TECHNICAL SUPPORT DOCUMENT FOR CANCER POTENCY FACTORS

APPENDIX C

Use of the Toxicity Equivalency Factor (TEF_{WHO-97} and TEF_{WHO-05}) Scheme for Estimating Toxicity of Mixtures of Dioxin-Like Chemicals

Updated by

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Outline of the presentation

- Introduction
- Toxic Equivalency Factors (TEFs)
- History of TEF development
- The basis of TEF methodology: The *Ah* receptor
- TEQ calculation: the assumption of additivity
- Uncertainties associated with the use of the TEF methodology
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Dioxin and dioxin-like compounds (DLCs)

- Dioxin (PCDDs) are chemically dibenzo-p-dioxins. One of the best known is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), while DLCs (PCBs and PCDFs) are a group of related chlorinated compounds.

- Dioxin and DLCs are ubiquitous global environmental contaminants (released from several industrial sources, including chemical manufacturing, combustion, and metal processing).

- Dioxin and DLCs are toxic, with a wide range of effects at low doses including carcinogenicity, immunotoxicity, reproductive and developmental toxicity, and endocrine toxicity.

Toxic Equivalency Factors (TEFs)

- **Some confusion regarding the definition of TEF. For example:**

  a) **As a relative potency value that is based on the results of several *in vivo* and *in vitro* studies;**

  b) **TEF as the relative potency of a compound relative to TCDD to cause a particular toxic or biological effect in a single study;**

  c) **TEF is frequently used to refer to an end point that is not a toxic response per se, such as binding affinity to the aryl hydrocarbon (Ah) receptor or induction of cytochrome P4501A1, although these biochemical effects may in some way associated with subsequent toxic responses.**

- **While the WHO TEF indicates an order of magnitude estimate of the toxicity of a compound relative to TCDD. The WHO TEF value has been derived using careful scientific judgment after considering all available scientific data.**

Scientific publications selection criteria for the WHO TEF

A. At least one PCDD, PCDF, or PCB congener and a reference compound must be included in the study.

B. Either TCDD or PCB 126 must be included as a reference compound in the same experiment or studied with the same experimental design by the same authors in another experiment.

C. The relevant end point should be affected by the congener studied as well as the reference compound.

Compound selection criteria for inclusion in the TEF concept

A. Show a structural relationship to the PCDDs and PCDFs;

B. Bind to the *Ah* receptor;

C. Elicit *Ah* receptor-mediated biochemical and toxic responses;

D. Be persistent and accumulate in the food chain.

For *in vitro* studies, the following experimental design is suggested to determine an REP (van den Berg *et al.*, 2006):

- **A vehicle group and at least four graded concentrations of a congener and four graded concentrations of 2,3,7,8-TCDD should be selected.**
- **For congener and 2,3,7,8-TCDD treatment groups, three of these concentrations should elicit a response that falls between the EC_{20} and EC_{80} for the congener and for 2,3,7,8-TCDD.**
- **At least one concentration should elicit a maximal response (EC_{100}), and the concentration-response curves should be parallel.**
- **The REP should be based on the EC_{50} of 2,3,7,8-TCDD and the EC_{50} of the congener.**

The following general guidelines for a future ideal dose-response study used to determine an *in vivo* REP (van den Berg *et al.*, 2006):

- A full dose-response curve for both the congener and for 2,3,7,8-TCDD should be determined.
- The congener and 2,3,7,8-TCDD should be administered by the same route to animals of the same species, strain, sex, and age, and the animals should be housed, fed the same diet, and maintained under the same conditions in the same laboratory.
- Ideally, the absolute maximal response (efficacy) should be similar for both the congener and for 2,3,7,8-TCDD and their dose-response curves should be parallel, but in practice, this is often not observed for various reasons.
- If the above dose-response criteria are met, the REP should be calculated by dividing the effective dose 50% (ED_{50}) of 2,3,7,8-TCDD by the ED_{50} of the congener.
- If full dose-response relationships are not attained and determination of ED_{50}'s is not possible, lowest observed effect doses or concentrations or benchmark doses could be used to determine the REP. However, such an REP has more uncertainty than if ED_{50}'s were used.

