCDD and 11 PCB congeners necessary to induce EROD activity in human and rat tumor cell lines. This study showed that the level of enzyme induction produced by cells exposed to individual PCB congeners was not constant across species, and that human cells were much less sensitive to dioxin-like PCB congeners than rat cells. Induction by individual PCB congeners was highly variable. For six of the 11 PCB congeners tested, no EROD induction was observed in human cells, despite the fact that induction was observed in the rat cells tested and WHO has assigned TEFs ranging from 0.00001 to 0.01 for them. While the relative potency of PCB congener 77 in human cells was slightly higher than its potency in rat cells, the potencies for PCB congeners 126 and 114 were substantially lower in human cells. In fact, for PCB congener 126, the observed potency was 50 times lower than the WHO TEF factor and 100 times lower than the potency observed in rat hepatoma cells. In addition, the relative potency of PCB congener 114 in human cells was lower than the potency in rat cells by more than a factor of three and was lower than the assigned TEF value of 0.0005 by more than a factor of eight.
Based on these data, and similar variations in response reported by Safe (1990) and Pohjanvirta et al. (1995), it can be concluded that there is substantial inter-species (as well as intra-species) variation in sensitivity of response to "dioxin-like" PCBs. In addition, it is clear that the TEFs calculated for PCB congeners in experiments with human cells can be much lower than those currently used in the TEF/TEQ approach to assess PCB toxicity. These factors further argue against the use of TEFs for risk assessments involving PCBs.

Reliability and Completeness of the Available Database

Finally, while not an inherent assumption of the TEF/TEQ approach, it is worth noting that that approach implicitly assumes that the available toxicological and epidemiological information for the individual PCB congeners, as well as their relationship to TCDD, is at least as reliable and complete as the information available for total PCBs and PCB Aroclors. This is not the case. There is a rich body of toxicological and epidemiological literature on total PCBs and PCB Aroclors, whereas the data on individual PCB congeners and their relationship to TCDD are relatively sparse and more uncertain. Hence, use of the TEF/TEQ approach unnecessarily involves far more uncertainties and has much less scientific support than evaluating the carcinogenic potential of PCBs based on the data for total PCBs or PCB Aroclors.

IV. Double Counting the Carcinogenic Potential of Dioxin-Like Congeners in PCB Mixtures

Under the TEF/TEQ approach, the available congener-specific data are used to estimate risks for the dioxin-like congeners through converting them to TCDD TEQs and then applying a CSF for TCDD. As discussed above, the risks from non-dioxin-like congeners are then estimated separately, using a CSF for PCBs — typically the upper-bound PCB CSF of 2 (mg/kg-day)^{-1} — and the two sets of risks are summed to provide an overall estimate of the carcinogenic risks of PCBs. This approach is not scientifically supportable and necessarily results in an overestimation of risks because it double counts the carcinogenic potency of the dioxin-like congeners in a PCB mixture.

The existing CSFs for PCBs (EPA, 1996a) characterize the carcinogenic potential of the entire PCB mixture, which includes both dioxin-like and non-dioxin-like congeners. Thus, if one evaluates the dioxin-like congeners using dioxin TEQs and then evaluates the non-dioxin-like components using a PCB CSF, the carcinogenic potential of the dioxin-like congeners is counted twice because their carcinogenic potential is already included in the CSF for PCBs. Even if the analysis subtracts out the concentrations of the dioxin-like congeners in making the risk calculations for the remaining PCBs, the double-counting still occurs because the calculated CSF for PCBs is based on toxicological studies of Aroclor mixtures that contained both dioxin-like and non-dioxin-like congeners. Indeed, EPA has attributed much of the so-called carcinogenic potency of PCB mixtures to the dioxin-like congeners (IRIS, 1998). Thus, the CSF of 2 (mg/kg-day)^{-1} is inclusive of the carcinogenic activity of both types of congeners and is much
too high to represent the carcinogenic potential of only the non-dioxin-like congeners. Without a CSF for non-dioxin-like PCBs, there is no defensible way to use both the TCDD CSF and the PCB CSF in the same assessment. Furthermore, as noted above, the toxicological and epidemiological databases for Aroclor PCBs are more reliable and complete than the databases for PCB congeners and thus should preferentially be used when a risk assessment includes Aroclor mixtures.