The criteria for inclusion or exclusion of an REP in this database (Haws et al., 2006) were accepted by the expert panel can be summarized as follows (van den Berg *et al.*, 2006):

- At least one test congener and a valid reference compound must have been included in the study or the reference compound must have been included in an identical experiment from the same laboratory, but in another study.
- The endpoint must have been an established *Ah*R-mediated response known to be affected by both the test congener and the reference compound.
- In the REP database, *in vivo* and *in vitro* studies were separated.
- Repetitive endpoints (i.e., measures of the same biological response) were identified in all studies in the database, and the most representative REP value was retained for reevaluation of a TEF.
- Those studies that used only a single-dose level of either the test and/or reference compound were filtered out of the REP database and not used in the TEF reevaluation process.
- Results from non-peer–reviewed studies were not used in reevaluating a TEF value and consequently did not contribute to the distribution of REPs for individual congeners.
- REPs based on biological responses that were statistically significant were included in the 2005 REP database and contributed to the distribution of REPs for individual congeners used to reevaluate TEFs. However, when there was a very limited data set for an individual congener, the panel also considered biological responses that were not statistically significant as part of the overall expert judgment in reevaluating a TEF value.
- REPs based on quantitative structure-activity relationship studies were included in the REP database.

TEFs and Toxic Equivalence (TEQ)

- Risk assessment for dioxin and DLCs uses a TEF approach, relating the potency of individual congeners to that of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).
- The TEF method is based on congener binding and activation of *Ah*-receptor-mediated enzyme activities.
- TEFs are used to calculate TEQ that is the sum of all individual congener's TEF multiplied by each congener's concentration in the mixture.
- Total Toxic Equivalence (TEQ) = $\sum_{n=1}^{k} (Cn \times TEFn)$

Major History of TEF development

- 1983. Ontario Ministry of Environment introduces the TEF concept, based on a common mechanism of action (activation of the *Ah*R) for PCDDs and PCDFs.
- 1986. California adopts "California TEFs" in TAC identification document for dioxins.
- 1988. North Atlantic Treaty Organization (NATO) presents international TEF (I-TEF) scheme for dioxins and PCDFs.
- 1989. U.S. EPA adopts the I-TEF scheme.
- 1993. ECEH and IPCS of the World Health Organization (WHO) proposed TEF values for 13 dioxin-like-PCBs including di-ortho congeners;
- 1997: California TAC program lists I-TEF in update.
- 1997: WHO developed TEF_{WHO-97}, a revised set of global consensus TEFs. The di-*ortho* PCBs were deleted.
- 1999. California's Hot Spots program includes I-TEF in formal TSD.
- 2003. California's Hot Spots program adopts TEF_{WHO-97}
- 2005; WHO develops TEF_{WHO-05}, a further revision of the consensus table.

The basis of TEF methodology: The *Ah* receptor

- **Many PCDDs, PCDFs, and dioxin-like-PCBs are sharing a common mechanism of action (*Ah* receptor binding) intimately related to similarities in their structural configuration.**
- **The mechanism of *Ah* receptor for these compounds is derived from research in three areas:**
  I. structure-activity relationships for receptor binding and induction of a variety of biochemical and toxicological responses;
  II. genetic studies using inbred mouse strains;
  III. studies at the molecular level that have elucidated key events in the actions of the receptor.

Polymorphism of the *Ah* Receptor and its ligands

- **Polymorphism of the *Ah* Receptor: generating great variability between intraspecies and interspecies;**
- **Ligands for the *Ah* Receptor:**
  1. **Dioxin and DLCs are anthropogenic ligands for the *Ah*R, while they are persistence and bioaccumulation in wildlife and humans;**
  2. **In contrast, naturally occurring *Ah*R ligands have short half-lives, but nevertheless have frequently been cited in criticism of the TEF methodology.**
  3. **Naturally occurring *Ah*R-ligands include: indole derivatives (indole-3-carbinol (I-3-C), 3,3'-diindolylmethane (DIM), indolocarbazoles (ICZs) etc.), heterocyclic aromatic amines (HAAs), and oxidized essential amino acids.**

Basis of TEQ calculation - the assumption of additivity

- The TEF/TEQ methodology is based on the scientific assumption that the *Ah*R mediates the biochemical and toxicological actions of DLCs.
- Another essential assumption in the development of the TEF methodology is the one of additive interactions.
- Although there are numerous scientific reports on the synergistic or antagonistic interaction of mixtures of DLCs and/or non-DLCs with TCDD, reports on the additive effects of DLCs predominate, especially under low doses of exposure.

Uncertainties associated with the use of the TEF methodology

- Quantifying uncertainty surrounding the TEF estimate is difficult.
- TEF estimates are generated from several sources of experimental data and for some congeners can vary by several orders of magnitude.
- This apparent variability has been attributed to different exposure regimens, test species, or purity of the test compound.
- WHO TEF 2005 reevaluation process used the refined TEF database published by Haws et al (2006) as a starting point, which will facilitate better characterization of the variability and uncertainty inherent in the data.
- Decisions about a TEF value were made based on a combination of unweighted relative effect potency (REP) distributions from Haws' database, WHO expert judgment, and point estimates.
- WHO TEF estimates are point estimates, derived from scientific semi-quantitative judgment based on examination of REP for various end points, which provide valuable insight in the estimation of TEQs.

Criticisms concerning the TEF approach mainly focus on four areas

- Non-additive interaction of dioxin-like-congeners when there is co-exposure to non-dioxin-like-congeners, particularly PCB 153;
- Differences in species responsiveness;
- Differences in the shape of the dose-response curves between individual *Ah*R agonists;
- Mono-*ortho* PCBs in the TEF concept.

Non-additive interaction with PCB 153

- Non-additive interactions in mixtures containing both PCDDs/Fs and specific *ortho*-substituted PCBs such as PCB 153 (a di-*ortho* PCB);
- Several "non-dioxin-like" PCBs, including PCB 153 and commercial PCBs exhibit "anti-dioxin" or *Ah*R antagonist activity;
- Non-additive interactions between PCB 153 and dioxin-like-PCBs were also reported by Harper *et al.* (1995);
- Zhao *et al.* (1997) reported an antagonistic interaction between PCB 153 and PCB 126.
- While PCB 153 is not on the WHO TEF list yet, although majority of publications, including NTP study, support the increased toxicity after co-exposure to PCB153 and DLCs.

Differences in species responsiveness

- Species differences in the functional responses to dioxin and DLCs could be important.
- Several factors, including pharmacokinetics/toxicokinetics, receptor distribution and affinity, agonistic action on receptor upon binding, etc. may be involved.
- There is a large difference of liver/adipose tissue distribution among species and dose levels used.
- However, most biological effects caused by DLCs occur at levels of DLCs that differ by less than one order of magnitude between species;
- In general, the binding affinity data of different *Ah*R ligands has limited usefulness as a predictor of agonist activity. Induction potency of CYP1A1 in cell culture for a number of *Ah*R ligands was poorly correlated with *Ah*R binding affinity *in vivo*.

Differences in the shape of the dose-response curves for individual *Ah* receptor agonists

- Several reports such as Schrenk *et al.* 1991 and van den Berg *et al.*, 2000, etc. mentioned that individual *Ah* receptor agonists may exhibits different dose-response curve shapes.
- However, for tests of *Ah*R activation *in vitro* were in a relatively simple fashion, dose-response slopes for potent PCDDs and PCDFs are generally reported to be similar. For example, the induction of CYP1A1 activity in hepatocytes by dioxin-like-PCBs generates dose-response curves with similar slopes.
- NTP evaluated the TEF approach in their 2-year rodent cancer bioassays and found that the shape of the dose–response curves for hepatic, lung, and oral mucosal neoplasms was the same in studies of the TCDD, PCB-126, PCDF alone, or a mixture of them.
- NTP also showed that use of the current WHO TEF values adequately predicted the increased incidence of liver tumors induced by exposure to the mixture (Walker et al., 2005).

Mono-*ortho* PCBs in the TEF concept

- DLCs include some mono-*ortho* PCBs, but not all of mono-*ortho* PCBs such as PCB 28;
- Di-, tri-, and tetra-*ortho* PCBs can share the non-*Ah*R-mediated pathway, which introduces more uncertainty in the risk assessment especially when considering end points common to both of *Ah*R and non-*Ah*R pathways;
- NAS (2006) reported that "Overall, even given the inherent uncertainties, the toxic equivalency factor (TEF) method provides a reasonable, scientifically justifiable, and widely accepted method to estimate the relative toxic potency of DLCs on human and animal health.