V. Use of an Uncertain CSF for TCDD

Use of the TEF/TEQ approach to evaluate PCBs is further undermined by the need to combine calculated TEQ dose estimates with an uncertain CSF for TCDD. EPA does not currently publish a CSF for TCDD in IRIS or HEAST and has never listed a CSF for TCDD on IRIS. A wide range of CSFs, spanning from 9,000 to 1,000,000 (mg/kg-day)$^{-1}$, have been proposed, with differences resulting from the selection of the low-dose extrapolation method model, the tumor classification scheme, and the cross-species scaling factor used (EPA, 1994, 2000; FDA, 1993, 1994; Keenan et al., 1991). In these circumstances, selection of any CSF within this range is associated with a high level of uncertainty. Indeed, in its review of EPA’s draft final Dioxin Reassessment, the Agency’s Science Advisory Board discussed the uncertainties associated with the available dose-response data and the extrapolation methods used, and stated that they could not “reach consensus on a single value for a dioxin potency factor” (EPA, 2001; p. 6).

There is no need to rely on the use of such a highly uncertain and controversial CSF for TCDD in evaluating the risks of PCBs. EPA has already developed conservative upper-bound CSFs for the more highly chlorinated PCB mixtures, ranging from 0.4 to 2 (mg/kg-day)$^{-1}$ (EPA, 1996a), which are based on bioassays and necessarily take into account the carcinogenic potency of the dioxin-like congeners. The highest of these upper-bound CSFs, 2 (mg/kg-day)$^{-1}$, was specifically identified (EPA, 1996a) as a conservative value for evaluating oral exposures (via food chain or soil/sediment pathways) and dermal exposures (via soil/sediment pathways when a dermal absorption factor is used) to Aroclors 1254 and 1260, which are the Aroclors found in the Housatonic River and its floodplain. As discussed in Section VI below, review of the human epidemiological and clinical evidence indicates that these CSFs overstate the carcinogenic potency of PCBs in humans. However, it is clear that that established approach for evaluating the dose-response of PCBs is superior to the TEF/TEQ approach, which relies on hypothetical structure/activity relationships, unproven toxic

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1 In prior comments to EPA on its planned human health risk assessment for the Housatonic River, General Electric has argued that there is no need for EPA to select any CSF for TCDD, since dioxins/furans can be evaluated through use of the dioxin Preliminary Remediation Goals previously established by EPA and the TEF/TEQ approach should not be used for PCBs. However, GE has also recommended that, if a CSF for TCDD must be selected, EPA should use a CSF of 30,000 (mg/kg-day)$^{-1}$. See Comments of the General Electric Company on EPA’s Human Health Risk Assessment Work Plan for the Lower Housatonic River (June 3, 1999) at pp. 20-22; Comments of the General Electric Company on EPA’s Final Human Health Risk Assessment Work Plan for Lower Housatonic River (June 12, 2000) at p. 11. GE continues to adhere to that position.
activity, and limited scientific foundation, and which unnecessarily introduces high levels of conservatism and uncertainty into the risk calculation.

VI. Inconsistency with Human Epidemiological and Clinical Evidence

The TEFs calculated by EPA and the risks predicted by the TEF/TEQ approach are also not borne out by the large body of human epidemiological and clinical literature on the potential cancer effects of PCBs. Numerous PCB-specific human mortality and cancer incidence studies have been performed over the last 25 years to evaluate potential associations between human occupational and/or environmental exposure to PCBs and various forms of cancer. A recent exhaustive review of this literature has evaluated these studies in the context of well-accepted criteria for causation, using a weight-of-evidence approach, to determine whether PCB exposure is causally related to an increased risk of human cancer (Golden and Shields, 2001) (Appendix B).4

This assessment reviewed and evaluated all the relevant human cancer studies available through March 2000 – which included 20 cancer mortality studies that investigated whether occupational exposure to PCBs is associated with cancer types of any kind, 21 clinical studies that investigated whether environmental exposure to PCBs is associated with an increased risk of breast cancer, and two studies that investigated potential associations between PCB exposure and endometrial cancer. These studies were evaluated using fundamental principles of “causation analysis” (which considers strength of association, dose-response relationship, specificity of association, consistency of association, biological plausibility, and temporally correct association), and were then assessed in an overall weight-of-evidence approach to answer the ultimate question of whether exposure to PCBs causes an increased risk of cancer. This weight-of-evidence approach utilizing the “causation analysis” principles is recognized and endorsed by EPA (EPA, 1996b), as well as the general scientific community, as a valid approach for distilling complex and discordant study results into a meaningful weight-of-evidence determination for risk assessment and risk management decisions.