Implication of the TEF methodology

- The use of the TEF method allows for a more accurate estimate of the health risks for exposure to the complex mixture of DLCs.

- However, something needs to be bearded in mind such as:
  - The profile of chemical constituents in a mixture could change as the released mixture moves away from its source and as it ages over time.
  - Other chemicals such as di-*ortho* PCBs (no *Ah*R-mediated pathway) and endogenous DLCs (not included in the WHO TEF) might bias the risk assessment estimate from the TEF methodology.
  - Thus, improvements to the TEF methodology should include risk assessment methods considering not only *Ah*R-mediated toxicological responses but also those mediated by other toxicological pathways.

Implication of the new WHO TEF methodology

- Many criteria for regulation of DLCs contamination are based on TEQs and a harmonized method is needed for worldwide comparisons.
- There may be changes to the total TEQ estimates from a variety of sources depending on the TEF scheme used.
- However, new WHO TEFs provide better results as more data considered by experts.

Conclusion

- The WHO TEF/TEQ methodology is currently the best available method for assessing risk of dioxin and DLCs in terms of *Ah* receptor mechanism, although some limitations exist.
- The TEF approach has been adopted by interested parties on condition that the TEF methodology remains an interim method and that it should be reevaluated periodically.
- OEHHA has used it in the Technical Support Document for Cancer Potency Factors for many years and will continue to use this current version until the next update or extension of the methodology appears.
- Since the exclusion of non-DLCs from the TEF methodology , the ultimate goal should aim to include both cancer and non-cancer effects of non-DLCs in order to have a more accurate estimate of the health risk caused by these persistent and bioaccumulative chemicals.
- At this point, it is important for public health protection that the most scientifically relevant and up-to-date TEF methodology be used.

Table 1. TEF values used or proposed in California

Congener	California TEF [a]	I-TEF [b]	TEF $_{WHO-97}$ [c]	TEF $_{WHO-05}$ [d]
PCDDs				
2,3,7,8-TCDD	1	1	1	1
1,2,3,7,8-PeCDD	1	0.5	1	1
1,2,3,4,7,8-HxCDD	0.03	0.1	0.1	0.1
1,2,3,6,7,8-HxCDD	0.03	0.1	0.1	0.1
1,2,3,7,8,9-HxCDD	0.03	0.1	0.1	0.1
1,2,3,4,6,7,8-HpCDD	0.03	0.01	0.01	0.01
1,2,3,4,6,7,8,9-OCDD		0.001	0.0001	0.0003
PCDFs				
2,3,7,8-TCDF	1	0.1	0.1	0.1
1,2,3,7,8-PeCDF	1	0.05	0.05	0.03
2,3,4,7,8-PeCDF	1	0.5	0.5	0.3
1,2,3,4,7,8-HxCDF	0.03	0.1	0.1	0.1
1,2,3,6,7,8-HxCDF	0.03	0.1	0.1	0.1
1,2,3,7,8,9-HxCDF	0.03	0.1	0.1	0.1
2,3,4,6,7,8-HxCDF	0.03	0.1	0.1	0.1
1,2,3,4,6,7,8-HpCDF	0.03	0.01	0.01	0.01
1,2,3,4,7,8,9-HpCDF	0.03	0.01	0.01	0.01
1,2,3,4,6,7,8,9-OCDF		0.001	0.0001	0.0003

Table 1 continues to next page

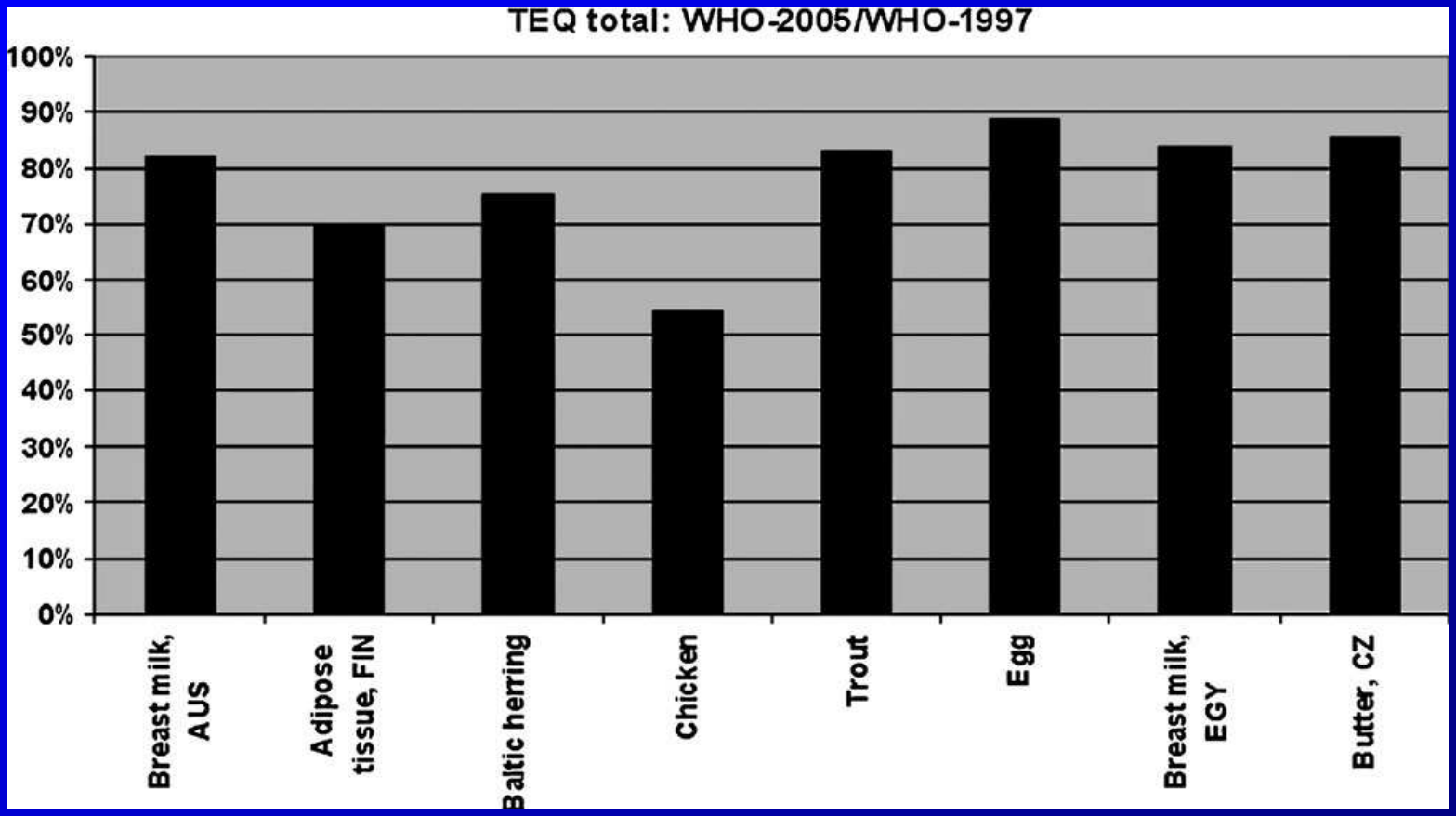
Table 1. TEF values used or proposed in California - *continued*

Congener		California TEF [a]	I-TEF [b]	TEF $_{WHO-97}$ [c]	TEF $_{WHO-05}$ [d]
PCBs (IUPAC #, Structure)					
77	3,3',4,4'-TCB			0.0001	0.0001
81	3,4,4',5-TCB			0.0001	0.0003
105	2,3,3',4,4'-PeCB			0.0001	0.00003
114	2,3,4,4',5-PeCB			0.0005	0.00003
118	2,3',4,4',5-PeCB			0.0001	0.00003
123	2',3,4,4',5-PeCB			0.0001	0.00003
126	3,3',4,4',5-PeCB			0.1	0.1
156	2,3,3',4,4',5-HxCB			0.0005	0.00003
157	2,3,3',4,4',5'-HxCB			0.0005	0.00003
167	2,3',4,4',5,5'-HxCB			0.00001	0.00003
169	3,3',4,4',5,5'-HxCB			0.01	0.03
170	2,2',3,3',4,4',5-HpCB			0	-
180	2,2',3,4,4',5,5'-HpCB			0	-
189	2,3,3',4,4',5,5'-HpCB			0.0001	0.00003

= Value introduced or changed

[a] CDHS, 1986 . [b] NATO/CCMS, 1989. [c] van Leeuwen, 1997. [d] Van den Berg, 2006.