Based on that approach, the assessment of the cancer mortality studies found that, even with occupational exposures to PCBs, which were generally many times greater than environmental exposures, there was insufficient evidence to establish that PCBs cause cancer in even those highly exposed workers. While there were some studies suggesting that occupational exposures might be associated with an increased risk of cancer, the results of these studies were either not credible or overwhelmingly offset by the results of larger or better-designed studies. Significantly, the results of follow-up studies that investigated the same study group more than once were consistent in not supporting the results from studies that reported an effect after looking at the study group only once. Overall, the weight of evidence did not support a causal association

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4 The copy of this report included in Appendix B includes, in Attachment A thereto, a list of the references for the studies reviewed. However, it does not include actual copies of those studies. Copies of those studies can be provided upon request.
between PCB exposure and any of the forms of human cancer studied, including liver cancer, rectal cancer, pancreatic cancer, malignant melanoma, hematologic cancer, gastrointestinal tract cancer, and "all cancers."

Similarly, the evaluation of the 21 clinical breast cancer studies, along with a number of the above-mentioned cancer mortality studies that included an investigation of breast cancer, revealed insufficient evidence that PCB exposure causes this type of cancer. In particular, the more recent and larger or better-designed studies have not supported an association between PCB exposure and breast cancer. The report thus concluded that the collective weight of evidence is that PCB exposure is not a causal risk factor for breast cancer. In addition, the two studies that investigated potential associations between PCB exposure and endometrial cancer concluded that there was no evidence for such an association.

Subsequent to the studies reviewed in the Golden and Shields (2001) assessment, two more recent studies have further supported the conclusion that PCBs are not causally related to breast cancer. In one recently reported study (which was one of the largest), Zheng et al. (2000) (Appendix C) concluded that "[t]he results do not support the hypothesis that DDE and PCBs increase the risk of breast cancer as encountered through environmental exposure." Likewise, the recent study by Demers et al. (2000) (Appendix D) concluded that, "[t]aken together, results from six large epidemiological studies reported during the last 2 years, including our own, provide little indication that organochlorine exposure is a risk factor for [breast cancer]."

In summary, a vast body of human epidemiological and clinical literature investigating the potential link between PCB exposure and cancer has been published. These studies have included both highly exposed worker populations as well as populations exposed to lesser environmental levels. In all instances where cancers have been reported and putatively associated with exposure to PCBs, subsequent studies, which were better designed, appropriately controlled for confounders, statistically more powerful, and otherwise more robust, did not confirm the original findings. The overall weight of evidence from these studies clearly supports the conclusion that PCBs do not cause cancer in humans.

This literature indicates that even the current bioassay-based CSFs for PCBs overstate the carcinogenic potency of PCBs in humans, and that it would be more appropriate to develop a revised CSF for PCBs based on these human studies. At a minimum, however, these studies demonstrate that the TEF/TEQ approach as applied to PCBs is unjustifiable, as it simply does not "fit" the empirical reality of the large-number of PCB-specific human cancer mortality and cancer incidence studies performed over the past quarter-century.

VII. Conclusions

Animal bioassays, in vitro experiments, AhR theory, and human epidemiological studies all strongly indicate that the TEF/TEQ approach substantially overestimates the
carcinogenic potency of PCBs. Because there is a paucity of data for many of the individual PCB congeners, the approach requires the use of myriad, unfounded assumptions about the similarities between those PCB congeners and TCDD, as well as an uncertain CSF for TCDD. These assumptions result in a high level of uncertainty and overestimation of carcinogenic potential when compared with empirical evidence.

For the reasons given in this paper, use of the TEF/TEQ approach to evaluate the cancer risks of PCBs in a human health risk assessment, such as that being conducted by EPA for the Housatonic River, is not currently defensible on a scientific basis. In addition, the use of that hypothetical, highly uncertain, and overly conservative methodology is not needed to evaluate such risks. EPA has already established a well-understood, conservative approach for evaluating cancer effects of PCBs using CSFs based on animal bioassays (EPA, 1996a). As discussed in Section VI, these animal bioassay-derived CSFs are themselves overly conservative in estimating potential carcinogenic risks to humans, and hence it would be more appropriate to develop a revised CSF for PCBs based on the human data. Nevertheless, use of the current CSFs for PCBs is at least based on empirical studies of PCB mixtures and thus, at this time, is more supportable than use of the TEF/TEQ approach.

References


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