Figure 2. Percentage of reduction in total TEQ levels calculated for the same biotic samples when WHO-05 TEFs rather than WHO-97 TEF are used



For each biotic sample shown, the height of the bar is the percentage that the total TEQ level determined using WHO-05 TEFs is of the total TEQ level determined using WHO-97 TEFs. Source: van den Berg *et al*., 2006.

Responses to the comments of Todd Abel on behalf of the Chlorine Chemistry Division of the American Chemistry Council

- ***OEHHA needs to include the most recent technical literature in its review of TEFs and TEF methodology (from cover letter)***

- **OEHHA has added/cited some new literatures in the document following public comments, which include references by Amakura Y, et. al. 2003; Connor KT, et. al. 2008; de Waard WJ, et. al. 2008; Degner SC, et. al. 2009; Giesy JP, et. al. 1998; Haws LC, et. al. 2006; Hong B, et. al. 2009; Huwe J, et. al. 2009; Jeuken A, et. al. 2003; NTP, 2006; Seegal RF, et. al. 2010; Simon T, et. al. 2008; Zhang S, et. al. 2003; and Zhang S, et. al. 2008. However, none of theses references would change the TEF method or values used in risk assessment for dioxin and dioxin-like chemicals (DLCs) based on the WHO TEF criteria.**

Responses to the comments of Todd Abel on behalf of the Chlorine Chemistry Division of the American Chemistry Council - *continued*

- ***the recent review of the TEF methodology by the National Academy of Sciences (NAS, 2006)***

➢ **OEHHA agrees with the statement in the National Academy of Sciences (NAS, 2006) report that "overall, even given the inherent uncertainties, the toxic equivalency factor (TEF) method provides a reasonable, scientifically justifiable, and widely accepted method to estimate the relative toxic potency of DLCs on human and animal health." (*http://www.ejnet.org/dioxin/nas2006.pdf*).**

Responses to the comments of Todd Abel on behalf of the Chlorine Chemistry Division of the American Chemistry Council - *continued*

- ***the recent 2-year cancer bioassays conducted by the National Toxicology Program (NTP) to evaluate the TEF methodology by assessing mixtures of dioxin-like compounds (NTP, 2006a-g; 2009)***

- **OEHHA has cited the National Toxicology Program (NTP, 2006) report. This report provides results of a series of studies in which rodents were exposed to either a single dioxin-like compound or mixtures of them for up to two years, and then evaluated for toxicity and carcinogenicity relative to TCDD. The NTP notes "Analysis of data from one group of completed studies confirms the assumption that the effects of the dioxin-like compounds in mixtures are additive. The number of cancer cases in the rats exposed to the mixture could be predicted accurately by adding the concentration of each compound, adjusted for its potency relative to TCDD using TEFs."**

  (*http://ntp.niehs.nih.gov/ntp/Factsheets/DioxFacts061.pdf*).

Responses to the comments of Todd Abel on behalf of the Chlorine Chemistry Division of the American Chemistry Council - *continued*

- ***the paper by Haws et al. (2006), which presented the refined database that served as the basis for the 2005 WHO review***

- **OEHHA recognizes that the WHO TEF 2005 reevaluation process had used the refined TEF database published by Haws et al. (2006) as a starting point, which facilitated better characterization of the variability and uncertainty inherent in the data (Haws, et al. 2006). Decisions about a TEF value were made based on a combination of unweighted relative effect potency (REP) distributions from Haws' database, expert judgment, and point estimates (Van den Berg, et al. 2006).**

Responses to the comments of Todd Abel on behalf of the Chlorine Chemistry Division of the American Chemistry Council - *continued*

- ***the USEPA (2008) document concerning the applications of TEFs in the assessment of ecological risk (which includes concepts that are directly applicable to both human health and ecological risk assessment)***

➢ **OEHHA knows the U.S. EPA's new draft (2009) for adopting the WHO 2005 TEF values at *http://www.epa.gov/raf/files/hhtef_draft_090109.pdf* and their final version was just released on January, 2011 at *http://www.epa.gov/osa/raf/files/tefs-for-dioxin-final-epa-100-r-10-005.pdf*.**

- ***additional publications that provide important new information concerning the mode of action, toxicity, and relative potency for various dioxin-like compounds, as well as the applicability of TEF methodology (e.g., Carlson et al., 2009; Connor et al., 2008; Simon et al., 2008; Zhang et al., 2008; Budinsky et al., 2006)***

➢ **OEHHA has cited some references and rejected others; please refer to our responses below and to comment 24 for further details.**

Responses to the comments of Patricia Kablach Casano on behalf of the General Electric Company

- ***The WHO TEFs are based on feeding studies and, consequently, should be used only to assess risks from dietary intake. Using the WHO TEFs to assess inhalation risks is not appropriate.***

- **Although human risk assessments ideally use human data or animal data that have the exact same exposure route as humans do, inhalation values can be generated from other routes (e.g., dietary) with proper conversion factors. The TEF methodology is not restricted to any particular exposure route. Its use in this way was endorsed by previous guidance issued under the Toxic Air Contaminants program (AB1807) and Air Toxics Hot Spots program (AB2588), as well as by the WHO and U.S. EPA.**

Responses to the comments of Patricia Kablach Casano on behalf of the General Electric Company - *continued*

- ***Basic assumptions upon which the WHO TEFs are based do not withstand scrutiny.***
  - ***The WHO TEFs assume that there are no differences in the response of humans and rodents to TCDD and PCBs, including PCB 126.***

- **The TEF methodology has been developed by a series of respected expert committees, of which the WHO 2005 TEF paper (van den Berg et al. 2006) is the latest report, and has been endorsed by a wide range of authorities including various California programs and the U.S. EPA. We concur with these generally accepted conclusions. The methodology does not claim that there is no difference between humans and animals, but rather uses the assumption that responses in animals are a reasonable analogue of the responses in humans. This is a basic assumption in toxicology.**

Responses to the comments of Patricia Kablach Casano on behalf of the General Electric Company - *continued*

- ***Repeated investigations have shown that:***
  - ***a) humans are an order of magnitude less sensitive to TCDD than responsive rodents;***
  - ***b) humans are two to three orders of magnitude less sensitive to the most toxic PCB – PCB 126 – than responsive rodents.***

➢ **OEHHA does not agree with these sweeping assertions, but in any case they relate to possible values of the TCDD potency rather than to the validity or implementation of the TEF methodology.**

Responses to the comments of Patricia Kablach Casano on behalf of the General Electric Company - *continued*

- ***The TEF approach assumes that the interactions of dioxinlike chemicals with the AH Receptor are additive (i.e., combining such chemicals increases toxicity).*** *- The assumption of additivity ignores competition among molecules to bind with the Ah receptor. Additivity has not been demonstrated across congeners and endpoints in animal studies.*

- **The additive property of dioxin-like effects was confirmed at low doses (NTP study), which is the important dose range for environmental risk assessment. However, as noted in our document, higher doses may show either competitive or synergetic effects.**

Responses to the comments of Patricia Kablach Casano on behalf of the General Electric Company - *continued*

- ***The WHO TEFs assume that the dose-response curves for dioxinlike PCBs are parallel to that for TCDD. Studies done by EPA's National Toxicology Project have shown that this assumption is invalid.***

➢ **The shape of the dose-response curve for TCDD and the DLCs may not be exactly the same. But the general consensus of the WHO expert committees and other scientifically informed commentators is that the similarities are sufficient to allow use of the TEF methodology in estimating risks from dioxin-like PCBs, at the low levels generally encountered in environmental exposure situations. OEHHA endorsed this approach in adopting the I-TEF methodology in 1999 and the WHO TEF methodology for dioxin-like PCBs in May 2009 after extensive public comment and peer review. The currently proposed action makes no change in this part of the established guidance.**

Responses to the comments of Patricia Kablach Casano on behalf of the General Electric Company - *continued*

- ***The WHO TEFs assume that there is a reliable estimate of the carcinogenicity of TCDD itself, but there is no scientific consensus on that cancer slope factor.***

➢ **OEHHA has a cancer slope factor for TCDD which was adopted after extensive peer review and public comment, and which is similar if not identical to values adopted by other regulatory agencies.**

- ***The WHO TEFs are not appropriate for body burden assessments.***

➢ **It is unclear what evidence the commenter is using as a basis for the assertion, and also what bearing it has on the proposal to update the TEF table to the latest version proposed by the WHO expert committee.**

Responses to the comments of Patricia Kablach Casano on behalf of the General Electric Company - *continued*

- ***Human epidemiological studies do not support the view that that there is a causal association between exposure to PCBs and cancer in humans. In fact, the epidemiological studies show that PCBs do not cause cancer in humans at environmental or occupational exposures.***

➢ **Although there is evidence for increased cancer risk/mortality from both occupational and environmental PCB exposures (De Roos et al., 2005; Demers et al., 2002; Nelson, 2005; Salehi et al., 2008), PCBs are classified as "probable human carcinogens" by the WHO and "class 2B" by the International Agency for Research on Cancer (IARC), based on insufficient human evidence (Carpenter, 2006), but sufficient evidence of carcinogenicity in animals. Both DL- and non-DL-PCB congeners can promote cancers (Knerr and Schrenk, 2006). It is important to recognize that non-positive results in studies of limited power cannot be used to "show that PCBs do not cause cancer".**

Responses to the comments of Patricia Kablach Casano on behalf of the General Electric Company - *continued*

- ***There is no validated method for performing the PCB congener analysis required to implement the TEF approach for PCBs. EPA's interlaboratory study demonstrates that Method 1668A, which purports to analyze all 219 PCB congeners, does not produce reliable data, and cannot be used consistently across labs.***

➢ **We acknowledge that the reliability and sensitivity of detection methods are a developing area of science and technology. However, there are plenty of examples in the literature, including some that were provided in the current revised draft of Appendix C, which show that useful results can be obtained with currently available methodology. Adoption or recommendation of analytical methods is not OEHHA's responsibility, but rather for the current purpose is undertaken by the California Air Resources Board.**

Responses to the comments of Patricia Kablach Casano on behalf of the General Electric Company - *continued*

- ***The TEFs were not developed in accordance with established principles for ensuring the reliability of science, including the principle that a review of a mass of relevant studies should include an exposition of the reasoning that led the reviewers to (1) include some studies and exclude others; (2) give more weight to some studies than to others; and (3) reach the conclusions that were drawn.***

➢ **OEHHA is satisfied that the WHO's expert committee's process and conclusions meet the accepted standards for expert evaluation and reporting, especially when the most recent report is considered in the context of an ongoing process of development and updating of the TEFs which is extensively reported in the scientific literature. However the important point in the present context is that OEHHA has considered use of this type of methodology on a number of previous occasions, starting with the original Toxic Air Contaminants document in 1986. It is on these deliberations, which used the statutorily mandated process of public comment and peer review, which OEHHA relies in applying the TEF methodology. The current proposal merely updates the table of values, without requiring or proposing any change to the underlying method.**

Responses to the comments of Patricia Kablach Casano on behalf of the General Electric Company - *continued*

- ***Appendix C purports to "update[] the background and methodology for use of the TEF method for dioxins and DL [dioxin-like]-compound[s]" as compared to the 2003 version of Appendix C. Appendix C does not, however, cite or discuss numerous relevant scientific papers that have been published since 2003.***

➢ **Appendix C does cite some related literature, but it is not intended as a general review paper and does not include papers not directly related to the proposed use of the TEF table. Appendix C describes the background, history, method, and usage of the WHO TEFs. The description of the methodology is the same as before except for including items related to the updating of some TEF values.**

Responses to the comments of Patricia Kablach Casano on behalf of the General Electric Company - *continued*

- ***OEHHA has framed its proposed TEF approach as "guidance," but it will effectively revise the Toxic Air Contaminant (TAC) listing and TAC health effects values for co-planar PCBs. Both the listing of TACs as well as the establishment of TAC health effects values are expressly subject to the California Administrative Procedure Act, Cal. Gov. Code §11340 et seq. ("CAPA"). Appendix C clearly was not adopted in accordance with the requirements of CAPA.***

➢ **OEHHA is making the current proposal as a revision to the Air Toxic Hot Spots guidelines required by Health and Safety Code section 44360. OEHHA is following the requirements of the law concerning preparation of the guidelines (see specifically, Health and Safety Code section 44360 (b)(2), which contains an exemption to the Administrative Procedure Act).**